

20-1025 (Lead); 20-1138 (Consolidated)

**UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT**

ENVIRONMENTAL HEALTH TRUST; CONSUMERS FOR SAFE CELL
PHONES; ELIZABETH BARRIS; THEODORA SCARATO

CHILDREN'S HEALTH DEFENSE; MICHELE HERTZ; PETRA BROKKEN;
DR. DAVID O. CARPENTER; DR. PAUL DART; DR. TORIL H. JELTER; DR.
ANN LEE; VIRGINIA FARVER, JENNIFER BARAN; PAUL STANLEY, M.Ed.

Petitioners

v.

FEDERAL COMMUNICATIONS COMMISSION;
UNITED STATES OF AMERICA

Respondents

Petition for Review of Order Issued by the
Federal Communications Commission

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SECTION 15

Evidence for Disruption by Modulation Role of Physical and Biological Variables in Bioeffects of Non-Thermal Microwaves for Reproducibility, Cancer Risk and Safety Standards 2012 Supplement

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ABSTRACT

Diverse biological responses to non-thermal (NT) microwaves (MW), including adverse health effects related to increased cancer risk, have been studied by multiple research groups all over the world. In approximately half of these studies, no any effects were found (negative studies), while the other half reported the NT MW effects (positive studies). This fact is often referred to as non-reproducibility of the NT MW effects. In most cases, such a conclusion is based on comparing studies, which significantly differ in important biological and physical variables/parameters. The aim of this chapter is to provide an overview of the complex dependence of the NT MW effects on various physical and biological parameters, which must be controlled in replication studies. To the aim of this paper, all studies available to the author, which included analysis of different variables/parameters and reported some positive NT MW response to be a reference for analyzing its dependence on physical and biological parameters, were included. Selection criteria included relevant experimental design, methodological quality and statistical analysis. Besides dependencies on carrier frequency, modulation, genotype, physiological traits, presence of radical scavengers and antioxidants, reported by many research groups, the emerging data suggest dependencies of the NT MW effects on polarization, intermittence and coherence time of exposure, static magnetic field, electromagnetic stray fields, sex, age, individual traits, cell density during exposure. This overview provides clear evidence that in most cases, the references to non-reproducibility of the NT MW effects are not correct. Unfortunately, most reviews and panels in the field do not include analysis of various biological variables and physical parameters when comparing the data on the NT MW effects from different studies. As result, misleading conclusion is often made that MW at NT levels produce no “reproducible” effects. Our analysis suggests that different (bandwidth, frequency, modulation, polarization) NT MW signals should be considered as separate agents in setting the safety standards. The data also indicate that duration of exposure may be as important as power density (PD) and specific absorption rate (SAR), and, therefore, the "dose" and duration of exposure should also be considered in safety standards along with PD/SAR. Further evaluation of the dependencies of NT MW effects on biological and physical variables/parameters are needed for understanding the mechanisms by which NT MW affect biological systems, planning *in vivo* and epidemiological studies, setting the safety standards, and minimizing the adverse effects of MW from mobile communication.

Keywords: non-thermal effects of microwaves, mobile (cellular) phones, safety standards.

List of Abbreviations:

Anomalous viscosity time dependence (AVTD); blood-brain barrier (BBB); catalase (CAT); Digital Enhanced (former European) Cordless Telecommunications (DECT); circularly polarized (CP); continuous wave (CW); Digital Advanced Mobile Phone System (DAMPS); discontinuous transmission (DTX); electroencephalographic (EEG); electromagnetic field (EMF); embryonic stem (ES) cells; ethidium bromide (EtBr); extremely low frequency (ELF); Gaussian Minimum Shift Keying (GMSK); Ginkgo biloba (Gb); Global System for Mobile Communication (GSM); glutathione peroxidase (GSH-Px); International Commission for Non-Ionizing Radiation Protection (ICNIRP); linearly polarized (LP); malondialdehyde (MDA); micronucleus (MN) assay; microwaves (MWs); N-acetyl-beta-d-glucosaminidase (NAG); nitric oxide (NO); non-thermal (NT); ornithine decarboxylase (ODC); phorbol ester 12-myristate 13-acetate (PMA); phosphorylated H2AX histone (γ -H2AX); power density (PD); regional cerebral blood flow (rCBF); Russian National Committee on Non-Ionizing Radiation Protection (RNCNIRP); specific absorption rate (SAR); static magnetic field (SMF); superoxide dismutase (SOD); Time Division Multiple Access (TDMA); tumor suppressor p53 binding protein 1 (53BP1); ultraviolet (UV); Universal Mobile Telecommunications System (UMTS).

I. THERMAL VERSUS NON-THERMAL EFFECTS

Exposures to electromagnetic fields vary in many parameters: power (specific absorption rate, incident power density), wavelength/frequency, near field/far field, polarization (linear, circular), continuous wave (CW) and pulsed fields (that include variables such as pulse repetition rate, pulse width or duty cycle, pulse shape, pulse to average power, etc.), modulation (amplitude, frequency, phase, complex), static magnetic field (SMF) and electromagnetic stray fields at the place of exposure, overall duration and intermittence of exposure (continuous, interrupted), acute and chronic exposures. With increased absorption of energy, so-called thermal effects of microwaves (MW) are usually observed that deal with MW-induced heating. Specific absorption rate (SAR) or power density (PD) is a main determinate for thermal MW effects. Several other physical parameters of exposure have been reported to be of importance for so-called non-thermal (NT) biological effects, which are induced by MW at intensities well below any measurable heating (Grundler, Jentzsch et al. 1988; Iskin 1990; Devyatkov, Golant et al. 1994; Pakhomov, Akyel et al. 1998; Adey 1999; Belyaev, Shcheglov et al. 2000; Betskii, Devyatkov et al. 2000; Banik, Bandyopadhyay et al. 2003; Grigoriev, Stepanov et al. 2003; Grigoriev 2004; Lai 2005; Belyaev 2010; Cifra, Fields et al. 2011) (Pakhomov and Murphy 2000).

Most often, current safety standards are based on thermal MW effects observed in short-term (acute) exposures. On the other hand, NT MW effects, especially those induced during prolonged (chronic) exposures, are accepted and taken into account for setting the national safety standards in some countries such as Russia (Grigoriev, Stepanov et al. 2003; Grigoriev 2004; Grigoriev, Nikitina et al. 2005). It should be noted that, in contrast to the ICNIRP (International Commission for Non-Ionizing Radiation Protection) safety standards (ICNIRP 1998) which are based on the acute thermal effects of MW, the standards adopted by the Russian National Committee on Non-Ionizing Radiation Protection (RNCNIRP) are based on experimental data from chronic (up to 4 month) exposures of animals to MW at various physical parameters including intensity, frequency and modulation, obtained from research performed in the former Soviet Union (Grigoriev, Stepanov et al. 2003; Grigoriev 2004; Grigoriev, Nikitina et al. 2005).

Since setting the current safety standards, the situation with exposure of the general population to MW has changed significantly. Nowadays, most of the human population is chronically exposed to MW signals from various sources including mobile phones and base stations. These exposures are characterized by low intensities, varieties and complexities of signals, and long-term durations of exposure that are comparable with a lifespan. So far, the “dose” (accumulated absorbed energy that is measured in radiobiology as the dose rate multiplied by exposure time) is not adopted for the MW exposures and SAR or PD is usually used for guidelines. To what degree SAR/PD can be applied to the nowadays NT MW chronic exposures is not known and the current state of research demands reevaluation of the safety standards (Grigoriev, Nikitina et al. 2005).

The literature on the NT MW effects is very broad. About half of available experimental studies report non-thermal biological effects of microwaves (Huss, Egger et al. 2007). There are four lines of evidence for the NT MW effects: (1) altered cellular responses in laboratory *in vitro* studies and results of chronic exposures *in vivo* studies (Grigoriev, Stepanov et al. 2003; Lai 2005; Cook, Saucier et al. 2006); (2) results of medical application of NT MW in the former Soviet Union countries (Sit'ko 1989; Devyatkov, Golant et al. 1994; Betskii, Devyatkov et al. 2000; Pakhomov and Murphy 2000; Pakhomov and Murphy 2000); (3) hypersensitivity to electromagnetic fields (EMF) ; (4) epidemiological studies suggesting increased cancer risks from using mobile phones longer than 10 years (Kundi, Mild et al. 2004; Lonn, Ahlbom et al. 2004; Hardell, Eriksson et al. 2005).

The first data on the NT effects of MW in so-called millimeter range (wavelength 1-10 mm in vacuum) was obtained by Vilenskaya and co-authors (Vilenskaya, Smolyanskaya et al. 1972) and Devyatkov (Devyatkov 1973). Highly resonant effects of ultra-weak MW (near 70 GHz) on the

induction of λ -phage were first established by Webb (Webb 1979), and subsequently corroborated (Lukashevsky and Belyaev 1990). In these and subsequent studies the observed spectra of MW action were found to have the following common properties: (1) the MW effects were strongly dependent on the frequency (frequency windows), (2) there was an associated power (intensity) threshold below which no effect was observed, and above which the effects of exposure depended only weakly on power over several orders of magnitude (so-called S-shaped or sigmoid dependence), (3) the occurrence of MW effects depended on the duration of exposure, a certain minimum duration of exposure was necessary for an effect to manifest itself. These important regularities of the NT MW effects have previously been reviewed (Postow and Swicord 1986; Grundler, Jentzsch et al. 1988; Golant 1989; Iskin 1990; Belyaev 1992; Devyatkov, Golant et al. 1994; Pakhomov, Akyel et al. 1998; Hyland 2000; Pakhomov and Murphy 2000).

The first investigations of the NT MW effects at lower frequency ranges were performed by several research groups in USSR (Presman, Iul et al. 1961; Presman 1963) and in USA by Frey (Frey 1967; Frey 1974), Blackman and colleagues (Blackman, Benane et al. 1980; Blackman, Benane et al. 1980; Joines and Blackman 1980) and Adey and colleagues (Adey, Bawin et al. 1982; Lin-Liu and Adey 1982). These groups found dependence of the NT MW effects on modulation. The effect of pulse-modulated MW was related to peak power, whereas average power was found to be relatively unimportant (Frey 1974). Frequency dependence of the MW effects have been reported (Frey 1974).

Since that time, other groups have confirmed and extended the main findings of these pioneering studies. Below, survey of recent studies, which evaluate dependence of the NT MW effects on physical parameters and biological variables, is provided.

II. FREQUENCY DEPENDENCE AND FREQUENCY WINDOWS

The effects of NT MW on DNA repair in *E. coli* K12 AB1157 were studied by the method of anomalous viscosity time dependence (AVTD) (Belyaev, Alipov et al. 1992; Belyaev, Alipov et al. 1992). The AVTD method is a sensitive technique to detect changes in conformation of nucleoids/chromatin induced by either genotoxic or stress factors (Belyaev and Harms-Ringdahl 1996; Belyaev, Shcheglov et al. 1996; Belyaev, Alipov et al. 1997; Sarimov, Malmgren et al. 2004; Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005). Significant inhibition of DNA repair was found when X-ray-irradiated cells were exposed to MW within the frequency ranges of 51.62-51.84 GHz and 41.25-41.50 GHz. The effects were observed within two “frequency windows”, both

displaying a pronounced resonance character with the resonance frequencies of 51.755 GHz and 41.32 GHz, respectively (Belyaev, Alipov et al. 1992; Belyaev, Alipov et al. 1992). Of note, these MW effects were observed at PD well below any thermal effects and could not be accounted for by heating. The frequency windows of resonance type have often been termed “resonances” as also will be used below.

The resonance frequency of 51.755 GHz was stable within the error of measurements, ± 1 MHz with decreasing the PD from $3 \cdot 10^{-3}$ to 10^{-19} W/cm² (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1996). At the same time, the half-width of the resonance decreased from 100 MHz to 3 MHz revealing an extremely sharp dependence on frequency ($Q \sim 10^4$). This sharp narrowing of the 51.755 GHz resonance with decreasing the PD from $3 \cdot 10^{-3}$ to 10^{-7} W/cm² followed by an emergence of new resonances, 51.675 ± 0.001 , 51.805 ± 0.002 , and 51.835 ± 0.005 GHz (Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997). The half-widths of all these resonances including the main one, 51.755 ± 0.001 GHz, were about 10 MHz at the PD of 10^{-10} W/cm². These data were interpreted in the framework of the model of electron-conformational interactions as a splitting of the main resonance 51.755 GHz by the MW field (Belyaev, Shcheglov et al. 1996).

The MW effects were studied at different PD and several frequencies around the resonance frequency of 51.675 GHz (Shcheglov, Belyaev et al. 1997). This resonance frequency was found to be stable, ± 1 MHz, within the PD range of 10^{-18} - 10^{-8} W/cm². Along with disappearance of the 51.675 GHz resonance response at the sub-thermal PD of 10^{-6} - 10^{-3} W/cm², a new resonance effect arose at 51.688 ± 0.002 GHz (Shcheglov, Belyaev et al. 1997). This resonance frequency was also stable within the PD range studied.

Taken together, the data on NT MW effects on chromatin (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997) suggested a sharp rearrangement of the frequency spectra of MW action, which was induced by the sub-thermal MW (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997). The half-widths of all three resonances depended on PD, changing either from 2-3 MHz to 16-17 MHz (51.675 GHz and 51.668 GHz resonances) or from 2-3 MHz to 100 MHz (51.755 GHz resonance) (Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997). The data indicated also that dependencies of half-width on PD might vary for different resonance frequencies.

Significant narrowing in resonance response with decreasing PD has been found when studying the growth rate in yeast cells (Grundler 1992) and chromatin conformation in thymocytes of rats (Belyaev and Kravchenko 1994). In the Gründler's study, the half-width of the resonance (near 41 GHz) decreased from 16 MHz to 4 MHz as PD decreased from 10^{-2} W/cm² to 5 pW/cm² (Grundler 1992).

Thus, the results of studies with different cell types indicate that narrowing of the resonance window upon decrease in PD is one of the general regularities in cell response to NT MW. This regularity suggests that many coupled oscillators are involved non-linearly in the response of living cells to NT MW as has previously been predicted by Fröhlich (Frohlich 1968).

Gapeev et al. studied effects of MW exposure (frequency range 41.75-42.1 GHz, frequency increment 50 MHz, PD 240 $\mu\text{W}/\text{cm}^2$) on the respiratory burst induced by calcium ionophore A23187 and phorbol ester 12-myristate 13-acetate (PMA) in the peritoneal neutrophils of mice (Gapeev, Safronova et al. 1996; Gapeyev, Safronova et al. 1997). MW inhibited the respiratory burst. MW effect displayed resonance-like dependence on frequency, the resonance frequency and half-width of the resonance being 41.95 GHz and 160 MHz, respectively ($Q=260$) (Gapeev, Safronova et al. 1996; Gapeyev, Safronova et al. 1997). In other studies, Gapeev et al. analyzed acute zymosan-induced paw edema in mice (Gapeyev, Mikhailik et al. 2008; Gapeyev, Mikhailik et al. 2009). MW exposure of animals at the PD of 0.1 mW/cm^2 resulted in decrease of the paw edema that was frequency-dependent in the range of 42-43 GHz.

Based on the extrapolation from the data obtained in the extremely high frequency range (30-300 GHz), the values for half-width of resonances at the frequency range of mobile phones (0.9–2 GHz) were estimated to be 1-10 MHz (Sarimov, Malmgren et al. 2004). Effects of GSM (Global System for Mobile Communication) MW on chromatin conformation and 53BP1 (tumor suppressor p53 binding protein 1)/ γ -H2AX (phosphorylated H2AX histone) DNA repair foci in human lymphocytes were studied in this frequency range (Sarimov, Malmgren et al. 2004; Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005; Belyaev, Markova et al. 2009). These MW effects depended on carrier frequency (Sarimov, Malmgren et al. 2004; Markova, Hillert et al. 2005; Belyaev, Markova et al. 2009). This dependence was replicated in independent experiments with lymphocytes from twenty six healthy and hypersensitive persons (Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005; Belyaev, Markova et al. 2009).

Tkalec and colleagues exposed duckweed (*Lemna minor L.*) to MW at the frequencies of 400, 900, and 1900 MHz (Tkalec, Malaric et al. 2005). The growth of plants exposed for 2 h to a 23 V/m electric field of 900 MHz significantly decreased in comparison with the control, while an electric field of the same strength but at 400 MHz did not have such effect. A modulated field at 900 MHz strongly inhibited the growth, while at 400 MHz modulation did not influence the growth significantly. At both frequencies, a longer exposure mostly decreased the growth and the highest electric field (390 V/m) strongly inhibited the growth. Exposure of plants to lower field strength (10 V/m) for 14 h caused a significant decrease at 400 and 1900 MHz while 900 MHz did not influence the growth. Peroxidase activity in exposed plants varied, depending on the exposure characteristics.

Observed changes were mostly small, except in plants exposed for 2 h to 41 V/m at 900 MHz where a significant increase (41%) was found. The authors concluded that MW might influence plant growth and, to some extent, peroxidase activity. However, the effects of MW strongly depended on the characteristics of the field exposure such as frequency and modulation. These dependences were replicated in further studies (Tkalec, Malaric et al. 2007; Tkalec, Malaric et al. 2009).

Remondini et al. analyzed changes in gene expression in human EA.hy926 endothelial cells using gene microarrays (Remondini, Nylund et al. 2006). Cells were exposed to MW (SAR 1.8-2.5 W/kg, 1 h exposure) either at 900-MHz GSM Basic mode or 1800-MHz GSM Basic mode. Exposure to 900 MHz resulted in up-regulation in 22 genes and down-regulation in 10 genes. No significant change in gene expression was observed after exposure to 1800 MHz.

III. NON-LINEARITY: SIGMOID INTENSITY DEPENDENCES AND POWER WINDOWS

Devyatkov with colleagues have found and published in Russian that wide variety of NT MW effects *in vitro* and *in vivo* display sigmoid dependence on intensity above certain intensity thresholds (Devyatkov 1973).

In English literature, one of the earliest observation of threshold in response to NT MW was published by Frey (Frey 1967). In this study, the threshold of 30 $\mu\text{W}/\text{cm}^2$ was found in the study by Frey on Brain stem evoked responses to RF in cats (Frey 1967). This value was 4 orders of magnitude lower than intensities needed to cause internal body temperature increase.

In their pioneering study on blood-brain barrier (BBB) permeability, Oscar and Hawkins exposed rats to MW at 1.3 GHz and analyzed BBB permeability by measuring uptake of several neutral polar substances in certain areas of the brain (Oscar and Hawkins 1977). A single, 20 min exposure, to continuous wave (CW) MW increased the uptake of D-mannitol at average power densities of less than 3 mW/cm^2 . Increased permeability was observed both immediately and 4 h after exposure, but not 24 h after exposure. After an initial rise at 0.01 mW/cm^2 , the permeability of cerebral vessels to saccharides decreased with increasing microwave power at 1 mW/cm^2 . Thus, the effects of MW were observed within the power window of 0.01- 0.4 mW/cm^2 . The findings on “power windows” for BBB permeability have been subsequently corroborated by the group of Persson and Salford (Salford, Brun et al. 1994; Persson, Salford et al. 1997). In their recent study, the effects of GSM MW on the permeability of the BBB and signs of neuronal damage in rats were investigated using a real GSM programmable mobile phone in the 900 MHz band (Eberhardt, Persson et al. 2008). The rats were exposed for 2 h at an SAR of 0.12, 1.2, 12, or 120 mW/kg .

Albumin extravazation and also its uptake into neurons increased after 14 d. The occurrence of dark neurons in the rat brains increased later, after 28 d. Both effects were seen already at 0.12 mW/kg with only slight increase, if any, at higher SAR values.

Sigmoid intensity dependences and power windows for the NT MW effects were observed in many other studies as previously reviewed (Postow and Swicord 1986; Grundler, Jentzsch et al. 1988; Golant 1989; Iskin 1990; Devyatkov, Golant et al. 1994; Blackman 2009).

Since 1980, there have been numerous reports of biological effects that show intensity “windows”, that is, regions of intensity that cause changes surrounded by higher and lower intensities that show no effects from exposure, see for review (Blackman 2009). These results mean that lower intensity is not necessarily less bioactive, or less harmful.

Olcerst et al. have reported that MW-induced increase in rubidium passive efflux did not increase monotonically with absorbed power (Olcerst, Belman et al. 1980). In fact, the highest exposure (SAR 390 mW/g) resulted in an increase, not statistically different from the lowest exposure level (SAR 100 mW/g). For sodium ions, at the greatest SAR of 390 mW/g, the effect was the smallest (Olcerst, Belman et al. 1980).

The data obtained in experiments with *E. coli* cells and rat thymocytes provided new evidence for sigmoid type of PD dependence and suggested that, similar to ELF effects, MW effects may be observed within specific “intensity windows” (Belyaev, Shcheglov et al. 1992; Belyaev and Kravchenko 1994; Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997). The most striking example of the sigmoid PD dependence was found at the resonance frequency of 51.755 GHz (Belyaev, Shcheglov et al. 1996). When exposing *E. coli* cells at the cell density of $4 \cdot 10^8$ cell/ml, the effect reached saturation at the PD of 10^{-18} - 10^{-17} W/cm² and did not change up to PD of 10^{-3} W/cm². In these experiments, the direct measurements of PD below 10^{-7} W/cm² were not available and lower PD was obtained using calibrated attenuators. Therefore, some uncertainty in the evaluation of the lowest PD was possible. The background MW radiation in this frequency range has been estimated to be 10^{-21} - 10^{-19} W/m²/Hz (Kolbun and Lobarev 1988). Based on the experimentally determined half-width of the 51.755 GHz resonance, 1 MHz (Belyaev, Shcheglov et al. 1996), the background PD was estimated as 10^{-19} - 10^{-17} W/cm² within the 51.755 GHz resonance. The resonance MW effects on *E. coli* cells were observed at the PD very close to the estimated background value (Belyaev, Shcheglov et al. 1993; Belyaev, Alipov et al. 1994; Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997; Shcheglov, Alipov et al. 2002). These data suggested that the PD dependence of MW effect at the specific resonance frequencies might have intensity threshold just slightly above the background level. Dependence of the MW effect on PD at one of the resonance frequencies, 51.675 GHz, had the shape of “intensity window” in the PD range

from 10^{-18} to 10^{-8} W/cm² (Shcheglov, Belyaev et al. 1997). It is interesting, that no MW effect at this resonance frequency was observed at sub-thermal and thermal PD. This type of PD dependence has supported hypothesis about possible rearrangement of the frequency MW spectra action by the MW field (Belyaev, Shcheglov et al. 1996). The position of the PD window varied between different resonance frequencies and depended on cell density during exposure of cells (Shcheglov, Belyaev et al. 1997). Despite some uncertainty in the evaluation of PD at the levels below 10^{-7} W/cm² in the referred studies the data indicated that NT MW at the resonance frequencies may result in biological effects at very low intensities comparable with intensities from base stations and other MW sources used in mobile communication.

Gapeev et al. have studied dependence of the MW effects at the resonance frequency of 41.95 GHz on the respiratory burst induced by calcium ionophore A23187 and PMA in the peritoneal neutrophils of mice (Gapeev, Safronova et al. 1996; Gapeyev, Safronova et al. 1997). Inhibitory effects of MW exposure has been observed at the PD of 0.001 mW/cm² and displayed sigmoid dependence on PD at higher power densities (Gapeev, Safronova et al. 1996; Gapeyev, Safronova et al. 1997). In other study, Gapeev et al. analyzed acute zymosan-induced paw edema in mice (Gapeyev, Mikhailik et al. 2009). MW exposure of animals at the frequency of 42.2GHz and exposure duration of 20 min decreased the paw edema. Sigmoid dependence of this effect on PD has been obtained with a maximum at the PD of 0.1 mW/cm².

French et al. exposed human astrocytoma cells to EMR at 835 MHz at a power density of either 40 mWcm² or 8.1 mWcm² (French, Donnellan et al. 1997). Lower power signal was more potent than high power signal. At the lower power density, it was observed that the rate of DNA synthesis decreased, and that the cells flattened and spread out in comparison to unexposed cultures. At higher power density there were no effects seen on cell proliferation, but alteration in cell morphology included increased cell spreading and also the appearance of actin-containing blebs at localized sites on the membrane. It was hypothesized that 835 MHz radiation at low power density may be affecting a signal transduction pathway involved in cell proliferation.

Sigmoid dependence of the negative impact of mobile phone usage on semen quality in human males was found in recent study analyzing motility, vitality, ROS generation by the whole cell, ROS generation by the mitochondria, oxidative DNA damage and DNA fragmentation (De Iuliis, Newey et al. 2009). Specifically, all of the responses examined showed an extremely rapid change at low SAR exposures that then reached a plateau at a point where around 30% of the sperm population was affected.

Hintzsche et al. have recently reported sigmoid dependence on PD in the range up to 4.3 mW/cm² for non-thermal effects of MW on mitotic spindle in human-hamster hybrid cells (Hintzsche, Jastrow et al. 2011).

Sun et al. have investigated the effects of exposure to a 1.8-GHz radiofrequency radiation (RFR) at different intensities on epidermal growth factor (EGF) receptor clustering and phosphorylation in human amniotic (FL) cells (Sun, Shen et al. 2012). The results showed that exposure to RFR at specific absorption rate (SAR) of 0.5, 1.0, 2.0, or 4.0 W/kg for 15 min significantly induced EGF receptor clustering and enhanced phosphorylation of the tyrosine-1173 residue in FL cells. The RFR effect displayed a sigmoid-dependence on SAR with a prominent plateau in the range of 0.5-4 W/kg and a threshold below 0.5 W/kg.

It should be mentioned that almost all biophysical mechanisms, which have previously been proposed to account for NT MW effects, predict thresholds in dependence of these effects in intensity (Grundler, Jentzsch et al. 1988; Golant 1989; Iskin 1990; Devyatkov, Golant et al. 1994; Golo 2005; Matronchik and Belyaev 2008).

To conclude, since 1970, there have been numerous reports of biological effects that show thresholds, sigmoid dependence of the NT MW effects on intensity and also “power windows”, that is, regions of intensity that cause changes surrounded by higher and lower intensities that show no effects from exposure. These results mean that: (i) lower intensity is not necessarily less bioactive, or less harmful; (ii) the NT effects may be observed at intensities above thresholds which are very close to background levels and similar to intensities from base stations.

IV. DOSE AND DURATION OF EXPOSURE

So far, the “dose” (accumulated absorbed energy that is measured in radiobiology as the dose rate multiplied by exposure time) is not adopted for the MW exposures and PD or SAR (dose rate analog in radiobiology) is usually used for guidelines. To what degree SAR/PD can be applied to the nowadays NT MW chronic exposures is not exactly known and the current state of research demands reevaluation of the safety standards (Grigoriev, Nikitina et al. 2005).

Based on mechanistic consideration of the NT MW effects, Frey has suggested that the toxicology model used by investigators was not the appropriate model on which to design MW experiments (Frey 1993). With chemical substance in a toxicology model, a dose-response relationship is usually observed: the greater the dose, the greater the effect. In analogy with toxicology, MW experiments tended to be designed with high doses and with little regard for other parameters such

as modulation and frequency. This might be one reason why many MW studies yielded so little useful information (Frey 1993).

The role of exposure duration in combination with dose rate/SAR for appearance and persistence of the NT MW effects have been analyzed by many research groups using various end-points.

Koveshnikova et al. exposed rats to pulsed MW (carrier frequency 3 GHz, pulse repetition 400 Hz, rectangular pulses of 2 μ s, power flux density, PD, of 100, 500 and 2500 μ W/cm²), during 60 days, 12 h/daily (Koveshnikova and Antipenko 1991) (is a determining factor 1991b). Chromosomal aberrations (CA) were analyzed in hepatocytes. Exposure was performed at three arrays of pulses so that 16, 29 or 48 arrays of pulses per 1 min were generated. The ratio of the obtained doses per animal was 1 : 1.8 : 3, correspondingly. Increased level of CA was generally observed at PD > 100 μ W/cm². Importantly, the differences between PD disappeared when the dose per animal increased. In particular, even the PD of 100 μ W/cm² induced CA at higher absorbed doses. These data support the notion that the absorbed dose may be an important parameter for estimation of risks.

Bozhanova with co-authors reported that the effect of cellular synchronization induced by NT MW depended on duration of exposure and PD (Bozhanova, Bryukhova et al. 1987). The dependence on duration of exposure fitted to exponential function. The important observation was that in order to achieve the same synchronization of cells, the decrease in PD could be compensated by the increase in the duration of exposure.

MW exposure of *E. coli* cells and rat thymocytes at PDs of 10⁻⁵-10⁻³ W/cm² resulted in significant changes in chromatin conformation if exposure was performed at resonance frequencies during 5-10 min (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1992; Belyaev and Kravchenko 1994). Decrease in the MW effects due to lowering the PD by orders of magnitude down to 10⁻¹⁴-10⁻¹⁷ W/cm² could be compensated by several-fold increase of exposure time to 20-40 min (Belyaev, Alipov et al. 1994). At the relatively longer duration of exposure, more than 1 h, and the lowest PD of 10⁻¹⁹ W/cm², the same effect was induced as at highest PDs and shorter durations (Belyaev, Alipov et al. 1994).

Kwee and Raskmark analyzed effects of MW at 960 MHz and various SARs, 0.021, 0.21, and 2.1 mW/kg on proliferation of human epithelial amnion cells (Kwee and Raskmark 1998). These authors found linear correlations between exposure time to MW at 0.021 and 2.1 mW/kg and the MW-induced changes in cell proliferation albeit no such clear correlation was seen at 0.21 mW/kg.

Peinnequin et al. have studied effects of 24 or 48 h MW 2.45 GHz exposure at non-thermal level, 5 mW/cm², on apoptosis in human T-cell line Jurkat clone E6-1 (Peinnequin, Piriou et al. 2000). MW affected Fas -, but neither butyrate- nor ceramide - induced apoptosis. This effect depended on exposure time and was observed only upon 48 h exposure.

Croft et al. have tested twenty-four subjects participated in a single-blind fully counterbalanced cross-over design, where both resting EEG and phase-locked neural responses to auditory stimuli were measured while a mobile phone (MP) was either operating or turned off (Croft, Chandler et al. 2002). MP exposure altered resting EEG, decreasing 1-4 Hz activity (right hemisphere sites), and increasing 8-12 Hz activity as a function of exposure duration. MP exposure also altered early phase-locked neural responses, attenuating the normal response decrement over time in the 4-8 Hz band, decreasing the response in the 1230 Hz band globally and as a function of time, and increasing midline frontal and lateral posterior responses in the 30-45 Hz band. The data have shown that active MPs affect neural function in humans and do so as a function of exposure duration.

Caraglia et al. have evaluated the in vivo effect of MW-EMF in human epidermoid cancer KB cells (Caraglia, Marra et al. 2005). It was found that MW-EMF induced time-dependent apoptosis (45% after 3 h) that was paralleled by an about 2.5-fold decrease of the expression of ras and Raf-1 and of the activity of ras and Erk-1/2.

Gapeyev et al. studied anti-inflammatory effect of low-intensity MW exposure (0.1 mW/cm²) using the model of acute zymosan-induced footpad edema in mice (Gapeyev, Mikhailik et al. 2008). Single whole-body MW exposure of mice at the frequencies of 42.2, 51.8, and 65 GHz after zymosan injection reduced both the footpad edema and local hyperthermia. At the frequency of 42.2 GHz the effect had sigmoid dependence on exposure duration with a maximum at 20-80 min. A linear dependence on the exposure duration with significantly lower increment was observed at a 10-fold less intensity (0.01 mW/cm²). However, this decrease in the effect was compensated by a slight increase in duration of exposure from 80 min to 120 min.

Recently, the negative impact of mobile phone usage on semen quality in human males was repeatedly found to correlate with the duration of exposure (Agarwal, Deepinder et al. 2008; Agarwal, Desai et al. 2009).

Gerner et al. exposed human fibroblasts to modulated GSM 1800 MHz at 2 W/kg (Gerner, Haudek et al. 2010). While short-term exposure within 2 hours did not significantly alter the proteome, an 8-h exposure caused a significant and reproducible increase in protein synthesis. Most of the proteins found to be induced were chaperones, which are mediators of protein folding. Heat-induced proteome alterations detectable with used proteome methodology would require heating

greater than 1°C. Because GSM-induced heating was less than 0.15°C, a heat-related response was excluded. These data further supported the notion that the exposure time seems to be a critical factor.

Differentiated astroglial cell cultures were exposed for 5, 10, or 20 min to either 900 MHz continuous waves or 900 MHz waves modulated in amplitude at 50 Hz (Campisi, Gulino et al. 2010). The strength of the electric field at the sample position was 10 V/m (rms). The irradiation conditions allowed the exclusion of any possible thermal effect. A significant increase in ROS levels and DNA fragmentation was found only after exposure of the astrocytes to modulated MW for 20 min. No evident effects were detected when shorter time intervals were used.

Adang et al. exposed Wistar albino rats to low-level RF during 21 months to two different microwave frequencies and exposure modes, 2 h a day, seven days a week (Adang, Remacle et al. 2009). After 14 and 18 months of exposure, the authors observed a significant increase in white blood cells and neutrophils of about 15% and 25%, respectively. Lymphocytes fell down after 18 months of exposure with about 15% compared to the sham-exposed group. No effects were observed at shorter duration of exposure. Exposure may probably have worked as a trigger and influenced the immune system, which reacted to this stressor by increasing the percentage of monocytes in the peripheral blood circulation.

Schrader et al. analysed production of spindle disturbances in FC2 cells, a human-hamster hybrid (A(L)) cell line, by MW with a field strength of 90 V/m at a frequency of 835 MHz (Schrader, Munter et al. 2008). Sigmoid dependence on time of exposure was observed with linear increase up to 30 min of exposure and saturation at longer exposures up to 2 h.

Markova et al. have found that inhibitory effect of MW on the 53BP1 foci leveled off at 1h-exposure (Markova, Malmgren et al. 2010). Human mesenchymal stem cells (MSC) and fibroblasts were exposed to MW at GSM 915 MHz/UMTS 1947 MHz and SAR of 37/39 mW/kg. No further increase in effects was observed both in MSC and fibroblasts at prolongation of exposure to 3 h. This data are in agreement with previous results obtained in human peripheral blood lymphocytes that MW effects were the same at 1-h and 2-h exposures (Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005).

Panagopoulos and Margaritis have studied the effects of different durations of a single (continuous), daily exposure, ranging from 1 min up to 21 min, to EMF from GSM 900 MHz (Global System for Mobile telecommunications) and DCS 1800 MHz (Digital Cellular System-referred to also as GSM 1800 MHz), on the reproductive capacity of *Drosophila melanogaster* (Panagopoulos and Margaritis 2010). The insects were exposed to each type of radiation at intensity of about 10 $\mu\text{W}/\text{cm}^2$, corresponding to a distance of 20 or 30 cm from the antenna of a DCS 1800 or

a GSM 900 mobile phone handset, respectively. The results show that the reproductive capacity decreases almost linearly with increasing exposure duration to both GSM 900 and DCS 1800 radiation, suggesting that short-term exposures to these radiations have cumulative effects. Additionally, the results show that GSM 900 MHz radiation is slightly more bioactive than DCS 1800 MHz radiation, at the same exposure durations and under equal radiation intensities.

In some studies, the prolonged MW exposures were associated with less prominent effects than shorter exposures (Nikolova, Czyz et al. 2005; Tkalec, Malaric et al. 2007; Markova, Malmgren et al. 2010). This type of dependence on exposure duration was explained by adaptation of the exposed biosystems to the MW exposure (Markova, Malmgren et al. 2010).

Esmekaya et al. exposed human peripheral blood lymphocyte to GSM modulated MW radiation at 1.8 GHz and SAR of 0.21 W/kg for 6, 8, 24 and 48 h (Esmekaya, Aytekin et al. 2011). The authors reported morphological changes in exposed lymphocytes. Longer exposure periods led to destruction of organelle and nucleus structures. Chromatin change and the loss of mitochondrial crista occurred in cells exposed to RF for 8 h and 24 h and were more pronounced in cells exposed for 48 h. RF exposure did not increase the temperature. The authors concluded that the greater damage occurred after longer periods of exposure to NT MW.

Tepe Çam and Seyhan have analyzed DNA damage in hair root cells of volunteers before and after they have used 900-MHz GSM mobile phone for 15 or 30 min. The 900-MHz GSM exposure significantly increased single-strand DNA breaks in cells of hair roots close to the position of phone at the heads of volunteers. 30 min talking by mobile phone induced more DNA damage than 15 min talking (Cam and Seyhan 2012).

Nazıroğlu et al. have measured cytosolic free Ca^{2+} in human leukemia cells during 1-24 h exposure to 2.45 GHz electromagnetic radiation at the average SAR of 1.63 W/kg (Nazıroğlu, Cig et al. 2012). Radiation induced increase of cytosolic free Ca^{2+} concentration was time-dependent and was highest at 24-h exposure.

In some studies, prolonged MW exposures were associated with less prominent effects than shorter exposures (Nikolova, Czyz et al. 2005; Tkalec, Malaric et al. 2007; Markova, Malmgren et al. 2010). This type of dependence on exposure duration was accounted for adaptation of the exposed systems to the MW exposure. The magnitude of adaptation depends on a number of biological variables that will be considered elsewhere.

In recent German study, 24 out of 60 participants were exposed to MW from base station at a power density of $< 60 \mu\text{W}/\text{m}^2$, 20 participants to $60 - 100 \mu\text{W}/\text{m}^2$, and 16 participants to more than $100 \mu\text{W}/\text{m}^2$ (Buchner and Eger 2011). The values of the stress hormones adrenaline and noradrenaline grew significantly during the first 6 months after starting the GSM base station; the

values of the precursor substance dopamine substantially decreased in this time period. The initial condition was not restored even after 1.5 years. Due to the not regulable chronic difficulties of the stress balance, the phenylethylamine levels dropped until the end of the investigation period. These effects show a dose-effect relationship.

Recently reported general indications of a dose-response relationship between chronic exposure to cellular phone MW and parotid gland malignancy indicate necessity of the dose approach at the epidemiological level (Duan, Zhang et al. 2011). For the first time in epidemiology of RF-induced tumors, Cardis et al. have used estimates of radio frequency energy deposition at the centre of tumors in the brain as a measure of MW dose (Cardis, Armstrong et al. 2011). An increased risk of glioma was seen in individuals at the highest quintile of radio frequency dose, though reduced risks were seen in the four lower quintiles. When risk was examined as a function of dose received in different time windows before diagnosis, an increasing trend was observed with increasing MW dose (for exposures 7 years or more in the past).

In conclusion, the data from different groups suggest that duration of exposure and dose may have significant role for the NT MW effects. In specially designed studies, reduction in dose rate/SAR could be compensated by prolongation of exposure time in order to achieve the same MW effect. The temporal nature of the MW effects contributes to the apparent lack of consistent results reported in the literature. Emerging epidemiology data indicate that the dose of MW exposure may correlate with the increased brain tumor risk.

V. TIME AFTER EXPOSURE

The MW effects on *E. coli* cells significantly depended on the post-exposure time (Belyaev, Shcheglov et al. 1993; Belyaev, Alipov et al. 1994; Shcheglov, Alipov et al. 2002). This dependence had an initial phase of increase about 100 min post-exposure followed by a phase, which was close to a plateau, around 100 min. A trend to decrease in effect was observed at longer times up to 300 min (Belyaev, Shcheglov et al. 1993; Shcheglov, Alipov et al. 2002).

Significant MW-induced changes in chromatin conformation were observed when rat thymocytes were analyzed in-between 30-60 min after exposure to MW (Belyaev and Kravchenko 1994). This effect nearly disappeared if the cells were incubated more than 80 min between exposure and analysis.

Gapeev et al. have studied dependence of the MW effect on the function of the mouse peritoneal neutrophils in dependence on duration of exposure at the frequency of 41.95 GHz and

the PD of $240 \mu\text{W}/\text{cm}^2$ (Gapeev, Safronova et al. 1996; Gapeyev, Safronova et al. 1997). This dependence had a bell-shaped form with the maximal effects at 20 - 40 min of exposure.

In recent studies, human lymphocytes from peripheral blood of healthy and hypersensitive to EMF persons were exposed to NT MW from the GSM mobile phones (Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005). NT MW induced changes in chromatin conformation similar to those induced by heat shock, which remained up to 24 h after exposure. It was found in the same and following studies that GSM MW at the carrier frequency of 915 MHz and UMTS (Universal Mobile Telecommunications System) MW at 1947.4 MHz inhibited formation of 53BP1/ γ -H2AX DNA repair foci and these adverse effects remained during 72 h after an 1-h exposure (Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005; Belyaev, Markova et al. 2009). The same group has reported that contrary to human fibroblast, which were able to adapt during chronic exposure to GSM/UMTS non-thermal MW, human stem cells did not adapt (Markova, Malmgren et al. 2010). Jorge-Mora et al. investigated the effects of MW 2.45 GHz radiation on the paraventricular nucleus (PVN) of the hypothalamus, extracted from brains of exposed rats (Jorge-Mora, Misa-Agustino et al. 2011). Expression of c-Fos was analyzed in rats exposed once or repeatedly (ten times in 2 weeks) to MW at non-thermal SAR of 0.0776 and 0.301 W/kg. High SAR triggered an increase of the c-Fos marker 90 min or 24 h after radiation, and low SAR resulted in c-Fos counts higher than in control rats after 24 h. Repeated irradiation at 0.0776 W/kg increased cellular activation of PVN by more than 100% compared to animals subjected to acute irradiation and to repeated non-irradiated repeated session control animals. The results suggest that the time of exposure to single or repeated doses of NT MW is a determining factor, though possibly not the only factor, in establishing the power levels that may produce a response.

Lu et al. have demonstrated that reactive oxygen species (ROS) plays an important role in the process of apoptosis in human peripheral blood mononuclear cell (PBMC), which is induced by the exposure to 900 MHz radiofrequency electromagnetic at the SAR of 0.4W/kg when the exposure lasts longer than two hours (Lu, Huang et al. 2012).

The data indicate that there is a time window for observation of the NT MW effects, which may be dependent on endpoint measured, cell type, duration and PD of exposure.

VI. COHERENCE TIME

MW exposure of L929 fibroblasts was performed by the group of Litovitz (Litovitz, Krause et al. 1993). MW at 915 MHz modulated at 55, 60, or 65 Hz approximately doubled ornithine

decarboxylase (ODC) activity after 8 h. Switching the modulation frequency from 55 to 65 Hz at coherence times of 1.0 s or less abolished enhancement, while times of 10 s or longer provided full enhancement. These results suggested that the microwave coherence effects are remarkably similar to those observed previously with extremely low frequency (ELF) magnetic fields by the same authors.

VII. INTERMITTENCE

Diem and colleagues exposed cultured human diploid fibroblasts and cultured rat granulosa cells to intermittent and continuous MW (1800 MHz; SAR 1.2 or 2 W/kg; different modulations; during 4, 16 and 24 h; intermittent 5 min on/10 min off or continuous exposure) (Diem, Schwarz et al. 2005). Comet assay was applied to analyze DNA single- and double-strand breaks. MW-induced effects occurred after 16 h exposure in both cell types and after different mobile-phone modulations. The intermittent exposure showed a stronger effect than continuous exposure.

Remondini et al. analyzed changes in gene expression in human HL-60 leukemia cells using gene microarrays (Remondini, Nylund et al. 2006). Cells were exposed to MW (SAR 1.0-1.3 W/kg, 1800 MHz DTX mode, 24 h exposure) either continuously or intermittently, 5 min ON/5 min OFF. Gene expression was affected by intermittent exposure but not continuous exposure.

Elhag et al. investigated effect of near field EMR from GSM mobile phones on the oxidant and antioxidant status in rats (Elhag, Nabil et al. 2007). Rats were subjected to either intermittent exposure (15 min/day for four days) or acute exposure for 1 h. Significant drop in the plasma concentration of vitamin C, vitamin E, vitamin A and reduced glutathione (GSH) was observed in both exposed groups as compared to controls. EMR exposure of rats produced a significant decrease in catalase (CAT) and superoxide dismutase (SOD) activities, with the values of these activities for acute-exposure group is significantly lower than those of intermittent exposure. The authors concluded that the effects of acute exposure to mobile phones on the rat's antioxidant status is significantly higher than those of intermittent exposure of the same type of radiation.

Chavdoula et al used a 6-min daily exposure of dipteran flies, *Drosophila melanogaster*, to GSM-900MHz (Global System for Mobile Telecommunications) mobile phone electromagnetic radiation (EMR), to compare the effects between the continuous and four different intermittent exposures of 6 min total duration on the insect's reproductive capacity as well as on the induction of apoptosis (Chavdoula, Panagopoulos et al. 2010). It was found that intermittent exposure, similar to continuous exposure, decreases the reproductive capacity and alters the actin-cytoskeleton network

of the egg chambers, another known aspect of cell death, and that this effect is due to DNA fragmentation. Intermittent exposures with 10-min intervals between exposure sessions proved to be almost equally effective as continuous exposure of the same total duration, whereas longer intervals between the exposures seemed to allow the organism the time required to recover and partly overcome the above-mentioned effects of the GSM exposure.

VIII. MODULATION

Several types of modulations used in mobile communication have previously been reviewed (Foster and Repacholi 2004; Blackman 2009; Juutilainen, Hoyto et al. 2011). In particular, the 2G signals use the Gaussian Minimum Shift Keying (GMSK) modulation, have a high coherence, extremely low frequency amplitude modulation spectra, high crest factor (pulsed signal) and a power regulation with an update in the order of seconds. In contrast, the 3G Wideband Code-Division Multiple Access (WCDMA) uses essentially Quadrature Phase Shift Keying (QPSK) modulation, has a low coherence and a broad-band extremely low frequency amplitude modulation spectrum.

While considering effect of modulation, all other parameters, which are important for appearance of biological effects induced by NT MW, should be taken into account. In particular it is useless to include in analysis the papers where no effects of NT MW were detected at all because usually these studies do not scan the parameters of exposure in wide range to enable detecting the NT MW effects. Even more importantly is to analyze separately different types of modulations because each type may result in its own specific effect. When such approach is used, clear evidence is emerging for the effects of specific modulations. For example, among three studies on cancer-relevant non-genotoxic endpoints, biological effects (apoptosis, altered cell proliferation, lipid peroxidation) were induced by GSM modulated signal but not by a CW signal (Juutilainen, Hoyto et al. 2011). All these studies involved combined exposure to RF fields and other agents, and found GSM-modulation-specific effects on apoptosis. Another example is increased power in the alpha band (8–12 Hz) of EEG, which has been consistently seen in several studies most of which have used GSM-type modulation and have found that signals with pulse modulation are more biologically active than CW fields, or that signals with higher degree of modulation (e.g., handset-like signals) are more biologically active than signals with lower degree of modulation (e.g., base station-like signals). Studies that have used only GSM-type signals have provided additional evidence for effects of modulated RF signals on human brain functions (van Rongen, Croft et al.

2009). Overall, the consistency of the positive findings indicates that there may be reproducible modulation-specific effects on the human central nervous system (Juutilainen, Hoyto et al. 2011). This result is consistent with the well-known notion that properly modulated RF may be a useful tool in experiments directed at understanding nervous system function (Frey 1967).

Using aforementioned approach, it became clear that significant body of papers where NT MW effects were observed and modulated and unmodulated signals were carefully compared revealed the differences. There is strong experimental evidence for the role of modulation in the diverse biological effects of NT MW both in vitro and in vivo (Lin-Liu and Adey 1982; Byus, Lundak et al. 1984; Dutta, Subramoniam et al. 1984; Byus, Kartun et al. 1988; Dutta, Ghosh et al. 1989; Veyret, Bouthet et al. 1991; Gapeev, Iakushina et al. 1997; Litovitz, Penafiel et al. 1997; Penafiel, Litovitz et al. 1997; Persson, Salford et al. 1997; d'Ambrosio, Massa et al. 2002; Huber, Treyer et al. 2002; Markkanen, Penttinen et al. 2004; Huber, Treyer et al. 2005). Examples include different types of modulation such as amplitude-, speech and phase modulations: (i) Amplitude modulation at 16 Hz, but not 60 Hz or 100 Hz, of a 450-MHz MW increased activity of ODC (Byus, Kartun et al. 1988). (ii) Speech-modulated 835-MHz MW produced no effect on ODC as compared to the typical signal from a TDMA (Time Division Multiple Access) digital cellular phone (Penafiel, Litovitz et al. 1997). (iii) Phase-modulated GSM-1800 MW (Gaussian Minimum Shift Keying, GMSK) at 1.748 GHz induced micronuclei in human lymphocytes while CW MW did not (d'Ambrosio, Massa et al. 2002).

Normal human lymphocytes were exposed for 5 days to continuous wave (CW) or pulsed wave (PW) 2450-MHz radiation at non-heating (37 degrees C) and various heating levels (temperature increases of 0.5, 1.0, 1.5, and 2 degrees C) (Czerska, Elson et al. 1992). The pulsed exposures involved 1-microsecond pulses at pulse repetition frequencies from 100 to 1,000 pulses per second at the same average SAR levels as the CW exposures. At non-heating levels, CW exposure did not affect lymphoblastoid transformation. At heating levels both conventional and CW heating enhanced transformation to the same extent and correlate with the increases in incubation temperature. PW exposure enhanced significantly transformation at non-heating levels. At heating levels PW exposure enhanced transformation to a greater extent than did conventional or CW heating. Authors concluded that PW 2450-MHz radiation acts differently on the process of lymphoblastoid transformation in vitro compared with CW 2450-MHz radiation at the same average SARs.

Bolshakov and Alexeev used microelectrode and voltage-clamp techniques to record spontaneous electrical activity and ionic currents of *Lymnea stagnalis* neurons during exposure to a 900-MHz field in a waveguide-based apparatus (Bolshakov and Alekseev 1992). The field was

pulse-modulated at repetition rates ranging from 0.5 to 110 pps, or it was applied as a continuous wave (CW). When subjected to pulsed waves (PW), rapid, burst-like changes in the firing rate of neurons occurred at SARs of a few W/kg. If the burst-like irregularity was present in the firing rate under control conditions, irradiation enhanced its probability of occurrence. The effect had a threshold SAR near 0.5 W/kg. CW radiation had no effect on the firing rate pattern at the same SAR. Thus, the effect was dependent on modulation. Mediator-induced, current activation of acetylcholine, dopamine, serotonin, or gamma-aminobutyric-acid receptors of the neuronal soma was not altered during CW or PW exposures and, hence, could not have been responsible for the bursting effect.

Gapeev and co-authors studied production of reactive oxygen species (ROS) in isolated peritoneal neutrophils of mice using a model of synergistic reaction of calcium ionophore A23187 and phorbol ester PMA (Gapeev, Iakushina et al. 1997; Gapeyev, Yakushina et al. 1998). MW exposure at 41.95 GHz, continuous wave mode and $50 \mu\text{W}/\text{cm}^2$, inhibited ROS production. MW modulated with the frequency of 1 Hz resulted in stimulation of the synergistic reaction. Modulation frequencies of 0.5, 2, 4, and 8 Hz did not cause significant effects, and modulation frequencies of 0.1, 16, and 50 Hz inhibited the synergistic reaction.

In other study, Gapeev et al. analyzed acute zymosan-induced paw edema in mice (Gapeyev, Mikhailik et al. 2009). MW exposure of animals at the PD of 0.1- 0.7 mW/cm^2 and some “effective” frequencies in the range of 42-43 GHz decreased the paw edema. Application of different modulation frequencies from the range of 0.03–100 Hz to MW exposure at the effective carrier frequency of 42.2 GHz did not lead to considerable changes in the effect. In contrast, modulation of MW at the “ineffective” carrier frequencies of 43.0 and 61.22 GHz by frequencies from the ranges of 0.07–0.1 and 20–30 Hz resulted in a maximal anti-inflammatory effects. The results suggested a complex dependence of the anti-inflammatory action of low-intensity MW on carrier and modulation frequencies.

Capri et al. evaluated the nonthermal effects of both a 900 MHz GSM signal and a 900 MHz CW RF field at low SARs (70–76 mW/kg average) on human peripheral blood mononuclear cells (PBMCs) *in vitro* (Capri, Scarcella et al. 2004). Data obtained from cells exposed to a GSM-modulated RF field showed a slight decrease in cell proliferation when PBMCs were stimulated with the lowest mitogen concentration and a slight increase in the number of cells with altered distribution of phosphatidylserine across the membrane. Data obtained from CW-exposed cultures showed no difference with respect to sham-exposed cultures in any of the end points studied.

Huber with coauthors investigated effects of MW similar to those used in mobile communication, a “base-station-like” and a “handset-like” signal (10 g tissue-averaged spatial peak-

SAR of 1 W/kg for both conditions), on waking regional cerebral blood flow (rCBF) in 12 healthy young men (Huber, Treyer et al. 2005). The effect depended on the spectral power in the amplitude modulation of the carrier frequency such that only “handset-like” MW exposure with its stronger low-frequency components but not the “base-station-like” MW exposure affected rCBF. This finding supported previous observations of these authors (Huber, Treyer et al. 2002) that pulse modulation of MW is of importance for changes in the waking and sleep EEG, and substantiated the notion that pulse modulation is crucial for MW-induced alterations in brain physiology.

Markkanen et al. exposed cdc48-mutated *Saccharomyces cerevisiae* yeast cells to 900 or 872 MHz MW, with or without exposure to ultraviolet (UV) radiation, and analyzed apoptosis (Markkanen, Penttinen et al. 2004). Amplitude modulated (217 pulses per second) MW significantly enhanced UV induced apoptosis in cells, but no effect was observed in cells exposed to unmodulated fields at the identical time-average SAR of 0.4 W/kg that was lower than the ICNIRP safety standards.

Persson and colleagues studied effects of MW of 915 MHz as CW and pulse-modulated with different pulse power and at various time intervals on permeability of the blood-brain barrier (BBB) in Fischer 344 rats (Persson, Salford et al. 1997). Albumin and fibrinogen were demonstrated immunochemically and classified as normal versus pathological leakage. The CW-pulse power varied from 0.001 W to 10 W and the exposure time from 2 min to 960 min. The frequency of pathological rats significantly increased in all exposed rats. Grouping the exposed animals according to the level or specific absorption energy (J/kg) gave significant difference in all levels above 1.5 J/kg. The exposure was 915 MHz MW either pulse modulated at 217 Hz with 0.57 ms pulse width, at 50 Hz with 6.6 ms pulse width, or CW. The frequency of pathological rats was significantly higher in MW-exposed groups than in controls and the frequency of pathological rats after exposure to pulsed radiation was significantly less than after exposure to CW.

In a study by Lypez-Martin et al. (Lopez-Martin, Brogains et al. 2009), GSM-exposed picrotoxin-pretreated rats showed differences in clinical and EEG signs, and in c-Fos expression in the brain, in comparison to picrotoxin-treated rats exposed to an equivalent dose of unmodulated radiation. Neither MW exposure caused tissue heating, so thermal effects could be ruled out. The most marked effects of GSM MW on c-Fos expression in picrotoxin-treated rats were observed in limbic structures, olfactory cortex areas and subcortical areas, the dentate gyrus, and the central lateral nucleus of the thalamic intralaminar nucleus group. Nonpicrotoxin-treated animals exposed to unmodulated radiation showed the highest levels of neuronal c-Fos expression in cortical areas. These results suggested a specific effect of the pulse GSM modulation on brain activity of a picrotoxin-induced seizure-proneness rat model.

Luukkonen et al. investigated effects of MW at 872 MHz and relatively high SAR value (5 W/kg) on intracellular reactive oxygen species (ROS) production and DNA damage in human SH-SY5Y neuroblastoma cells. The experiments also involved combined exposure to MW and menadione, a chemical inducing intracellular ROS production and DNA damage. Both CW and a pulsed signal similar to that used in GSM mobile phones were used. Exposure to the CW radiation increased DNA breakage in comparison to the cells exposed only to menadione. Comparison of the same groups also showed that ROS level was higher in cells exposed to CW RF radiation at 30 and 60 min after the end of exposure. No effects of the GSM-like modulated signal were seen on either ROS production or DNA damage.

Hinrikus et al. (Hinrikus, Bachmann et al. 2008) evaluated the effects of MW (450 MHz) pulse-modulated at the frequencies of 7, 14 and 21 Hz on human electroencephalographic (EEG) rhythms. The field power density at the scalp was 0.16 m W/cm^2 . Modulated microwaves caused an increase in the average EEG alpha (17%) and beta (7%) power but the theta rhythm remained unaffected. Increases in the EEG alpha and beta power were statistically significant during the first half-period of the exposure interval (30 s) at the modulation frequencies of 14 and 21 Hz. The authors concluded that the effect of the 450-MHz MW modulated at 7, 14 and 21 Hz varies depending on the modulation frequency.

Hoyto et al. exposed human SH-SY5Y neuroblastoma and mouse L929 fibroblast cells to MW (SAR of 5 W/kg) at 872 MHz using continuous-waves (CW) or a modulated GSM-like signal under isothermal conditions (Hoyto, Luukkonen et al. 2008). Menadione was used to induce reactive oxygen species, and tert-butylhydroperoxide (t-BOOH) was used to induce lipid peroxidation. Two statistically significant differences related to MW exposure were observed: Lipid peroxidation induced by t-BOOH was increased in SH-SY5Y (but not in L929) cells, and menadione-induced caspase 3 activity was increased in L929 (but not in SH-SY5Y) cells. Both differences were statistically significant only for the GSM-modulated signal.

Franzellitti et al. exposed human trophoblast HTR-8/SVneo cells to MW at 1.8 GHz CW and differently modulated GSM signals (GSM-217Hz, (speaking only): and GSM-Talk (34% of speaking and 66% of hearing):) during 4 - 24 h (Franzellitti, Valbonesi et al. 2008). The inducible HSP70C transcript was significantly enhanced after 24 h exposure to GSM-217 Hz signals while being reduced after 4 and 16 h exposure to GSM-Talk signal. In another study of the same group, HTR-8/SVneo cells were exposed for 4, 16 or 24 h to 1.8 GHz continuous wave (CW) and different GSM signals, namely GSM-217 Hz and GSM-Talk (intermittent exposure: 5 min field on, 10 min field off). The alkaline comet assay was used to evaluate primary DNA damages and/or strand breaks due to uncompleted repair processes in HF-EMF exposed samples. The amplitude-

modulated signals GSM-217 Hz and GSM-Talk induced a significant increase in comet parameters in trophoblast cells after 16 and 24 h of exposure, while the un-modulated CW was ineffective (Franzellitti, Valbonesi et al. 2010).

Only CW RF resulted in statistically significant effect on immune system of the exposed rats (Campisi, Gulino et al. 2010). In this study, primary rat neocortical astroglial cell cultures were exposed to MW for 5, 10, or 20 min to either 900 MHz continuous waves or 900 MHz waves modulated MW in amplitude at 50 Hz using a sinusoidal waveform and 100% modulation index. The strength of the electric field (rms value) at the sample position was 10 V/m. A significant increase in ROS levels and DNA fragmentation was found only after exposure of the astrocytes to modulated EMF for 20 min. No evident effects were detected when shorter time intervals or continuous waves were used. The irradiation conditions allowed the exclusion of any possible thermal effect. The results show the importance of the amplitude modulation in the interaction between EMF and neocortical astrocytes (Campisi, Gulino et al. 2010).

There are studies where similar effects of modulated and CW MW were observed. Adang et al. exposed Wistar albino rats to low-level CW and pulse-amplitude modulated RF during 21 months at 970 MHz (Adang, Remacle et al. 2009). Similar effects on immune system were observed in both groups.

Significant amount of *in vivo* studies under varying parameters of exposure (intensity, frequency, exposure time, modulation, intermittence) have been performed in Russia/Soviet Union and published in Russian. Retrospective analysis of 52 Russian/Soviet *in vivo* studies with animals (mice, rats, rabbits, guinea pigs) on chronic exposure to MW has recently been published (Grigoriev, Stepanov et al. 2003). In these studies, various endpoints were measured up to 4 month of chronic exposure including analysis of: weight of animal body, histological analysis and weight of tissues, central nervous system, arterial pressure, blood and hormonal status, immune system, metabolism and enzymatic activity, reproductive system, teratogenic and genetic effects. Based on their analysis, the authors concluded that: “exposure to modulated MW resulted in bioeffects, which can be different from the bioeffects induced by CW MW; exposure to modulated MW at low intensities (non-thermal levels) could result in development of unfavorable effects; direction and amplitude of the biological response to non-thermal MW, both *in vitro* and *in vivo*, depended on type of modulation; often, but not always, modulated MW resulted in more pronounced bioeffects than CW MW; the role of modulation was more pronounced at lower intensity levels”.

One review of the Russian/Soviet studies on the role of modulation on MW effects is available in English (Pakhomov and Murphy 2000). The authors conclude that “a number of good-quality studies have convincingly demonstrated significant bioeffects of pulsed MW. Modulation

often was the factor that determined the biological response to irradiation, and reactions to pulsed and CW emissions at equal time-averaged intensities in many cases were substantially different". Since that time, more studies have been published in Russian which show the role of modulation in experimnts with animals (Dolgacheva, Semenova et al. 2000; Pashovkina and Akoev 2000; Pashovkina and Akoev 2001; Pashovkina and Akoev 2001; Akoev, Pashovkina et al. 2002).

In conclusion, significant amount of in vitro and in vivo studies from different research groups, although not universally reported, clearly indicated dependence of the NT MW effects on modulation.

IX. POLARIZATION

Polarization is a property of electromagnetic waves that describes the orientation of their oscillations versus direction of propagation. In most cases, electromagnetic wave propagates in free space as a transverse wave - the polarization is perpendicular to the wave's direction of propagation. The electric field may be oriented in a single direction (linear polarization), or it may rotate as the wave propagates (circular or elliptical polarization). In the latter cases, the oscillations can rotate either towards the right (right-handed polarization) or towards the left (left-handed polarization) in the direction of propagation.

The effects of circularly polarized (CP) MW were studied in *E. coli* cells at the frequencies from two frequency windows (resonances) that were identified using linearly polarized (LP) MW, within the frequency ranges of 51.62-51.84 GHz and 41.25-41.50 GHz (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1992). At the resonance frequency of 51.76 GHz, right-handed CP MW inhibited repair of X-ray-induced DNA damages (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1992). In contrast to right-handed polarization, left-handed CP MW had virtually no effect on the DNA repair, while the efficiency of LP MW was in-between of two circular polarizations. Inversion in effectiveness of circular polarizations was observed at another resonance frequency, 41.32 GHz. In contrast to the frequency of 51.76 GHz, left-handed CP MW at 41.32 GHz significantly inhibited DNA repair, while right polarization was almost ineffective. MW of the same CP affected cells at several frequencies tested within each resonance, alternative CP being almost ineffective (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1992; Belyaev, Shcheglov et al. 1992). Therefore, specific sign of effective CP, either left- or right-, was the attribute of each resonance. Two different types of installations, based on either spiral waveguides (Belyaev, Shcheglov et al. 1992) or quarter-wave mica plates (Belyaev, Alipov et al. 1992; Belyaev,

Shcheglov et al. 1992; Shcheglov, Belyaev et al. 1997; Ushakov, Shcheglov et al. 1999; Ushakov, Alipov et al. 2005), were used to produce CP MW. Similar results were observed regardless the way of producing the MW of different polarizations.

Pre-irradiation of *E. coli* cells to X-rays inverted the sign of effective polarization (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1992). This inversion was observed for two different resonances, 41.32 and 51.76 GHz. Neither resonance frequencies, nor half-widths of the resonance changed during the inversions in effective CPs. The effects of left- and right-handed CP MW become the same at 50 cGy (Belyaev, Alipov et al. 1992). At this dose, about one single stranded DNA break per haploid genome was induced. X-ray-induced DNA breaks result in relaxation of the supercoiled DNA-domains. It is known that the majority of DNA in living cells has a right-handed helicity (B-form) but a minor part, in order of 1 %, may alternate from the B-form with the form of left-handed helix (Z-form). Supercoiling is connected with transitions between right B-form to left Z-form in these DNA sequences. Therefore, the data suggested that difference in biological effects of polarized MW might be connected with DNA helicity and supercoiling of DNA-domains.

Supercoiling of DNA-domains is changed during cell cycle because of transcription, replication, repair, and recombination. It can also be changed by means of DNA-specific intercalators such as ethidium bromide (EtBr). EtBr changes supercoiling and facilitates the transition of DNA sequences from Z-form to B-form. Preincubation of *E. coli* AB1157 cells with EtBr inverted the effective polarization at the resonance frequency of 51.755 GHz and right-handed MW became more effective than left polarization (Ushakov, Shcheglov et al. 1999). EtBr changed the supercoiling of DNA-domains starting at a concentration of 1 µg/ml as measured with the AVTD in different cell types including *E. coli* (Belyaev, Shcheglov et al. 1996; Belyaev, Alipov et al. 1997; Belyaev, Eriksson et al. 1999). These data provided further evidence that DNA may be a target for the NT MW effects.

The effects of MW on conformation of nucleoids in *E. coli* cells have recently been studied at the power flux density of 100 µW/cm² (Ushakov, Alipov et al. 2006). Linearly polarized MW resulted in significant effects within specific frequency windows of resonance type in the range of 51-52 GHz. The distances between frequency windows were about 55-180 MHz. Only one of the two possible circular polarizations, left-handed or right-handed, was effective at each frequency window. The sign of effective circular polarization alternated between frequency windows.

While most data on the role of polarization in MW effects on chromatin have been obtained by the same research group (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1992; Belyaev, Shcheglov et al. 1992; Alipov, Belyaev et al. 1993; Belyaev, Alipov et al. 1993; Belyaev, Shcheglov et al. 1993; Belyaev and Kravchenko 1994; Shcheglov, Belyaev et al. 1997; Ushakov,

Shcheglov et al. 1999; Ushakov, Alipov et al. 2005; Ushakov, Alipov et al. 2006), recent data of others corroborated our findings at least partially (Shckorbatov, Pasiuga et al. 2009). These authors analyzed the condensation of chromatin in human buccal epithelium cells and human fibroblasts by the method of vital indigo carmine staining. MW induced chromatin condensation in dependence on polarization (Shckorbatov, Pasiuga et al. 2009). The same research group investigated the effects influence of linear and left-handed and right-handed elliptically polarized MW at 36.65 GHz on chromatin in human fibroblast nuclei (Shckorbatov, Pasiuga et al. 2010). Microwave irradiation at 10 and 100 $\mu\text{W}/\text{cm}^2$ induced chromatin condensation. The right-handed elliptically polarized radiation was more active than the left-handed polarization.

Obviously, the difference in effects of right- and left polarizations could not be explained by the heating or by the mechanism dealing with “hot-spots” due to unequal SAR distribution. The data about the difference in effects of differently polarized MW, the inversion of effective circular polarization between resonances and after irradiation of cells with X-rays and incubation with EtBr provided strong evidence for the non-thermal mechanisms of MW effects. These data suggested chiral asymmetry in the target for the NT MW effects, one of which is presumably chromosomal DNA (Belyaev, Alipov et al. 1992), and selection rules on helicity if quantum-mechanical approach is applied (Belyaev, Shcheglov et al. 1992).

Lai and Singh have consistently reported that circularly polarized MW exposure at 2450 MHz induced DNA damage in brain cells of the exposed rats (Lai and Singh 1995; Lai and Singh 1996; Lai and Singh 1997). Replication studies have also tested circularly polarized MW exposure at 2450 MHz and no induced DNA damage was reported (Malyapa, Ahern et al. 1997; Malyapa, Ahern et al. 1998; Lagroye, Anane et al. 2004). All these replication studies have used another exposure system. However, handedness of circular polarization has not been described neither in original study, no in replications. If the handedness was different between studies it could reasonably account for inconsistency.

In some studies, MW of circular polarization with undefined handedness were used, but the obtained effects were not compared with alternative circular polarization or linear polarization (Bartsch, Kupper et al. 2010).

XI. ELECTROMAGNETIC ENVIRONMENT

It is very likely that background EMF might be of importance for the MW effects. This hypothesis is based on the experimental observations that SMF, ELF magnetic fields, and MW at

low intensities induced similar effects in cells under specific conditions of exposure (Belyaev, Alipov et al. 1999; Belyaev, Shcheglov et al. 2000; Belyaev and Alipov 2001; Binhi, Alipov et al. 2001; Belyaev, Hillert et al. 2005). Despite very little has been achieved for mechanistic explanation of such effects, there are attempts to consider the effects of EMF in a wide frequency range in the frames of the same physical models (Chiabrera, Bianco et al. 1991; Matronchik, Alipov et al. 1996; Chiabrera, Bianco et al. 2000; Binhi 2002; Panagopoulos, Karabarbounis et al. 2002; Matronchik and Belyaev 2005; Matronchik and Belyaev 2008).

Litovitz and colleagues found that the ELF magnetic noise inhibited the effects of MW on ODC in L929 cells (Litovitz, Penafiel et al. 1997). The ODC enhancement was found to decrease exponentially as a function of the noise root mean square amplitude. With 60 Hz amplitude-modulated MW, complete inhibition was obtained with noise levels at or above 2 μ T. With the DAMPS (Digital Advanced Mobile Phone System) cellular phone MW, complete inhibition occurred with noise levels at or above 5 μ T. Further studies by the same group revealed that the superposition of ELF noise inhibited hypoxia de-protection caused by long term repeated exposures of chick embryos to MW (Di Carlo, White et al. 2002).

The effect of a magnetic noise on microwave-induced spatial learning deficit in the rat was investigated by Lai (Lai 2004). Rats were exposed to MW (2450 MHz CW, PD 2 mW/cm², average whole-body SAR 1.2 W/kg) alone or in combination with noise exposure (60 mG). Microwave-exposed rats had significant deficit in learning. Exposure to noise alone did not significantly affect the performance of the animals. However, simultaneous exposure to noise significantly attenuated the microwave-induced spatial learning deficit. The author concluded that simultaneous exposure to a temporally incoherent magnetic field blocks MW-induced spatial learning and memory deficits in the rat (Lai 2004).

Lai and Singh studied combined effects of a temporally incoherent magnetic noise (45 mG) and MW (CW 2450 MHz, PD 1 mW/cm², average whole-body SAR of 0.6 W/kg) in rat brain cells (Lai and Singh 2005). MW exposure induced significant DNA breakages as measured with both neutral and alkaline comet assays. Exposure to noise alone did not significantly affect cells. However, simultaneous noise exposure blocked the MW-induced effects.

Burch et al. have analyzed the relationship between cellular telephone use and excretion of the melatonin metabolite 6-hydroxymelatonin sulfate (6-OHMS) in two populations of male electric utility workers (Study 1, $n=149$; Study 2, $n=77$) (Burch, Reif et al. 2002). Participants collected urine samples and recorded cellular telephone use over 3 consecutive workdays. Personal 60-Hz magnetic field (MF) and ambient light exposures were characterized on the same days. A repeated measures analysis was used to assess the effects of cellular telephone use, alone and combined with

MF exposures, after adjustment for age, participation month and light exposure. No change in 6-OHMS excretion was observed among those with daily cellular telephone use >25 min in Study 1 (5 worker-days). Study 2 workers with >25 min cellular telephone use per day (13 worker-days) had lower creatinine-adjusted mean nocturnal 6-OHMS concentrations ($p=0.05$) and overnight 6-OHMS excretion ($p=0.03$) compared with those without cellular telephone use. There was also a linear trend of decreasing mean nocturnal 6-OHMS/creatinine concentrations ($p=0.02$) and overnight 6-OHMS excretion ($p=0.08$) across categories of increasing cellular telephone use. A combined effect of cellular telephone use and occupational 60-Hz MF exposure in reducing 6-OHMS excretion was also observed in Study 2. The authors concluded that exposure-related reductions in 6-OHMS excretion were observed in Study 2, where daily cellular telephone use of >25min was more prevalent. Prolonged use of cellular telephones may lead to reduced melatonin production, and elevated 60-Hz MF exposures may potentiate the effect.

Yao and colleagues investigated the influence of the GSM-like MW at 1.8 GHz on DNA damage and intracellular reactive oxygen species (ROS) formation in human lens epithelial cells (hLECs) (Yao, Wu et al. 2008). DNA damage examined by alkaline comet assay was significantly increased after 3 W/kg and 4 W/kg radiation, whereas the double-strand breaks (DSB) evaluated by γ -H2AX foci were significantly increased only after 4 W/kg radiation. Significantly elevated intracellular ROS levels were detected in the 3-W/kg and 4-W/kg groups. After exposure to 4 W/kg for 24 hours, hLECs exhibited significant G₀/G₁ arrest. All the effects were blocked when the MW exposure was superposed with a 2 μ T electromagnetic noise. The authors concluded that superposed electromagnetic noise blocks MW-induced DNA damage, ROS formation, and cell cycle arrest.

It has previously been reported that resonance effects of MW on *E. coli* cell depend on the magnitude of static magnetic field at the place of MW exposure (Belyaev, Alipov et al. 1994). This dependence was explained by the model of electron-conformational interactions that also predicted possible shift of resonance frequencies in dependence on SMF (Belyaev, Shcheglov et al. 1996).

More recently, Ushakov with co-authors exposed *E. coli* cells to MW at the PD of 10^{-10} W/cm² and the frequencies of 51.675, 51.755 and 51.835 GHz (Ushakov, Alipov et al. 2005). In this study, cells were exposed to MW at various values of SMF within the range of geomagnetic field: 22, 49, 61, or 90 μ T. The authors observed that the effects of MW exposure on the conformation of nucleoids depended on the SMF during exposure.

Gapeev et al. analyzed effects of MW (41.85-42.1 GHz, frequency increment 50 MHz, PD 50 μ Bt/cm², 20 min exposure) on synergistic reaction of calcium ionophore A23187 and phorbol ester PMA in activation of the respiratory burst of the peritoneal neutrophils of mice (Gapeev,

Iakushina et al. 1997). The MW exposure was performed at various SMF. At a SMF of 50 μT , the authors observed frequency-dependent inhibition of the synergetic reaction with maximal effect at the frequency of 41.95 GHz. In the same frequency range, frequency-dependent activation of the synergetic reaction with a maximal effect at the frequency of 42.0 GHz was found at a SMF of 95 μT . The authors concluded that increasing the SMF from 50 to 95 μT resulted in the inversion of ten MW effects and the shift of the resonance frequency by 50 MHz (Gapeev, Iakushina et al. 1997; Gapeev, Iakushina et al. 1999). Moreover, these effects of MW at the 41.95 GHz and 42.0 GHz were not found at the SMF of ± 1 , 28.3, 75.5 or 117.3 μT suggesting that the NT MMW effects may appear only at specific values of SMF (Gapeev, Iakushina et al. 1997; Gapeev, Iakushina et al. 1999).

During 1997–2008, Bartsch et al. have performed two long-term (I and II) and two life-long (III and IV) experiments analyzing the effect of chronic exposure to a low-intensity GSM-like signal (900 MHz pulsed with 217 Hz, 100 $\mu\text{W}/\text{cm}^2$ average power flux density, 38–80 mW/kg SAR for whole body) on health and survival of unrestrained female Sprague-Dawley rats kept under identical conditions (Bartsch, Kupper et al. 2010). Radiofrequency continued up to 37 months. In experiment I no adverse health effects of chronic RF-exposure were detectable, neither by macroscopic nor detailed microscopic pathological examinations. Also in experiment II no apparent macroscopic pathological changes due to treatment were apparent. In the course of two complete survival experiments (2002–2005; 2005–2008) median survival was significantly shortened under RF-exposure in both experiments by 9.06% (95% CI 2.7 to 15.0%) ($p=0.0064$); i.e by 72 days in experiment III and 77 days in experiment IV (Bartsch, Kupper et al. 2010). Based on their thorough analysis of possible reasons for variability in RF effects from year to year, the authors assumed that these variations follow the course of solar activity within the 11-years' sunspot cycle which, according to their reported observations, seems to affect pineal melatonin secretion which is an integral part of endogenous defense against cancer. The activity of the sun may influence laboratory animals via changes in the geomagnetic field, which is omnipresent and perceived by specific receptors, e.g. retinal melanopsin, also involved in the light-mediated synchronization of the SCN (central circadian clock of the brain) and controlling the circadian secretion of pineal melatonin.

The observations indicating dependence of the NT MW effects on SMF and EMF stray field may be of significant interest for further development of physical theory for the NT MW effects and development of safe mobile communication.

XII. CELL-TO-CELL INTERACTION IN RESPONSE TO MICROWAVES

The effects of NT MW at the resonance frequency of 51.755 GHz on conformation of nucleoids in *E. coli* cells were analyzed with respect to cell density during exposure (Belyaev, Alipov et al. 1994). The per-cell-normalized effect of MW increased by a factor of 4.7 ± 0.5 on average if cell density increased by one order of magnitude, from $4 \cdot 10^7$ to $4 \cdot 10^8$ cell/ml. These data suggested a co-operative nature of cell response to MW, which is based on cell-to-cell interaction during exposure. This suggestion was in line with the observed partial synchronization of cells after exposure to MW.

The co-operative nature of cell response to MW at the resonance frequency of 51.755 GHz was confirmed in further studies with *E. coli* cells (Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997; Shcheglov, Alipov et al. 2002). In addition, dependence of the per-cell-normalized effect on cell density was found for two other resonances, 51.675 GHz and 51.688 GHz. These data suggested that dependence on cell density during exposure is a general attribute of the resonance response of *E. coli* cells to NT MW. At the cell density of $4 \cdot 10^8$ cells/ml, the average intercellular distance was approximately 13 μm that is 10 times larger than the linear dimensions of *E. coli* cells (Belyaev, Alipov et al. 1994; Shcheglov, Alipov et al. 2002). Therefore, no direct physical contact seemed to be involved in the cell-to-cell interaction. Two mechanisms, biochemical and electromagnetic, were considered to account for the co-operative nature in the resonance response to weak EMF in wide frequency range including ELF, MW and ionizing radiation (Belyaev 1993; Belyaev, Alipov et al. 1994; Alipov, Shcheglov et al. 2003). The first one, biochemical, is based on release of secondary chemical messengers (ions, radicals, or molecules) by those cells, which were directly targeted. Via diffusion, these messengers can induce response in other cells. The second mechanism, electromagnetic, is based on reemission of secondary photons. According to this mechanism, reemitted photons can induce response in other cells if the intercellular distance is shorter than the length of photon absorption. The experimental data on MW effects fitted better to the electromagnetic mechanism but a combination of two mechanisms was also possible (Belyaev, Alipov et al. 1994; Shcheglov, Alipov et al. 2002). In particular, radicals with prolonged lifetimes might be involved in the observed cell-to-cell communication during response to EMF (Belyaev, Alipov et al. 1998).

The absorption length of photons with the frequencies of 10^{12} - 10^{13} Hz corresponds to the intracellular distance at the cell density of $5 \cdot 10^8$ cell/ml, at which saturation in the dependences of EMF effects on cell density was observed (Belyaev, Alipov et al. 1994; Belyaev, Alipov et al. 1995; Belyaev, Alipov et al. 1998; Shcheglov, Alipov et al. 2002). Such photons may be involved in cell-

to-cell communication according to the electromagnetic mechanism and in agreement with the prediction of Fröhlich that biosystems support coherent excitations within frequency range of 10^{11} - 10^{12} Hz (Frohlich 1968). From this point of view, cell suspension may respond to NT MW as a whole. In this case, the number of the exposed cells should be large enough to facilitate cell-to-cell communication during the responses to MW at specific parameters of exposure such as frequency, modulation, and polarization. Interestingly, the cell density for saturation of both MW and ELF effects was about $5 \cdot 10^8$ cell/ml that is close to cell densities in soft tissues of eukaryotes (Belyaev, Alipov et al. 1998; Shcheglov, Alipov et al. 2002). Such density of cells in the tissues may be important for regulation of living systems by electromagnetic cell-to-cell communication. Cellular membranes and DNA have been considered as possible sources of coherent excitations and photons, which may be involved in electromagnetic cell-to-cell communication (Frohlich 1968; Belyaev, Shcheglov et al. 1996; Belyaev, Alipov et al. 1998).

PD dependences of the MW effect at the 51.755 GHz resonance frequency were considerably different between two cell densities, $4 \cdot 10^7$ cells/ml and $4 \cdot 10^8$ cells/ml (Belyaev, Shcheglov et al. 1996). However, the resonance frequency of 51.755 GHz did not shift with the changes in cell density. The half-width of the 51.755 GHz resonance did not depend on cell density either. Contrary to the 51.755 GHz resonance response, the half-width of the 51.675 GHz resonance depended on cell density (Shcheglov, Belyaev et al. 1997). The data suggested that intracellular interaction during the NT MW exposures at some specific frequencies might affect sub-cellular targets for NT MW. This target is presumably chromosomal DNA that is organized in the DNA-domains (Belyaev, Alipov et al. 1992; Belyaev, Alipov et al. 1993; Matronchik and Belyaev 2005).

In all studies concerning dependence of the MW effects on cell density, the cells occupied a negligible part of the exposed volume and could not change the absorption of MW even at the highest cell densities (Belyaev, Alipov et al. 1994; Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997; Shcheglov, Alipov et al. 2002). Striking difference in the cell responses at various cell densities provided further evidence for non-thermal mechanism of the observed MW effects.

Significant MW effect on synchronization of *Saccharomyces carlsbergensis* yeast cells were observed by Golant and co-authors (Golant, Kuznetsov et al. 1994). Exposure to MW at $30 \mu\text{W}/\text{cm}^2$ and 46 GHz induced synchronization as measured by cell density and bud formation. The authors assumed that MW induced cell-to-cell interaction resulting in the observed synchronization.

Possible role of intrinsic electromagnetic fields in cell-to-cell communication and mechanisms of their generation have recently been reviewed (Cifra, Fields et al. 2011).

XIII. GENETIC BACKGROUND AND CELL TYPE

Belyaev et al. have studied effects of MW on *E. coli* cells of three isogenic strains with different length of chromosomal DNA (Belyaev, Alipov et al. 1993). Bacterial chromosomal DNA in the cells of N99 wild type stain was lengthened by inserting DNA from λ and $\lambda imm^{434} bio^{10}$ phages. Two strains were obtained with increased length of chromosomal DNA, N99(λ) and N99($\lambda, \lambda imm^{434} bio^{10}$). The cells of these 3 strains were exposed to MW 10^{-10} at W/cm² and 10-17 frequencies within the ranges of 41.24-41.37 GHz and 51.69-51.795 GHz. The changes in chromatin conformation were analyzed before and after exposure. Clear resonance responses to MW were observed for each strain in both frequency ranges. However, each strain had its own resonance frequency, which were statistically significantly different between strains. All resonances had the same amplitude and half-width (Belyaev, Alipov et al. 1993). In each frequency band, all 3 resonances had the same effective circular polarization: right-handed in the 41.24-41.37 GHz band and left-handed within 51.69-51.795 GHz. All these data have led to conclusion that lengthening of chromosomal DNA resulted in shifting the resonance MW spectra of action. Importantly, these shifts in resonance frequencies could not be explained by the genetic activity of the inserted DNA. On the other hand, theoretical consideration based on oscillations of the DNA-domains regarding a whole nucleoid provided a good correlation between the increasing in the DNA length and the shifts in resonances (Belyaev, Alipov et al. 1993). A detailed analysis of MW effects on the cells of another *E. coli* strain, AB1157, at 10^{-10} W/cm² and various frequencies within 51.69-51.795 GHz, revealed the resonance frequency of 51.755 ± 0.001 GHz (Belyaev, Shcheglov et al. 1996). This value was statistically significantly different from the resonance frequency of 51.765 ± 0.002 in response of *E. coli* N99 cells to MW in the same frequency range (Belyaev, Shcheglov et al. 1996). It should be noted that both strains, AB1157 and N99, are considered as wild type strains. Nevertheless, these strains are different in their genotypes by several gene markers (Lukashevsky and Belyaev 1990; Belyaev, Alipov et al. 1992). These data provided evidence that cells of different origin, even being considered as wild type cells, might have different resonance responses to NT MW because of differences in their genotypes.

Stagg with colleagues exposed tissue cultures of transformed and normal rat glial cells to modulated MW (TDMA that conforms to the North American digital cellular telephone standard) at 836.55 MHz (Stagg, Thomas et al. 1997). Results from DNA synthesis assays differed for these two cell types. Sham-exposed and MW-exposed cultures of primary rat glial cells showed no significant differences for either log-phase or serum-starved condition. C6 glioma cells exposed to MW at 5.9

$\mu\text{W/g}$ SAR (0.9 mW/cm^2) exhibited small (20-40 %) but significant increases in 38 % of [^3H]-thymidine incorporation experiments.

Repacholi with co-authors chronically exposed wild-type mice and E mu-Pim1 transgenic mice, which are moderately predisposed to develop lymphoma spontaneously, to plane-wave pulse-modulated MW at 900 MHz with a pulse repetition frequency of 217 Hz and a pulse width of 0.6 ms (Repacholi, Basten et al. 1997). Incident power densities were $2.6\text{-}13 \text{ W/m}^2$ and SARs were $0.008\text{-}4.2 \text{ W/kg}$, averaging $0.13\text{-}1.4 \text{ W/kg}$. The lymphoma risk was found to be significantly higher in the exposed transgenic mice. No effects were seen in the wild type mice.

Markkanen with colleagues found that MW affected the UV-induced apoptosis in *Saccharomyces cerevisiae* yeast cells KFY437 (cdc48-mutant) but did not modify apoptosis in KFY417 (wild-type) cells (Markkanen, Penttinen et al. 2004).

Czyz with colleagues exposed pluripotent embryonic stem (ES) cells of wild-type and deficient for the tumor suppressor p53 to pulse modulated GSM MW at 1.71 GHz (Czyz, Guan et al. 2004). Two dominant GSM modulation schemes (GSM-217 and GSM-Talk), which generate temporal changes between GSM-Basic (active during talking phases) and GSM-DTX (discontinuous transmission, which is active during listening phases thus simulating a typical conversation), were applied to the cells at and below the ICNIRP safety standards, 2 and 1.5 W/kg . GSM-217 MW induced a significant upregulation of mRNA levels of the heat shock protein hsp70 of p53-deficient ES cells differentiating in vitro, paralleled by a low and transient increase of c-jun, c-myc, and p21 levels in p53-deficient, but not in wild-type cells. These data further substantiated the notion that the genetic background determines cellular responses to GSM MW.

Nylund and Leszczynski have examined cell response to MW (900 MHz GSM-like signal, average SAR of 2.8 W/kg) using two human endothelial cell lines: EA.hy926 and EA.hy926v1 (Nylund and Leszczynski 2006). Gene expression changes were examined using cDNA Expression Arrays and protein expression changes were examined using 2-DE and PDQuest software. The same genes and proteins were differently affected by exposure in each of the cell lines.

Remondini et al. analyzed changes in gene expression in six human cell lines by gene microarrays (Remondini, Nylund et al. 2006). Cells were exposed to MW at 900 MHz GSM Basic mode, SAR $1.8\text{-}2.5 \text{ W/kg}$, 1 h exposure. Most cell lines responded to GSM-900 MHz, except for the CHME5 human microglial cells.

Rat1 and HeLa human cells were subjected to RF exposure at a frequency of 875 MHz with an intensity of 0.07 mW/cm^2 (Friedman, Kraus et al. 2007). In Rat1 cells, phosphorylation peaked at 15 min after irradiation and returned to basal level within 30 min, whereas, in HeLa cells, peak phosphorylation was at 5 min after stimulation and decreased thereafter. Increases in Hb-

EGF release upon mobile phone irradiation were detected in both Rat1 and HeLa cell lines, although the amount released from irradiated HeLa cells was much higher than that released from Rat1 cells.

Zhao et al. studied whether expression of genes related to cell death pathways are dysregulated in primary cultured neurons and astrocytes by exposure to MW from GSM cell phone at the frequency of 1900 MHz for 2 h (Zhao, Zou et al. 2007). Microarray analysis and real-time RT-PCR have shown up-regulation of caspase-2, caspase-6 and Asc (apoptosis associated speck-like protein containing a card) gene expression in neurons and astrocytes. Up-regulation occurred in both "on" and "stand-by" modes in neurons, but only in "on" mode in astrocytes. Additionally, astrocytes showed up-regulation of the Bax gene. The authors concluded that even relatively short-term exposure to the cell phone radiation can up-regulate elements of apoptotic pathways in cells derived from the brain, and that neurons appear to be more sensitive to this effect than astrocytes.

Hoyto et al. analyzed the effects of MW exposure on cellular ornithine decarboxylase (ODC) activity in fibroblasts, two neural cell lines and primary astrocytes (Hoyto, Juutilainen et al. 2007). Several exposure times and exposure levels were used, and the fields were either unmodulated or GSM-like-modulated. Murine L929 fibroblasts, rat C6 glioblastoma cells, human SH-SY5Y neuroblastoma cells, and rat primary astrocytes were exposed to RF radiation at 872 MHz in a waveguide exposure chamber equipped with water cooling. Cells were exposed for 2, 8, or 24 hours to CW MW or to a GSM type signal pulse modulated at 217 Hz. ODC activity in rat primary astrocytes was decreased statistically significantly and consistently in all experiments performed at two exposure levels (1.5 and 6.0 W/kg) and using GSM modulated or CW radiation. In the secondary cell lines, ODC activity was generally not affected. The authors concluded that ODC activity was affected by MW exposure in rat primary neural cells, but the secondary cells used in this study showed essentially no response. In further studies by the same group, the difference in response of human SH-SY5Y neuroblastoma and mouse L929 fibroblast cells to a GSM-modulated MW at 872 MHz was replicated (Hoyto, Luukkonen et al. 2008).

Human cultured fibroblasts of three different donors and three different short-term human lymphocyte cultures were exposed to UMTS-like MW at 1950 MHz and the SAR below safety limit of 2 W/kg by Schwarz et al. (Schwarz, Kratochvil et al. 2008). The alkaline comet assay and the micronucleus assay were used to analyze genotoxic effects. UMTS exposure increased the comet tail factor (CTF) and induced centromere-negative micronuclei in human cultured fibroblasts in a dose and time-dependent way. No UMTS effect was obtained with lymphocytes, either unstimulated or stimulated with phytohemagglutinin. The authors concluded that UMTS exposure may cause genetic alterations in some but not in all human cells in vitro.

Del Vecchio et al. have tested viability, proliferation, and vulnerability of neural cells, after continuous radiofrequency (RF) electromagnetic fields exposure (global system for mobile telecommunications (GSM) modulated 900 MHz signal at a specific absorption rate (SAR) of 1 W/kg and maximum duration 144 h) generated by transverse electromagnetic cells. Two cellular systems, SN56 cholinergic cell line and rat primary cortical neurons were used (Del Vecchio, Giuliani et al. 2009). Exposure to RF did not change viability/proliferation rate of the SN56 cholinergic cells or viability of cortical neurons. Co-exposure to RF exacerbated neurotoxic effect of hydrogen peroxide in SN56, but not in primary cortical neurons, whereas no cooperative effects of RF with glutamate and 25-35AA beta-amyloid were found. These data suggest that only under particular circumstances (cell type and type of co-exposure) exposure to GSM modulated, 900MHz signal act as a co-stressor for oxidative damage of neural cells.

Gerner et al. exposed four different human cell types exposed to modulated GSM 1800 MHz at 2 W/kg (Gerner, Haudek et al. 2010). While short-term exposure did not significantly alter the proteome, an 8-h exposure caused a significant increase in protein synthesis in Jurkat T-cells and human fibroblasts, and to a lesser extent in activated primary human mononuclear cells (Gerner, Haudek et al. 2010). Quiescent (metabolically inactive) mononuclear white blood cells, did not detectably respond to GSM 1800 MHz. Most of the proteins found to be induced were chaperones, which are mediators of protein folding. Heat-induced proteome alterations detectable with used proteome methodology would require heating greater than 1°C. Because GSM-induced heating was less than 0.15°C, a heat-related response was excluded.

Dragicevic et al. evaluated brain mitochondrial function in aged Tg mice and non-transgenic (NT) littermates following 1 month of daily exposure to EMF at 918 MHz frequency, involved modulation with Gaussian minimal-shift keying (GMSK) signal, and SAR levels that varied between 0.25 and 1.05 W/kg (Dragicevic, Bradshaw et al. 2011). The cognitively-important brain areas of cerebral cortex and hippocampus in EMF-exposed mice exhibited clear increases in maximum mitochondrial respiration, while the striatum and amygdala were unaffected. For Tg mice, long-term EMF treatment induced a dramatic reduction in mitochondrial ROS levels in both cerebral cortex and hippocampus, but not in striatum or amygdala. By contrast, NT mice given EMF treatment did not show significant changes in ROS levels within any of the four brain areas analyzed. Therefore, EMF treatment reduced ROS levels selectively in Tg mice and selectively in cognitively-important brain areas.

Finally, it follows from the emerging data that MW effects are dependent on genotype and cell-type. These dependences may explain, at least partly, the discrepancies among studies from

different laboratories and demand careful selection of biological objects in designing the replication studies.

XIV. SEX-AND AGE-RELATED DIFFERENCES

There are few studies consistently indicating that MW may exert a sex-related influence on brain activity.

Papageorgiou and co-authors investigated the sex-related influence of MW similar to that emitted by GSM900 mobile phones on brain activity (Papageorgiou, Nanou et al. 2004). Baseline EEG energy of males was greater than that of females, and exposure to MW decreased EEG energy of males and increased that of females. Memory performance was invariant to MW exposure and sex influences.

Smythe and Costall reported the effects of mobile phone exposure on short- and long-term memory in male and female subjects (Smythe and Costall 2003). The results showed that males exposed to an active phone made fewer spatial errors than those exposed to an inactive phone condition, while females were largely unaffected. These results further indicated that mobile phone exposure has functional consequences for human subjects, and these effects appear to be sex-dependent.

Nam and colleagues exposed volunteers of both sex to MW emitted by a CDMA cellular phone for half an hour (Nam, Kim et al. 2006). Physiological parameters such as systolic and diastolic blood pressures, heart rate, respiration rate, and skin resistance were simultaneously measured. All the parameters for both groups were unaffected during the exposure except for decreased skin resistance of the male subjects (Nam, Kim et al. 2006).

Güler et al. exposed infant female and male white rabbits to 1800 MHz GSM like RF signal at SAR of 1.8 W/kg for 15 min/day during 7-14 days (Guler, Tomruk et al. 2012). Lipid peroxidation levels in the liver tissues of female and male infant rabbits increased under RF radiation exposure. Liver 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels of female rabbits exposed to RF radiation were also found to increase when compared with the levels of non-exposed infants. However, there were no changes in liver 8-OHdG levels of male rabbits under RF exposure.

Santini et al. have performed a survey study on symptoms experienced during use of digital cellular phones using questionnaire of 161 students and workers in a French engineering school (Santini, Seigne et al. 2001). A significant increase in concentration difficult ($p < 0.05$) was reported by users of 1800-MHz (DCS) cellular phones compared to 900-MHz (GSM) phone users.

In users of cellular phones, women significantly ($p < 0.05$) complained more often of sleep disturbance than men. This sex difference for sleep complaint was not observed between women and men non-users of cellular phone. The use of both cellular phones and VDT significantly increased concentration difficulty. Digital cellular phone users also significantly ($p < 0.05$) more often complained of discomfort, warmth, and picking on the ear during phone conversation in relation with calling duration per day and number of calls per day. The complaint warmth on the ear might be a signal to users for stopping the call.

Prevalence of women (usually around 70%) among subjects, which report hypersensitivity to electromagnetic fields of wide frequency range including MW, may also provide indirect evidence for the gender-dependent effects of MW.

In his pioneering study concerning age in cancer risk from MW exposure, Hardell and colleagues found that the highest risks were associated with >5-year latency period in the youngest age group studied, 20-29-year, for analog phones (OR = 8.17, 95% CI = 0.94-71), and cordless phones (OR = 4.30, 95% CI = 1.22-15) (Hardell, Mild et al. 2004). Of note, no participants of age less 20 years were involved on this study. In further studies from the Hardell's group, highest risk was found in the age group <20 years at time of first use of wireless phones (Hardell and Carlberg 2009; Hardell, Carlberg et al. 2009).

Nam with co-authors reported that skin resistance in teenagers decreased by exposure to CDMA MW from cellular phones whereas no effects were seen in adults (Nam, Kim et al. 2006).

Capri et al. analyzed CD25, CD95, CD28 molecules in unstimulated and stimulated CD4+ e CD8+ T cells in vitro (Capri, Salvioli et al. 2006). Peripheral blood mononuclear cells (PBMCs) from young and elderly donors were exposed or sham-exposed to RF (1,800 MHz, SAR 2 W/kg) with or without mitogenic stimulation. No significant changes in the percentage of these cell subsets were found between exposed and sham-exposed lymphocytes in both young and elderly donors. Nevertheless, RF exposure induced a slight, but significant, downregulation of CD95 expression in stimulated CD4+ T lymphocytes from elderly, but not from young donors. This age-related result is noteworthy given the importance of such molecule in regulation of the immune response.

XV. INDIVIDUAL TRAITS

Shckorbatov et al. investigated electrokinetic properties of cell nuclei and condensation of heterochromatin in human buccal epithelium cells in response to MW at 42.2 GHz (Shckorbatov,

Grigoryeva et al. 1998). MW exposure decreased electric charge of cell nuclei and an increased chromatin condensation in dependence on individual traits of donors.

Individual variability in effects of GSM and UMTS MW on chromatin conformation and 53BP1/ γ -H2AX DNA repair foci was observed in studies with lymphocytes from hypersensitive to EMF subjects and healthy persons (Sarimov, Malmgren et al. 2004; Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005; Belyaev, Markova et al. 2009). The same individual variability was reported for response of chromatin condensation human lymphocytes to ELF magnetic fields (Sarimov, Alipov et al. 2011). This variability correlated with initial state of chromatin in the exposed cells (Sarimov, Alipov et al. 2011). Thus, the data from two different research groups have indicated that the NT MW effects on human cells depended on initial state of chromatin that individually varied between subjects.

Zotti-Martelli with colleagues exposed peripheral blood lymphocytes from nine different healthy donors for 60, 120 and 180 min to CW MW with a frequency of 1800 MHz and PD of 5, 10, and 20 mW/cm² and analyzed DNA damage using micronucleus (MN) assay (Zotti-Martelli, Peccatori et al. 2005). Both spontaneous and induced MN frequencies varied in a highly significant way among donors, and a statistically significant increase of MN, although rather low, was observed dependent on exposure time and PD. The data analysis highlighted a wide inter-individual and reproducible variability in the response.

Hinrikus et al. (Hinrikus, Bachmann et al. 2008) evaluated the effects of pulse-modulated MW (450 MHz) on human EEG rhythms. Thirteen healthy volunteers were exposed to MW; the field power density at the scalp was 0.16 mW/cm². Differences were found in individual sensitivity to exposure. Increases in the EEG beta power appeared statistically significant in the case of four subjects. In other study, the same authors confirmed and extended their observations on individual sensitivity to exposure with pulse-modulated MW. The experiments were carried out on four different groups of healthy volunteers. A 450-MHz MW modulated at 7 Hz (first group), 14 and 21 Hz (second group), 40 and 70 Hz (third group), 217 and 1000 Hz (fourth group) frequencies was applied. MW exposure, SAR 0.303 W/kg, increased the EEG energy. The proportion of subjects significantly affected was similar in all groups except for the 1000 Hz group: in the first group 16% at 7 Hz modulation; in the second group 31% at 14 Hz modulation and 23% at 21 Hz modulation; in the third group 20% at 40 Hz and 13% at 70 Hz modulation; in the fourth group 16% at 217 Hz and 0% at 1000 Hz modulation frequency.

Sannino et al. evaluated the induction of micronuclei in response to MW (900 MHz, average SAR of 1.25 W/kg) exposure and subsequent treatment with mitomycin C in peripheral blood lymphocytes from five human volunteers (Sannino, Sarti et al. 2009). MW exposure reduced the

level of mitomycin C –induced micronuclei in cells collected from four donors (i.e., responders). However, the effect of MW was not observed in the remaining donor (i.e., non-responder). The overall data indicated the existence of heterogeneity in the MW response among individuals.

Human sensitivity to radio frequency (RF) standing waves was tested using a movable reflecting wall (Huttunen, Hanninen et al. 2009). When the reflector was moved, the position of the maximums of the standing waves changed and the electromagnetic intensity changed in the body of the standing test subject. The computer with an AD-converter registered the signals of the hand movement transducer and the RF-meter with 100MHz dipole antennas. A total of 29 adults of different ages were tested. There were 9 persons whose hand movement graphs included features like the RF-meter. Six showed responses that did not correlate with the RF-meter. There were also 14 persons who did not react at all. Sensitive persons seem to react to crossing standing waves of the RF signals.

To conclude, while only few studies were performed, to evaluate individual sensitivity, the obtained results indicate dependence of response to MW exposure on individual traits.

XVI. PHYSIOLOGICAL VARIABLES: STAGE OF CELL GROWTH, TEMPERATURE, OXYGEN, DIVALENT METALS

The importance of physiological variables, which may include all conditions of cell culture growth such as aeration, the composition of the growth and exposure media, on NT MW effects has previously been reviewed (Grundler, Jentzsch et al. 1988). Since that time, significant body of new data has been accumulated unequivocally supporting the role of physiological variables for the NT MW effects, which should be carefully taken into account when replicating the original studies.

Belyaev et al. have reported that both value and direction of the MW effects strongly depended on the phase of culture growth, at which *E. coli* cells were exposed to CP or LP MW (100 $\mu\text{W}/\text{cm}^2$) at the resonance frequencies of 41.32 GHz and 51.76 GHz (Belyaev, Shcheglov et al. 1993; Belyaev, Alipov et al. 1994). At logarithmic phase of growth, MW resulted in condensation of nucleoids. In contrast, MW exposure decondensed nucleoids in cells if exposure was performed at the stationary phase of growth. It is known, that the state of nucleoid condensation depends on cell activity. In stationary cells nucleoids are more condensed compared to logarithmic cells that divide actively. It was concluded that MW are able to either stimulate or inhibit activity of the cells in dependence on stage of growth, stationary or logarithmic, respectively. Higher variability in effects was observed for logarithmic phase and effects were more stable for the stationary phase

that is characterized by partial synchronization of cells (Belyaev, Shcheglov et al. 1993; Belyaev, Alipov et al. 1994). There was no effect at all if cells were exposed at the end of the logarithmic phase where the MW effects changed their direction from inhibition to stimulation (Belyaev, Alipov et al. 1994). Another peculiarity was observed at the very beginning of the logarithmic stage, where the condensation of chromatin induced by MW was relatively weak. The AVTD data were confirmed by the electrophoretic analysis of proteins bound to DNA (Belyaev, Shcheglov et al. 1993). The effect in the stationary phase was characterized by a decrease in the quantity of several DNA-bound proteins with molecular weights of 61, 59, 56, 26, and 15 kDa. In contrast, abundance of some DNA-bound proteins, 61, 56, 51 and 43 kDa increased after exposure at the logarithmic phase. The decrease or increase in the abundance of DNA-bound proteins correlated with the observed changes in the state of nucleoids, decondensation or condensation, respectively.

Shcheglov et al. have studied effects of MW at the PD range of 10^{-18} to $3 \cdot 10^{-3}$ W/cm² stationary on logarithmic and stationary cells at various cell densities (Shcheglov, Alipov et al. 2002). Relatively weak response to MW was observed in exponentially growing cells. Partially synchronized stationary cells were more sensitive, especially at the cell densities above 10^8 cell/ml. The data suggested that the co-operative responses of cells to MW vary in dependence on phase of growth.

Recent data by Ushakov and colleagues indicated that the MW effects on *E. coli* cells depended on concentration of oxygen in the cell suspension during exposure (Ushakov, Alipov et al. 2005). This dependence might suggest that oxygen concentration should be indicated in order to improve reproducibility in replication studies.

Biological systems have been shown to be very sensitive to perturbations at conditions where critical components are at phase transition points, governed by local temperature, ionic strength and pH. This phenomenon was demonstrated by independent laboratories using 2.45-GHz MW radiation associated with a phase transition in lipid-protein complexes around 20-25 °C (Olcerst, Belman et al. 1980; Fisher, Poznansky et al. 1982; Liburdy and Vanek 1985; Allis and Sinha-Robinson 1987; Liburdy and Vanek 1987).

Fisher et al. have reported an effect of low-level 2450-MHz MW on total and ouabain-sensitive $^{24}\text{Na}^+$ flux from human erythrocytes. Erythrocytes washed and loaded with $^{24}\text{Na}^+$ were exposed at an absorption rate of 2.0-3.0 mW/ml suspension in a waveguide system under temperature- controlled conditions for 1 or 2 hr. Experiments were run in parallel, with exposed and sham- irradiated (control) samples, at various temperatures between 7 and 35°C. Continuous-wave electromagnetic radiation at 2450 MHz had a significant effect on $^{24}\text{Na}^+$ efflux, but only in the temperature range 22-25°C. Total efflux increased an average of 23%; this was the result of an

increase in the ouabain-insensitive component (mean, 33%) and a decrease in the ouabain-sensitive portion (mean, 18%). These results indicated increased passive Na^+ efflux and decreased ATPase-mediated Na^+ efflux in erythrocytes exposed to low-level microwaves at 22-25°C (Fisher, Poznansky et al. 1982).

Liburdy and Vanek have shown that MW-induced protein shedding is oxygen and temperature dependent (Liburdy and Vanek 1987). Microwaves (2450 MHz, 60 mW/g) resulted in the release or shedding of at least 11 low-molecular-weight proteins (<31,000 Da) from rabbit erythrocytes maintained in physiological buffer. This release was oxygen dependent and occurred in 30 min for exposures conducted within the special temperature region of 17-21°C, which is linked to a structural or conformational transition in the cell membrane. Shedding of 26,000 and 24,000 Da proteins was unique to MW treatment, with enhanced release of 28,000 and < 15,000 Da species upon MW exposure. Two-dimensional isoelectric focusing revealed that proteins of < 14,000 Da shed during microwave treatment exhibited a pI of 6.8-7.3 not seen in sham-treated cells. When erythrocytes were maintained at 17-21°C in the absence of divalent cations, release of 28,000-31,000 and < 14,000 Da components was detected. This indicated that cation-bridge stability may be important for release of these proteins. The results provided evidence that MW alter erythrocyte protein composition at temperatures linked to a transition in the cell membrane and that destabilization of salt bridges may play a role in an interaction mechanism for protein release (Liburdy and Vanek 1987).

The ATPase activity in human red blood cell membranes was investigated in vitro as a function of temperature and exposure to 2,450-MHz continuous wave microwave radiation to confirm and extend a report of Na^+ transport inhibition under certain conditions of temperature and exposure (Allis and Sinha-Robinson 1987). Assays were conducted spectrophotometrically during microwave exposure with a custom-made spectrophotometer-waveguide apparatus. Temperature profiles of total ATPase and Ca^{+2} ATPase (ouabain-inhibited) activity between 17 and 31 degrees C were graphed as an Arrhenius plot. Each data set was fitted to two straight lines which intersect between 23 and 24 degrees C. The difference between the total and Ca^{+2} ATPase activities, which represented the Na^+/K^+ ATPase activity, was also plotted and treated similarly to yield an intersection near 25 degrees C. Exposure of membrane suspensions to electromagnetic radiation, at a dose rate of 6 W/kg and at five temperatures between 23 and 27 degrees C, resulted in an activity change only for the Na^+/K^+ ATPase at 25 degrees C. The activity decreased by approximately 35% compared to sham-irradiated samples. A possible explanation for the unusual temperature/microwave interaction was proposed (Allis and Sinha-Robinson 1987).

Therefore, temperature may be an important variable, which should be taken into account while analyzing response of cells to MW.

Similar to the effects of ELF (Belyaev, Alipov et al. 1999), the MW effects were reported to be dependent on concentration of divalent ions (Gapeev, Iakushina et al. 1997).

In conclusion, physiological parameters such as stage of cell growth, temperature, oxygen an divalent ions temperature may be an important variable, which should be taken into account while analyzing response of cells to MW.

XVII. ANTIOXIDANTS AND RADICAL SCAVENGERS

Oxidative stress caused by biological, chemical and physical factors has been associated with increased risk of human cancer at various sites. Human cells induce and/or activate several oxidant generating enzymes that produce high concentrations of diverse free radicals and oxidants. These reactive species can damage DNA, RNA, lipids and proteins, leading to increased mutations and altered function of enzymes and proteins, thus contributing to the multistage carcinogenesis process. Control of oxidative stress is being explored as an approach to chemoprevention of human cancers (IARC 2002).

It is well known that endogenous (intracellular) free radicals, which are collectively called reactive oxygen species (ROS), arise from mitochondrial oxidative metabolism and other reactions in cells (Pollycove and Feinendegen 2003). The estimated average generation rate is $\sim 10^9$ ROS per cell per day (Beckman and Ames 1998), which results in 10^6 oxidative DNA damage, 10^5 SSBs and 0.1 DSBs per cell per day (Pollycove and Feinendegen 2003).

In their pioneering study, Lai and Singh described the effects of MW on the rat brain cells as measured using a microgel electrophoresis assay (Lai and Singh 1996). These effects were significantly blocked by treatment of rats either with the spin-trap compound N-tert-butyl- α -phenylnitron or with melatonin, both agents being free radical scavengers and antioxidants (Lai and Singh 1997). These data suggested that free radicals might be involved in the effects of MW. The ability of scavengers and antioxidants has been tested by many other research groups and in all cases, this treatment inhibited the reported TN MW effects.

Oktem and colleagues exposed rats to MW from GSM900 mobile phone with and without melatonin treatment (Oktem, Ozguner et al. 2005). Malondialdehyde (MDA), an index of lipid peroxidation, and urine N-acetyl-beta-d-glucosaminidase (NAG), a marker of renal tubular damage, were used as markers of oxidative stress-induced renal impairment. Superoxide dismutase (SOD),

catalase (CAT), and glutathione peroxidase (GSH-Px) activities were studied to evaluate changes in antioxidant status. In the MW-exposed group, while tissue MDA and urine NAG levels increased, SOD, CAT, and GSH-Px activities were reduced. Melatonin treatment inhibited these effects. The authors concluded that melatonin might exhibit a protective effect on mobile phone-induced renal impairment in rats.

Ozguner and colleagues exposed Wistar-Albino rats to MW from GSM900 mobile phone with and without melatonin and analyzed histopathologic changes in skin (Ozguner, Aydin et al. 2004). MW induced increase in thickness of stratum corneum, atrophy of epidermis, papillomatosis, basal cell proliferation, granular cell layer (hypergranulosis) in epidermis and capillary proliferation. Impairment in collagen tissue distribution and separation of collagen bundles in dermis were all observed in exposed animals as compared to the control group. Most of these changes, except hypergranulosis, were prevented with melatonin treatment. The authors concluded that exposure to GSM900 MW caused mild skin changes and melatonin treatment could reduce these changes. In other studies of the same group, the ability of melatonin to reduce various MW-induced effects was confirmed and inhibitory potential of the antioxidant caffeic acid phenethyl ester (CAPE) was reported (Ozguner, Altinbas et al. 2005; Ozguner, Oktem et al. 2005; Ozguner, Oktem et al. 2005; Ozguner, Bardak et al. 2006).

Ayata et al. analyzed the effects of 900 MHz MW with and without melatonin on fibrosis, lipid peroxidation, and anti-oxidant enzymes in rat skin (Ayata, Mollaoglu et al. 2004). The levels of MDA and hydroxypyroline and the activities of SOD, GSH-Px, and CAT were studied. MDA and hydroxypyroline levels and activities of CAT and GSH-Px were increased significantly in the exposed group without melatonin and decreased significantly in the exposed group with melatonin. SOD activity was decreased significantly in the exposed group and this decrease was not prevented by the melatonin treatment. The authors assumed that the rats irradiated with MW suffer from increased fibrosis and lipid peroxidation and that melatonin can reduce the fibrosis and lipid peroxidation caused by MW.

Ilhan with co-authors investigated oxidative damage in brain tissue of rats exposed to GSM900 MW with and without pretreatment with Ginkgo biloba (Gb) (Ilhan, Gurel et al. 2004). MW induced oxidative damage measured as: (i) increase in MDA and nitric oxide (NO) levels in brain tissue, (ii) decrease in brain SOD and GSH-Px activities, and (iii) increase in brain xanthine oxidase and adenosine deaminase activities. These MW effects were prevented by the Gb treatment. Furthermore, Gb prevented the MW-induced cellular injury in brain tissue revealed histopathologically. The authors concluded that reactive oxygen species may play a role in the

adverse effects of GSM900 MW and Gb prevents the MW-induced oxidative stress by affecting antioxidant enzymes activity in brain tissue.

Guney et al. examined 900 MHz mobile phone-induced oxidative stress that promotes production of ROS and investigated the role of vitamins E and C, which have antioxidant properties, on endometrial tissue against possible 900 MHz mobile phone-induced endometrial impairment in rats (Guney, Ozguner et al. 2007). The animals were randomly grouped (eight each) as follows: 1) Control group (without stress and EMR, Group I), 2) sham-operated rats stayed without exposure to EMR (exposure device off, Group II), 3) rats exposed to 900 MHz EMR (EMR group, Group III) and 4) a 900 MHz EMR exposed + vitamin-treated group (EMR + Vit group, Group IV). A 900 MHz EMR was applied to EMR and EMR + Vit group 30 min/day, for 30 days. Endometrial levels of nitric oxide (NO, an oxidant product) and malondialdehyde (MDA, an index of lipid peroxidation), increased in EMR exposed rats while the combined vitamins E and C caused a significant reduction in the levels of NO and MDA. Likewise, endometrial superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) activities decreased in EMR exposed animals while vitamins E and C caused a significant increase in the activities of these antioxidant enzymes. In the EMR group histopathologic changes in endometrium, diffuse and severe apoptosis was present in the endometrial surface epithelial and glandular cells and the stromal cells. Diffuse eosinophilic leucocyte and lymphocyte infiltration were observed in the endometrial stroma whereas the combination of vitamins E and C caused a significant decrease in these effects of EMR. It is concluded that oxidative endometrial damage plays an important role in the 900 MHz mobile phone-induced endometrial impairment and the modulation of oxidative stress with vitamins E and C reduces the 900 MHz mobile phone-induced endometrial damage both at biochemical and histological levels.

Koylu et al. studied the effects of MW on the brain lipid peroxidation in rats, and the possible protective effects of melatonin on brain degeneration induced by MW (Koylu, Mollaoglu et al. 2006). The levels of lipid peroxidation in the brain cortex and hippocampus increased in the MW group compared with the control group, although the levels in the hippocampus were decreased by combined administration of MW and melatonin. Brain cortex lipid peroxidation levels were unaffected by melatonin treatment. The authors concluded that melatonin may prevent MW-induced oxidative stress in the hippocampus by strengthening the antioxidant defense system.

Balci et al. exposed albino Wistar rats to mobile-phone-emitted radiation and analyzed oxidant/antioxidant balance in corneal and lens tissues. The results of this study suggest that mobile telephone radiation leads to oxidative stress in corneal and lens tissues and that antioxidants such as vitamin C can help to prevent these effects (Balci, Devrim et al. 2007).

Sokolovic et al. evaluated the intensity of oxidative stress in the brain of Wistar rats chronically exposed to MW from mobile phones (SAR = 0.043-0.135 W/kg) during 20, 40 and 60 days (Sokolovic, Djindjic et al. 2008). A significant increase in brain tissue malondialdehyde (MDA) and carbonyl group concentration was found. Decreased activity of catalase (CAT) and increased activity of xanthine oxidase (XO) remained after 40 and 60 days of MW exposure. Melatonin treatment significantly prevented the increases in MDA content and XO activity in the brain tissue after 40 days of exposure while it was unable to prevent the decrease of CAT activity and increase of carbonyl group contents. The authors concluded that exposure to the mobile phone MW caused oxidative damage in the brain and that treatment with melatonin significantly prevented this oxidative damage.

Gajski and Garaj-Vrhovac investigated the radioprotective effect of bee venom against DNA damage induced by 915-MHz microwave radiation (SAR of 0.6 W/kg) (Gajski and Garaj-Vrhovac 2009). Whole blood lymphocytes of Wistar rats are treated with 1 mg/mL bee venom 4 hours prior to and immediately before irradiation. Standard and formamidopyrimidine-DNA glycosylase (Fpg)-modified comet assays were used to assess basal and oxidative DNA damage produced by ROS. Bee venom decreased basal and oxidative DNA damage induced by microwave radiation. The difference between the comet assay results in the presence and in the absence of Fpg-enzyme suggested that oxidative stress is responsible for the DNA damage induced by microwave radiation. Among other possible mechanisms, antioxidant activity of bee venom may likely account for the radioprotective effect.

Esmekaya et al. analyzed effects of 1.8 GHz GSM alone and in combination with Ginkgo biloba (EGb 761) pre-treatment in human peripheral blood lymphocytes (Esmekaya, Aytekin et al. 2011). RF exposure significantly increased frequency of sister chromatid exchanges (SCE) and inhibited cell viability. No temperature difference was observed between sham control and RF exposed cells, so the observed effects may be considered as non-thermal. EGb 761 pre-treatment significantly reduced both RF effects. The authors concluded that EGb 761 had a protective role against RF induced mutagenesis.

Ozgun et al investigated oxidative damage and antioxidant enzyme status in the liver of guinea pigs exposed to mobile phone-like radiofrequency radiation (RFR) and the potential protective effects of N-acetyl cysteine (NAC) and epigallocatechin-gallate (EGCG) on the oxidative damage (Ozgun, Gler et al. 2010). Nine groups of guinea pigs were used to study the effects of exposure to an 1800-MHz Global System for Mobile Communications (GSM)-modulated signal (average whole body Specific Absorption Rate (SAR) of 0.38W/kg, 10 or 20 min per day for seven days) and treatment with antioxidants. Significant increases in malondialdehyde (MDA) and total

nitric oxide (NO) levels and decreases in activities of superoxide dismutase (SOD), myeloperoxidase (MPO) and glutathione peroxidase (GSH-Px) were observed in the liver of guinea pigs after RFR exposure. NAC treatment induced increase in hepatic GSH-Px activities, whereas EGCG treatment alone attenuated MDA level. Extent of oxidative damage was found to be proportional to the duration of exposure. Authors concluded that the adverse effect of RFR may be related to the duration of mobile phone use. NAC and EGCG may protect the liver tissue against the RFR-induced oxidative damage and enhance antioxidant enzyme activities.

Female rats were exposed to a mobile phone signal (900 MHz), the mobile phone plus vitamin C group was exposed to a mobile phone signal (900 MHz) and treated orally with vitamin C (Imge, Kilicoglu et al. 2010). Malondialdehyde (MDA), antioxidant potential (AOP), superoxide dismutase, catalase (CAT), glutathione peroxidase (GSH-Px), xanthine oxidase, adenosine deaminase (ADA) and 5'nucleotidase (5'-NT) were analyzed in brain tissues. MW exposure caused an inhibition in 5'-NT and CAT activities. GSH-Px activity and the MDA level were also found to be reduced in the mobile phone group but not significantly. Vitamin C caused a significant increase in the activity of GSH-Px and non-significant increase in the activities of 5'-NT, ADA and CAT enzymes. The results suggest that vitamin C may play a protective role against detrimental effects of mobile phone radiation in brain tissue.

To conclude this section, several studies consistently show that supplementation with antioxidants and radical scavengers can reduce MW effects. In other words, the level of radicals should be considered as an important parameter for the NT MW effects. Moreover, these studies indicate that induction of radicals is one of the key events in bioeffects of NT MW.

XVIII. CO-EXPOSURE

Zmyslony et al have studied effects of 930 MHz continuous wave (CW) electromagnetic field, 1.5 W/kg, on the reactive oxygen species (ROS) level in rat lymphocytes (Zmyslony, Politanski et al. 2004). Acute (5 and 15 min) exposure did not induce ROS. However, this exposure increased effect of FeCl₂, 10 µg/ml.

Co-exposure to RF (global system for mobile telecommunications (GSM) modulated 900MHz signal at a specific absorption rate (SAR) of 1 W/kg and maximum duration 144 h) exacerbated neurotoxic effect of hydrogen peroxide in SN56, but not in primary cortical neurons (Del Vecchio, Giuliani et al. 2009). These data suggest that only under particular circumstances

(cell type and type of co-exposure) exposure to GSM modulated, 900MHz signal act as a co-stressor for oxidative damage of neural cells.

XIX. REPLICATION STUDIES

Obviously, not taking into account the dependences of NT MW effects on a number of physical parameters and biological variables may result in misleading conclusions regarding the reproducibility of these effects. Especially important might be the observations that NT MW could inhibit or stimulate the same functions dependent on conditions of exposure (Pakhomov, Akyel et al. 1998). Under different conditions of exposure, MW either increased or decreased the growth rate of yeast cells (Grundler, Jentzsch et al. 1988), the radiation-induced damages in mice (Sevast'yanova 1981), the respiratory burst in neutrophils of mice (Gapeev, Iakushina et al. 1997), the condensation of nucleoids in *E coli* cells (Belyaev, Shcheglov et al. 1993; Belyaev, Alipov et al. 1994) and human lymphocytes (Sarimov, Malmgren et al. 2004). Potentially bi-directional effects of MW should be taken into account in replication studies.

In some cases when the conditions were kept in strict control, the effects we reproduced. Highly resonant effects of ultra-weak MW (near 70 GHz) on the induction of λ -phage were first established by Webb (Webb 1979), and subsequently corroborated (Lukashevsky and Belyaev 1990).

Despite of considerable body of studies with NT MW in biology, only a few studies were performed to independently replicate the original data on the NT MW effects. It should be noted, that these replications are usually not completely comparable with the original studies because of either missing description of important parameters of exposure or significant differences in these parameters between original study and replication. One well-known attempt to replicate the results of Gründler was the study by Gos and co-authors (Gos, Eicher et al. 1997). No MW effects were observed in this replication study. However, the deviations from the Gründler's protocol might be a simple reason for poor reproducibility. For example, synchronized cells were used in studies of Gründler. Contrary to the Gründler's original protocol, Gos used exponentially growing cells. If the MW effects in yeast cells are dependent on stage of growth, cell density and intercellular interactions as it has been described for *E. coli* cells (Belyaev, Shcheglov et al. 1993; Belyaev, Alipov et al. 1994; Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997), no response should be expected in the logarithmic phase of growth. Gos and colleagues used *S. cerevisiae* strain with the auxotrophy mutations for leucine and uracil. Gründler used the wild type strain. It might

suggest another cause for the deviations between the data of Gründler and Gos. Despite orientation of SMF in respect to electric and magnetic components of MW was the same, the values of SMF were different. The stray ELF field was 120 nT in the study by Gos, that is higher than usually observed background fields, < 50 nT. The spectral characteristics of the background fields, which were described only in the study by Gos, might be also different. In addition, the conditions of cell cultivation might vary between studies; for example, the data on oxygen concentration in media used in both studies are not available.

Lai and Singh have consistently reported that circularly polarized MW exposure at 2450 MHz induced DNA damage in brain cells of the exposed rats (Lai and Singh 1995; Lai and Singh 1996; Lai and Singh 1997). Replication studies have also tested circularly polarized MW exposure at 2450 MHz and no induced DNA damage was reported (Malyapa, Ahern et al. 1997; Malyapa, Ahern et al. 1998; Lagroye, Anane et al. 2004). All these replication studies have used another exposure system. However, handedness of circular polarization has not been given neither in original study, no in replications. If the handedness was different between studies it could reasonably account for inconsistency.

Most reviews of the experimental studies do not include analysis of various biological variables and physical parameters when comparing the data on the NT MW effects from different studies. As result, misleading conclusion is often made that MW at NT levels produce no "reproducible" effects.

XX. SIMILARITY OF MICROWAVE AND ELF EFFECTS

Mobile phones not only expose the user to RF EMF but also to ELF EMF (Linde and Mild 1997; Heath, Jenvey et al. 1998; Jokela, Puranen et al. 2004; Ilvonen, Sihvonen et al. 2005; Cook, Saucier et al. 2006; Perentos, Iskra et al. 2007). Perentos et al. have recently measured and characterized the ELF magnetic field from several commercial GSM handsets (the RF characteristics being already well understood) using different probes which covered frequency range from static magnetic fields ("0 Hz") to 2 GHz. Peak ELF fields at the front sides of 5 commercial GSM phones were assessed and a maximum of 22.4 μ T was reported (Perentos, Iskra et al. 2008). The main ELF component at the 217 Hz was about 1 μ T at the distance of 3 cm from the handset front side. The overall pulse peak was 4.2 times greater than the 217 Hz component. 217 Hz magnetic field decreased with distance and reached 0.3 μ T approximately at 5 cm from the front handset side. The overall ELF pulse peak produced by all ELF components was 4.2 times greater

than the 217 Hz component. The ELF fields higher 0.3 μT have consistently been shown to correlate with increased risk of children leukemia in several studies covering European countries, USA and Japan (Kabuto, Nitta et al. 2006; Yang, Jin et al. 2008). Similar to RF, ELF has been classified by the IARC as possible carcinogen "2B". It has been known for long time that weak ELF fields and NT MW result to similar effects with significant overplaying of molecular biological pathways for their appearance (Adey 1981; Blank and Goodman 2009; Davanipour and Sobel 2009). Multiple data on ELF biological effects at intensities below the ICNIRP standards are available showing their complex dependence of the ELF effects on biological and physical variables (Belyaev, Alipov et al. 1999; Blank and Goodman 2009; Phillips, Singh et al. 2009; Sarimov, Alipov et al. 2011). In particular, stress response, molecular pathways for generation of reactive oxygen species (ROS), increased sensitivity of stem cells, and inhibition of melatonin production (Burch, Reif et al. 2000) were suggested as mechanisms which link observed increase in cancer risks and effects of exposure at the cellular level. EMF effects in a wide frequency range from ELF to MW have been considered in the frames of the same physical models (Chiabrera, Bianco et al. 1991; Matronchik, Alipov et al. 1996; Chiabrera, Bianco et al. 2000; Binh 2002; Panagopoulos, Karabarbounis et al. 2002; Matronchik and Belyaev 2005; Matronchik and Belyaev 2008).

In many cases, because of ELF modulation and additional ELF fields created by the MW sources, for example by mobile phones, it is difficult to distinguish the effects of exposures to ELF and MW. Therefore, these combined exposures and their possible cancer risks should be considered in combination.

XXI. CANCER RISK ASSESSMENT FROM MECHANISTIC POINT OF VIEW

At present, a new situation has arisen when a significant part of the general population is exposed chronically (much longer than previously investigated durations of exposures) to NT MW from different types of mobile communication including GSM and UMTS/3G phones and base stations, WLAN (Wireless Local Area Networks), WPAN (Wireless Personal Area Networks such as Bluetooth), DECT (Digital Enhanced (former European) Cordless Telecommunications) wireless phones (Joseph, Frei et al. 2010). Multiple sources of mobile communication result in chronic exposure of general population to MW at the non-thermal levels. These exposures are characterized by low intensities, varieties and complexities of signals, and long-term durations of exposure that are comparable with a lifespan.

Most of the real signals that are in use in mobile communication have not been tested so far. Very little research has been done with real signals and for durations and intermittences of exposure that are relevant to chronic exposures from mobile communication. In some studies, so-called “mobile communication-like” signals were investigated that in fact were different from the real exposures in such important aspects as intensity, carrier frequency, modulation, polarization, duration and intermittence.

Emerging evidence suggests that the SAR concept, which has been widely adopted for safety standards, is not useful alone for the evaluation of health risks from NT MW of mobile communication. The role of other exposure parameters such as frequency, modulation, polarization, duration, and intermittence of exposure should be taken into account.

IARC has recently classified RF as a ‘Possible Human Carcinogen’ (Class 2B) (Baan, Grosse et al. 2011). Contrary to other panels, such as ICNIRP, whose members dismiss the NT MW effects based on their “non-reproducibility” and lack of comprehensive mechanisms, the IARC working group included scientists, which argued for existence of non-thermal effects and their complex dependence on variety of biological and physical parameters which should be included in consideration. By its classification, IARC has justified implementation of the Precautionary Principle, confirmed the existence of non-thermal effects that can cause health risks, and indicated that the current safety standards are insufficient to protect health.

The data about the effects of MW at super low intensities and significant role of duration of exposure in these effects along with the data showing that adverse effects of NT MW from GSM/UMTS mobile phones depend on carrier frequency and type of the MW signal suggest that MW from base-stations/masts, wireless routers, WI-FI and other wireless devices and exposures in common use today can also produce adverse effects at prolonged durations of exposure.

So far, most laboratory and epidemiological studies did not control important features of the NT MW effects and therefore, only limited conclusion regarding health effects of MW from mobile communication can be drawn from these studies. The group of Hardell was the first epidemiologic studying separately the MW signals from cordless phones, analogue phones and digital phones (Hardell, Hansson Mild et al. 2001; Hardell, Hansson Mild et al. 2003; Hardell, Eriksson et al. 2005; Hardell and Hansson Mild 2005). This approach is valid from the mechanistic point of view.

Nowadays, it is almost impossible to select control unexposed groups because the whole population in many countries is exposed to wide range of MW signals from various sources such as mobile phones, base stations/masts, WLAN, WPAN, DECT wireless phones and given that duration of exposure (at least 10 years for cancer latency period) is also important for the effects of NT MW along PD/SAR. Exposure from downlink sources (base stations *etc.*) may contribute up to

90% of total environmental outdoor-urban exposure in European countries while exposure to DECT phone is comparable to exposure to mobile phones (Frei, Mohler et al. 2009; Frei, Mohler et al. 2010; Joseph, Frei et al. 2010). In other words, there are no unexposed control groups available for epidemiologic studies in the developed countries. Substantial variation in relative ratio of downlink and uplink signals between countries (Joseph, Frei et al. 2010) can at least partially account for differences in epidemiologic data because of variation in exposure of control groups to downlink signals.

While several national registers (Norway, Australia, Finland, Denmark) report increased incidence of brain cancer, US and Swedish ones do not. This inconsistency may be accounted by deficit in reporting of tumors to the Swedish Cancer Registry (Hardell and Carlberg 2009).

Importantly, because the signals are completely replaced by other signals faster than once per 10 years, duration comparable with latent period, epidemiologic studies can not provide basement for assessment of upcoming new signals.

As far as different types of MW signals (carrier frequency, modulation, polarization, far and near field, intermittence, coherence, *etc.*) may produce different effects, cancer risks should ideally be estimated for each MW signal separately. In other words, one type of MW signal would correspond to one chemical compound. That means, for example, that each from 124 signals involved in GSM uplink mobile communication should be separately evaluated to fit situation accepted for estimation of cancer risks from chemical compounds.

It now appears that most, if not all, adult tissues and organs including blood and brain contain stem cells (Metcalf and Ferguson 2008). Almost all hematopoietic and solid neoplasms arise from cancer stem cells that are dysfunctional versions of a normal stem cells. Current models for radiation carcinogenesis have paid much attention to the stochastic process of energy deposition in cells, but accumulating evidences have shown that the nature of the target cells, i.e. tissue stem cells and progenitor cells, needs to be taken into consideration (Niwa 2010; Richardson 2011). Stem cell self-renewal and progenitor differentiation is regulated by the specialized microenvironment—or “niche”—in which these cells reside (Alvarez-Buylla and Lim 2004) and which regulate stem cells (Morrison and Spradling 2008; Johansson, Cappello et al. 2010; Kim and Shivdasani 2012; Sugiyama and Nagasawa 2012). Importance of stem cells for carcinogenesis, challenges the definition of volume for SAR determination in safety standards. Instead of random distribution of targets for carcinogenesis, localized distribution of SAR in stem cells and niches is needed. Because very small size of the niches in different tissues including the brain (Kazanis 2012), the SAR averaging should be performed at volumes much less than currently accepted 10 g. Decreasing the sensitive volume to the stem cell niches with sizes down to 10 μm (Richardson 2011) may likely

put almost all mobile phones out of the current safety standards, even given that they are only based on thermal effects and do not consider any other parameters except for SAR. From point view of stem cell organization, the volume of SAR determination may be especially important for setting the safety standards for children. During brain development, most stem cells and their niches are spatially ephemeral and temporally transient as the cellular and molecular “puzzle” behind neurogenesis and morphogenesis is “assembled” and “disassembled” at a dazzling pace. In contrast, in the adult, neural stem cells and their niches are retained in restricted regions with their local developmental processes occurring for the life (Alvarez-Buylla and Lim 2004).

It should be anticipated that some part of the human population, such as children, pregnant women and groups of hypersensitive persons could be especially sensitive to the NT MW exposures.

XXII. CONCLUSIONS

Non-thermal effects of microwaves depend on variety of biological and physical parameters that should be taken into account in setting the safety standards. These exposures can cause health risk. The current safety standards are insufficient to protect from non-thermal microwave effects. Emerging evidence suggests that the SAR concept, which has been widely adopted for safety standards, is not useful alone for the evaluation of health risks from NT MW of mobile communication. Other parameters of exposure, such as frequency, modulation, duration, dose should be taken into account. New standards should be developed based on knowledge of mechanisms of non-thermal effects. Importantly, because the signals of mobile communication are completely replaced by other signals faster than once per 10 years, duration comparable with latent period, epidemiologic studies cannot provide basement for cancer risk assessment from upcoming new signals. Precautionary Principle should be implemented while new standards are in progress. In many cases, because of ELF modulation and additional ELF fields created by the MW sources, for example by mobile phones, it is difficult to distinguish the effects of exposures to ELF and MW. Therefore, these combined exposures and their possible cancer risks should be considered in combination. It should be anticipated that some part of the human population, such as children, pregnant women and groups of hypersensitive persons could be especially sensitive to the non-thermal microwave exposures.

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SECTION 20

Findings in Autism (ASD) Consistent with Electromagnetic Fields (EMF) and Radiofrequency Radiation (RFR)

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Part 1 - INTRODUCTION

The premise of this review is that although scant attention has been paid to possible links between electromagnetic fields and radiofrequency exposures (EMF/RFR) and Autism Spectrum Disorders (ASDs), such links probably exist. The rationale for this premise is that the physiological impacts of EMF/RFR and a host of increasingly well-documented pathophysiological phenomena in ASDs have remarkable similarities. Additional support may be found in the parallels between the rise in reported cases of ASDs and the remarkable increases in EMF/RFR exposures over the past few decades. Reviewing these similarities does not prove that these parallels imply causality – that kind of research has not been done. Moreover, the physiological processes affected by EMF/RFR are also impacted by other environmental factors. Yet EMF/RFR does not need to be a unique contributor to ASDs to add significantly to system overload ('allostatic load') and dysfunction. Even so these pathophysiological overlaps do suggest that the potential for an EMF/RFR-ASD connection should be taken seriously, and that their vulnerable biological features may make many with ASDs more likely to experience adverse EMF/RFR impacts. This is a sufficient basis to recommend that precautionary measures should be implemented and respected, that further research should be prioritized, and that policy level interventions based on existing and emerging data should be designed and pursued. Moreover, pursuing this link could help us understand ASDs better and find more ways to improve the lives of people with ASDs and of so many others.

A. How are biology and behavior related?

Considering a potential link between ASDs and EMF/RFR (or indeed of any potential contributor to incidence or pathogenesis) requires taking account of the evolution that has been occurring in our understanding of the relationship between ASD's behavioral and biological features. ASDs were first labeled as 'autism' in 1943 by Leo Kanner, a child psychiatrist who extracted several key behavioral features, related to communication and social interaction challenges and a tendency toward restricted interests and repetitive behaviors, characteristic of all 11 of the children in his first case series (Kanner 1943). Although in the seven decades since this condition was first constructed as a category there has been some modification of the way these behavioral features have been characterized, ASDs are still defined behaviorally, although sensory issues such as hypo- or hyper-reactivity have recently been included in the diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders or DSM-V) (American Psychiatric Association 2000, 2013, May).

1. Transduction is fundamental but poorly understood

Yet in considering how an environmental factor such as EMF/RFR could lead to autism and/or influence its severity or incidence, we need to think about how underlying biology is transduced into changes in nervous system electrical activity, and how these in turn generate the set of behaviors we have categorized as ‘autism.’ {Herbert, 2005 #757} This means not taking behaviors as given, or as purely determined by genetics, but exploring the full range of biology that generates these features and challenges.

2. More than brain

Although ‘autism’ has long been considered to be a psychiatric or neurological brain-based disorder (Rapin and Katzman 1998; Polleux and Lauder 2004), it has become undeniable that people diagnosed with ASDs often also have a multitude of biological features – including systemic pathophysiological disturbances (such as oxidative stress, mitochondrial dysfunction and metabolic and immune abnormalities) (Ming et al. 2012; Tsaluchidu et al. 2008; Pieczenik and Neustadt 2007; Gonzalez et al. 2011) as well as symptomatic medical comorbidities (such as gastrointestinal distress, recurrent infections, epilepsy, autonomic dysregulation and sleep disruption) (Nikolov et al. 2009; Kotagal and Broomall 2012; Kaartinen et al. 2012; Daluwatte et al. 2012; Tuchman and Cuccaro 2011; Canitano 2007; Malow 2004; Kang and Barnes 2013; Jyonouchi et al. 2011) – in addition to the core defining behaviors – and many of these occur commonly (Kohane et al. 2012). The problem has been that no one such biological feature has turned out to be present in every single person carrying an ASD diagnosis – and they are not specific to ASDs, either. Moreover there has been much variability in many of the features of autism – not only between individuals but in many cases within individuals at different points in time or under different circumstances. Because of this variability, the relevance of many of these biological features has been dismissed as secondary and not intrinsically related to the ‘autism.’ Instead, many have considered the behavioral features as fundamental not only to how autism manifests and is defined but also to the core intrinsic nature of ASDs, even though the biological basis of these behaviors has by no means been established.

3. Heterogeneity: More Genetic and Environmental than Physiological

It is not as if this variability is unique to the ‘environmental side.’ At the present time over 800 genes have been associated with ASDs, and over 100 different rare genetic syndromes are frequently accompanied by ASD, with no clear specific unifying mechanism uniting this remarkable heterogeneity (Trikalinos et al. 2006; Ring et al. 2008; Pelphrey et al. 2011; Mandell 2011; Hall et al. 2012; Bill and Geschwind 2009).

Similarly a large number of potential environmental contributors are under investigation ranging from toxicants and Vitamin D deficiency or failure to take prenatal vitamins to air pollution and stress or infection in pregnancy (Whitehouse et al. 2012; Kocovska et al. 2012; Schmidt et al. 2011; Landrigan 2010; Roberts et al. 2007; Shelton, Hertz-Picciotto, and Pessah 2012; Becerra et al. 2012; Volk et al. 2011). Yet at the physiological level a smaller set of disturbances are showing up as common across substantial numbers of people with ASDs – and in fact not uniquely to ASDs but also in myriad other chronic conditions whose prevalence also appears to be increasing (Bilbo, Jones, and Parker 2012; Knox 2010). Prominent among these are immune disturbances including inflammation, mitochondrial dysfunction, and oxidative stress, as well as toxic body burden. Vulnerability to all of these can be increased mildly or substantially by a variety of often common genetic mutations, but may remain latent without the overlay of environmental triggers. Conversely, with substantial enough environmental input, genetic vulnerability may not be necessary.

4. Mechanism is more than correlation

Just HOW biological features might be related to the behavioral features that have up until now defined ASDs has not been clarified; until recently the main research effort regarding pathophysiology in ASDs has been to establish the presence of these phenomena in the first place. Even so, some correlations between biological and behavioral features have been identified – e.g. a higher level of immune abnormalities correlates with more aberrant behaviors (Wei et al. 2012; Careaga and Ashwood 2012; Jyonouchi et al. 2011; Ashwood et al. 2011; Heuer et al. 2008; Zerrate et al. 2007; Curran et al. 2007). Still, such correlations in themselves do not explain the *mechanisms* by which the *transduction of pathophysiology into behavior* might actually occur. In order to do that, an important component would be to study the relationship between systemic pathophysiology and nervous system electrophysiology.

5. EMF/RFR research may help us understand how ASDs ‘work’

Assessing the potential contribution of EMF/RFR to ASDs puts this question of the nature of the pathophysiology-behavior transduction into an interesting and provocative light since the brain is simultaneously a tissue-based physical organ that can be compromised by cellular pathophysiology as well as altered developmental processes, and an information processing system that operates through networks of synchronized electrical oscillations (brain waves) – and EMF/RFR impacts may occur directly at both of these levels. To date the emphasis in ASD research has largely been on ‘structure-function’ relationships that have been anatomy-centered. This research has generated correlations between brain structures and behaviors, and has found some genetic correlates as well, but it has made assumptions that these phenomena are rooted in genetics and genetically perturbed molecular structures and substances. This leads to

targeting the molecular level with pharmaceuticals, but not to the broader agenda of understanding environmental or physiological contributions or dynamic features of brain and behavior. Thus, exploring how EMF/RFR impacts ASDs may help to force the question of how these pathophysiological and electrophysiological/information processing levels actually interact, and how anatomy may in many ways be a product rather than a cause of physiology.

B. Time courses of mechanisms

For the most part, researchers have looked for causes of autism in mechanisms that occur early and create permanent change or damage. This approach is logical if one assumes that genetic influences are overwhelmingly predominant, and ‘autism’ is a fixed lifelong trait. However evidence is emerging that ASDs may in many respects be more state-like and variable than trait-like and fixed.

1. Plasticity

One of the remarkable shifts in conceptual thinking about ASDs is an appreciation of its brain plasticity (Helt et al. 2008). Growing numbers of reports of improvement and loss of diagnosis, reversal of neurological symptoms in a growing number of mouse models of genetic syndromes that in humans prominently feature autism (Cobb, Guy, and Bird 2010; Ehninger et al. 2008; Goebel-Goody et al. 2012; Henderson et al. 2012; Kaphzan et al. 2012; Liu, Huang, and Smith 2012; Mehta, Gandai, and Siegel 2011; Paylor et al. 2008; Rotschafer et al. 2012; Sato et al. 2012; Suvrathan et al. 2010), short-term pharmaceutically induced improvement in brain connectivity (Narayanan et al. 2010), and transient reversal or abeyance of symptomatology under various circumstances (including fever, fluid-only diet, and certain antibiotic treatments (Sandler et al. 2000; Curran et al. 2007)) – all of these throw into question the long-standing assumption that we are simply dealing with a ‘broken brain.’ Indeed, how could a ‘broken brain’ produce markedly improved function with such a short turnaround time? (Herbert 2009) Such a time frame cannot possibly be accounted for by remodeling of the brain’s anatomical substrate. ‘Brain waves’ and their synchronization, on the other hand, could easily vary over short time periods. Looking into physiological and environmental modulators not only of brain development but also of everyday brain function becomes increasingly imperative.

In addition, documentation of average to superior intelligence in most people with autism (Edelson 2006; Dawson et al. 2007), as well as of domains of perceptual superiority (Soulieres, Zeffiro, et al. 2011; Soulieres, Dawson, et al. 2011; Samson et al. 2011; Soulieres et al. 2010; Soulieres et al. 2009; Mottron et al. 2006; Mottron 2004; Bertone et al. 2005; Perreault et al. 2011), call into question the long-standing assumption that ASDs are intrinsically or for the most part associated with cognitive deficits – another strike against the outdated ‘deficit’ or ‘broken brain’ model.

2. Mechanisms that operate actively throughout the lifecourse

One particularly valuable lesson about ASDs that can be learned from looking at how EMF/RFR affects underlying biology is that these impacts are by no means confined to early development. We already have clinical reports of ‘intermittent autism’ – for example, some children with mitochondrial disease who have ups and downs of their bioenergetics status ‘have autism’ on their bad days but don’t display autistic features on their good days (Korson 2007). These children with their vulnerable, barely compensated mitochondria seem to be teetering right at the brink of the interface of metabolic and electrophysiological dysfunction, tipping back and forth on this knife edge. It makes one wonder what everyday exposures – allergens, infection, pesticide on the school playground, even perchance EMF/RFR – might contribute to the bad days (with their loss of electrophysiological optimization, probably on account of insufficient energy to drive fully integrated brain function), and conversely how many choices exist in everyday life that could tilt things in the direction of more good days (by helping to stabilize more optimal nervous system performance) (Herbert and Weintraub 2012).

The short time course needed for biologically effective EMF/RFR ‘doses’ to lead to observable impacts reflects that these exposures can affect cells without obstruction (unlike many chemical agents), and create impacts within minutes. This type of mechanism may also give us fresh and important ways of understanding the short-term variability – the good days and the bad days – that are so common in ASD even in those who do not have a formal diagnosis of mitochondrial disease.

3. Pathophysiology and Allostatic Load

Based on these considerations, the strategy to be pursued in this examination of a potential EMF/RFR - ASD link is to review the many parallels between underlying biology, or pathophysiology, in ASDs and the impacts of EMF/RFR on living organisms. EMF/RFR exposures have demonstrated impacts at just about every level at which biology and physiology have been shown to be disrupted in ASDs. EMF/RFR has been shown to potentiate the impact of various toxicants when both exposures occur together (Juutilainen, Kumlin, and Naarala 2006); this may be additive or more than additive. This suggests that EMF/RFR may synergize with other contributors and make things worse. With many different environmental factors piling on to a much smaller number of environmentally vulnerable physiological mechanisms (Herbert 2010), one must consider that the model of ‘allostatic load’ – the sum total of stressors and burdens – may be central to understanding how the many risk factors interact to create autism – and to create a spectrum of levels of severity across so many of ASD’s associated features. A cascade of exposures interacting with vulnerabilities can potentially lead to a tipping point for an individual, such as the phenomenon of autistic regression experienced by a substantial subset of people with ASDs. When exposures increase at the population

level, we are likely to see trends of increase in the number of people passing that tipping point and getting diagnosed. EMF/RFR exposures have increased several thousand-fold or more in the past two decades from wireless technology innovations that have unplanned side effects from pulsed RFR, a newly classified human carcinogen (Baan et al, 2011). Nearly six billion people globally own wireless phones, for example. Many hundreds of thousands more are exposed to wireless whole-body transmissions from wireless antenna facilities (Sage and Carpenter, BioInitiative 2012 Report, Section 24). For this as well as for physiological reasons allostatic loading as a viable concept for the study of ASDs should reasonably address EMF/RFR as one of the collection of exposures of relevance to the overall stress load, since it is now a chronic and unremitting exposure in daily life at environmentally relevant levels shown to cause bioeffects from preconception and pregnancy through infancy, childhood and the whole lifecourse.

In an article entitled “Unrelenting Stress is Toxic,,: The New Scientist (28 July 2012) describes stress in an eloquent way:

“Unrelenting stress is toxic because it can turn the body’s defense system against itself. Neuroendocrinologist Bruce McEwen at Rockefeller University in New York says the stress response that evolved to protect us from harm can be hijacked and actually cause harm when the stress level never abates. In a normal situation, the introduction of stress causes the body to deliver a boost of energy – by sending a surge of glucose to the muscles – and to increase heart rate, blood pressure and breathing to get oxygen to the muscles in hurry. At the same time, blood vessels constrict and clotting factors increase – ready to slow bleeding in case you are wounded. These responses are a part of a fight-or-flight survival kit, and once the stress has passed, these should subside. But for people under unrelenting stress, this response never quite switches off – leaving sugar levels unregulated, high blood pressure, increase risk of blood clots, depressed sex drive and an immune system buckling under the strain. Prolonged exposure to stress hormones can have other effects as well, including affecting the brain by altering the structure of the neurons and their connections, which in turn can influence behaviour and hormonal processes.”

This passage refers to effects on the hypothalamo-pituitary-adrenal axis {Aldad, 2012 #2034}, but as will be discussed in the Part II, equally important is cellular stress from stress proteins (heat shock protein HSP) and from oxidative stress generated at very low-intensity EMF and RFR levels as detailed in the BioInitiative 2012 Update, Section 7 by Martin Blank, PhD) {Blank, 2012 #2467}. Both are significant kinds of stress that can add body-burdens via allostatic loading.

Part II - PARALLELS IN PATHOPHYSIOLOGY

This section will review parallels in pathophysiology between ASDs and impacts of EMF/RFR. It will begin with a review of mechanisms of direct impact at the level of molecules, cells, tissues and genes. It will then move on to consider how these levels of damage lead to degradation of the integrity of functional systems including mitochondrial bioenergetics, melatonin, immune function and nervous system physiology. The review of parallels will conclude with a discussion of electromagnetic signaling and synchronized oscillation from membranes to nervous system, treating ‘aberrant’ neural systems and somatic function and behaviors as consequences or ‘outputs’ of disturbed underlying physiology to which EMF/RFR is a plausible contributor.

A. DAMAGE: MEANS AND DOMAINS

ASDs have been conceptualized as ‘neurodevelopmental’ which has focused attention on how genes and environment could alter brain development. This leads to the unstated presumption that virtually everything important about the brain in ASDs has to do with differences in the way it was formed. In genetics this has led to a hunt for neurodevelopmental genes. There is no question that environmental impacts can alter brain development, and impact brain function across the lifespan. This chapter begins the work to systematically rectify the omission of EMF/RFR as one environmental contributor in ASDs.

However the influence of the environment on neurodevelopmental conditions such as ASDs does not stop there. Evidence is accumulating showing that increased expression of genes associated with physiological dysregulation, as well as single-nucleotide polymorphisms (SNPs) associated with these issues, may be if anything more prominent than alterations of ‘neurodevelopmental’ genes (Lintas, Sacco, and Persico 2012). In a study of gene expression in ASDs, Down syndrome and Rett syndrome, these authors state, *“Our results surprisingly converge upon immune, and not neurodevelopmental genes, as the most consistently shared abnormality in genome-wide expression patterns. A dysregulated immune response, accompanied by enhanced oxidative stress and abnormal mitochondrial metabolism seemingly represents the common molecular underpinning of these neurodevelopmental disorders.”* Others have also found pathophysiology-related genes as figuring most prominently in alterations of gene expression in ASD (Kong et al. 2012; Jung, Kohane, and Wall 2011; Voineagu et al. 2011; Waly et al. 2012). SNPs associated with methylation abnormalities, impaired glutathione synthesis and mitochondrial dysfunction also have been identified as significant risk factors.

Genetics may create risk, but the actual nervous system and health consequences probably come from dysfunction at the physiological level. Evidence for pathophysiological dysfunction in ASDs increasingly abounds. In particular, a growing body of literature documents immune aberrations, low total and reduced glutathione levels, lower activity of the anti-oxidative stress system and mitochondrial dysfunction. These phenomena may be both genetically and environmentally modulated. As will be discussed further below, they are certainly pertinent to the neurodevelopment of the brain, which has been by far the dominant focus autism research, but it does not stop there as they can significantly modulate brain function in real time, as well as shape the function of the entire organism, including the autonomic system, the cardiovascular, endocrine, immune, gastrointestinal and reproductive systems and more.

1. Cellular Stress

Oxidative Stress

Autism (ASD) research indicates that oxidative stress may be a common attribute amongst many individuals with autism. In the past decade the literature on this has moved from a trickle to a flood. Studies document reduced antioxidant capacity, increased indicators of oxidative stress and free radical damage, alterations in nutritional status consistent with oxidative stress, altered lipid profiles, and pertinent changes not only in blood but also in brain tissue. Associations of ASDs with environmental exposures such as air pollution and pesticides are indirectly supportive as well, since such exposures are linked in other literature to oxidative stress (Kanthasamy et al. 2012; Roberts et al. 2010; Knox 2010; Rose, Melnyk, Trusty, et al. 2012; Rose, Melnyk, Pavliv, et al. 2012; Ghanizadeh et al. 2012; Frustaci et al. 2012; Rossignol and Frye 2011; Adams et al. 2011, 2011; Mostafa et al. 2010; Zecavati and Spence 2009; Yao et al. 2006; Naviaux 2012; Chauhan and Chauhan 2006; Chauhan, Chauhan, and Brown 2009).

Reactive oxygen species are produced as a normal consequence of mitochondrial oxidative metabolism as well as other reactions, but when their number exceeds the cell's antioxidant capacity a situation of oxidative stress develops. It is certainly the case that oxidative stress can be a consequence of exposures to chemical toxicants, or of the interactive impacts of toxicants, nutritional insufficiencies and genetic vulnerabilities. This set of risk factors has received considerable attention for the potential roles each component and various possible combinations could play in causing or exacerbating autism.

Less often mentioned in the ASD pathophysiology literature is that it is also well established that EMF/RFR exposures can be associated with oxidative damage. Published scientific papers that demonstrate the depth of EMF and RFR evidence reporting oxidative damage in human and animal models are profiled in Section 6 (Genotoxicity) of this BioInitiative 2012 Report and in the BioInitiative Report (2007),

both by Henry Lai, PhD {Lai, 2012 #2548}{Lai, 2007 #2549}. These cellular effects can occur at low-intensity, legal levels of exposure that are now 'common environmental levels' for pregnant women, the fetus, the infant, the very young child, and the growing child as well as for adults. Electromagnetic fields (EMF) can enhance free radical activity in cells (Lai and Singh 2004; De Iuliis et al. 2009) particularly via the Fenton reaction, and prolonging the effect causes a larger increase, indicating a cumulative effect. The Fenton reaction is a catalytic process of iron to convert hydrogen peroxides, a product of oxidative respiration in the mitochondria, into hydroxyl free radical, which is a very potent and toxic free radical (Lai, in the BioInitiative Report 2007) {Lai, 2007 #2549}. Free radicals damage and kill organelles and cells by damaging macromolecules, such as DNA, protein and membrane components.

Further indications of a link to oxidative stress are findings that EMF and RFR at very low intensities can modulate glutamate, glutathione and GABA, and affect mitochondrial metabolism. Alterations in all these substances and processes have been documented in ASDs (Bristot Silvestrin et al. 2012; Brown et al. 2012; Choudhury, Lahiri, and Rajamma 2012; Essa et al. 2012; Oberman 2012; Yang and Pan 2012; Chauhan, Audhya, and Chauhan 2012; Frustaci et al. 2012; Main et al. 2012; Pecorelli et al. 2012; Rose, Melnyk, Pavliv, et al. 2012; Rose, Melnyk, Trusty, et al. 2012; Waly et al. 2012; Banerjee et al. 2012; Coghlan et al. 2012; Enticott et al. 2012; Kang and Barnes 2013; Mendez et al. 2012; Piton et al. 2012; Anitha, Nakamura, Thanseem, Matsuzaki, et al. 2012; Anitha, Nakamura, Thanseem, Yamada, et al. 2012; Gargus 2008; Giulivi et al. 2010; Hadjixenofontos et al. 2013; Napolioni et al. 2011; Rossignol and Frye 2011). Campisi et al (2010) report that increased glutamate levels from 900 MHz cell phone frequency radiation on primary rat neocortical astroglial cell cultures induced a significant increase in ROS levels and DNA fragmentation after only 20 min with pulsed RFR at non-thermal levels (Campisi et al. 2010).

Fragopoulou et al (2012) conducted proteomics analysis of proteins involved in brain regulation in mice as a consequence of prolonged exposure to EMF(Fragopoulou et al. 2012). They identified altered expression of 143 proteins, ranging from as low as 0.003 fold downregulation up to 114 fold overexpression with affected proteins including neural function-related proteins including Glial Fibrillary Acidic Protein (GFAP), alpha-synuclein, Glia Maturation Factor beta (GMF), apolipoprotein E (apoE)), heat shock proteins, and cytoskeletal proteins (i.e., neurofilaments and tropomodulin), as well as proteins of brain metabolism such as aspartate aminotransferase and glutamate dehydrogenase. The authors pointed out that oxidative stress was consistent with some of these changes.

Aberrations in glutathione metabolism and deficiencies in reserves of reduced glutathione are increasingly associated with ASDs, both systemically and in the brain. The parallel with EMF/RFR impacts here is strong, since glutathione reduction associated with

EMF/RFR is reported in at least twenty three relevant research studies in both human and animal studies since 1998, including the following citations (Shapiro et al. 2012; Ozgur, Guler, and Seyhan 2010; Ozguner et al. 2005; Moustafa et al. 2001; Kesari, Kumar, and Behari 2011; Jelodar, Akbari, and Nazifi 2012; Hoyto et al. 2008; Guney et al. 2007; Esmekaya, Ozer, and Seyhan 2011; Atasoy et al. 2012){Al-Demegh, 2012 #2624}{Kumaf, 2010 December #2619}{Meral, 2007 #2627}{Oktem, 2005 #2074}{Ozguner, 2006 #2625} It is increasingly appreciated that glutathione is a final common pathway, a critical piece of environmentally vulnerable physiology, as glutathione reserves are compromised by an enormous number of environmental stressors, so that the cumulative impact upon glutathione may be far greater than could be predicted by the magnitude of any specific exposure (Lee, Jacobs, and Porta 2009), which supports an allostatic loading model.

Also of note are studies showing that the effects of EMF/RFR can be reduced by supplementation with antioxidants and radical scavengers. As an example, Vitamins E and C reduced adverse impacts on rat endometrium from 900MHz EMR exposure (Guney et al. 2007). Gingko biloba has also prevented mobile phone-induced increases in malondialdehyde and nitric oxide levels in brain tissue as well as decreases in brain superoxide dismutase and glutathione peroxidase activities and increases in brain xanthin oxidase and adenosine deaminase activities, and treated rats were spared the histopathological cell injury found in the untreated rats (Ilhan et al. 2004). Substantial further literature on antioxidants and radical scavengers is reviewed in Section 15 in Belyaev's contribution to the Bioinitiative 2012 Report (Belyaev 2012).

Stress Protein (Heat Shock Protein) Responses

Another well-documented effect of exposure to low- intensity ELF and RFR is the creation of stress proteins (heat shock proteins) that signal a cell is being placed under physiological stress) (Weisbrot et al. 2003; Velizarov, Raskmark, and Kwee 1999; Leszczynski et al. 2004; Leszczynski et al. 2002; de Pomerai et al. 2000; Daniells et al. 1998; Blank and Goodman 2004). Heat shock proteins are in a family of inducible proteins that are initiated when any increased need for protection from stray electrons occurs (Padmini 2010; Bottoni, Giardina, and Scatena 2009). The HSP response is generally associated with heat shock, exposure to toxic chemicals and heavy metals, and other environmental insults. HSP is a signal of cells in distress. Plants, animals and bacteria all produce stress proteins to survive environmental stressors like high temperatures, lack of oxygen, heavy metal poisoning, and oxidative stress. It should also be noted that the generation of HSP stress proteins can have constructive medical applications, such as protection from reperfusion of the heart following ischemic injury (George et al. 2008). Another concomitant impact of cellular stress can be protein misfolding, which has been documented in association with exposure to EMF/RFR. (Bohr and Bohr 2000; Mancinelli et al. 2004)

Although a number of papers have demonstrated increases in HSPs in people with ASDs (El-Ansary and Al-Ayadhi 2012; Evers, Cunningham-Rundles, and Hollander 2002; El-Ansary, Ben Bacha, and Kotb 2012; Walker, Segal, and Aschner 2006; Vojdani et al. 2004), it has been investigated far less often than oxidative stress. Part of the research needed to study possible influences of EMF/RFR on ASDs would be to study this more carefully.

2. Membranes and Channels

Cell membranes and Lipid peroxidation

Cell and organelle membranes play roles in partitioning cells from the extracellular milieu as well as in sustaining boundaries and regulating flow of materials between cellular compartments needing different metabolic parameters for their activities. They also play critical roles in maintaining electrical differences and the flow of electricity.

Adey (2002) summarized studies that report cell membranes as the site of initial field transductive coupling.

“Collective evidence points to cell membrane receptors as the probable site of first tissue interactions with both ELF and microwave fields for many neurotransmitters (Mironova et al. 1994), hormones (Liburdy 1995; Ishido, Nitta, and Kabuto 2001), growth- regulating enzyme expression (Byus, Pieper, and Adey 1987; Chen et al. 2000; Litovitz et al. 1993) (Penafiel et al. 1997), and cancer-promoting chemicals (Cain, Thomas, and Adey 1993; Mevissen, Haussler, and Loscher 1999). In none of these studies does tissue heating appear involved causally in the responses. Physicists and engineers have continued to offer microthermal, rather than athermal, models for these phenomena (Barnes 1996; Astumian, Weaver, and Adair 1995), with views that exclude consideration of cooperative organization and coherent charge states, but it is difficult to reconcile experimental evidence for factors such as modulation frequency-dependence and required duration of an amplitude-modulated signal to elicit a response (coherence time) (Litovitz et al. 1993) with models based on the equilibrium dynamics of tissue heating.” (Adey 2002)

Membranes are well-known targets of oxidative stress. Membrane damage is a major route through which free radical damage proliferates through the cellular system. Lipid peroxidation of membranes most often affects polyunsaturated fatty acids such as EPA and DHA which are the most abundant and vulnerable lipids in the brain where the damage they sustain can have serious impacts – DHA is 40% of brain tissue. Lipid peroxidation of membranes has been identified as an effect of EMF/RFR in multiple studies (Desai, Kesari, and Agarwal 2009; Phelan et al. 1992). A variety of other mechanisms for membrane alteration related to EMF/RFR have been intimated in the

literature. Physicochemical properties of membranes such as phase transition of phosphatidylcholine can be shifted by nonthermal effects of microwave radiation (Beneduci et al., 2012). Membrane potential and currents may also be impacted by pulsed radiofrequency fields (Linz et al., 1999). This has been observed graphically in altered cellular movement in *Paramecium caudatum*, with these cells becoming broader, with a broader-appearing cytopharynx, with their pulse vesicles having difficulty in expelling their content outside the cell, and with less efficient movement of cilia (Cammaerts et al. (2011) which the authors suggested might be due to targeting of the cellular membrane. The impacts on this unicellular organism may help us imagine what the impact of EMF/RFR might be on cells with some structural similarities, such as columnar epithelial cells and ciliated cells in mucosal surfaces in the respiratory system, digestive tract, uterus and fallopian tubes and central spinal cord.

Indications of lipid peroxidation of membranes has been documented in ASDs, including malonaldehyde and isoprostanes, as well as alteration of membrane phospholipids and prostaglandins (Pecorelli et al. 2012; El-Ansary et al. 2010; El-Ansary, Ben Bacha, and Kotb 2012; Zhang, Sun, et al. 2012; Yao et al. 2006; Al-Gadani et al. 2009; Chauhan and Chauhan 2006; Ming, Stein, et al. 2005; Zoroglu et al. 2004). In one study the isoprostane levels showed a bimodal distribution with the majority of ASD subjects showing moderate increase but a smaller group showing dramatic increases (Ming, Stein, et al. 2005). Thromboxane, reflecting platelet activation, was also elevated in one study (Yao et al. 2006). Given that this phenomenon has been identified in many people with ASDs, it is plausible that such individuals will likely be more vulnerable to having such cellular injuries caused, worsened or both by EMF/RFR exposures.

Calcium channels

Of particular prominence in the EMF/RFR physiological impact literature is the impact on calcium channels and signaling. Calcium signaling is ubiquitous in biological systems ranging from single-celled organisms to the most sophisticated functioning of our nervous and immune systems. This signaling takes place through a myriad of mechanisms within and between cells. The exquisite tuning of organisms is influenced by the precision of functioning of these systems, with even subtle disturbances having the potential to ramify in a nonlinear fashion through a system causing larger-scale disturbances elsewhere. EMF/RFR exposures have been shown to create disturbances in calcium signaling through a variety of mechanisms, including membrane leakage (Nesin et al. 2012), alteration of calcium-binding proteins and GFAP reactivity (Maskey et al. 2012; Maskey et al. 2010), and altered ultrastructural distribution of calcium and calcium-activated ATPases after exposure (Kittel et al. 1996).. Adey (2002) provided an overview of key studies on calcium efflux and the importance of calcium in cell signalling. *“Early studies described calcium efflux from brain tissue in response to ELF exposures (Bawin and Adey 1976; Blackman et al. 1985), and to ELF-modulated RF*

fields (Bawin and Adey 1976) (Blackman 1979) (Blackman et al. 1985; Dutta, Ghosh, and Blackman 1989). Calcium efflux from isolated brain subcellular particles (synaptosomes) with dimensions under 1.0 μm also exhibit an ELF modulation frequency-dependence in calcium efflux, responding to 16 Hz sinusoidal modulation, but not to 50 Hz modulation, nor to an unmodulated RF carrier (Lin-Liu and Adey 1982). In the same and different cell culture lines, the growth regulating and stress responsive enzyme ornithine decarboxylase (ODC) responds to ELF fields (Byus et al. 1988; Litovitz et al. 1993) and to ELF-modulated RF fields (Byus, Pieper, and Adey 1987) (Litovitz et al. 1993) (Penafiel et al. 1997) .” (Adey 1994)

Dutta et al (1992) reported:

“Radio-frequency electromagnetic radiation (RFR) at 915 and 147 MHz, when sinusoidally amplitude modulated (AM) at 16 Hz, has been shown to enhance release of calcium ions from neuroblastoma cells in culture. The dose-response relation is unusual, consisting of two power-density “windows” in which enhanced efflux occurs, separated by power-density regions in which no effect is observed. To explore the physiological importance of these findings, we have examined the impact of RFR exposure on a membrane-bound enzyme, acetylcholinesterase (AChE), which is intimately involved with the acetylcholine (ACh) neurotransmitter system. Neuroblastoma cells (NG108), exposed for 30 min to 147-MHz radiation, AM at 16 Hz, demonstrated enhanced AChE activity, as assayed by a procedure using ^{14}C -labeled ACh. Enhanced activity was observed within a time window between 7.0 and 7.5 h after the cells were plated and only when the exposure occurred at power densities identified in a previous report as being effective for altering the release of calcium ions. Thus RFR affects both calcium-ion release and AChE activity in nervous system-derived cells in culture in a common dose-dependent manner.” (Dutta et al. 1992)

The prominence of these calcium signaling impacts of EMF/RFR are striking when considered in relation to ASD pathophysiology, where such alterations have been proposed as of central importance. Calcium channels play an important role in regulating neuronal excitability, whose disturbance during development has been thought by many to be potentially contributory to the development of ASDs, as well as to the often associated vulnerability to seizures. Gene alterations have been identified associated with a number of voltage-gated calcium channels in ASDs Smith, 2012 #1451}(Krey and Dolmetsch 2007; Pasca et al. 2011; Gargus 2009; Lu et al. 2012). However, based on an examination of patient laboratory and phenotype data it has been argued that aberrant calcium signaling could be downstream: Palmieri and Persico (2010) suggest that “*an abnormal neuroimmune response as a relevant player in elevating intracellular Ca^{2+} levels, deranging neurodevelopment, driving oxidative stress, and ultimately affecting synaptic function and neural connectivity especially in long-range neuronal pathways*

physiologically responsible for integrated information processing.” (Palmieri and Persico 2010) Peng and Jou (2010) have in turn shown how increased intracellular calcium can cause oxidative stress, and a vicious circle: “...mitochondrial ROS [reactive oxygen species]rise can modulate Ca²⁺ dynamics and augment Ca²⁺ surge. The reciprocal interactions between Ca²⁺ induced ROS increase and ROS modulated Ca²⁺ upsurge may cause a feedforward, self-amplified loop creating cellular damage far beyond direct Ca²⁺ induced damage.” (Peng and Jou 2010)

Environmental as well as genetic routes to calcium signaling dysfunction have been identified (Pessah and Lein 2008) including chemicals such as the polyaromatic hydrocarbons. PCB-95 in particular modulates the calcium-dependent signaling pathway responsible for activity-dependent dendritic growth {Wayman, 2012 #2550;Wayman, 2012 #2551}. In fact, once a genetic mutation has been associated with altering a critical signaling pathway and conferring risk for autism, chemicals or other environmental agents can be identified that target the same pathways and also confer ASD risk. Stamou et al. (2012) have reviewed this strategy of identifying multiple mechanisms converging on common signaling pathways regarding Ca(2+)-dependent mechanisms as well as extracellular signal-regulated kinases (ERK)/phosphatidylinositol-3-kinases (PI3K) and neuroligin-neurexin-SHANK (Stamou et al. 2012). From this point of view, there may be no particular reason to privilege genetic mutations in their contribution to a disturbance of calcium signaling, since whether this function becomes derailed due to a genetic mutation, from a chemical toxin or from EMF/RFR perturbation of calcium signaling, the functional effect is comparable. Moreover if a person is subject to multiple triggers all of which have calcium signaling impacts, the gene-environment interactions may lead to impacts that could be less, the same as or more than any one contributor alone might create.

3. Junctions and Barriers

The damage discussed so far has been at the molecular and subcellular level. However impacts from this level reverberate up to larger scales in the system. Where membranes create boundaries between cells and subcellular compartments, barriers do this at a larger scale. Cells become capable of forming barriers between each other through tight junctions which block substances and cells from ‘slipping through the cracks,’ so to speak, between the cells. Conversely, gap junctions are subcellular structures providing openings that allow physical passage of materials between cells otherwise separated by membranes.

It appears that such connections between cells can also be altered by electromagnetic fields and radiofrequency exposures, at least under certain circumstances. High frequency magnetic fields have been observed to be associated with a sharp decrease in

intercellular gap junction-like structures, in spite of increased gene expression for pertinent proteins {Cervellati, 2009 #1449}. Changes in tight junctions have been observed upon exposure to microwave and x-ray irradiation {Palfia, 2001 #1458}.

A number of papers in the ASD research field document problems pertinent to junctions. Connexin abnormalities have been documented in neuropathological studies (Fatemi et al. 2008). and MacFabe and colleagues identified lipid alterations associated with oxidative stress, membrane fluidity and the modulation of gap junction coupling (Thomas et al. 2012). Decrease in platelet endothelial cell adhesion molecule-1 were reduced and this reduction correlated with repetitive behavior and abnormal brain growth; adhesion molecules modulate permeability and signaling at the blood-brain barrier as well as leukocyte infiltration into the central nervous system (Onore et al. 2012).

EMF and RFR might also compromise biologically important barrier structures that separate blood flow from organs like the brain (Salford et al, BioInitiative Report 2012, Section 10) {Salford, 2012 #2477}. This raises important questions regarding whether other 'barriers' that keep blood flow separate from the gut (gut-blood barrier), or the placenta (blood-placenta barrier) or the eye (ocular-blood barrier) may also be rendered pathologically leaky, and allow albumin, toxins, pro-inflammatory cytokines and infectious agents to cross this barrier into the intestines (invoking immune responses) and impacting the developing fetus {Somosy, 1993 #1470}. While there are a fair number of negative studies, there are also many studies showing an association between EMF/RFR and pathological leakage of the blood-brain barrier (BBB), as well as evidence in animal studies of damage to brain cells and damage to or death of neurons. Such leakage has been shown to be potentiated by physiological factors such as diabetes and insulin (Gulturk et al 2010) and has also potentiated viral lethality in a dose-dependent fashion (Lange et al, 1991). Many of the positive findings were associated with non-thermal exposures comparable to normal cell phone radiation exposure {Salford, 1994 #2553; Salford, 2003 #2552} {Salford, 2007 #2629; Salford, 1992 #2628} {Eberhardt, 2008 #1428} {Nittby, 2009 #2307; Nittby, 2008 #2556}. There are scattered reports of increased permeability across other membranes and barriers, such as the blood-testicle barrier in mice (Wang, 2008; wang et al., 2010) and the rat liver canalicular membrane {Lange, 1993 #2557}. A 1992 study by Kues et al. reported that *"studies in our laboratory have established that pulsed microwaves at 2.45 GHz and 10 mW/cm² are associated with production of corneal endothelial lesions and with disruption of the blood-aqueous barrier in the non-human primate eye."* (Kues et al. 1992) A recent study showing impact of high-frequency electromagnetic fields on trophoblastic connexins (Cervellati et al. 2009) may indicate the vulnerability of the placenta and placental barrier function to electromagnetic fields. A thorough review and methodological discussion of literature regarding EMF/RFR impacts on the BBB is provided by Salford in Section 10 of the BioInitiative 2012 Report {Salford, 2012 #2477}.

According to a review by Zlokovic, *"BBB breakdown, due to disruption of the tight junctions, altered transport of molecules between blood and brain and brain and blood, aberrant angiogenesis, vessel regression, brain hypoperfusion, and inflammatory responses, may initiate and/or contribute to a "vicious circle" of the disease process, resulting in progressive synaptic and neuronal dysfunction and loss in disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and others."* (Zlokovic 2008). The integrity of the BBB can be compromised by oxidative stress which can lead to increased permeability (Parathath, Parathath, and Tsirka 2006). The resultant extravasation of albumin into brain parenchyma can be excitotoxic and neurotoxic (Hassel, Iversen, and Fonnum 1994; Eimerl and Schramm 1991).

The evidence suggesting possible existence of barrier function compromise in people with ASDs is largely indirect. The existence of brain neuroinflammation in ASDs has been documented in a growing number of studies (Boso et al. 2006; El-Ansary and Al-Ayadhi 2012; Young et al. 2011), and this is known to be associated with BBB permeability (Erickson, Dohi, and Banks 2012; Janigro 2012; Takeshita and Ransohoff 2012). In a review of clinical MRI findings in ASDs 19/59 showed white matter signal abnormalities (Boddaert et al. 2009), which in other settings have been associated with cerebral hypoperfusion, though not necessarily in the same locations as the hyperintensities (Vardi et al. 2011) {Brickman, 2009 #2581}. Blood flow abnormalities, predominantly hypoperfusion, documented in a few dozen PET and SPECT studies, could also be caused by and/or associated with physiological phenomena associated with vascular permeability as will be revisited below. Increased intestinal permeability has been documented (although its absence has also been documented) (de Magistris et al. 2010; Lucarelli et al. 1995; D'Eufemia et al. 1996; Horvath and Perman 2002; White 2003; Robertson et al. 2008; Souza et al. 2012) and discussed in the context of food exposures, particularly gluten (Silva et al. 2012; Sapone et al. 2011; Visser et al. 2009; Simpson et al. 2009; Fasano 2009; Lammers et al. 2008; De Angelis et al. 2006). The reactivity to large numbers of different foods clinically observed in many children with autism has been framed by some as a manifestation of indiscriminate exposure of the immune system and the brain to food proteins on account of intestinal permeability as well as BBB permeability (Theoharides and Doyle 2008). This reactivity could in turn feed in to aberrant immune responsivity which in turn could further amplify barrier vulnerability {Fasano, 2009 #654}.

A number of studies have made an association between an increased risk of having a child with autism and maternal infection during pregnancy. This phenomenon looks like it is a result of the maternal immune system response rather than being due to an impact deriving from a specific infectious agent; but the potential for an accompanying compromise of the placental barrier is also conceivable in this setting. Under these

circumstances the fetal risk of exposure to maternal blood toxins, cytokines and stress proteins in-utero could potentially be increased if placenta barrier (BPB) function were impaired. The integrity, or compromise thereto, of the maternal-fetal interface via the placenta is an important modulator of brain development (Hsiao and Patterson 2012).

4. Genetic Alterations and Reproductive Impacts

Because of the high heritability of autism that was calculated from the concordance rates of monozygotic (identical) vs. dizygotic (fraternal) twins found in by a series of small twin studies performed some decades ago, the overwhelming emphasis in recent decades in autism research has been on genetics, and on finding linkages between genes, brain and behavior. As mentioned earlier, this point of view also promotes more of a structural/anatomical orientation than a bioelectric/physiological orientation. Along with this emphasis it has seemed obvious to people just looking at the stubborn persistence of symptoms in affected individuals that ASDs are inborn, lifelong brain defects. From this vantage point there would be no reason to think about the transduction of pathophysiology – whether acquired or genetic or some combination – to brain and hence behavior (or, more broadly, neurocognitive function). Thus the research agenda of looking for gene-brain-behavior correlations has seemed both self-evident and sufficient.

In recent years the genetic premises of this seemingly obvious framing of autism as overwhelmingly genetic have been undermined at several levels. (The undermining of the brain premises will be discussed beyond what was covered in Part I in later sections.) First the number of reported cases is increasing, making it more difficult to maintain that ASDs are purely genetic because these increases can only be partly explained away by greater awareness or other data artifacts (King and Bearman 2009; Hertz-Picciotto and Delwiche 2009). Second, the complexity of the ways we understand how genes might relate to autism has grown, from an expectation a decade ago that a small number of genes (even less than a dozen) would explain everything to an identification of close to a thousand genes associated with autism, as well as ‘de novo’ mutations present in ASD children but not their parents and even ‘boutique’ mutations not shared beyond an individual family. Out of over a hundred genetic syndromes in which autism commonly occurs, it is unclear what the pertinent genetic mutations and rearrangements have in common to account for the shared association with ASDs (Anney et al. 2010; Betancur 2011). Moreover, a recent twin study that was much larger than any of the prior such studies identified a modest genetic role but a substantial environmental role (Hallmayer et al. 2011). Also of interest, a Swedish study of identical twins and schizophrenia grouped into monozygotic (shared placenta) and dizygotic (each had its own placenta) showed 60% concordance for schizophrenia diagnosis for monozygotic twins but only 10.7% concordance for dizygotic twins (Davis, Phelps, and Bracha 1995); though this work has not yet been replicated in ASD twins, in principle it opens the door to non-genetic

interpretations of any concordance figures that have generally been assumed to be indicators of heritable genetics. The authors of this study interpreted their findings as consistent with data on viral infection as a contributor to schizophrenia risk (a possibility also entertained in ASDs (Patterson 2012; Teixeira and Barichello 2012; Atladottir et al. 2012, 2012; Hornig et al. 1999)), but one could also consider the possibility of differences in the dichorionic cases in the integrity of the placental barrier.

All of this calls into question the idea that genetics can be presumed to be the ‘cause’ of autism simply based upon heritability calculations, and upgrades the importance of looking not only at the environment and environmentally vulnerable physiology, but also at acquired mutations. There is certainly progress being made through genetic research to the identification of networks of genes and mechanisms on which genes converge (Voineagu et al. 2011), but environmental mechanisms converge on these mechanisms too (Stamou et al. 2012), and the mechanisms are what drive the impacts.

Genotoxicity

One route through which environmental impacts may influence an organism’s status is by changing genes through mutation – that is, by genotoxicity. This has been proposed as a mechanism for the generation of ‘de novo’ mutations (found in children but not their parents) being found in ASDs (Kinney et al. 2010) and increasingly in other settings as well, making mutations something that needs to be accounted for rather than simply assuming they are associated with normal, stable variation. Reviews and published scientific papers on genotoxicity and EMF report that both ELF-EMF and RFR exposures can be considered genotoxic – i.e., damaging to DNA – under certain conditions of exposure, including under conditions of intermittent and/or chronic ELF and RFR exposure that are of low-intensity and below current world safety standards (Ruediger 2009; Ivancsits et al. 2005; Diem et al. 2005; Blank and Goodman 2011; Phillips, Singh, and Lai 2009; REFLEX 31 May 2004; Sage and Carpenter 2009; Lai and Singh 2004). Types of genetic damage reported have included DNA fragmentation and single- and double-strand DNA breaks, micronucleation and chromosome aberrations, all of which indicate genetic instability. Genotoxic impacts of EMF/RFR are further reviewed in the BioInitiative Working Group 2007 contribution by Lai as well as in Section 6 of the present Bioinitiative Report {Lai, 2007 #2549; Lai, 2012 #2548}.

The European research program REFLEX (Risk Evaluation of Potential Environmental Hazards From Low-Energy Electromagnetic Field Exposure Using Sensitive in vitro Methods – a 5FP EU project) documented many changes in normal biological functioning in tests on DNA at exposure levels below existing public safety standards (REFLEX 31 May 2004). Some of the key findings included:

- Gene mutations, cell proliferation and apoptosis which are caused by or result in altered gene and protein expression profiles. The convergence of these events is required for the development of all chronic diseases.
- Genotoxic effects and a modified expression of numerous genes and proteins after EMF exposure could be demonstrated with great certainty.
- Genotoxic effects produced by RF-EMF in fibroblasts, HL- 60 cells, granulosa cells of rats and neural progenitor cells derived from mouse embryonic stem cells.
- Response of cells to RF exposure between SAR levels of 0.3 and 2 W/Kg with a significant increase in single- and double-strand DNA breaks and in micronuclei frequency.
- A clear demonstration of increase in intracellular generation of free radicals in HL-60 cells accompanying RF-EMF exposure.
- The observation that the induced DNA damage was not based on thermal effects, which raises concerns about the thermal-based environmental safety limits for ELF-EMF exposure.

These impacts could be contributors to a role for genetics in ASDs that does not derive from only inheritance but also from environmental and epigenetic influences. Moreover, in the light of the great heterogeneity of genetic findings in ASD alongside the documented impacts of EMF/RFR upon many other levels of pathophysiology than simply genetics, it becomes worth reflecting whether genetics might not be the primary problem but instead, in many cases at least, just one of many levels of collateral damage from environmental impacts. Whatever genetic variants a person carries may bias their system toward specific vulnerability, or may contribute more generically by increasing entropy and molecular disorder; in either capacity they may aggravate the situation but may not be part of the main cause.

Contributors to Genotoxicity

Oxidative Stress and free radical damage to DNA

Oxidative stress and excessive free radical production are very well known to be potentially genotoxic. They can be a consequence of myriad environmental factors, including but by no means limited to EMF/RFR. The DNA damage that can result could very well be one cause of ‘de novo’ mutations. Although there is not a consensus at this time about the rates or causes of *de novo* mutations in ASDs, and using present methods of detection are only found in a small percentage of individuals with ASDs, given the potential contribution of environmentally triggered oxidative stress and free radical damage that we know is present in at least large numbers of people with ASDs, a serious investigation of the potential contribution of EMF and RFR to de novo mutations in ASD seems warranted, given the large increase in exposure to these phenomena accompanying the massively increased non-ionizing radiation exposures in daily life due to

electrification and the global saturation of RFR from wireless technologies (BioInitiative 2012 Report, Section 24, Public Health Implications, Sage and Carpenter) (Sage and Carpenter 2012).

Challenge to DNA repair mechanisms

Reduced DNA repair may contribute to increased risk of cancers, but it may also contribute to a variety of other diseases and disturbances of growth and development. When the rate of damage to DNA exceeds the rate at which DNA can be repaired, there is the possibility of retaining mutations and initiating pathology. Failure to trigger DNA damage repair mechanisms, or incomplete or failed repair, may be a consequence of a variety of commonplace stressors, including EMF/RFR exposure. A decrease in DNA repair efficiency has been reported to result from exposure to low-intensity RFR in human stem cells, and other cells. Mobile phone frequency GSM exposure at the frequency of 915 MHz consistently inhibited DNA repair foci in lymphocytes (Markova et al. 2005; Belyaev et al. 2005; Belyaev, Markova, and Malmgren 2009). Belyaev, Markova and colleagues (2005) Markova et al. (2009) reported that very low-intensity microwave radiation from mobile phones inhibits DNA repair processes in human stem cells. A significant reduction in 53BP1 ((tumor suppressor p53 binding protein 1) foci was found in cells exposed to microwave radiofrequency radiation within one hour of exposure. Fibroblast cells were impacted in this fashion but adapted over time, whereas stem cells were similarly affected (inhibited 53BP1 foci) but did not adapt to microwave radiation during chronic exposure (Markova et al. 2005; Belyaev et al. 2005). Additional challenges to DNA repair mechanisms include not only toxicants and other damaging inputs but also nutritional insufficiencies of substances important to the proper functioning of DNA repair mechanisms, including Vitamin D, essential fatty acids, and minerals such as selenium and molybdenum (Christophersen and Haug 2011). The high possibility that various such contributors may combine supports an ‘allostatic load’ model of environmental injury and genotoxicity. Also note the overlap between nutritional risk factors for oxidative stress and for impaired DNA repair mechanisms. This supports a vicious circle model where the more oxidative damage to the genome, the less the cells will be prepared to deal with it successfully. It can also work the other way around – nutrients can attenuate the degree of damage; instances of this will be discussed in the Melatonin section below.

Chromatin condensation

Chromatin condensation is another hallmark of damage from EMF and RFR. Orderly chromatin condensation is a normal part of cell division, but it can also be provoked pathologically. The work of Markova, Belyaev and others has repeatedly shown that RFR exposure can cause chromatin condensation. Belyaev (1997) reported that super-low intensity RFR resulted in changes in genes, and chromatin condensation of DNA at intensities comparable to exposures from cell towers (typically at RFR levels of 0.1 to 1.0

uW/cm²) (Belyaev, Alipov, and Harms-Ringdahl 1997). Significant microwave-induced changes in chromatin conformation were observed when rat thymocytes were analyzed in-between 30-60 min after exposure to MW (Belyaev and Kravchenko 1994). This effect nearly disappeared if the cells were incubated more than 80 min between exposure and analysis.

In recent studies, human lymphocytes from peripheral blood of healthy and hypersensitive to EMF persons were exposed to non-thermal microwave radiation (NT MW) from the GSM mobile phones (Belyaev et al. 2005; Markova et al. 2005). NT MW induced changes in chromatin conformation similar to those induced by heat shock, which remained up to 24 h after exposure. The same group has reported that contrary to human fibroblast cells, which were able to adapt during chronic exposure to GSM/UMTS low intensity RFR exposure, human stem cells did not adapt (Belyaev, Markova, and Malmgren 2009).

Researchers have recently identified large numbers of “spontaneous genetic glitches,” or de novo mutations, more likely to be transmitted by fathers than by mothers to their children (Neale et al. 2012; O’Roak et al. 2012; Sanders et al. 2012). These glitches are widely distributed across the genome, with their location rather than their size conferring risk. The Eichler team at the University of Washington found that 39% of the 126 most severe or disruptive mutations map to a network associated with chromatin remodeling that has already been ranked as significant amongst autism candidate genes (O’Roak et al. 2012). Whether the prominence of chromatin-related gene mutations can be related in any meaningful way to the impacts of EMF/RFR on chromatin condensation is not possible to say at this point in time and this apparent parallel between ASDs and EMF/RFR may be a pure coincidence, though an intriguing one worth looking into further, including regarding how these mutations and the chromatin-remodeling impacts of EMF/RFR exposure may interact.

Gonadal and germline impacts

De novo mutations have been shown to be more of a problem related to paternal age (O’Roak et al. 2012; Paul, Nagano, and Robaire 2011; Iossifov et al. 2012; Cantor et al. 2007; Alter et al. 2011), and this may be related to the impact of environmental factors such as EMF/RFR on the stem cell genome, particularly in sperm which have no DNA repair capacity. Vulnerability of testes and ova, and of sperm and egg cells, relates to the tissue milieu in which damage to the germline can take place, as well as on the greater vulnerability of stem cells. Several international laboratories have replicated studies showing adverse effects on sperm quality, motility and pathology in men who use and particularly those who wear a cell phone, PDA or pager on their belt or in a pocket (Agarwal et al. 2008; Agarwal et al. 2009; Wdowiak, Wdowiak, and Wiktor 2007; De Iuliis et al. 2009; Fejes et al. 2005; Aitken et al. 2005) Kumar, 2012). Other studies

conclude that usage of cell phones, exposure to cell phone radiation, or storage of a mobile phone close to the testes of human males affect sperm counts, motility, viability and structure (Aitken et al, 2004; Agarwal et al, 2007; Eroglu et al., 2006). Animal studies have demonstrated oxidative and DNA damage, pathological changes in the testes of animals, decreased sperm mobility and viability, and other measures of deleterious damage to the male germ line (Dasdag et al. 1999; Yan et al. 2007; Otitoloju et al. 2010; Salama et al. 2009) Behari et al, 2006; Kumar et al, 2012). Of note, altered fatty acids consistent with oxidative stress have been found in sperm cells in male infertility (Zalata et al. 1998; Zalata, Hafez, and Comhaire 1995).

There are fewer animal studies that have studied effects of cell phone radiation on female fertility parameters. Panagopoulous et al. 2012 report decreased ovarian development and size of ovaries, and premature cell death of ovarian follicles and nurse cells in *Drosophila melanogaster* (Panagopoulos 2012). Gul et al (2009) report rats exposed to stand-by level RFR (phones on but not transmitting calls) caused decrease in the number of ovarian follicles in pups born to these exposed dams (Gul, Celebi, and Ugras 2009). Magras and Xenos (1997) reported irreversible infertility in mice after five (5) generations of exposure to RFR at cell phone tower exposure levels of less than one microwatt per centimeter squared ($\mu\text{W}/\text{cm}^2$) (Magras and Xenos 1997).

Implications of genotoxicity

The issue of genotoxicity puts the contribution of genetic variation into a different light – as something that needs to be accounted for, not necessarily assumed as the starting point. In this regard it has been speculated that the apparent higher rates of autism in Silicon Valley, discussed in the past as related to ‘geek genes’ (Silberman 2001), might be conditioned by higher levels of exposure to EMF/RFR. The relationship between the greater vulnerability of male sperm than of female eggs to adverse effects of EMF/RFR exposure and the marked (4:1) predominance of paternal origin of de novo point mutations (4:1 bias), also deserves further careful attention (O’Roak et al. 2012).

5. Implications of Damage

We have reviewed parallels between ASD and EMF/RFR in molecular, cellular and tissue damage, including cellular stress (oxidative stress, the heat shock response and protein misfolding), injury of membranes, aberrant calcium signaling, and compromise of junctions and barriers. The genotoxicity of EMF/RFR was reviewed in relation to issues of environmental contributions to autism and of the phenomenon of de novo mutations. The compromise of the tissue substrate appears to have many commonalities in ASDs and in EMF/RFR exposures. Also notable was the possibility of attenuating some of the damage through increasing antioxidant status.

These commonalities come to mind in considering the implications of a recent study documenting arrest of symptomatology in a mouse model of Rett syndrome through a bone marrow transplant of wild-type microglia (Derecki et al. 2012; Derecki, Cronk, and Kipnis 2012). The introduction of these competent microglia cells did not directly target the neuronal defect associated with the MECP2 gene mutation; instead the benefits of the transplant were diminished through inhibition of phagocytosis. Phagocytosis involves removing debris. This suggests that while research has focused on how specific molecular defects, particularly in the synapse, may contribute to Rett pathophysiology, there may also be an important contribution from cellular debris, misfolded proteins and other disordered cellular structure and function. Such disorder could be accumulating in cells under the conditions of pathophysiological disarray reviewed above. This has potentially broad implications for other genetic disorders, as well as for conditions like ASDs which are for the most part idiopathic. Based on this study as well as on the levels of damage just reviewed, problems in cells that are pertinent to ASDs most likely go beyond any specific defect introduced by a mutation. Additionally it is conceivable that many of the mutations may be not part of normal background variation but instead collateral damage from the same environmental factors that are also driving the damage to the pathophysiology. It is also encouraging that at least some of the damage and dysfunction was reversible by a generic cellular mechanism (phagocytosis), and this could have broad significance for idiopathic ASDs as well, along with other conditions involving related pathophysiological challenges.

B. DEGRADATION OF SYSTEM INTEGRITY

In the setting of molecular, cellular and tissue damage, one would predict that the organization and efficiency of a variety of organelles, organs and systems would also be degraded. EMF/RFR exposures yield a stressful situation of chronically interrupted homeostasis. Here we will review disturbances from EMF/RFR in systems (including include oxidative and bioenergetics metabolism, immune function and electrophysiological oscillations) that include molecular and cellular components subject to the kinds of damage discussed in the previous section. We will review disturbances that have been associated with EMF/RFR, and consider the parallel disturbances that have been documented in ASDs.

1. Mitochondrial Dysfunction

Mitochondria are broadly vulnerable, in part because the integrity of their membranes is vital to their optimal functioning – including channels and electrical gradients, and their membranes can be damaged by free radicals which can be generated in myriad ways. Moreover, just about every step in their metabolic pathway can be targeted by environmental agents, including toxicants and drugs, as well as mutations (Wallace and Starkov 2000). This supports an allostatic load model for conditions in which

mitochondrial dysfunction is an issue, which includes ASDs as well as myriad other chronic conditions.

Mitochondria are commonly discussed in terms of the biochemical pathways and cascades of events by which they metabolize glucose and generate energy. But in parallel with this level of function there also appears to be a dimension of electromagnetic radiation that is part of the activity of these organelles. For example, electromagnetic radiation can be propagated through the mitochondrial reticulum, which along with the mitochondria has a higher refractive index than the surrounding cell and can serve to propagate electromagnetic radiation within the network (Thar and Kuhl 2004). It is also the case that *“The physiological domain is characterized by small-amplitude oscillations in mitochondrial membrane potential ($\Delta\psi(m)$) showing correlated behavior over a wide range of frequencies.... Under metabolic stress, when the balance between ROS [reactive oxygen species, or free radicals] generation and ROS scavenging [as by antioxidants] is perturbed, the mitochondrial network throughout the cell locks to one main low-frequency, high-amplitude oscillatory mode. This behavior has major pathological implications because the energy dissipation and cellular redox changes that occur during $\Delta\psi(m)$ depolarization result in suppression of electrical excitability and Ca^{2+} handling...”* (Aon, Cortassa, and O'Rourke 2008). These electromagnetic aspects of mitochondrial physiology and pathophysiology could very well be impacted by EMF/RFR.

There are also a variety of types of mitochondrial damage that have been documented in at least some of the studies that have examined the impacts of EMF/RFR upon mitochondria. These include reduced or absent mitochondrial cristae (Khaki et al. 2006; Lahijani, Tehrani, and Sabouri 2009; Esmekaya et al. 2011), mitochondrial DNA damage (Xu et al. 2010), swelling and crystallization (Lahijani, Tehrani, and Sabouri 2009), alterations and decreases in various lipids suggesting an increase in their use in cellular energetics (Chernysheva 1987), damage to mitochondrial DNA (Xu et al. 2010), and altered mobility and lipid peroxidation after exposures (Wang et al. 2002). Also noted has been enhancement of brain mitochondrial function in Alzheimer's transgenic mice and normal mice (Dragicevic et al. 2011). The existent of positive as well as negative effects gives an indication of the high context dependence of exposure impacts, including physical factors such as frequency, duration, and tissue characteristics; these are intensively reviewed in Belyaev's contribution to BioInitiative 2012 in Section 15 (Belyaev 2012).

The idea that mitochondrial dysfunction might be common in ASDs met with a fair bit of consternation, and many professionals have preferred to limit their consideration to mitochondrial disorders with proven genetic mutations. However the concept of mitochondrial dysfunction is better established in other areas of medicine, with thousands

of papers and hundreds of reviews carrying “mitochondrial dysfunction” in their titles. By now there is a large amount of evidence for biochemical and other abnormalities in a large portion of children with autism that are consistent with mitochondrial dysfunction (Giulivi et al. 2010; Palmieri et al. 2010; Pastural et al. 2009). Recently published postmortem brain tissue studies that have added a new dimension of evidence for mitochondrial abnormalities in ASDs will be reviewed in the section on alteration of brain cells below.

Some have called the mitochondrial issues most commonly seen in ASDs ‘secondary mitochondrial dysfunction’ (Zecavati and Spence 2009; Rossignol and Frye 2011) to indicate that it results from environment insults and/or other pathophysiological dysfunction rather than directly from genetics (Hadjixenofontos et al. 2012); the already discussed potential for EMF/RFR to damage channels, membranes and mitochondria themselves could contribute in a number of ways to degrading mitochondrial function without a basis in genetic mutation, as could toxicant exposures and immune challenges. In a meta-analysis of studies of children with ASD and mitochondrial disorder, the spectrum of severity varied, and 79% of the cases were identified by laboratory not associated with genetic abnormalities (Rossignol and Frye 2011). *“Substantial percentages of autistic patients display peripheral markers of mitochondrial energy metabolism dysfunction, such as (a) elevated lactate, pyruvate, and alanine levels in blood, urine and/or cerebrospinal fluid, (b) serum carnitine deficiency, and/or (c) enhanced oxidative stress.....In some patients, these abnormalities have been successfully explained by the presence of specific mutations or rearrangements in their mitochondrial or nuclear DNA. However, in the majority of cases, abnormal energy metabolism cannot be immediately linked to specific genetic or genomic defects.”* (Palmieri and Persico 2010)

2. Melatonin Dysregulation

Melatonin, mitochondria, glutathione, oxidative stress

Melatonin is well-known for its role in regulation of circadian rhythms, but it also plays important metabolic and regulatory roles in relation to cellular protection, mitochondrial malfunction and glutathione synthesis. (Leon et al. 2005; Luchetti et al. 2010; Limon-Pacheco and Gonsebatt 2010) *“It is known that melatonin scavenges oxygen and nitrogen-based reactants generated in mitochondria. This limits the loss of the intramitochondrial glutathione and lowers mitochondrial protein damage, improving electron transport chain (ETC) activity and reducing mtDNA damage. Melatonin also increases the activity of the complex I and complex IV of the ETC, thereby improving mitochondrial respiration and increasing ATP synthesis under normal and stressful conditions.”* (Leon et al. 2005) It also helps prevent the breakdown of the mitochondrial membrane potential, decrease electron leakage, and thereby reduce the formation of

superoxide anions. (Hardeland 2005) Pharmacological doses of melatonin not only scavenge reactive oxygen and nitrogen species, but enhance levels of glutathione and the expression and activities of some glutathione-related enzymes. (Limon-Pacheco and Gonshebbatt 2010; Gupta, Gupta, and Kohli 2003)

Melatonin can attenuate or prevent some EMF/RFR effects

Melatonin may have a protective effect in the setting of some EMF/RFR exposures, apparently in relation to these functions just described. EMF/RFR can impact melatonin; one example is exposure to 900-MHz microwave radiation promoted oxidation, which reduced levels of melatonin and increased creatine kinase and caspase-3 in exposed as compared to sham exposed rats (Kesari, Kumar, and Behari 2011).

Further types of adverse impacts can be seen in the next set of examples, but what is interesting is that melatonin can attenuate or prevent them. In an experiment exposing rats to MW from a GSM900 mobile phone with and without melatonin treatment to study renal impacts (Oktem et al. 2005), the untreated exposed rats showed increases of lipid peroxidation markers as reduction of the activities of superoxide dismutase, catalase and glutathione peroxidase indicating decrement in antioxidant status. However these negative effects were inhibited in the exposed rats treated with melatonin. Melatonin also inhibited the emergence of preneoplastic liver lesions in rats exposed to EMFs (Imaida et al. 2000). The development of DNA strand breaks was observed in RFR exposed rats; this DNA damage was blocked by melatonin (Lai and Singh 1997). Exposure of cultured cortical neurons to EMF led to an increase in 8-hydroxyguanine in neuronal mitochondria, a common biomarker of DNA oxidative damage, along with a reduction in the copy number of mitochondrial DNA and the levels of mitochondrial RNA transcripts; but these effects could all be prevented by pretreatment with melatonin (Xu et al. 2010). In a study of skin lesion induced by exposure to cell phone radiation, the skin changes in the irradiated group (which included thicker stratum corneum, epidermal atrophy, papillomatosis, basal cell proliferation, increased epidermal granular cell layer and capillary proliferation, impaired collagen tissue distribution and separation of collagen bundles in dermis) were prevented (except for hypergranulosis) by melatonin treatment (Ozguner et al. 2004). Melatonin as well as caffeic acid phenylethyl ester (an antioxidant) both protected against retinal oxidative stress in rats exposed long-term to mobile phone irradiation (Ozguner, Bardak, and Comlekci 2006). Nitric oxide (NO) was increased in nasal and sinus mucosa in rats after EMF exposure, with this NO possibly acting as a defense mechanism suggesting tissue damage; but this was prevented by pretreatment with melatonin (Yariktas et al. 2005). Melatonin treatment significantly prevented the increase in the MDA (malondialdehyde, a marker of lipid peroxidation) content and XO (xanthine oxidase) activity in rat brain tissue after 40 days of exposure, but it was unable to prevent the decrease of CAT activity and increase of carbonyl group contents (Sokolovic et al. 2008).

Of note, the melatonin production of infants in isolettes in neonatal intensive care units appears to be impacted by the high ELF-EMF environment, in that when infants were removed from those exposures they showed an increase in melatonin levels (Bellieni, Tei, et al. 2012). There is an increased prevalence of ASDs in children who were born prematurely (Indredavik et al. 2010; Indredavik et al. 2008; Johnson et al. 2011; Johnson et al. 2010; Johnson and Marlow 2011; Lampi et al. 2012; Limperopoulos 2009, 2010; Limperopoulos et al. 2008; Matson, Matson, and Beighley 2011; Pinto-Martin et al. 2011). There are many potential prematurity-associated factors that could contribute to increased risk for ASDs, but electromagnetic exposure might be one of them worthy of further consideration, as it could be modified; conversely, such exposures in vulnerable infants are likely to have much broader impacts beyond reducing melatonin synthesis.

Melatonin and autism

Based on the commonality of both sleep disorders and low melatonin levels, Bourgeron (2007) proposed that synaptic and clock genes are important in ASDs, and that future studies should investigate the circadian modulation of synaptic function (Bourgeron 2007). A number of melatonin-related genetic variants have been identified as associated with ASDs. Polymorphisms, deletions and polymorphisms in the ASMT gene, which encodes the last enzyme of melatonin synthesis, have been found (Pagan et al. 2011; Jonsson et al. 2010; Melke et al. 2008), and variations have been found as well for melatonin receptor genes (Chaste et al. 2010; Pagan et al. 2011; Jonsson et al. 2010). CYP1A2 polymorphisms have been found in slow melatonin metabolisers, in whom melatonin levels are aberrant and initial response to melatonin for sleep disappeared in a few weeks (Braam et al. 2012).

Regarding melatonin status in people with ASDs, a recent meta-analysis summarized the current findings as indicating that “1) *Physiological levels of melatonin and/or melatonin derivatives are commonly below average in ASD and correlate with autistic behavior*, 2) *Abnormalities in melatonin-related genes may be a cause of low melatonin levels in ASD*, and 3) *...treatment with melatonin significantly improves sleep duration and sleep onset latency in ASD.*” (Rossignol and Frye 2011) The meta-analysis also showed that polymorphisms in melatonin-related genes in ASD could contribute to lower melatonin concentrations or an altered response to melatonin, but only in a small percentage of individuals, since pertinent genes were found in only a small minority of those screened.

Autism AND Melatonin AND Glutathione

Whereas PubMed searches for “autism AND melatonin” and “autism AND glutathione” each coincidentally yielded 72 citations, and “melatonin AND glutathione” yielded 803 citations, the search for “autism AND melatonin AND glutathione” yielded zero citations. This is interesting given the strong connection of melatonin and glutathione metabolically, as discussed above, alongside of the strongly established interest in both

glutathione and melatonin in ASD research and increasingly in clinical practice. Hopefully one contribution of an investigation of EMF/RFR links to ASDs will be to help bring attention to this relationship, which may help identify potential environmental and physiological causes for low melatonin in those without pertinent mutations. Of pertinence, tryptophan hydroxylase (TPH2) – the rate limiting enzyme in the synthesis of serotonin, from which melatonin is derived – is extremely vulnerable to oxidation, and tends to misfold when its cysteine residues are oxidized, with the enzyme being converted to a redox-cycling quinoprotein (Kuhn and Arthur 1999; Kuhn and Geddes 1999; Kuhn et al. 2011; Kuhn and Arthur 1997).

3. Disturbed Immune Function

There is by now a broad appreciation of the presence of immune disturbances in ASDs, to the point where there is an emerging discussion of ASDs as neuroimmune disorders (Bilbo, Jones, and Parker 2012; Persico, Van de Water, and Pardo 2012). Research identifying immune features in ASDs spans from genetics where risk genes have been identified to epigenetics where altered expression of immune genes is being reported as prominent in ASD epigenetics (Kong et al. 2012; Waly et al. 2012; Lintas, Sacco, and Persico 2012), and also includes prenatal infectious and immune disturbances as risk factors for autism as well as other neurodevelopmental and neuropsychiatric diseases as well as other conditions such as asthma (Patterson 2011; Smith et al. 2007; Fox, Amaral, and Van de Water 2012). Immune disturbances in infants and children with ASD are heterogeneous, with some but not all manifesting autoimmunity (Soumiya, Fukumitsu, and Furukawa 2011; Martin et al. 2008). Anecdotally, recurrent infection is common while on the other hand some get sick less often than their peers. It is common for people with autism to have family members with immune or autoimmune diseases (Croen et al. 2005). The immune system is turning out to have an important role in brain development (Bilbo and Schwarz 2012; Schwarz and Bilbo 2012; Boksa 2010). As mentioned, glial activation associated with brain immune response has been identified in a growing number of studies. Whether or not EMF/RFR contributes to these features of ASDs causally, based on the evidence below regarding immune impacts of EMF/RFR exposure (which is also reviewed much more thoroughly by Johansson in Section 8 of the present Bioinitiative Report) (Blank 2012), it is certainly plausible that such exposures could serve as aggravating factors.

Low-intensity exposures

It is clear that the body's immune defense system responds to very low-intensity exposures. Chronic exposure to factors that increase allergic and inflammatory responses on a continuing basis is likely to be harmful to health, since the resultant chronic inflammatory responses can lead to cellular, tissue and organ damage over time. We are increasingly appreciating the extent to which many chronic diseases are related to chronic

immune system dysfunction. Disturbance of the immune system by very low-intensity electromagnetic field exposure is discussed as a potential underlying cause for cellular damage and impaired healing (tissue repair), which could lead to disease and physiological impairment (Johansson 2009; Johansson 2007).

Both human and animal studies report that exposures to EMF and RFR at environmental levels associated with new technologies can be associated with large immunohistological changes in mast cells as well as other measures of immune dysfunction and dysregulation. Mast cells not only can degranulate and release irritating chemicals leading to allergic symptoms; they are also widely distributed in the body, including in the brain and the heart, which might relate to some of the symptoms commonly reported in relation to EMF/RFR exposure (such as headache, painful light sensitivity, and cardiac rhythm and palpitation problems).

Consequences of immune challenges during pregnancy

As mentioned, infection in pregnancy can also increase the risk of autism and other neurodevelopmental and neuropsychiatric disorders via maternal immune activation (MIA). Viral, bacterial and parasitic infections during pregnancy are thought to contribute to at least 30% of cases of schizophrenia (Brown and Derkits 2010). The connection of maternal infection to autism is supported epidemiologically, including in a Kaiser study where risk was associated with psoriasis and with asthma and allergy in the second trimester (Croen et al. 2005), and in a large study of autism cases in the Danish Medical registry (Atladdottir et al. 2010) with infection at any point in pregnancy yielding an adjusted hazard ratio of 1.14 (CI: 0.96-1.34) and when infection occurred during second trimester the odds ratio was 2.98 (CI: 1.29-7.15). In animal models, while there is much variation in study design, mediators of the immune impact appear to include oxidative stress, interleukin-6 and increased placental cytokines (Smith et al. 2007; Patterson 2009; Boksa 2010). Garbett et al. (2012) commented on several mouse models of the effects of MIA on the fetal brain that *“The overall gene expression changes suggest that the response to MIA is a neuroprotective attempt by the developing brain to counteract environmental stress, but at a cost of disrupting typical neuronal differentiation and axonal growth.”* (Garbett et al. 2012). Maternal fetal brain-reactive autoantibodies have also been identified in some cases (Braunschweig et al. 2012; Braunschweig and Van de Water 2012; Fox, Amaral, and Van de Water 2012; Goines et al. 2011; Wills et al. 2009; Wills et al. 2011; Zimmerman et al. 2007).

Although we have evidence of immune impacts of EMF/RFR, the impact of repeated or chronic exposure to EMF and RFR during pregnancy is poorly studied; could this trigger similar immune responses (cytokine production) and stress protein responses, which in turn would have effects on the fetus? Although this has been poorly studied, we do have data that very low cell phone radiation exposures during both human and mouse

pregnancies have resulted in altered fetal brain development leading to memory, learning, and attention problems and behavioral problems (Aldad et al. 2012).

Potential immune contributions to reactivity and variability in ASDs

Immune changes in ASDs appear to be associated with behavioral change (Shi et al. 2003; Ashwood et al. 2008; Ashwood et al. 2011; Breece et al. 2012; Heuer et al. 2008), but the mechanisms are complex and to date poorly understood (Careaga and Ashwood 2012) and likely will need to be elucidated through systems biology methods that capture multisystem influences on the interactions across behavior, brain and immune regulation (Broderick and Craddock 2012), including electrophysiology.

Two of the particularly difficult parts of ASDs are the intense reactivity and the variability in assorted symptoms such as tantrums and other difficult behaviors. Children with ASDs who also have gastrointestinal symptoms and marked fluctuation of behavioral symptoms have been shown to exhibit distinct innate immune abnormalities and transcriptional profiles of peripheral blood monocytes (Jyonouchi et al. 2011). It is worth considering EMF/RFR exposures could be operating through related mechanisms so as to add to allostatic loading in ways that exacerbate behavior. In Johansson 2006 and 2007 a foundation is provided for understanding how chronic EMF/RFR exposure can compromise immune function and sensitize a person to even small exposures in the future (Johansson 2007; Johansson et al. 2006). Johansson discusses alterations of immune function at environmental levels resulting in loss of memory and concentration, skin redness and inflammation, eczema, headache, and fatigue. Mast cells that degranulate under EMF and RFR exposures and substances secreted by them (histamine, heparin and serotonin) may contribute to features of this sensitivity to electromagnetic fields (Johansson et al. 2006). Theoharides and colleagues have argued that environmental and stress related triggers might activate mast cells, causing inflammatory compromise and leading to gut-blood-brain barrier compromise, seizures and other ASD symptoms (Theoharides et al. 2012, 2010), and that this cascade of immune response and its consequences might also be triggered in the absence of infection by mitochondrial fragments that can be released from cells in response to stimulation by IgE/anti-IgE or by the proinflammatory peptide substance P (Zhang, Asadi, et al. 2012).

Seitz et al. (2005) reviewed an extensive literature on electromagnetic hypersensitivity conditions reported to include sleep quality, dizziness, headache, skin rashes, memory and concentration impairments related to EMF and RFR {Seitz, 2005 #2582}. Some of these symptoms are common in ASDs, whether or not they are due to EMF/RFR exposure, and the experience of discomfort may be hard to document due to difficulties with self-reporting in many people with ASDs.

Johansson (2007, 2009) also reports that benchmark indicators of immune system allergic and inflammatory reactions occur under exposure conditions of low-intensity non-

ionizing radiation (immune cell alterations, mast cell degranulation histamine-positive mast cells in biopsies and immunoreactive dendritic immune cells) (Johansson 2007; Johansson 2009). In facial skin samples of electro- hypersensitive persons, the most common finding is a profound increase in mast cells as monitored by various mast cell markers, such as histamine, chymase and tryptase (Johansson et al. 2001). In ASDs, infant and childhood rashes, eczema and psoriasis are common, and they are common in family members as well (Bakkaloglu et al. 2008).

4. Alteration of and damage to cells in the brain

Brain cells have a variety of ways of reacting to environmental stressors, such as shape changes, metabolic alterations, upregulation or downregulation of neurotransmitters and receptors, other altered functionality, structural damage, production of un-metabolizable misfolded proteins and other cellular debris, and apoptosis; these range along a spectrum from adaptation to damage and cell death. These types of alterations can be looked at in animals under controlled conditions, but in human beings direct cellular examination can only be done on surgical biopsy tissue – which is hardly ever available in people with ASDs – or after death, at which point there has been a whole lifetime of exposures that are generally impossible to tease apart if there were even motivation to do so. This complicates the comparison of brain cell and tissue-related pathophysiology between what is seen in ASDs and what is associated with EMF/RFR exposures.

Brain cells

Impact of EMF/RFR on cells in the brain has been documented by some of the studies that have examined brain tissue after exposure, although the interpretation of inconsistencies across studies is complicated by sometimes major differences in impact attributable to differences in frequencies and duration of exposure, as well as to differences in resonance properties of tissues and other poorly understood constraints on cellular response. These studies and methodological considerations have been reviewed in depth in Belyaev, 2012 in section 15 of the 2012 BioInitiative Report (Belyaev 2012), as well as by Salford et al. (2012) in Section 10 (Salford, Nittby, and Persson 2012). A few examples of observations after exposure have included dark neurons (an indicator of neuronal damage), as well as alteration of neuronal firing rate (Bolshakov and Alekseev 1992), and upregulation of genes related to cell death pathways in both neurons and astrocytes (Zhao, Zou, and Knapp 2007). Astrocytic changes included increased GFAP and increased glial reactivity (Chan et al. 1999; Ammari et al. 2008; Ammari et al. 2010; Brillaud, Piotrowski, and de Seze 2007), as well as astrocyte-pertinent protein expression changes detected by Fragopoulou et al, 2012 as mentioned above. Also observed has been a marked protein downregulation of the nerve growth factor glial maturation factor beta (GMF) which is considered as an intracellular signal transduction regulator in astrocytes, which could have significant impact on neuronal-glial interactions as well as

brain cell differentiation and tumor development. Diminution of Purkinje cell number and density has also been observed, (Ragbetli et al. 2010) including in two studies of the impacts of perinatal exposure {Albert, 1981 #2584; Albert, 1981 #2583}. Promotion of pro-inflammatory responses in EMF-stimulated microglial cells has also been documented (Yang et al. 2010).

Neuropathology findings in ASDs have been varied and have been interpreted according to various frameworks ranging from a regionalized approach oriented to identifying potential brain relationships to ASD's behavioral features (Amaral, Schumann, and Nordahl 2008) to identifying receptor, neurotransmitter and interneuron abnormalities that could account for an increased excitation/inhibition ratio {Levitt, 2009 #551} {Geschwind, 2007 #2586} {Anney, 2010 #423} {Casanova, 2006 #2587} {Rubenstein, 2003 #809}. Studies have documented a range of abnormalities in neurons, including altered cellular packing in the limbic system, reduced dendritic arborization, and reductions in limbic GABAergic systems. Over the past decade a shift has occurred from presuming that all pertinent brain changes occurred prior to birth, to an acknowledgement that ongoing cellular processes appear to be occurring not only after birth but well into adulthood. (Bauman and Kemper 2005) One of the reasons for this shift was the observation that head size (as well as brain weight and size) was on average larger in children with autism, and the head sizes of children who became diagnosed with autism increased in percentile after birth {Herbert, 2005 #642}.

Neuroinflammation, glial activation and excitotoxicity

Although much attention has been paid in ASD brain literature to specific regions manifesting differences in size and activity in comparison to those without ASDs, there are other observations that are not strictly regional in nature, such as more widely distributed scaling differences (e.g. larger brains, wider brains, increased white matter volume, along with altered functional connectivity and coherence to be discussed below). Recently more studies have appeared identifying pathophysiological abnormalities such as neuroinflammation, mitochondrial dysfunction and glutathione depletion in brain tissue. Neuroinflammation was first identified in a study of postmortem samples from eleven individuals aged 5-44 who had died carrying an ASD diagnosis, in which activated astrocytes and microglial cells as well as abnormal cytokines and chemokines were found. Other research has identified further astrocyte abnormalities include, altered expression of astrocyte markers GFAP abnormalities including elevation, antibodies, and altered signaling {Laurence, 2005 #1729; Singh, 1997 #1730} (Fatemi et al. 2008). Increased microglia activation and density as well as increased myeloid dendritic cell frequencies have also been documented. (Vargas et al. 2005; Breece et al. 2012; Tetreault et al. 2012), as has abnormal microglial-neuronal interactions (Morgan et al. 2012). Recently through use of the PET ligand PK11105 microglial activation was found to be significantly higher in multiple brain regions in young adults with ASDs (Suzuki et al.

2013). Genes associated with glial activation have been documented as upregulated. Garbett et al measured increased transcript levels of many immune genes, as well as changes in transcripts related to cell communication, differentiation, cell cycle regulation and chaperone systems (Garbett et al. 2008). Voineagu and colleagues performed transcriptomic analysis of autistic brain and found a neuronal module of co-expressed genes which was enriched with genetically associated variants, and an immune-glial module showing no such enrichment for autism GWAS signals (Voineagu et al. 2011).

Neuroinflammation also does not appear to be strictly localized in a function-specific fashion, and it may contribute both to more broadly distributed and more focal features for tissue-based reasons. It may be that brain regions with particular prominence in ASDs may have distinctive cellular characteristics – e.g. the amygdala (Baron-Cohen et al. 2000; Dziobek et al. 2010; Hall et al. 2010; Mercadante et al. 2008; Nordahl et al. 2012; Otsuka et al. 1999; Schulkin 2007; Schumann and Amaral 2006; Schumann et al. 2009; Truitt et al. 2007; Zirlinger and Anderson 2003), which may have a larger or more reactive population of astrocytes (Johnson, Breedlove, and Jordan 2010) or the basal ganglia which may have greater sensitivity to even subtle hypoxia or perfusion abnormalities. In this case it may be the histology of these areas that makes them vulnerable to environmental irritants, and this may contribute to how environmental factors such as EMF/RFR might trigger or aggravate some of ASD's features. More widely distributed brain tissue pathology be part of what leads to differences in ASDs in brain connectivity. However these types of tissue-function relationships have been poorly investigated. The contribution of tissue differences is one of the physical considerations covered by Belyaev (2012) in Section 15 of the 2012 BioInitiative Report {Belyaev, 2012 #2324}.

Various signs of mitochondrial dysfunction and oxidative stress have also been identified in the brain. Findings include downregulation of expression of mitochondrial electron transport genes (Anitha, Nakamura, Thanseem, Matsuzaki, et al. 2012) or deficit of mitochondrial electron transport chain complexes (Chauhan et al. 2011), brain region specific glutathione redox imbalance (Chauhan, Audhya, and Chauhan 2012), and evidence of oxidative damage and inflammation associated with low glutathione redox status (Rose, Melnyk, Pavliv, et al. 2012). Oxidative stress markers were measured as increased in cerebellum (Sajdel-Sulkowska, Xu, and Koibuchi 2009).

Additional support for the presence of tissue pathophysiology-based changes in brains of people with ASDs comes from the various studies documenting reduction in Purkinje cell numbers (Whitney et al. 2009; Whitney et al. 2008; Bauman and Kemper 2005; Shi et al. 2009; Blatt and Fatemi 2011; Fatemi et al. 2002; Fatemi et al. 2012), possibly due to oxidative stress and an increased excitation/inhibition ratio that could potentially be acquired (Fatemi et al. 2012). Also of note are changes in the glutamatergic and GABAergic systems, which when imbalanced can disturb the excitation/inhibition ratio

and contribute to seizure disorders; reductions in GABA receptors as well as in GAD 65 and 67 proteins that catalyse the conversion of glutamate into GABA have been measured. (Yip, Soghomonian, and Blatt 2007, 2008, 2009) A consensus statement on the cerebellum in ASDs stated that, “*Points of consensus include presence of abnormal cerebellar anatomy, abnormal neurotransmitter systems, oxidative stress, cerebellar motor and cognitive deficits, and neuroinflammation in subjects with autism.*” (Fatemi et al. 2012)

Some indirect corroboration for these findings has come from neuroimaging, where the initial hypothesis regarding the tissue basis of the larger size of brains in so many people with autism – that it was due to a higher density of neurons and more tightly packed axons – came under question with the emergence of contradictory findings, well reviewed a few years ago by Dager and colleagues (Dager et al. 2008). These include reduced rather than increased density of NAA (n-acetylaspartate, a marker of neuronal integrity and density that is produced in the mitochondria), reduced rather than increased fractional anisotropy suggesting less tightly packed axonal bundles (Bode et al. 2011; Cascio et al. 2012; Mak-Fan et al. 2012; Travers et al. 2012; Walker et al. 2012; Wolff et al. 2012){Sundaram, 2008 #2588} and greater rather than lower diffusivity, all of which may be more consistent with lower density of tissue and tissue metabolites and more fluid, which could be consistent with neuroinflammation and/or oxidative stress. The early postnatal development of such lower fractional anisotropy and increased diffusivity was measured in the process of occurring recently, in the first large prospective longitudinal imaging study of infants, who trended from 6 months to 2 years in the direction of these findings becoming more pronounced – but still with substantial overlap with those infants who did not develop autism (Wolff et al. 2012). This trend was consistent with prior studies showing increase in head size after birth, and added some information about what was happening in the brain to drive this size increase, although due to its methods it could only indirectly address the possibility that emergence during the first few years of life of tissue pathophysiology disturbances such as neuroinflammation might be contributing to these trends (Herbert 2012).

There is also substantial variability across many different types of brain findings. Of interest is that a number of functional brain imaging and electrophysiology studies have identified greater heterogeneity in response to stimuli between individuals in the ASD group than individuals in the neurotypical control group (Muller et al. 2003; Dinstein et al. 2012). This may make more sense from the point of view of non-linear response – i.e. a disproportionality between output and input (as well as state and context sensitivity), in a pathophysiologically perturbed brain system. Nonlinearity has also been a significant methodological issue in EMF/RFR research because linear methods of study design and data analysis have often been insensitive to effects, whereas nonlinear methods have been argued to show greater sensitivity (Carrubba and Marino 2008; Marino, Wolcott,

Chervenak, Jourdain, Nilsen, Frilot, et al. 2001; Marino and Frilot 2003; Carrubba et al. 2006; Carrubba et al. 2012; Marino, Nilsen, and Frilot 2003; Marino, Wolcott, et al. 2001, 2001; Carrubba et al. 2007; Marino et al. 2000){Bachmann, 2005 #2072} .

The presence of various types of tissue pathophysiology both in findings in postmortem tissue from individuals with ASDs and in documented impacts of EMF/RFR exposure are intriguing and suggest overlap in processes involved. But it is not really possible to infer any specific agent of injury from cellular responses since for the most part these are not specific but rather are stress or repair responses generic to a variety of triggers. It is important to entertain how environmental agents could contribute to brain changes in ASDs, and how these changes may develop over progress over time after the earliest periods in brain development. EMF/RFR exposures could be preconceptional, prenatal or postnatal – or all of the above; it is conceivable that this could be the case in ASDs as well.

Altered development

There is some evidence for altered brain and organism development in relation to EMF/RFR exposure. Aldad et al. 2012 exposed mice in utero to cellular telephones, with resultant aberrant miniature excitatory postsynaptic currents, dose-responsive impaired glutamatergic synaptic transmission onto layer V pyramidal neurons of the prefrontal cortex (Aldad et al. 2012). Lahijani exposed preincubated chicken embryos to 50 Hz EMFs, and made the following morphological observations: “*exencephalic embryos, embryos with asymmetrical faces, crossed beak, shorter upper beak, deformed hind limbs, gastroschisis, anophthalmia, and microphthalmia. H&E and reticulin stainings, TEMS, and SEMs studies indicated EMFs would create hepatocytes with fibrotic bands, severe steatohepatitis, vacuolizations, swollen and extremely electron-dense mitochondria, reduced invisible cristae, crystalized mitochondria with degenerated cristae, myelin-like figures, macrophages engulfing adjacent cells, dentated nuclei, nuclei with irregular envelopes, degenerated hepatocytes, abnormal lipid accumulations, lipid droplets pushing hepatocytes' nuclei to the corner of the cells, abundant cellular infiltrations cellular infiltrations inside sinusoid and around central veins, disrupted reticulin plexus, and release of chromatin into cytosol,, with partially regular water layers,*” and attributed cell damage to elevated free radical induced cell membrane disruptions (Lahijani, Tehrani, and Sabouri 2009).

Although it is of great interest to characterize the changes in development associated with ASDs, it is also difficult to do in human beings because at present diagnosis is not possible until at least 2-3 years after birth. By now there have been a lot of prospective studies of infants at high risk for autism, but the in vivo brain imaging and electrophysiology data from these studies is only starting to be published, and so the for now the main sources of information are still inference backwards from post-mortem or

imaging data, and animal models, both of which have clear limitations. Thus it is impossible to seek precise parallels here between what we know about the development of ASDs compared with the impacts of EMF/RFR exposures.

Nevertheless it is of real concern that such exposures have elicited some of the brain tissue changes that have been documented, both in early development and subsequently. Already noted above is the question of whether high exposures of neonates to monitoring equipment may affect the melatonin levels of neonates (Bellieni, Tei, et al. 2012); these exposures also impact heartrate variability . There are no studies yet on infants exposed to baby surveillance monitors or DECT wireless phones. However there are good laboratory testing studies yielding actual measurements of these devices that conclude: *“Maximum incident field exposures at 1m can significantly exceed those of base stations (typically 0.1 - 1 V/m). At very close distances the derived or reference exposure limits are violated” for baby surveillance monitors and DECT phones.* Further, the authors conclude that, based on very strictly controlled laboratory testing of everyday devices like baby monitors and some cordless phones *“(W)orse case peak spatial SAR values are close to the limit for the public or uncontrolled environments, e.g., IEEE802.11b and Bluetooth Class I”.*(Kuhn et al. 2012) Even exposure of the fetus to laptop computer wireless emissions through the pregnant mother’s use of them may on her lap involve induction of strong intracorporeal electric current densities from the power supply possibly even more than the device itself (Bellieni, Pinto, et al. 2012).

Brain Blood Flow and metabolism

Cerebral perfusion and metabolism abnormalities have been identified in close to 2 dozen papers studying autistic cohorts. Cerebral perfusion refers to the quantity of blood flow in the brain. Abnormal regulation of cerebral perfusion is found in a range of severe medical conditions including tumors, vascular disease and epilepsy. Cerebral hypoperfusion has also been found in a range of psychiatric disorders (Theberge 2008). Neurocognitive hypotheses and conclusions, as well as localization of perfusion changes, have been heterogeneous across these papers. Hypoperfusion or diminished metabolism has been identified in frontal regions {George, 1992 #2565} {Gupta, 2009 #2575} {Degirmenci, 2008 #2563} {Wilcox, 2002 #2578} {Galuska, 2002 #2564} {Ohnishi, 2000 #2571}, temporal lobes {Boddaert, 2002 #2558} {Burroni, 2008 #2559} {Degirmenci, 2008 #2563} {Galuska, 2002 #2564} {George, 1992 #2565} {Hashimoto, 2000 #2566} {Ohnishi, 2000 #2571} {Ryu, 1999 #2573} {Starkstein, 2000 #2576} {Zilbovicius, 2000 #2579}, as well as a variety of subcortical regions including basal ganglia {Degirmenci, 2008 #2563} {Ryu, 1999 #2573} {Starkstein, 2000 #2576}, cerebellum {Ryu, 1999 #2573}, limbic structures {Ito, 2005 #2568} {Ohnishi, 2000 #2571} and thalamus {Ito, 2005 #2568} {Ryu, 1999 #2573} {Starkstein, 2000 #2576} – i.e., in a widely distributed set of brain regions. It is interesting to note that even with this regional variation in localization, most of these publications showed that

cerebral perfusion was *reduced*; in the only one of those studies reporting some areas of localized hyperfusion, these areas were found in the middle of areas in the frontal pole and temporal lobe that were hypoperfused {McKelvey, 1995 #2570}, Only one study showed no difference in perfusion between autistic and control subjects {Herold, 1988 #2567}. Possibly because virtually all of these studies were oriented toward testing neuropsychological rather than pathophysiological hypotheses, there were no probes or tests reported to unearth the tissue level alterations that might be underlying these reductions in blood flow in these brains.

While a large number of animal studies have documented BBB abnormalities from EMF/RFR exposures, only a few PET studies have been performed evaluating EMF exposure effects upon brain glucose metabolism. Volkow et al. performed PET scans both with and without EMF exposure (50 min of GSM-900 with maximum SAR of 0.901 W/kg), and the participants were blinded to the exposure situation (Volkow et al. 2011). A 7% increase in metabolism in the exposure situation compared to controls was identified regionally on the same side of the head as where the mobile phone was placed, in the right orbitofrontal cortex and in the lower part of the right superior temporal gyrus . The strength of the E-field from the phones correlated positively with the brain activation, which the authors hypothesized was from an increase in brain neuron excitability. . A subsequent smaller study by Kwon et al. demonstrated not increased but decreased brain ¹⁸FDG uptake after GSM-900 exposure, this time in the temporoparietal junction (Kwon et al. 2011).

Many possible mechanisms could be involved in the metabolic and perfusion abnormalities identified, ranging from altered neuronal activity that was hypothesized in the Volkow et al. (2011) ⁸FDG PET study to narrowing of vascular lumen in the setting of reduced perfusion. Underlying tissue pathophysiology-based phenomena could influence the measurable metabolism and perfusion abnormalities, via mechanisms such as excitotoxicity, cell stress response, constriction of capillary lumen by activated astrocytes, volume effects of vascular extravasation, subtle alterations in blood viscosity due to immune or oxidative stress-associated blood chemical changes, with other possibilities as well. Given the types of damage at the cellular level covered in this pathophysiology section so far – including oxidative stress, membrane and barrier function damage and poorly functioning channels, which occur both in ASDs as a consequence of EMF/RFR exposure, and given the heterogeneity of localization of abnormalities in the autism perfusion papers as well as considerations of nonlinearity, it may not be so surprising that the results in the two PET studies of human impacts of EMF exposure were not consistent.

6. Electrophysiology perturbations

At this stage the argument we hit a key pivot point, where we look at how the alterations in molecular, cellular and systems physiological function, which occur in the brain as well as in the body, impact the transduction into the electrical signaling activities of the brain and nervous system. Certainly the cells and tissues whose physiological challenges we have already discussed provide the material substrate for the electrical activity. Although ASD behaviors are influenced by many factors, they must in principle be mediated through nervous system electrophysiology.

If the cells responsible for generating synapses and oscillatory signaling are laboring under cellular and oxidative stress, lipid peroxidation, impaired calcium and other signaling system abnormalities, then mitochondrial metabolism will fall short, all the more so because of the challenges from the immune system which in turn be triggered to a major extent by environment. How well will synapses be generated? How well will immune-activated and thereby distracted glial cells be able to modulate synaptic and network activity? (Tasker et al. 2012; Eroglu and Barres 2010; Bilbo and Schwarz 2009; Fields 2006)

At present we are in the early stages of being able to formulate these questions well enough to address them. We do know that microglial activation can impact excitatory neurotransmission mediated by astrocytes (Pascual et al. 2012). We do know that the cortical innate immune response increases local neuronal excitability and can lead to seizures (Rodgers et al. 2009; Gardoni et al. 2011). We do know that inflammation can play an important role in epilepsy (Vezzani et al. 2011). We know less about lower levels of chronic or acute pathophysiological dysfunction and how they may modulate and alter the brain's electrophysiology.

Seizures and Epilepsy

EEG signals in ASDs are abnormal on a variety of levels. At the most severe level, EEGs show seizure activity. In addition to the association of some severe epilepsy syndromes (e.g. Landau Kleffner, tuberous sclerosis) with autism, the risk of epilepsy is substantially higher in people with ASDs than in the general population, with a large subset of these individuals experiencing seizure onset around puberty, likely in relation to aberrations in the dramatic and brain-impactful hormonal shifts of that phase of life. Although less than 50% of people clearly have seizures or epilepsy, a much larger number have indications of epileptiform activity, and an even larger percent have subclinical features that can be noted by a clinical epileptologist though not necessarily flagged as of clinical concern.

Epileptic seizures can be both caused by and cause oxidative stress and mitochondrial dysfunction. Seizures can cause extravasation of plasma into brain parenchyma (Mihaly and Bozoky 1984; Librizzi et al. 2012; Marchi et al. 2010; van Vliet et al. 2007; Yan et al. 2005) which can trigger a vicious circle of tissue damage from albumin and greater

irritability, as discussed above. Evidence suggests that if a BBB is already disrupted, there will be greater sensitivity to EMF/RFR exposure than if the BBB were intact (Tore et al. 2002; Tore et al. 2001), suggesting that such exposures can further exacerbate vicious circles already underway.

The combination of pathophysiological and electrophysiological vulnerabilities has been explored in relation to the impact of EMF/RFR on people with epilepsy – which, as discussed above, is a lot more common in ASDs than in the general population.. EMF/RFR exposures from mobile phone emissions have been shown to modulate brain excitability and to increase interhemispheric functional coupling (Vecchio et al. 2012; Tombini et al. 2012). In a rat model the combination of picrotoxin and microwave exposure at mobile phone-like intensities led to a progressive increase in neuronal activation and glial reactivity, with regional variability in the fall-off of these responses three days after picrotoxin treatment (Carballo-Quintas et al. 2011), suggesting a potential for interaction between a hyperexcitable brain and EMF/RFR exposure.

One critical issue here is nonlinearity and context and parameter sensitivity of impact. In one study, rat brain slices exposed to EMF/RFR showed reduced synaptic activity and diminution of amplitude of evoked potentials, while whole body exposure to rats led to synaptic facilitation and increased seizure susceptibility in the subsequent analysis of neocortical slices (Varro et al. 2009). Another study unexpectedly identified enhanced rat pup post-seizure mortality after perinatal exposure to a specific frequency and intensity of exposure, and concluded that apparently innocuous exposures during early development might lead to vulnerability to stimuli presented later in development (St-Pierre et al. 2007)

Sleep

Sleep involves a profound change in brain electrophysiological activity, and EEG abnormalities including disrupted sleep architecture figure in sleep challenges in ASD. Sleep symptoms include bedtime resistance, sleep onset delay, sleep duration and night wakings, and sleep architecture can involve significantly less efficient sleep, less total sleep time, prolonged sleep latency, and prolonged REM latency (Buckley et al. 2010; Giannotti et al. 2011), with these sleep problems being worse in children with ASDs who regressed than in those who did not regress into their autism {Giannotti, 2011 #1611}. EEG abnormalities have also been associated with EMF/RFR exposure, including disrupted sleep architecture as well as changes in sleep spindles and in the coherence and correlation across sleep stages and power bands during sleep {Borbely, 1999 #2165}{Huber, 2003 #2166}.

Sleep disturbance symptoms are also common in both situations. Insomnia is commonly reported in people who are chronically exposed to low-level wireless antenna emissions. Mann (1996) reported an 18% reduction in REM sleep, which is key to memory and

learning functions in humans. In ASDs sleep difficulties are highly pervasive and disruptive not only to the affected individual but also to their whole family due to the associated problems such as noise and the need for vigilance.

The multileveled interconnections involved in the modulation of sleep exemplify the interconnectedness of the many levels of pathophysiology reviewed here: *“Extracellular ATP associated with neuro- and glia-transmission, acting via purine type 2 receptors, e.g., the P2X7 receptor, has a role in glia release of IL1 and TNF. These substances in turn act on neurons to change their intrinsic membrane properties and sensitivities to neurotransmitters and neuromodulators such as adenosine, glutamate and GABA. These actions change the network input-output properties, i.e., a state shift for the network.”* (Clinton et al. 2011) With disturbance simultaneously at so many of these levels, it is not surprising that sleep dysregulation is nearly universal in ASDs, and common in the setting of EMF/RFR exposures.

Quantitative electrophysiology

While clinical reading of EEG studies is done visually, a growing number of studies are examining EEG and MEG data using digital signal processing analysis, and often using data collected in controlled research settings with high density array equipment and carefully designed stimuli paradigms. In these settings a variety of abnormalities have been identified other than epileptic. These include abnormalities in the power spectrum, i.e. the distribution of power over the different frequencies present, with some studies showing impaired or reduced gamma-and activity (Sun et al. 2012; Rojas et al. 2008){Rippon, 2007 #2585} and others showing reduction of spectral power across all bands (Tierney et al. 2012) while still others showed increased high-frequency oscillations (Orekhova et al. 2007). Abnormalities in coherence and synchronization between various parts of the brain have been found (Muller 2008; Muller et al. 2011; Wass 2011), comparable to abnormal functional connectivity measured by fMRI (Just et al. 2004) but measurable using EEG or MEG with higher temporal resolution {Duffy, 2012 #2593}{Isler, 2010 #1421}{Murias, 2007 #2591;Murias, 2007 #2590}{Coben, 2008 #2592}. Several studies have identified reduced complexity and increased randomness in EEGs of people with autism (Lai et al. 2010; Catarino et al. 2011), as well as an increase in power but a reduction in coherence (Isler et al. 2010; Mathewson et al. 2012). Some electrophysiological metrics are emerging as potential discriminators between brain signal from individuals with ASDs and those who are neurotypical, such as a wavelet-chaos-neural network methodology applied to EEG signal (Ahmadlou, Adeli, and Adeli 2010).

EMF/RFR also has impacts at levels of brain function measurable by these techniques. At various frequencies and durations of exposure it has been noted to impact alpha and beta rhythms (Hinrikus et al. 2008), to increase randomness (Marino, Nilsen, and Frilot 2003;

Marino and Carrubba 2009), to alter power, to modulate interhemispheric synchronization (Vecchio et al. 2007), to alter electrical activity in brain slices (Tattersall et al. 2001) and to alter the patterns of coordination (spectral power coherence) across the major power bands (Hountala et al. 2008). Bachman et al. (2006) showed statistically significant changes in EEG rhythms and dynamics occurred in between 12% and 20% of healthy volunteers {Bachmann, 2006 #2069}. In children, exposures to cell phone radiation have resulted in changes in brain oscillatory activity during some memory tasks [97,102].

Sensory processing

At the symptomatic level issues with sensory processing are highly prevalent in ASDs. Phenomenology can include hypersensitivity to external stimuli, hyposensitivity to internal sensations and difficulty localizing sensation including pain, and difficulty processing more than one sensory channel at one time. (Robledo, Donnellan, and Strandt-Conroy 2012; Perry et al. 2007; Sacco et al. 2010) There is now electrophysiological evidence of abnormalities at early (brainstem) stages of sensory processing, as well as in later stages of processing that occur in the cortex. Some studies have shown lower and some longer latencies of response to an auditory stimulus. Domains of perception where the performance of people with ASDs is superior to that of neurotypical individuals have been identified. (Marco et al. 2011) *“It is obvious...that sensory processing abnormalities in ASD are distributed rather than localized; sensory abnormalities in ASD obviously span multiple dimensions of latency, adaptation, magnitude and behavior abnormalities, with both enhanced and impaired behavior associated with aberrant cortical responses. Given this diversity in findings, the heterogeneity of ASD, and broad variability seen over and over again in the ASD groups almost irrespective of the study, it is hard to imagine that one single theory could account for all of these observations.... It is therefore probable that several mechanisms and neuronal abnormalities, most likely at multiple levels (from single neurons through to inter-area connections), all contribute to varying degrees to the abnormal sensory processing observed in ASD. It is also likely that no single mechanism is unique to one sensory modality, which is why we see such a widely distributed range of abnormalities across modalities.”* (Kenet 2011)

It is also possible that the mechanisms may not simply be neural – they may also be modulated by glial, metabolic, immune, perfusional and other physiological processes and physical properties as well. Yet although there is some consideration of the pathophysiology-sensory function interaction (Kern et al. 2010), it has basically not been fleshed out in studies of ASDs with experimental designs integrating pathophysiological and electrophysiology.

Kenet et al. (2010) demonstrated environmental vulnerability of sensory processing in the brain by the exposure of rat dams to noncoplanar polychlorinated biphenyls (PCBs), during gestation and for three subsequent weeks of nursing {Kenet, 2011 #1852}.

“Although the hearing sensitivity and brainstem auditory responses of pups were normal, exposure resulted in the abnormal development of the primary auditory cortex (A1). A1 was irregularly shaped and marked by internal nonresponsive zones, its topographic organization was grossly abnormal or reversed in about half of the exposed pups, the balance of neuronal inhibition to excitation for A1 neurons was disturbed, and the critical period plasticity that underlies normal postnatal auditory system development was significantly altered. These findings demonstrate that developmental exposure to this class of environmental contaminant alters cortical development.” (Kenet et al. 2007).

This study may be particularly relevant for EMF/RFR exposures, as the noncoplanar PCBs were discussed above as targeting calcium signaling as do EMF/RFR exposures – i.e. they both converge upon a common cellular mechanism (Pessah and Lein 2008; Stamou et al. 2012), justifying exploring the hypothesis that the outcomes one might expect from EMF/RFR could be similar.

Autonomic dysregulation

Although there are a fair number of negative studies regarding the impact of EMF/RFR exposure on the autonomic nervous system, increased HRV and autonomic disturbances have been documented (Andrzejak et al. 2008; Szmigielski et al. 1998; Bortkiewicz et al. 2006; Graham et al. 2000; Saunders and Jefferys 2007). Buchner and Eger (2010), in a study in rural Germany of the health impacts of exposures from a new base station yielding novel exposure to EMF/RFR, saw a significant elevation of the stress hormones adrenaline and noradrenaline during the first six months with a concomitant drop in dopamine, with a failure to restore the prior levels after a year and a half. These impacts were felt by the young, the old and the chronically ill, but not by healthy adults (Buchner and Eger 2011).

Effects on the neonate are also evident. Bellieni et al (2008) found that heart rate variability is adversely affected in infants hospitalized in isolettes or incubators where ELF-EMF levels are in the 0.8 to 0.9 μT range (8 to 9 mG). Infants suffer adverse changes in heart rate variability, similar to adults (Bellieni et al. 2008). This electromagnetic stress may have lifelong developmental impacts, based on a study showing that in utero beta 2 agonist exposure can potentially induce a permanent shift in the balance of sympathetic-to-parasympathetic tone (Witter et al. 2009).

Meanwhile clinical observation and a growing body of literature support a major role for stress in ASDs (Anderson and Colombo 2009; Anderson, Colombo, and Unruh 2012; Daluwatte et al. 2012; Ming et al. 2011), with variability amongst individuals in the severity of the stress response but a tendency to have high tonic sympathetic arousal at

baseline (Hirstein, Iversen, and Ramachandran 2001; Toichi and Kamio 2003; Ming, Julu, et al. 2005; Mathewson et al. 2011; Cheshire 2012; Chang et al. 2012).

The impact of EMF/RFR exposure can also be greatly influenced by the stress system status of the individual being exposed. Tore et al. sympathectomized some of his rats before exposure to GSM, to simulate cell phone exposure (Tore et al. 2002; Tore et al. 2001). Salford et al. (2012) reviewed the results:

*“Comparing the animals, which had been subjected to ganglionectomy, to the other animals, Töre et al. made an interesting observation: as expected, albumin extravasation was more prominent in the sympathectomised sham-exposed rats as compared to normal exposed rats. This was due to the fact that the sympathectomised rats were in a chronic inflammation-prone state with hyper-development of pro-inflammatory structures, such as the parasympathetic and sensory inputs as well as mast cells, and changes in the structure of the blood vessels. Such an inflammation-prone state has a well-known effect on the BBB leakage. However, when comparing sham-exposed sympathectomised rats to GSM-exposed sympathectomised rats, a remarkable increase in albumin leakage was present in the GSM exposed sympathectomised rats compared to the sham rats. **In the GSM-exposed sympathectomised rats, both brain areas and the dura mater showed levels of albumin leakage resembling those observed in positive controls after osmotic shock.**[emphasis added] Indeed, more attention should be paid to this finding, since it implicates that the sensitivity to EMF-induced BBB permeability depends not only on power densities and exposure modulations, but also on the initial state of health of the exposed subject.” (Salford, Nittby, and Persson 2012)*

This dramatically greater impact on an autonomically and immunologically vulnerable set of animals raises concerns since the vulnerabilities of these animals bear some resemblance to the pathophysiological challenges of individuals with ASDs.

The interconnection between stress and brain connectivity (or coherence) in ASDs is brought out by Narayanan et al. (2010) in a pilot study testing the impact of the beta blocker propranolol on brain functional connectivity measured using functional MRI (Narayanan et al. 2010). A fairly immediate increase in functional connectivity was noted from propranolol – but not from nadolol which has the same vascular effects but does not cross the BBB. Propranolol decreases the burden of norepinephrine, thereby reducing the impact of stress systems on brain processing, and the authors interpreted these effects as creating an improvement of the brain’s signal-to-noise ratio (Hasselmo, 1997 #2594), allowing it to utilize and coordinate more remote parts of its networks. This suggests that stressors such as EMF/RFR, by adding non-biologically meaningful noise to the system, might have the opposite effects, degrading coherent integration.

C. DE-TUNING OF THE BRAIN AND ORGANISM

1. Electromagnetic signaling, oscillation and synchrony are fundamental, and vulnerable

While electrophysiological activity is an intrinsic property of the nervous system, electromagnetic signaling are vital parts of every cell and of molecular structure.

“All life on earth has evolved in a sea of natural low-frequency electromagnetic (EM) fields. They originate in terrestrial and extraterrestrial sources. The ever-growing use of electric power over the last century has sharply modified this natural environment in urban environments. Exposure to power-frequency fields far stronger than the natural environment is now universal in civilized society.”
(Adey 1994)

Adey published some of the earliest scientific studies on the “cooperativity” actions of cells in communication. Studies showing us that the flux of calcium in brain tissue and immune cells is sensitive to ELF-modulated radiofrequency fields is actually telling us that some of the most fundamental properties of cells and thus of our existence can be modulated by EMF/RFR.

*“...in first detection of environmental EM fields in tissues, there appears to be a general consensus that the site of field action is at cell membranes. Strands of protein are strategically located on the surface of cells in tissue, where they act as detectors of electrical and chemical messages arriving at cell surfaces, transducing them and transmitting them to the cell interior. The structural basis for this transductive coupling by these protein strands is well known. Through them, cell membranes perform a triple role, in **signal detection, signal amplification, and signal transduction to the cell interior.**”* (Adey 1994)
Communication between cells through gap junctions, which is a means of “metabolic cooperation,” is also vulnerable to disruption, as discussed earlier.

Oscillation is also a universal phenomenon, and biological systems of the heart, brain and gut are dependent on the cooperative actions of cells that function according to principles of non-linear, coupled biological oscillations for their synchrony, and are dependent on exquisitely timed cues from the environment at vanishingly small levels (Buzsaki 2006; Strogatz 2003). The key to synchronization is the joint actions of cells that co-operate electrically - linking populations of biological oscillators that couple together in large arrays and synchronize spontaneously according to the mathematics described for Josephson junctions (Brian Josephson, the 1993 Nobel prize winner for this concept). This concept has been professionally presented in journal articles and also popularized in a book by Prof. Steven Strogatz, a mathematician at Cornell University who has written

about ‘sync’ as a fundamental organizing principle for biological systems (Strogatz 2001) (Strogatz 2003).

“Organisms are biochemically dynamic. They are continuously subjected to time-varying conditions in the form of both extrinsic driving from the environment and intrinsic rhythms generated by specialized cellular clocks within the organism itself. Relevant examples of the latter are the cardiac pacemaker located at the sinoatrial node in mammalian hearts and the circadian clock residing at the suprachiasmatic nuclei in mammalian brains. These rhythm generators are composed of thousands of clock cells that are intrinsically diverse but nevertheless manage to function in a coherent oscillatory state. This is the case, for instance, of the circadian oscillations exhibited by the suprachiasmatic nuclei, the period of which is known to be determined by the mean period of the individual neurons making up the circadian clock. The mechanisms by which this collective behavior arises remain to be understood.” (Strogatz 2003)

The brain contains a population of oscillators with distributed natural frequencies, which pull one another into synchrony (the circadian pacemaker cells). Strogatz has addressed the unifying mathematics of biological cycles and external factors disrupt these cycles. This also applies to mitochondria:

“Organisation of mitochondrial metabolism is a quintessential example of a complex dissipative system which can display dynamic instabilities. Several findings have indicated that the conditions inducing instabilities are within the physiological range and that mild perturbations could elicit oscillations. Different mathematical models have been put forth in order to explain the genesis of oscillations in energy metabolism. One model considers mitochondria as an organised network of oscillators and indicates that communication between mitochondria involves mitochondrial reactive oxygen species (ROS) production acting as synchronisers of the energy status of the whole population of mitochondria. An alternative model proposes that extramitochondrial pH variations could lead to mitochondrial oscillations.” (Iotti, Borsari, and Bendahan 2010)

The field of bioelectromagnetics has studied exposure to very low levels of electromagnetic frequencies.

These exposures can alter critical properties of chemical reactions. *“In a chemical reaction, the bond breaks and each partner reclaims its electron from the bond, moving away to encounter a new partner. It is now an unattached, highly reactive free radical. Reforming a bond requires a meeting between two radicals with opposite electron spins, the union producing a singlet pair. The*

lifetime of free radicals is typically short, in the range of microseconds to nanoseconds. It is in this brief period that imposed magnetic fields may alter the rate and amount of product of a chemical reaction. Since the effect is only on the kinetics of chemical reactions, they are known as magnetokinetic effects (Steiner and Ulrich, 1989). They occur only in nonthermal states of biomolecular systems, defined as an insensitivity to random thermal interactions during the brief period of their existence (Walleczek, 1994). They are a consequence of a coherent quantum-mechanical step which accompanies free radical formation.” (Adey 1994)

Not just chemical reactions but synchronous biological oscillations in cells (pacemaker cells) can be disturbed and disrupted by artificial, exogenous environmental signals, which can lead to desynchronization of neural activity that regulates critical functions (including metabolism) in the brain, gut and heart and circadian rhythms governing sleep and hormone cycles (Strogatz, 1987). Buzsaki in his book *Rhythms of the Brain* (2006) says “*rhythms can be altered by a wide variety of agents and that these perturbations must seriously alter brain performance.*” (Buzsaki 2006)

Disturbance can get increasingly disruptive as more damage occurs and more systems are thrown out of kilter and out of cooperativity. One can think of the kindling model in which repeated induction of seizures leads to longer and more severe seizures and greater behavioral involvement. The combination of disruptive and stimulatory effects of biologically inappropriate EMF/RFR exposures could contribute to disruption of synchronized oscillation and cooperativity at a myriad of levels but particularly in the brain, and this may contribute to the loss of coherence and complexity in the brain in autism, as well as dysregulation of multiple other bodily systems. Strogatz points out that there are many more ways of being desynchronized than being synchronized {Strogatz, 2003 #1969}. It has even been suggested that autism itself could be due to brain desynchronization {Welsh, 2005 #528}.

2. Behavior as an “emergent property”

Although from a pathophysiological point of view one might hypothesize that a brain with greater indications of oxidative stress along with immune activation and mitochondrial dysfunction might generate different oscillatory activity than a brain in which those pathophysiological features were absent, to date almost no attention has been paid to testing this hypothesis in ASD or neurodevelopmental and neuropsychiatric conditions more generally. From this vantage point it would make sense to propose that the compromised whole body health status of at least many with ASDs would make it harder for them to maintain the resilience of their brain cells and brain activities in the face of potentially disruptive exposures. Yet the investigation of how this might occur remains a largely unexplored frontier. But from the point of view of making sense of the

brain impact of environmental challenges – including but not limited to EMF-RFR – this investigation is crucial.

The pathophysiological perspective that guides this review would suggest a move away from considering the behavioral manifestations of ASDs as core ‘traits,’ *Instead behaviors may be better understood as ‘outputs’ or emergent properties – what the brain and body produce – when their physiological attributes are altered* in these fashions for whatever reasons – be they genetic, environmental or many combinations of both (Anderson 2009, 2008; Sieb 2004; Smith and Thelen 2003; Custodio et al. 2007; Herbert 2012). Sleep and consciousness have also been considered ‘emergent properties’ (Krueger et al. 2008; Krueger and Obal 2003). Brain oscillatory activity is critical for organizing behavior, and it arises from cells and subcellular features that are shaped by the environment and can act differently based on their functional status as well as on account of external sensory or psychosocial stimuli.

In particular, a) brain oscillatory activity is intimately connected with underlying cellular, metabolic and immune status, b) EMF/RFR is capable of perpetrating changes at each of these levels, and c) problems at each of these levels can make other problems worse. And as mentioned earlier, EMF/RFR and various toxicants can co-potentiate damage (Juutilainen and Kumlin 2006; Juutilainen, Kumlin, and Naarala 2006; Verschaeve et al. 2006; Ahlbom et al. 2008; Hoyto et al. 2008; Juutilainen 2008; Luukkonen et al. 2009; Markkanen, Juutilainen, and Naarala 2008), amplifying allostatic load.

Put together, all of this implies that the combination of these EMF/RFR impacts may quite plausibly significantly contribute both to how ASDs happen in individuals and to why there are more reported cases of ASDs than ever before (with studies showing that not all of this increase can be written off as artifact (King and Bearman 2009; Hertz-Picciotto and Delwiche 2009)).

The hopeful side of this framing of the problem comes from moving beyond the increasingly anachronistic idea that autism is determined overwhelmingly by genetic code about which we can do little or nothing. An emerging model that explains much more of what we now know frames ASDs as the dynamic, active outcomes of perturbed physiological processes – again, more like a chronic but changeable ‘state’ than a ‘trait.’ In the latter model, one is empowered to strongly reduce exposures and to make aggressive constructive environmental changes – particularly in diet and nutrition, given their protective potency discussed above (Herbert and Weintraub 2012). In this way allostatic load can be reduced, physiological damage can be repaired, homeostasis can be restored and resilience and optimal function can be promoted.

PART III: IMPLICATIONS

A. SUMMARY

In the above review, the case has been made that ASDs involve physiological challenges at multiple levels, and that these challenges are paralleled in the physiological impacts of EMF/RFR exposure. Evidence has also been presented to suggest that the many levels of damage and degradation of physiological and functional integrity are profoundly related to each other. Although autism spectrum disorders (ASDs) are defined by problems with behavior, communication, social interaction and sensory processing, under the surface they also involve a range of disturbances of underlying biology that find striking parallels in the physiological impacts of electromagnetic frequency and radiofrequency exposures (EMF/RFR). At the cellular and molecular level many studies of people with ASDs have identified oxidative stress and evidence of free radical damage, evidence of cellular stress proteins, as well as deficiencies of antioxidants such as glutathione. Elevated intracellular calcium in ASDs can be associated with genetic mutations but more often may be downstream of inflammation or chemical exposures. Cell membrane lipids may be peroxidized, mitochondria may function poorly, and immune system disturbances of various kinds are common. Brain oxidative stress and inflammation as well as measures consistent with blood-brain barrier and brain perfusion compromise have been documented. Changes in brain and autonomic nervous system electrophysiology can be measured and seizures are far more common than in the population at large. Sleep disruption and high levels of stress are close to universal. In parallel, all of these phenomena have also been documented to result from or be modulated by EMF/RFR exposure. Moreover, some people with ASDs have de novo mutations (that their parents do not have), and EMF/RFR exposures could contribute to this due to their potential genotoxicity. EMF/RFR exposure during pregnancy may send spurious signals to developing brain cells during pregnancy, altering brain development during critical periods, and may increase oxidative stress and immune reactivity that can increase risk for later developmental impairments, with further disruption later in development increasing risk, physiological dysregulation and severity of outcome.

All of this does not prove that EMF/RFR exposures cause autism, but it does raise concerns that they could contribute by increasing risk, and by making challenging biological problems and symptoms worse in these vulnerable individuals. Placed alongside the dramatic rise in reported cases of ASDs, that parallels the dramatic rise in deployment of wireless technologies, a strong case can be made for aggressively investigating links between ASDs and EMR/RFR, and minimizing exposures for people with autism as well as families preconceptionally, during pregnancy, and around infants and children at home, at school, and in health care centers and hospitals.

These arguments have implications for how we understand what ASDs ‘are’ and how they work. These implications call upon us to take the environmental contribution very seriously, which involves on the one hand a sobering appreciation of the vast array of exposures that can contribute to risk via perturbed development and physiological degradation, and on the other hand a sense that there are powerful things we can do to improve the situation.

B. EXPOSURES AND THEIR IMPLICATIONS

Several thousand scientific studies over four decades point to serious biological effects and health harm from EMF and RFR as are intensively reviewed in the many detailed sections of this BioInitiative Report. These studies report genotoxicity, single-and double-strand DNA damage, chromatin condensation, loss of DNA repair capacity in human stem cells, reduction in free-radical scavengers (particularly melatonin), abnormal gene transcription, neurotoxicity, carcinogenicity, damage to sperm morphology and function, effects on behavior, and effects on brain development in the fetus of human mothers that use cell phones during pregnancy. Cell phone exposure has been linked to altered fetal brain development and ADHD-like behavior in the offspring of pregnant mice.

1. Exposures have outpaced precautions

There is no question that huge new exposures to EMF/RFRs have occurred over the past few decades. As discussed extensively in other parts of this Bioinitiative 2012 update {Sage, 2012 #2595}, there is much concern that regulations to date have been based on a very limited sense of the pertinent biology, and particularly that limiting concern to thermal impacts is no longer valid since there is a wealth of evidence by now that non-thermal impacts can be biologically very powerful.

Only in the last two decades have exposures to RFR and wireless technologies become so widespread as to affect virtually every living space, and affect every member of societies around the world. Even as some disease patterns like brain tumors from cell phone use have become ‘epidemiologically visible’, there are no comprehensive and systematic global health surveillance programs that really keep up to report EMF/RFR health trends (Fragopoulou et al. 2010).

“The deployment of new technologies is running ahead of any reasonable estimation of possible health impacts and estimates of probabilities, let alone a solid assessment of risk. However, what has been missing with regard to EMF has been an acknowledgement of the risk that is demonstrated by the scientific studies. There is clear evidence of risk, although the magnitude of the risk is uncertain, and the magnitude of doing nothing on the health effects cost to society is similarly uncertain. This situation is very similar to our history of dealing with

the hazards of smoking decades ago, where the power of the industry to influence governments and even conflicts of interest within the public health community delayed action for more than a generation, with consequent loss of life and enormous extra health care costs to society.” (Sage and Carpenter 2009).

2. The population’s exposure has increased

Given the range of physiological impacts described in Part 2, the very rapid global deployment of both old and new forms of emerging wireless technologies in the last two decades needs aggressive evaluation from a public health perspective.

In the United States, the deployment of wireless infrastructure (cell tower sites) to support cell phone use has accelerated greatly in the last decades. The Cellular Telephone Institute of America (CTIA) estimated that in 1997 there were only 36,650 cell sites in the US; but increased rapidly to 131,350 in June 2002; 210,350 in June 2007 and 265,561 in June 2012 {Roche, 2012 #2614; Cellular Telephone Industry of America (CTIA), 2012 June #2615}. About 220,500 cell sites existed in 2008 {Reardon, 2007 #2613} {Cellular Telephone Industry of America (CTIA), 2012 June #2615} {Anonymous, 2005 May 20 #2618}. These wireless facilities for cellular phone voice and data transmission produce RFR over broad areas in communities and are an involuntary and unavoidable source of radiofrequency radiation exposure. Other new RFR exposures that didn’t exist before are from WI-FI access points (hotspots) that radiate 24/7 in cafes, stores, libraries, classrooms, on buses and trains, and from personal WI-FI enabled devices (iPads, tablets, PDAs, etc).

Not surprisingly, the use of cell phones has a parallel growth trend. In the late 1980s and early 1990’s, only a few percent of the US population were cell phone users. By 2008, eighty-four percent (84%) of the population of the US owned cell phones [16]. CTIA reports that wireless subscriber connections in the US increased from 49 million in June 1997 to 135 million in June 2002 to 243 million in June 2007 to 322 million in June 2012 {Roche, 2012 #2614; Cellular Telephone Industry of America (CTIA), 2012 June #2615}. This represents more than a 100% penetration rate in the US consumer market, up from just a few percent in the early 1990’s. The number of wireless subscribers in June 1997 was 18%; in June 2002 it was 47%; in June 2007 it was 81% and in June 2012 it is 101%.

The annualized use of cell phones in the US was estimated to be 2.23 trillion minutes in 2008 [16] and 2.296 trillion minutes in 2010 (CITA, 2012). There are 6 billion users of cell phones world- wide in 2011 up from 2.2 billion in 2008 [17] and many million more users of cordless phones.

The number of US homes with *only* wireless cell phones has risen from 10.5% in 2007 to 31.6% in June of 2012 {Roche, 2012 #2614; Cellular Telephone Industry of America

(CTIA), 2012 June #2615}. There are no statistics for June 1997 nor for June 2002, since landline (non-wireless) phone use predominated. The shift to wireless communications, more minutes of use, and reliance on cell and cordless phones rather than corded phones is an extremely revealing measure of new EMF and RFR exposures for both adults and children.

3. Infants, children and childbearing families are highly exposed and vulnerable

With regard to children, the spread of cell towers in communities, often placed on pre-school, church day-care, and school campuses, means that young children may have hundreds of thousands of times higher RF exposures in home and school environments than existed even 20-25 years ago. In addition, the nearly universal switch to cordless and cell phones, and away from corded landline phones, means close and repetitive exposures to both EMF and RFR in the home. Wireless laptops and wireless internet in schools, and home offices and for homework mean even more chronic exposures to RFR, a designated IARC 2B Possible Human Carcinogen {International Agency for Research on Cancer of the World Health Organization, 2011 May #2616} {Baan, 2011 #2598} . The great utility of handheld devices as communication aids and sources of information and satisfaction for people on the autism spectrum may come with a concerning underbelly.

Exposures prior to conception or during pregnancy and infancy are also important to consider. These exposures can come from faulty wiring, proximity to power lines, or high-frequency transients from a proximate transformer on a utility pole, or internal sources of pulsed RFR in the home (examples include an electronic baby monitor in the crib, a wireless router in the next room, a DECT phone that pulses high emissions of RFR on a continuous basis 24/7, or conversion to all compact fluorescent bulbs that produce significant 'dirty electricity' for occupants due to low-kilohertz frequency fields on electrical wiring and in ambient space. Sick and vulnerable infants in neonatal intensive care units are heavily exposed from being surrounded by equipment, with negative metabolic and autonomic consequences documented and other likely consequences needing further investigation (Bellieni et al. 2008; Bellieni, Tei, et al. 2012).

Wireless phones and laptops exposures produce extremely low frequency pulses from the battery of the wireless device {Sage, 2007 #2611} (Sage and Carpenter 2009) and the exposures to pulsed radiofrequency microwave radiation when the wireless device is transmitting or receiving calls and emails.

Especially since EMF/RFR exposures are already classified as IARC 2B Possible Human Carcinogens, we should be actively investigating these sources of damage to DNA that could reasonably result in 'de novo mutations' but also be aware that common

environmental exposures from EMF and RFR might play a role in the higher rates of concordance for autism (ASD) among twins and siblings.

Researchers also should be aware that common environmental exposures from EMF and RFR might play a role in the higher rates of autism (ASD) among twins and siblings, not solely because of maternal use of wireless devices during pregnancy and paternal sperm exposure to wireless devices peri-conception; but also because such oxidative damage to DNA can occur at levels introduced into the world of the fetus, and young developing infant and child via baby surveillance monitoring devices in the crib and wireless devices in the home. The deployment of technologies poses risks to human fertility and reproduction capacity, to the fetus, to children and adults (Sage and Carpenter 2009).

4. ASD Risk and Genomic Damage to Future Generations

Barouki and Grandjean (2012) make a persuasive case that public health interventions are critically needed in early childhood development to prevent adult diseases that appear decades later (Barouki et al. 2012). Although they do not include EMF or RFR but only chemicals, they do say that physiological stressors, which EMF and RFR certainly have been established to be, should be reduced during critical development windows. They say: *“The current pandemic of non-communicable diseases and the increased prevalence of important dysfunctions demand an open interrogation of why current interventions appear insufficient. We now know that disease risk can be induced very early in the life course and that it is modifiable by nutrients and environmental chemical exposures (along with drugs, infections, and other types of stresses)”*.

Part II of this chapter documents the detailed scientific basis for considering EMF/RFR exposures to be of significance to the ASDs crisis. Public health interventions are warranted now to protect the genetic heritage of humans, as well as the other stocks of genetic material in wildlife and plants in the face of what appears to be on-going impairment of these genomes. The risk of genomic damage for future generations is sufficiently documented to warrant strong preventative action and new public safety limits that observe EMF/RFR levels shown to cause adverse effects.

5. De-Tuning the Organism

Genetic mutations may lead to cancer and other diseases in the present and future generations, but the exposures that are capable of creating genotoxic impacts also compromise physiological function. Even genotoxicity can have not only specific but also non-specific effects due to inefficiencies, misfolded proteins, and cellular debris, as discussed in the section “Implications of Damage” at the end of the first part of Part II, regarding the rescue of a mouse model of Rett syndrome through enabling a probably generic process of microglial phagocytosis, critical to debris removal, rather than through

correcting some specific molecular defect of the synapse (Derecki et al. 2012; Derecki, Cronk, and Kipnis 2012).

In the present setting, where the argument about the pertinence of the cascade of physiological and genotoxic compromises to autism includes the degradative impact on oscillatory synchronization, it is also worth considering that oscillation is a property of living and even physical systems much more generally, and not just of brain oscillatory networks (Strogatz 2003). Under certain circumstances, phase transitions occur and synchronization emerges, often rather quickly rather than gradually – more like a state change than a gradual trend. On the other hand, as mentioned, synchronization can be lost, and there are an enormous number of ways for a system to be de-synchronized, which may relate to the heterogeneity amongst people with ASD that so vexes researchers.

In the setting of autism, a baby gestated or developing as a neonate in a milieu with excessively elevated EMF/RFR exposures is bound to have interference with the normal development processes, including the organization of information and experience in the brain. This baby's environment also often nutritional insufficiencies (processed denatured pesticide-laden food low in antioxidants, minerals and essential fatty acids essential to cellular protection). The baby's gestational period may have been complicated by the mother's own health issues such as conditions like obesity and diabetes {Krakowiak, 2012 #2617} which converge on inflammation, oxidative stress and other common forms of physiological dysregulation associated with or even just eating nutrient-depleted, pesticide-laden processed food. The exquisite 'tuning up' of the brain and body as it develops will integrate and respond to the environmental inputs it receives, and is particularly sensitive to environmental miscues (whether chemical like endocrine disruptors, EMF/RFR, or other hostile environmental conditions whether hostile or nurturing). To the extent that the baby is burdened with more disorganized or hostile cues than nurturing and organizing cues, that baby may lose resiliency and become more physiologically vulnerable –perhaps approaching a tipping point into decompensation.

From a systems point of view, the phenomenon of 'autistic regression' may occur after an accumulation of multisystem signaling interference leading to a tipping point of loss of some vital systems synchronization and increase in randomization. EMF/RFR exposures could plausibly contribute both to this vulnerability and to the decompensation/desynchronization process – as could other stressors such as infection, toxicity, acute stress. The vulnerability, then, is the 'allostatic load' – the total burden of stressors pressing toward disorganization. The tipping point may come in a variety of ways but upon investigation one is likely to find that unless it is a severe stressor it is not triggered simply by a single source of stress in an otherwise blissfully healthy child, but rather is the "straw that breaks the camel's back" laid atop a prior accumulation of 'allostatic load.'

C. CONCLUSIONS AND RECOMMENDATIONS

1. Change our deployment of EMF/RFR

The deployment of RFR from wireless technologies has incredible momentum, and it has made many things easier and many other things possible for the first time. On the other hand this momentum can interfere with setting up the technology in a fashion truly respectful of biological tolerances. Other sections in the Bioinitiative 2012 update will address recommendations and guidelines for increasing the safety profile. This will undoubtedly provoke controversy. The problems will not get settled immediately, and transformation to healthier arrangements will take time.

“There is no question that global implementation of the safety standards proposed in the Bioinitiative Report, if implemented abruptly and without careful planning, have the potential to not only be very expensive but also disruptive of life and the economy as we know it. Action must be a balance of risk to cost to benefit. The major risk from maintaining the status quo is an increasing number of cancer cases, especially in young people, as well as neurobehavioral problems at increasing frequencies. The benefits of the status quo are expansion and continued development of communication technologies. But we suspect that the true costs of even existing technologies will only become much more apparent with time. Whether the costs of remedial action are worth the societal benefits is a formula that should reward precautionary behavior.” (Sage and Carpenter 2009)

2. Encourage precautions right now based on present knowledge

In the meantime many people have already started taking precautionary measures, and more will wish to do so. Physicians and health care people should raise the visibility of EMF/RFR as a plausible environmental factor in clinical evaluations and treatment protocols. Reducing or removing EMF and wireless RFR stressors from the environment is a reasonable precautionary action given the overall weight of evidence.

- Children with existing neurological problems that include cognitive, learning, attention, memory, or behavioral problems should as much as possible be provided with wired (not wireless) learning, living and sleeping environments,
- Special education classrooms should aim for 'no wireless' conditions to reduce avoidable stressors that may impede social, academic and behavioral progress.
- All children should reasonably be protected from the physiological stressor of significantly elevated EMF/RFR (wireless in classrooms, or home environments).
- School districts that are now considering all-wireless learning environments should be strongly cautioned that wired environments are likely to provide better learning and teaching environments, and prevent possible adverse health consequences for both students and faculty in the long-term.

- Monitoring of the impacts of wireless technology in learning and care environments should be performed with sophisticated measurement and data analysis techniques that are cognizant of the non-linear impacts of EMF/RFR and of data techniques most appropriate for discerning these impacts.
- There is sufficient scientific evidence to warrant the selection of wired internet, wired classrooms and wired learning devices, rather than making an expensive and potentially health-harming commitment to wireless devices that may have to be substituted out later, and
- Wired classrooms should reasonably be provided to all students who opt-out of wireless environments.

Undoubtedly risks and the above recommendations will be dismissed by those poised to benefit from the sale of these new systems. Many people also feel that new possibilities have opened up to themselves and the world through wireless technologies. But the public needs to know that these risks exist, that transition to wireless should not be presumed safe, and that it is very much worth the effort to minimize exposures that still provide the benefits of technology in learning, but without the threat of health risk and development impairments to learning and behavior in the classroom.

Broader recommendations also apply, related to reducing the physiological vulnerability to exposures, reduce allostatic load and build physiological resiliency through high quality nutrition, reducing exposure to toxicants and infectious agents, and reducing stress (Herbert and Weintraub 2012), all of which can be implemented safely based upon presently available knowledge.

3. Build an environmentally physiologically centered research program in ASDs as a platform for investigating the EMR/RFR-ASD linkage

This review has been structured around the physiological parallels between ASDs and the impacts of EMF/RFR. What is missing from the autism research agenda is some cross-study of these two bodies of research evidence. To do this we will need both a recognition of the importance of these risks, and a collaborative multi-site research program centered around a “middle-out” physiological approach that can incorporate the the gene-brain-behavior agenda that has dominated ASD research into a broader framework (Herbert 2013). While the middle-out approach is an emerging framework in systems biology that can incorporate complexity and nonlinear, multileveled modeling (Cristofolini et al. 2008; de Graaf et al. 2009; Majumder and Mukherjee 2011; Vinga et al. 2010; Walker and Southgate 2009), the gene-brain-behavior approach has been based on an expectation of linear mapping across the levels on which it focuses, but instead the systems involved appear to be much more complex, and the physiological levels largely

left out of this linear approach are critically important to helping people with ASDs because they will help not only with understanding how environment impacts function but also with identifying leverage points.

4. Take the evidence as a call to action

Both EMF and RFR exposures are already classified as IARC 2B Possible Human Carcinogens. The substantial scientific literature on EMF and RFR effects on DNA, on immune and blood-brain barrier disruption, on stress proteins, on circadian rhythms and hormone dysregulation, and on cognition, sleep, disruption of neural control and altered brainwave activity all argue for reduction of exposures now, and better coordinated research in these areas.

All relevant environmental conditions should be given weight in defining and implementing prudent, precautionary actions to protect public health, including EMF and RFR. Evidence is sufficient to add EMF/RFR prominently to the list of exposures that can degrade the human genome, and impair normal development, health and quality of our physiology. With the rising numbers people with ASDs and other childhood health and developmental disorders, we cannot afford to ignore this component of risk to our children and vulnerable populations. When the risk factors are largely avoidable or preventable, ignoring clear evidence of large-scale health risks to global populations poses unnecessary and unacceptable risks. Taking this evidence as a call to action will be challenging and disruptive in the short term, but constructive in the longer term as we learn to use EMF/RFR in healthier ways.

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BioInitiative-Neurological; Percent Comparison, Effect vs No Effect
in Neurological Effect Studies; 2019

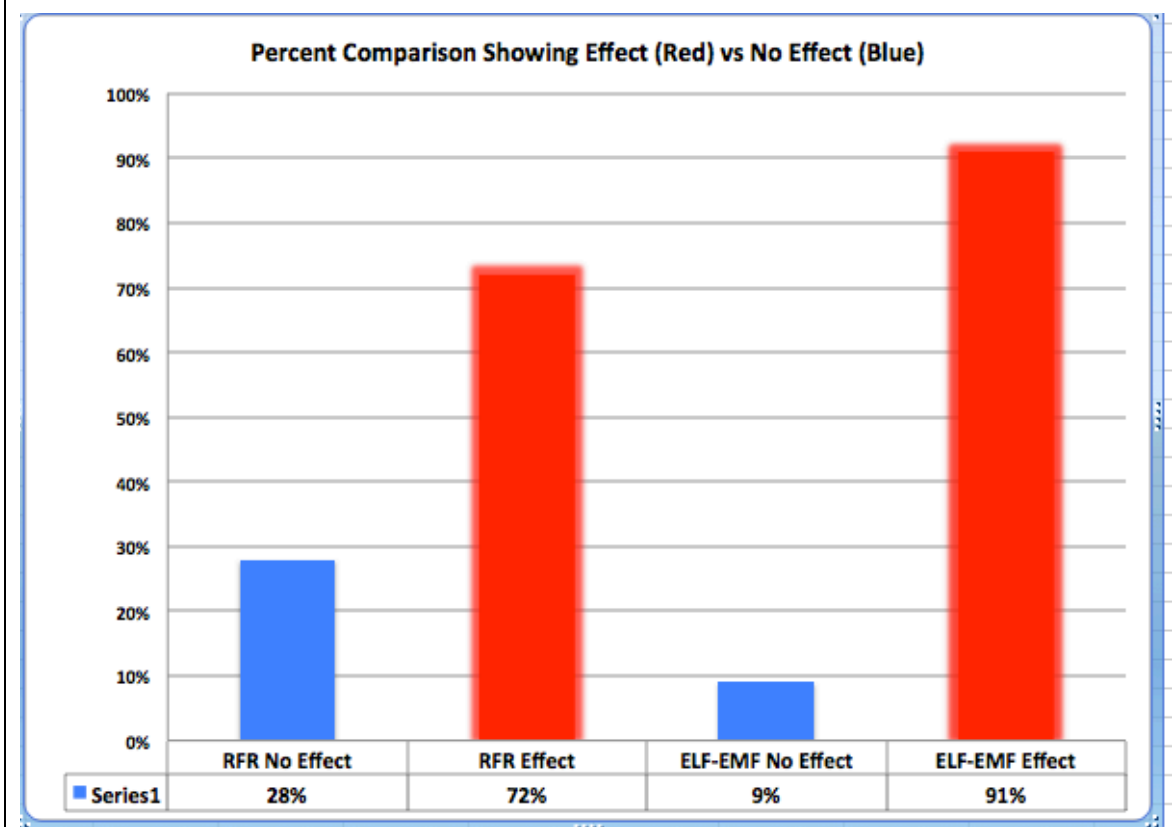
Percent Comparison Showing Effect vs No Effect in Neurological Effect Studies**BioInitiative Report Research Summaries Update,****August 2019****Chapter 8, Neurological Effects****Neurological Effects of Radiofrequency Radiation**

Of 305 total studies: (E= 222 (72%); NE= 83 (28%))

Neurological Effects of Static Fields and ELF-EMF

Of 229 total studies: (E= 208 (91%); NE= 21 (9%))

(E = reported effect; NE = reported no significant effect)



BioInitiative-Neurological; Research Summaries, RFR Neurological
Effects (Section 8), 2007-2017; 2017

October, 2017

Neurological effects of nonionizing electromagnetic fields

Introduction

Neurological effects are caused by changes in the nervous system. Factors that act directly or indirectly on the nervous system causing morphological, chemical, or electrical changes in the nervous system can lead to neurological effects. The final manifestation of these effects can be seen in psychological changes, e.g., memory, learning, and perception. The nervous system is an electrical organ. Thus, it should not be surprising that exposure to electromagnetic fields could lead to neurological changes. Morphological, chemical, electrical, and behavioral changes have been reported in animals and cells after exposure to nonionizing electromagnetic fields (EMF) across a range of frequencies. The consequences of physiological changes in the nervous system are very difficult to assess. We don't quite understand how the nervous system functions and reacts to external perturbations. The highly flexible nervous system could easily compensate for external disturbances. On the other hand, the consequence of neural perturbation is also situation-dependent. An EMF-induced change in brain electrical activity, for instance, could lead to different consequences depending on whether a person is watching TV or driving a car.

The following is a summary of the research literature on the neurological effects of EMF exposure published between 2007-2014. The literature on radiofrequency and extremely-low frequency EMFs are placed in two separate sections. Each section has a discussion and a list of publications with abstracts. Summary sentences in the abstracts are underlined for reader convenience. Where additional information is relevant, some earlier papers, or papers not specifically related to neurological effects, are also included with citations contained within the discussion.

In this paper, as in the update paper on genetic effects, analyses show that there are more publications showing effects than no effects with the recent neurological literature. With E representing a biological effect, and NE representing no biological effects, the recent literature finds RFR-neurological effects at: E=222 publications (72%); NE=83 publications (28%); and ELF-neurological effects at: E=117 (89%); NE=14 (11%).

Section 1: Neurological effects of Radiofrequency Radiation (RFR) (2007-2017)

Discussion

- (1) There are many new studies on human subjects. Many of them are on changes in brain electrical activities after acute exposure to cell phone radiation. Bak et al (2010) reported effects on event-related potentials. Maganioti et al. (2010) further reported

that RFR affected the gender-specific components of event-related potentials (see also Hountala et al., 2008). Croft et al (2008) reported changes of the alpha-wave power of EEG. The same authors (Croft et al., 2010) further reported that effects differed between various new cell phone transmission systems, which have different signaling characteristics. They observed effects after exposure to second generation (2G), but not third generation (3G) radiation, whereas Leung et al. (2011) found similar EEG effects with both 2G and 3G radiations. Ghosn et al. (2015) also reported GSM EMF affected alpha band of resting human EEG. Lustenberger et al. (2013) found increased slow-wave activity in humans during exposure to pulse-modulated RF EMF toward the end of the sleep period. Vecchio and associates reported that cell phone RFR affected EEG and the spread of neural synchronization conveyed by interhemispherical functional coupling of EEG rhythms (Vecchio et al., 2007) and enhanced human cortical neural efficiency (Vecchio et al., 2012a). Naziroglu et al. (2009) reported a significant change in cortical EEG spikes in rats after chronic RFR exposure. RFR exposure modulated the spontaneous low frequency fluctuations in some brain regions (Lv et al., 2013) and the synchronization patterns of EEG activation across the whole brain (Lv et al., 2014) in humans. An interesting finding is that RFR could interact with the activity of brain epileptic foci in epileptic patients (Tombini et al., 2012; Vecchio et al., 2012b). However, no significant effect on EEG was reported by Parentos et al. (2007) or Trunk et al. (2013, 2014), and Kleinlogel et al. (2008 a, b) also reported no significant effects on resting EEG and event-related potentials in humans after exposure to cell phone RFR. Roggeveen et al. (2015 a,b) reported significant changes in several bands of human EEG and detection of radiation peaks when exposed to the RFR from a 3G mobile phone. These effects were observed only when the phone was placed on the ear, and not on the heart. Yang et al. (2016) reported a reduction in spectral power in the alpha and beta bands in the frontal and temporal cortical regions of humans exposed to LTE cell phone radiation. Furthermore, Krause et al. (2007) reported no significant effect of cell phone radiation on brain oscillatory activity, and Inomata-Terada et al. (2007) concluded that cell phone radiation does not affect the electrical activity of the motor cortex.

- (2) There are studies on the interaction of cell phone radiation on EEG during sleep. Changes in sleep EEG have been reported by Hung et al. (2007), Regel et al. (2007), Lowden et al (2011), Schmid et al. (2012), and Loughran et al. (2012), whereas, no significant effect was reported by Fritzer et al (2007), Mohler et al. (2010, 2012) and Nakatani-Enomoto et al. (2013). Loughran et al. (2012) provided an interesting conclusion in their paper: "These results confirm previous findings of mobile phone-like emissions affecting the EEG during non-REM sleep. Importantly, this low-level effect was also shown to be sensitive to individual variability. Furthermore, this indicates that "previous negative results are not strong evidence for a lack of an effect..." More recently, Lustenberg et al. (2015) reported RFR-exposure-related increases in delta-theta EEG frequency range in several fronto-central brain areas in humans during nREM sleep. Increase in REM sleep (Pelletier et al., 2012) and increases in duration and frequency of slow-wave sleep (Pelletier et al., 2014) have been reported in developing rats after chronic RFR exposure. Mohammed et al. (2013) reported a disturbance in REM

sleep EEG in the rat after long term exposure (1 hr/day for 1 month) to a 900-MHz modulated RFR.

- (3) With these electrophysiological changes in the brain, what behavioral effects have been reported? The outcomes are summarized in the tables below. The animal studies are mostly studies on rodents (i.e., rat and mouse).

Human studies that showed behavioral effects:

	Behavior studies/results	Exposure duration
Danker-Hopfe et al. (2015)	Sleep of individuals can be affected differently- showing both improvements and deteriorations.	During sleep
de Tommaso et al. (2009)	Reduction in behavioral arousal	10 min
Deniz et al. (2017)	Poorer attention in high exposure group	Low (<30 min/day) vs high (>90min/day) mobile phone exposure
Hung et al. (2007)	Sleep latency	30 min
Leung et al. (2011)	Cognitive functions	10 min
Luria et al. (2009)	Spatial working memory (In a subsequent study (Hareuveny et al., 2011), the authors indicated that some of the effects observed may not be related to RFR exposure.)	60 min
Lustenberger et al. (2013)	Sleep-dependent motor-task performance improvement	All-night
Mortazavi et al. (2012)	Decreased reaction time	10 min
Mortazavi et al. (2013)	Decreased reaction time; poorer short-term memory performance	Occupational exposure to military radar radiation
Movvahedi et al. (2014)	Better short-term memory in elementary school students	10 min

Redmayne et al. (2013)	Well-being	Use of cellphone and cordless phone
Regel et al. (2007)	Cognitive functions	30 min
Schoeni et al. (2015)	A change in memory performance	Based on cumulative duration of wireless phone use and RF-EMF dose over one year
Thomas et al. (2010b)	Overall behavioral problems in adolescents	
Vecchio et al. (2012b)	Enhanced cognitive-motor processes	45 min
Vecsei et al. (2013)	Thermal pain threshold	30 min
Wiholm et al. (2009)	'Virtual' spatial navigation task	150 min
Yogesh et al. (2014)	Sleep disturbance, latency and day dysfunction especially in females	> 2h/day of mobile phone use
Zheng et al. (2014)	Inattention in adolescents	Use of cell phone

Human studies that did not show behavioral effects:

	Behavior studies/results	Exposure duration
Calvente et al. (2016)	No definite conclusion can be drawn on cognitive and behavioral functions of 10-year old boys	Environmental RFR 100 kHz to 6 GHz; root mean square 285.94 $\mu\text{W}/\text{cm}^2$; maximum power density 2759.68 $\mu\text{W}/\text{cm}^2$
Cinel et al. (2007)	Order threshold task	40 min
Cinel et al. (2008)	Subjective symptoms	40 min
Curcio et al. (2008)	Reaction time task, sequential figure tapping task	3 x 15 min
Curcio et al. (2012)	Somatosensory task	40 min
Danker-Hopfe et al. (2011)	Effect on sleep	

Eltiti et al. (2009)	Cognitive functions	50 min
Fritzer et al. (2007)	Sleep and cognitive functions	During sleep
Haarala et al. (2007)	Cognitive functions	90 min
Irlenbusch et al. (2007)	Visual discrimination threshold	30 min
Kleinlogel et al. (2008a)	Well being	30 min
Loughran et al. (2013)	Cognitive effects and EEG	30-60 min
Malek et al. (2015)	Cognitive functions in sensitive humans	Short-term
Mohler et al. (2010, 2012)	Effect on sleep	
Nakatani-Enomoto et al. (2013)	Effect on sleep	3 hr
Redmayne et al. (2016)	Cognitive functions	Use of cellular and cordless phone in 8-11 years old children
Riddervold et al. (2008)	Trail making B test	45 min
Roser et al. (2016)	No change behavioral problem and concentration capacity	Self reported and operator-recorded wireless communication device use
Sauter et al. (2011)	Cognitive functions	7 hr 15 min in two episodes
Sauter et al. (2015)	Cognitive functions and well-being	2.5 hr
Schmid et al. (2012a)	Cognitive functions	30 min
Schmid et al. (2012b)	Cognitive functions	30 min
Trunk et al. (2013)	Automatic deviance detection processes	30 min
Trunk et al. (2014)	Reaction time to a stimulus	15 min
Unterlechner et al. (2008)	attention	90 min
Wallace et al. (2012)	Cognitive functions	10- 50 min (whole body

		exposure)
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Animal studies that showed behavioral effects:

	Behavior studies/results	Exposure duration
Aldad et al. (2012)	Hyperactive, impaired memory	In utero
Arendash et al. (2010, 2012)	Improved cognitive behavior	Daily, 2-6 months
Banaceur et al. (2013)	Improved cognitive functions in mouse model of Alzheimer's disease	2 hr/day for a month
Barthélemy et al. (2016)	Memory, emotionality, and locomotion in plus maze and open field	15 min or 45 min
Bouji et al. (2012)	Contextual emotional behavior deficit	15 min
Cammaerts et al. (2012)	Olfactory and/or visual memory deficit in ants	
Cammaerts et al. (2013)	Change in food collection behavior in ants	180 hr
Cammaerts et al. (2014)	Changes in locomotor and general behaviors in ants	Repeated 10 min exposure
Choi and Choi (2016)	Delayed hyperactivity-like behavior	9-11 weeks
Daniels et al. (2009)	Decreased motor activity	
Deshmukh et al. (2013)	Impaired cognitive functions	2 hr/day, 30 days
Deshmukh et al. (2015)	Impaired cognitive functions	2 hr/day, 180 days
Deshmukh et al. (2015)	Impaired cognitive functions	2 hr/day. 90days
Fragopoulou et al. (2010)	Spatial memory deficit	2 hr/day, 4 days
Hao et al. (2012)	Learning and memory deficit	6 hr/day, 5 days/wk, 10 wk

Hassanshahi et al. (2017)	Impaired object recognition	12 hr/day. 30 days
Hu et al. (2014)	Spatial memory deficit	15 min/day, 14 days
İkinci et al. (2013)	Learning behavior deficit	Prenatal exposure
Júnior et al. (2014)	Stress behavioral patterns	25 sec every 2 min for 3 days
Kim et al. (2017)	Hyperactivity-like behavior	5 hr/day for 12 weeks
Kumar et al. (2009)	hypoactivity	50 missed call/day, 4 wk
Kumlin et al. (2007)	Improved learning and memory	2 hr/day. 5 days/wk, 5 wk
Lee and Yang (2014)	Increased anxiety-like behavior	Continuously during embryonic development of medakas
Lee et al. (2015)	Fish locomotor activity after feeding	RFR from a cell phone
Li et al. (2014)	Spatial learning and memory deficits	6 min 3 times a week up to 6 weeks
Lu et al. (2012)	Spatial memory deficit	3 hr/day, 30 days
Maaroufi et al. (2013)	Spatial learning and memory deficit	1 hr/day, 21 days
Mathur (2008)	Analgesic effect	2 hr/day, 45 days
Megha et al. (2012)	Cognitive functions	2 hr/day, 30 days
Mohammed et al. (2013)	Increased latency of REM sleep	1 hr/day for 1 month
Narayanan et al. (2009)	Learning deficit	50 missed call/day, 4 wk
Narayanan et al. (2010)	Passive avoidance deficit	50 missed call/day, 4 wk
Narayanan et al. (2012)	Elevated plus maze-emotionality test deficit	1 hr/day for 28 days
Narayanan et al. (2015)	Spatial memory deficit	1 hr/day for 28 days
Nirwane et al. (2016)	Change in social behavior, anxiety behavior, learning	1 hr/day for 14 days

	impairment	
Nittby et al. (2008)	Reduced memory functions	2 hr/wk, 55 wk
Ntzouni et al. (2011)	Non-spatial memory deficit	90 min/day, 17 days
Ntzouni et al. (2013)	Spatial and non-spatial memory deficit	90 min/day, 66-148 days
Odacı et al. (2013)	Motor function	Prenatal exposure
Othman et al. (2017)	Deficits in neuromotor maturation mainly in male offspring	Prenatal exposure
Pelletier et al. (2012)	Food intake increase; sleep parameters; increase food intake	5 weeks (23.5 hr/day)
Pelletier et al. (2014)	Preferred to sleep in a different temperature environment than controls; sleep parameters	5 weeks (23.5 hr/day)
Qiao et al. (2014)	Spatial memory deficit	5 min
Qin et al. (2014)	Learning and memory deficits	2 hr/day, 30 days
Razavinasab et al. (2014)	Learning and memory deficits	In utero
Saikhedkar et al. (2014)	Learning and memory deficits	4 hr/day, 15 days
Sarapultseva et al. (2013)	Motor activity in protozoa	0.05-10 hr
Schneider and Stangassinger (2014)	Social memory effect	Life-long up to 6 months
Sharma et al. (2013)	Spatial memory deficit	2 hr/day, 30 days
Sharma et al. (2017)	Spatial memory deficit	2 hr/day, 15 days
Shehu et al. (2015)	Anxiety-like behavior	10 min call per day for 4 weeks
Sokolovic et al. (2012)	Anxiety-related behavior	4 hr/day for 20, 40, 60 days
Tang et al. (2015)	Spatial long-term memory deficit	3 hr/day for 28 days

Vácha et al. (2009)	Magnetoreception in cockroach	
Wang et al. (2013)	Spatial memory deficit	6 min
Wang et al. (2014)	Spatial learning and memory deficits	6 min
Wang et al. (2017)	Increased recognition memory	30 min
Zhang et al. (2014)	Increased anxiety-related behavior; memory and learning deficits in male offsprings.	In utero exposure

Animal studies that did not show behavioral effects:

	Behavior studies/results	Exposure duration
Ammari et al. (2008c)	spatial memory	15 min/day, 8 or 24 wk
Fasseas et al. (2014)	Chemotaxis, short-term memory	Various lengths of time
Haghani et al. (2013)	Motor function	6 hr/day during gestation period
Shirai et al. (2014)	Spatial memory and motor functions	Multi-generation

Almost all the animal studies reported effects, whereas more human studies reported no effects than effects. This may be caused by several possible factors: (a) Humans are less susceptible to the effects of RFR than are rodents. (b) It may be more difficult to do human than animal experiments, since it is, in general, easier to control the variables and confounding factors in an animal experiment. (c) In the animal studies, the cumulative exposure duration was generally longer and studies were carried out after exposure, whereas in the human studies, the exposure was generally one time and testing was done during exposure. This raises the question of whether the effects of RFR are cumulative. This consideration could have very important implication on real life human exposure to EMF. However, it must be pointed out that neurophysiological and behavioral changes have been reported in both animals and humans after acute (one time) exposure to RFR, and most of the EEG studies mentioned above are acute exposure experiments. (In the 2007-2014 papers listed below, see those marked '(E)'

and not classified as 'CE'). (d) In the animal studies, the effects studies were mostly learning and memory functions. The hippocampus in the brain, particularly the cholinergic system, plays a major role in learning and memory functions. Various studies indicated that RFR affected electrical activities/morphology/chemistry of the hippocampus in animals (Aboul Ezz et al., 2013; Ammari et al., 2010; Barcal et al., 2007; Barthélémy et al., 2016; Baş et al., 2009, 2013; Carballo-Quintas et al., 2011; Choi and Choi, 2016; Erdem Koç et al., 2016; Fragopoulous et al., 2012; Gökçek-Saraç et al., 2017; Hao et al., 2012; Hassanshahi et al., 2017; Hu et al., 2014; İkinci et al., 2013; Kesari et al., 2011; Kim et al., 2016; Li et al., 2014; Lopez-Martin et al., 2009; Lu et al., 2012; Maskey et al., 2010 a,b, 2012; Megha et al., 2015; Mugunthan et al., 2016; Narayanan et al., 2010, 2015; Ning et al., 2007; Nittby et al., 2008; Odaci et al., 2008; Razavinasab et al., 2014; Şahin et al., 2015; Saikhedkar et al., 2014; Sharma et al., 2017; Tang et al., 2015; Tong et al., 2013; Wang et al., 2013, 2014; Wang H. et al., 2017; Wang K. et al., 2017; Xiong et al. 2015; Xu et al., 2017; Yang et al., 2012). (Reports on effects of the hippocampus can also be found in the ELF section below). As early as 1987, we have reported that RFR affected cholinergic system in the hippocampus of the rat (Lai H, Horita A, Chou CK, Guy AW. Low-level microwave irradiation affects central cholinergic activity in the rat. *J Neurochem.* 48:40-45, 1987). Thus, it is not surprising that 'learning and memory' functions are affected in the rodents by RFR. In the human studies listed above, the most common effect studied was cognitive function. Since the exposure in most of these human studies was localized in the brain, particularly in the temporal cortical area, it is questionable whether the psychological tests used were appropriate. Interestingly, there are several reports indicating a beneficial effect of RFR on cognitive functions in animal models of Alzheimer's disease (Arendash et al., 2010, 2012; Banaceur et al., 2013).

- (4) There are studies on the effects of cell phone radiation and the auditory system. Most research (Bhagat et al., 2016; Gupta et al., 2015; Kwon 2009, 2010a, b; Parazzini et al., 2009; Stefanics et al., 2007, 2008) reported no effects, which seems to agree with the pre-2007 studies in this area. However, there are two reports by Kaprana et al. (2011) and Khullar et al (2013) showing effects on auditory brainstem response, two papers by Panda et al (2010, 2011) that concluded: "Long-term and intensive GSM and CDMA mobile phone use may cause damage to cochlea as well as the auditory cortex.", and a paper (Mandala et al., 2013) reporting effect on auditory-evoked cochlear nerve response. Maskey and Kim (2014) reported a decrease in neurotrophins that are important in the regulation of neuron survival in the superior olivary complex, a neural component of the auditory system, in mice after chronic exposure to RFR. Velayutham et al. (2014) reported hearing loss in cell phone users and Sudan et al. (2013) observed weak associations between cell phone use and hearing loss in children at age 7. These effects may not be caused by the radiation. However, there is a study (Seckin et al., 2014) showing structural damage in the cochlea after prenatal exposure to RFR. And, Ozgur et al. (2015) reported neuronal degeneration in the cochlear nucleus of the auditory system in the rat after chronic exposure to RFR. Çeliker et al. (2016) reported no significant change in auditory brainstem responses, but increases in neuronal

degeneration and apoptosis in the cochlear nucleus in rats exposed to a 2100-MHz field for 30 days.

- (5) There are several studies that showed neurological changes in humans after use of wireless devices, but those changes apparently were not caused by exposure to the radiation. Abramson et al. (2009) reported changes in cognitive functions in young adolescents. ("The accuracy of working memory was poorer, reaction time for a simple learning task shorter, associative learning response time shorter and accuracy poorer in children reporting more mobile phone voice calls"). Arns et al. (2007) observed more focused attention in frequent cell phone users, which was probably a "cognitive training effect". Yuan et al. (2011) reported morphological changes in the brain of adolescents with "internet addiction disorder".
- (6) There are several studies showing differential effects of different waveforms. This is an important consideration in understanding how EMF interacts with living organisms and nonthermal effects. Croft et al. (2010) reported that 2G, but not 3G, cell phone radiation affected resting EEG. Hung et al. (2007) showed that 2, 8, 217 Hz-modulated RFR differentially affected sleep. Lopez-Martin et al. (2009) reported that modulated and non-modulated RFR had different effects on gene expression in the brain. Nylund et al. (2010) found that different carrier-frequencies (900 MHz verses 1800 MHz) had different effects on protein expression. Schmid et al. (2012) concluded that "modulation frequency components (of a RFR) within a physiological range may be sufficient to induce changes in sleep EEG". Mohammed et al (2013) reported that EEG power spectrum during REM sleep is more susceptible to modulated RFR than the SWS. Schneider and Stangassinger (2014) reported different effects of 900-MHz and 1.966-GHz EMFs on social memory functions in the rat. Zhang et al. (2008) reported that an intermittent exposure to RFR had a more potent effect on gene expression in the brain than a continuous exposure. Apparently, ELF-modulation plays a role on determining the biological effects of RFR. Indeed, in the following section on the neurological effects of ELF EMF, one can find many studies showing EEG and behavioral effects in animals after exposure to ELF fields (Capone et al., 2009; Carrubba et al., 2007, 2010; Cook et al., 2009; Corbacio et al., 2011; Cvetkovic and Cosic, 2009; Legros et al., 2012; Perentos et al., 2008; Ross et al., 2008; Shafiei et al., 2012, 2014; Shin et al., 2007, 2011; Stevens, 2007). This is of considerable importance, since all cell phone signals are modulated by low frequency components.
- (7) On the neurological effects of RFR, there are several papers indicating that oxidative stress played a role in the effects observed: Akbari et al., 2014; Boderia et al., 2015; Cetin et al., 2014; Dasdag et al., 2009, 2012; Del Vecchio et al., 2009; Deshmukh et al., 2013a; Dragicevic et al., 2011; Eser et al., 2013; Gao et al., 2013; Ghazizadeh et al., 2014; Hidisoglu et al., 2016; Hu et al., 2014; Imge et al., 2010; Jing et al., 2012; Kesari et al., 2011; Kim et al., 2016; Liu et al., 2011; Maaroufi et al., 2013; Megha et al., 2012; Meral et al., 2007; Motawi et al., 2014; Narayanan et al., 2014; Nazıroğlu et al., 2009, 2012; Nirwane et al., 2016; Othman et al., 2017; Qin et al., 2014; Saikhedkar et al., 2014;

Sharma et al., 2017; Shehu et al., 2015; Sokolovic et al., 2009; Xu et al., 2010. (Dragicevic et al. (2011) reported a decrease in mitochondrial free radical production in the hippocampus and cerebral cortex of the mouse after RFR exposure.) There was one study (Poulletier de Gannes et al, 2011) that found no significant oxidative stress in brain cells after exposure to Enhanced Data rate for GSM Evolution (EDGE) signal. Kang et al (2013) reported that “neither combined RF radiation alone nor combined RF radiation with menadione or H₂O₂ influences the intracellular ROS level in neuronal cells.” The mediating roles of cellular free radicals and oxidative status on the biological effects of EMF are worth looking into.

- (8) An important issue that has been extensively debated in the media is whether children are more vulnerable to the effect of cell phone radiation than adults? The claim that children have thinner skulls and thus absorb more energy is not valid. And the claim that a child's head absorbs more energy from a cell phone is also debatable. It is quite possible that the pattern of energy distribution of cell phone energy absorption in the head is significantly different between a child and an adult (cf. Christ A, Kuster N. Differences in RF energy absorption in the heads of adults and children. *Bioelectromagnetics*. Suppl 7:S31-44. 2005; Christ A, Gosselin MC, Christopoulou M, Kühn S, Kuster N. Age-dependent tissue-specific exposure of cell phone users. *Phys. Med. Biol.* 55(7):1767-1783, 2010; Gandhi OP, Morgan LL, de Salles AA, Han YY, Herberman RB, Davis DL. Exposure limits: the underestimation of absorbed cell phone radiation, especially in children. *Electromagn. Biol. Med.* 31(1):34-51, 2012). Scientific data on whether a child is biologically more vulnerable to cell phone radiation is sparse. In the 2007-2014 literature that I surveyed, there are several studies that indicate that animals (including humans) of different ages respond differently to cell phone radiation. Bouji et al. (2012) reported differences in neuro-immunity, stress, and behavioral responses to GSM signals between ‘young adult’ (6 weeks-old) and ‘middle age’ (12 month-old) rats. Croft et al. (2010) showed that GSM signals affected certain electrical activities of the brain in young human adults (19-40 years old) but not in adolescents (13-15 years old) or elderly (55-70 years old) subjects. Leung et al. (2011) reported that performance in a cognitive test was affected by GSM signal in adolescents but not in young or old human subjects. Noor et al. (2011) reported differences in neurochemical responses to 900-MHz RFR between adult and young rats. And, Vecchio et al. (2010) found differences in brain electric activities between young and elderly human subjects responding to GSM signals. It must be pointed out that although these studies reported an age-dependent effect of cell phone radiation, they do not necessarily imply that children are more vulnerable to cell phone radiation than adults. (See also: Sekeroğlu V, Akar A, Sekeroğlu ZA. Cytotoxic and genotoxic effects of high-frequency electromagnetic fields (GSM 1800 MHz) on immature and mature rats. *Ecotoxicol Environ Saf.* 80:140-144, 2012.) There are several papers showing effects of exposure to RFR during perinatal periods on the development and functions of the nervous system (Aldad et al., 2012; Bas et al., 2013; Cetin et al., 2014; Divan et al., 2008, 2011, 2012; Erdem Koç et al., 2016; Gao et al., 2013; Haghani et al., 2013; İkinci et al., 2013; Jing et al., 2012; Kokturk et al., 2013; Lee and Yang, 2014; Odaci et al., 2008, 2013; Ragbetli et al., 2010;

Razavinasab et al., 2014; Zareen et al., 2009; Zhang et al., 2014). The cerebellum seems to be a structure especially vulnerable to the exposure (Eser et al. 2013; Haghani et al., 2013; Kokturk et al., 2013; Ragbetli et al., 2010). Chen et al. (2014) reported that exposure to an 1800-MHz RFR impaired neurite outgrowth of embryonic neural stem cells, which play a critical role in brain development. More recently, Xu et al. (2017) reported that effect of exposure to a 1800-MHz field on stem and progenitor cell proliferation in the hippocampus of mouse depended on the age of the animal.

- (9) In many of these studies, a cell phone was used in the exposure of animals and humans. But information on how the cell phone was activated, in many instances, was not provided. Thus, the amount of energy deposited in the body was not known. Some studies used the phone in 'stand-by' mode. Kjell Mild and his associates reported that when a stationary cell phone is on 'stand-by' mode, it actually infrequently emits a very small amount of energy (Mild KH, Andersen JB, Pedersen GF. Is there any exposure from a mobile phone in stand-by mode? *Electromagn Biol Med.* 31(1):52-56, 2012).
- (10) I think that a few words should be said about 'thermal' and 'nonthermal' effects. It is not easy to conclude that an RFR effect is 'nonthermal', because of the uneven distribution of the energy in the body. On the other hand, it is also not easy to prove that an effect is 'thermal'. There is an important criterion for the proof of 'nonthermal' effect. It is 'modulation effect'. If you expose an animal or cells at the same frequency and SAR (thus, the same distribution and amount of energy) but at different modulations (i.e., energy is delivered with different time sequences) and produce different effects, then it is good proof of a nonthermal effect. Most studies do not include different modulations. Thus, the effects reported by these studies cannot be concluded as 'nonthermal'. There are some studies, however, that reported different biological effects with RFRs of the same frequency and intensity but different modulations (see point #6 above and the section on 'genetic effects', and some of my earlier papers). From these; I would conclude that nonthermal effects probably exist. Another important argument for EMF nonthermal effects is that low-level ELF-EMF can produce biological effects. The energy carried by ELF-EMF is very small and thermal effect is unlikely. (High intensity ELF-EMF can produce electric currents in the body and possibly heating.) The 'thermal/nonthermal' distinction is purely a scientific question. In public exposure policy, we only need to know at what level of exposure an effect occurs. Exposure guideline should be set based on it, and it doesn't matter whether the effect is thermal or nonthermal.

Section 2: Neurological effects of extremely low frequency electromagnetic fields (ELF EMF) (2007-2014)

Discussion

The following is a summary of the research literature on the neurological effects of ELF EMF published in 2007-2014. (In most studies, even only magnetic field was mentioned; there was

no explicit statement that electric fields had been eliminated. In most ELF EMF exposure systems used in laboratory system, electric fields were also generated unless grounding was done. Thus, cells or animals were actually exposed to both magnetic and electric fields.)

1. Neurotransmitters are chemicals that carry (transmit) signals from one nerve cell to another. Neurotransmitters are released from one nerve cell and react with molecules called receptors on another nerve cell. The reaction alters the activity of the second nerve cell. Activities in nerve cell could also change the properties of these receptors (mainly by changing the concentration or the affinity of the receptors to neurotransmitters). In the updated EMF literature, all the studies are on the effects of ELF EMF exposure on neurotransmitter receptors. Manikonda et al. (2007), Li et al. (2014) and Duan et al. (2014) reported effects of chronic ELF EMF exposure on NMDA receptors in the hippocampus of rodents. Salunke et al. (2013) reported that ELF EMF-induced anxiety in the rat involved NMDA receptors in the brain. There is a report on effects of magnetic field serotonin and dopamine receptors in the brain of the rat (Janac et al., 2009). Frilot et al. (2014) reported a change in NMDA receptor-mediated electrical activity in the rat brain after exposure a 60-Hz EMF. Changes in a subtypes of serotonin receptors 5HT(2A) in the prefrontal cortex was reported. However, Masuda et al. (2011) reported that another types of serotonin receptor 5HT (1B) was not significantly affected after magnetic field exposure in an in vitro experiment. The research were trying to replicate two experiments carried out previously showing magnetic field exposure affected 5HT(1B) receptor. Some of the co-authors of the Musuda study were actually co-authors of one of these earlier studies. However, the 5HT (2A) receptors , particularly in the frontal cortex, are believed to be related to the psychiatric syndromes of depression in humans. The serotonergic system is also implicated in the nociceptive effect of static magnetic field (Hernádi and László, 2014). Kitaoka et al. (2013) and Szemerszky et al. (2010) did report depression-like behavior in mice and rats, respectively, after chronic exposure to magnetic fields. There are two reports on dopamine receptors. Shin et al. (2007, 2011) reported an increase in D-1 dopamine receptors and activity in the striatum of the rat after magnetic field exposure. Dopamine in the striatum is involved in Parkinson's disease. Wang et al. (2008) reported that ELF magnetic fields potentiated morphine-induced decrease in D-2 dopamine receptors. The implication of these data is not readily clear. Both D-1 and D-2 dopamine receptors in the brain are involved in depression and drug addiction. Salunke et al. (2014) reported no significant change in serotonin and dopamine levels in the cortex, hippocampus, and hypothalamus of the mouse after chronic exposure to an ELF magnetic field. Level (concentration) of a transmitter usually does not provide much information on the function and activity of a transmitter system. However, these authors observed obsessive compulsive disorder-like behavior in the exposed mice, which could be relate to a change in nitric oxide in the brain. There is one study on the cholinergic system. Ravera et al. (2010) reported changes in the enzyme acetylcholinesterase in cell membrane isolated from the cerebellum after magnetic field exposure. Interesting, these researchers also reported 'frequency window' effects in their experiment. Window effects, i.e., effects are observed at a certain range(s) of EMF frequency or

intensity, were first reported by Ross Adey and Susan Bawin and Carl Blackman in the 1980s. A recently study by Fournier et al. (2012) reported an 'intensity window' effect of ELF magnetic field on neurodevelopment in the rat. The cholinergic systems in the brain play a major role in learning and memory functions. There were a series of studies carried out more than a decade ago showing effects of ELF magnetic field on the cholinergic systems, e.g., Lai and Carino (1999) (60-Hz magnetic field and central cholinergic activity: effects of exposure intensity and duration. *Bioelectromagnetics* 20:284-289, 1999). Not many studies have been carried out in recent years to further investigate the effects of EMF on this important neurological function. Another important neurotransmitter function that has been shown to be affected by magnetic field is the endogenous opioid systems (Hernádi and László, 2014; Murugan and Persinger, 2014).

2. Behavioral effects of ELF EMF have been further substantiated in recent research. These included: changes in locomotor activity (Balassa et al., 2009; Dimitrijevic et al., 2014; Janac et al., 2012; Legros et al., 2012; Murugan and Persinger, 2014; Raus et al., 2012b; Sakhnini et al., 2012; Shin et al., 2007, 2011; Todorovic et al., 2012), learning and memory functions (Che et al., 2007; Corbacio et al., 2011; Cui et al., 2012; Duan et al., 2013; Fournier et al., 2012; Fu et al., 2008; Harakawa et al., 2008; He et al., 2011; Liu et al., 2008b; Sun et al., 2010), anxiety (Balassa et al., 2009; He et al., 2011; Korpınar et al., 2012; Liu et al., 2008a; Salunke et al., 2013); Autism-relevant social abnormalities (Alsaeed et al., 2014), depression-like behavior (Kitaoka et al., 2013; Szemerszky et al., 2011), perception (Ross et al., 2008), cognitive dysfunction (Davanipour et al., 2014), emotional state (Stevens, 2007), sleep quality (Hung et al., 2007; Liu et al., 2014; Monazzam et al., 2014), and comb building in hornets (Ishay et al., 2007). Since different behavioral effects have been observed in different exposure conditions, species of animals, and testing paradigms, they provide the strongest evidence that exposure to ELF EMF can affect the nervous system.
3. In some of these observed neurological effects, oxidative changes (free radicals) again seemed to play a role (Akdag et al., 2010, 2013; Akpınar et al., 2013; Cho et al., 2012; Chu et al., 2011; Ciejka et al., 2011; Deng et al., 2013; Coskun et al., 2009; Cui et al., 2012; Cui et al., 2012; Di Loreto et al., 2009; Duan et al., 2013; Falone et al., 2008; Kantar Gok et al., 2014; Liu et al., 2014; Manikonda et al., 2013; Martinez-Samano et al., 2012; Rauš Balind et al., 2014; Reale et al., 2014; Salunke et al., 2014; Selaković et al., 2013; Tassel et al., 2012a, Turkozer et al., 2008). Increase in free radicals causes cellular damages. Most of these effects are changes in enzymes involved in maintenance of oxidative balance in cells. A paper by Falone et al. (2008) reported an interesting finding. The researchers observed that, after magnetic field exposure, the brain of young rats showed an increase in anti-oxidative enzymes and defense against oxidative damage, whereas that of old rat showed a decrease. Thus, aging may make an individual more susceptible to the detrimental effects of ELF EMF. There are other factors that could affect an animal's response to ELF EMF. Janac et al. (2012) reported age-dependent effects of ELF EMF on locomotor activity in the Gerbils. Reyes-Guerrero et al. (2010)

found that the fields affected olfactory bulb estrogen receptors in female but not in male rats. Sun et al. (2010) reported that, after in ovo (in the egg) exposure to ELF EMF, chicks showed memory deficit only when they were under stress. Indeed, Lahijani et al. (2011) reported histological changes in the brain of chicks exposed to ELF EMF in ovo.

4. The possible medical applications of ELF EMF should be given more attention. Several studies indicate that ELF EMF could enhance recovery of functions after nervous system damage and have protective effects against development of neurodegenerative diseases. Cuccurazzu et al. (2010) reported an ELF EMF-induced neurogenesis and repair of the nervous system after damage. Choi et al. (2014) reported stimulation of neural differentiation in human bone marrow mesenchymal stem cells by extremely low-frequency electromagnetic fields, which may be a mean for the treatment for neurodegenerative diseases. Ben Yakir-Blumkin et al. (2014) reported a protective effect of static magnetic field on primary cortical neurons from induced apoptosis. Kumar et al. (2010) and Das et al. (2012) showed an enhanced restoration of functions after spinal injury in the rat. Kumar et al. (2013) further showed that ELF EMF exposure restored spinal cord injury-induced tonic pain and changes in neurotransmitter concentrations in the brain of the rat. Maestú et al. (2013) reported improvement in pain sensation in fibromyalgia patients after magnetic field stimulation. A possible beneficial effect on cerebral ischemia has been reported by Rauš Balind et al. (2014). Piacentini et al. (2008) reported a promotion of neural differentiation by ELF EMF. Kim et al. (2013) and Bai et al. (2013) reported stimulation by ELF EMF on neural differentiation of stem cells. Effects on stem cells and hippocampal neurogenesis also have been reported by Podda et al. (2013) and Leone et al. (2014). Protective effects of ELF EMF have been reported by Raus et al (2012a, b) after cerebral ischemia, Tassel et al. (2012a, b) on the development of Huntington's Disease, and Manjhi et al. (2013) on spinal cord injury induced osteoporosis. Marchesi et al. (2014) reported a potential cytoprotective effect exerted by LF-EMF in neurodegenerative diseases such as Alzheimer's Disease. Furthermore, Cvetkovic et al. (2009) reported alteration of EEG by application of certain frequencies of magnetic fields. This may be useful in the treatment of certain neurological disorders such as sleep and psychiatric disorders. Static magnetic field has been shown by Wang et al. (2010) to act like an anti-Parkinson drug. Static magnetic field also has been shown to have antiangiogenesis property (Wang Z, Yang P, Xu H, Qian A, Hu L, Shang P. Inhibitory effects of a gradient static magnetic field on normal angiogenesis. *Bioelectromagnetics*. 30(6):446-453, 2009), which can be translated into an anticancer activity. Use of ELF EMF for cancer treatment has been extensively investigated. There is a study showed that pulsed electromagnetic fields turned on adenosine receptors in brain cancer cells that inhibit cancer growth (Vincenzi F, Targa M, Corciulo C, Gessi S, Merighi S, Setti S, Cadossi R, Borea PA, Varani K. The anti-tumor effect of A₃ adenosine receptors is potentiated by pulsed electromagnetic fields in cultured neural cancer cells. *PLoS One* 7(6):e39317, 2012). Interesting, this effect was not observed when normal brain cells were exposed to magnetic field. The waveform of the fields may play an important role in the effect produced. There are several studies on pulsed (instead of sinusoidal) magnetic fields (Aldinucci et al., 2009; Capone et al.,

2009; Cook et al. 2009; Glover et al., 2009) and complex fields (Ross et al., 2008). It has been speculated that intermittent EMF or fields that have a transient nature could be more biologically potent than constant fields. The conditions and parameters of the fields that could produce either detrimental or beneficial effects need further investigation. Furthermore, it is still not clear whether acute (one time) exposure would elicit effects different from chronic/repeated exposure. In the 2007-2014 literature, there are many studies investigated the effects of chronic/repeated exposure. The study by Liu et al. (2008a) indicates that duration of exposure could be an important factor.

5. The majority of the studies used magnetic fields above 0.1 mT (1 gauss; the highest was 8 mT). The intensities are much higher than those in the public environment. Thus, caution should be taken in extrapolating the high-intensity cell and animal studies to environmental human exposure situation. Exposure to magnetic fields of 0.4 μ T (0.0004 mT) has been implication in an increased risk of childhood leukemia. And, the recent report by Li et al. (Li DK, Ferber JR, Odouli R, Quesenberry CP Jr. A Prospective Study of In-utero Exposure to Magnetic Fields and the Risk of Childhood Obesity. *Sci Rep.* 2:540, 2012) on an increased risk of obesity of humans exposed prenatally to magnetic field at 0.25 μ T (0.00025 mT). There is also a report of a blood pressure lowering effect in humans with mild-to-moderate hypertension after exposure to magnetic fields at 1 μ T (0.001mT) (Nishimura T, Tada H, Guo X, Murayama T, Teramukai S, Okano H, Yamada J, Mohri K, Fukushima M. A 1- μ T extremely low-frequency electromagnetic field vs. sham control for mild-to-moderate hypertension: a double-blind, randomized study. *Hypertens Res.* 34(3):372-377, 2011.) Apparently, humans are sensitive to magnetic field at level less than 1 μ T. There are a study by Ross et al (2008) showing 'perception' alteration in human subjects exposed to magnetic field at 10 nT (0.00001 mT), a study by Fournier et al (2012) on effect of brain development in the rat at 30 nT (0.00003 mT), and a study by Stevens (2007) indicating changes in emotional states in humans exposed to 8-12 Hz magnetic field at 5 μ T (0.005 mT). These data do suggest magnetic fields at very low intensities could cause neurological effects in humans. In the 1990s, there was a series of more than 20 studies published by Reuven Sandyk showing that pulsed magnetic fields at pT (1 pT = 0.000000001 mT) levels could have therapeutic effects on Parkinson's disease and multiple sclerosis (see e.g., Sandyk R. Reversal of cognitive impairment in an elderly Parkinsonian patient by transcranial application of picotesla electromagnetic fields. *Int J Neurosci.* 91(1-2):57-68, 1997, or, search for 'Sandyk R' in the PubMed.) However, Sandyk's findings have never been independently confirmed.
6. In summary, both RF and ELF EMF affect neurological functions and behavior in animals and humans. There is no definite data showing that these effects are detrimental to human health. However, since effects have been observed, it is advisable that one should limit one's exposure to EMF.

Literature on neurological effects of radiofrequency radiation (2007-2017)

Below is a key to abbreviations used throughout the following list of abstracts for recent papers published since 2007 and serve as my comments to help the reader identify the significance of each paper.

(E)-effect observed; **(NE)**- no significant effect observed; **HU**- human study; **AS**- animal study; **CS**-cell study; **LI**- low intensity/cell tower; **CE**- chronic/repeated exposure; **BE**- behavioral effect; **DE**- developmental effect; **CC**- cellular effects; **CH**-chemical changes; **ME**- morphological effect; **PE**-physiological effect; **EE**- electrophysiological effect; **OX**- oxidative changes; **AD**- age-dependent effect; **SL**- effect on sleep; **MA**- possible medical application; **WS**- waveform specific effect; **IA**- interaction with other factors.

(E) Abdel-Rassoul G, El-Fateh OA, Salem MA, Michael A, Farahat F, El-Batanouny M, Salem E. Neurobehavioral effects among inhabitants around mobile phone base stations. *Neurotoxicology*. 28(2):434-440, 2007. **(HU, CE, BE, LI, SL)**

BACKGROUND: There is a general concern on the possible hazardous health effects of exposure to radiofrequency electromagnetic radiations (RFR) emitted from mobile phone base station antennas on the human nervous system. AIM: To identify the possible neurobehavioral deficits among inhabitants living nearby mobile phone base stations. METHODS: A cross-sectional study was conducted on (85) inhabitants living nearby the first mobile phone station antenna in Menoufiya governorate, Egypt, 37 are living in a building under the station antenna while 48 opposite the station. A control group (80) participants were matched with the exposed for age, sex, occupation and educational level. All participants completed a structured questionnaire containing: personal, educational and medical histories; general and neurological examinations; neurobehavioral test battery (NBTB) [involving tests for visuomotor speed, problem solving, attention and memory]; in addition to Eysenck personality questionnaire (EPQ). RESULTS: The prevalence of neuropsychiatric complaints as headache (23.5%), memory changes (28.2%), dizziness (18.8%), tremors (9.4%), depressive symptoms (21.7%), and sleep disturbance (23.5%) were significantly higher among exposed inhabitants than controls: (10%), (5%), (5%), (0%), (8.8%) and (10%), respectively (P<0.05). The NBTB indicated that the exposed inhabitants exhibited a significantly lower performance than controls in one of the tests of attention and short-term auditory memory [Paced Auditory Serial Addition Test (PASAT)]. Also, the inhabitants opposite the station exhibited a lower performance in the problem solving test (block design) than those under the station. All inhabitants exhibited a better performance in the two tests of visuomotor speed (Digit symbol and Trailmaking B) and one test of attention (Trailmaking A) than controls. The last available measures of RFR emitted from the first mobile phone base station antennas in Menoufiya governorate were less than the allowable standard level. CONCLUSIONS AND RECOMMENDATIONS: Inhabitants living nearby mobile phone base stations are at risk for developing neuropsychiatric problems and some changes in the performance of neurobehavioral functions either by facilitation or inhibition. So, revision of standard guidelines for public exposure to RER from mobile phone base station antennas and

using of NBTB for regular assessment and early detection of biological effects among inhabitants around the stations are recommended.

(E) Aboul Ezz HS, Khadrawy YA, Ahmed NA, Radwan NM, El Bakry MM. The effect of pulsed electromagnetic radiation from mobile phone on the levels of monoamine neurotransmitters in four different areas of rat brain. Eur Rev Med Pharmacol Sci. 17(13):1782-1788, 2013. (AS, CE, CH)

BACKGROUND: The use of **mobile** phones is rapidly increasing all over the world. Few studies deal with the effect of electromagnetic radiation (EMR) on monoamine neurotransmitters in the different brain areas of adult rat. AIM: The aim of the present study was to investigate the effect of EMR on the concentrations of dopamine (DA), norepinephrine (NE) and serotonin (5-HT) in the hippocampus, hypothalamus, midbrain and medulla oblongata of adult rats.

MATERIALS AND METHODS: Adult rats were exposed daily to EMR (frequency 1800 MHz, specific absorption rate 0.843 W/kg, power density 0.02 mW/cm², modulated at 217 Hz) and sacrificed after 1, 2 and 4 months of daily EMR exposure as well as after stopping EMR for 1 month (after 4 months of daily EMR exposure). Monoamines were determined by high performance liquid chromatography coupled with fluorescence detection (HPLC-FD) using their native properties. RESULTS: The exposure to EMR resulted in significant changes in DA, NE and 5-HT in the four selected areas of adult rat brain. CONCLUSIONS: The exposure of adult rats to EMR may cause disturbances in monoamine neurotransmitters and this may underlie many of the adverse effects reported after EMR including memory, learning, and stress.

***(E) Abramson MJ, Benke GP, Dimitriadis C, Inyang IO, Sim MR, Wolfe RS, Croft RJ. Mobile telephone use is associated with changes in cognitive function in young adolescents. Bioelectromagnetics. 30(8):678-686, 2009. (HU, BE) (*Effects observed probably not caused by exposure to RFR.)**

As part of the Mobile Radiofrequency Phone Exposed Users' Study (MoRPhEUS), a cross-sectional epidemiological study examined cognitive function in secondary school students. We recruited 317, 7th grade students (144 boys, 173 girls, median age 13 years) from 20 schools around Melbourne, Australia. Participants completed an exposure questionnaire based on the Interphone study, a computerised cognitive test battery, and the Stroop colour-word test. The principal exposure metric was the total number of reported mobile phone voice calls per week. Linear regression models were fitted to cognitive test response times and accuracies. Age, gender, ethnicity, socio-economic status and handedness were fitted as covariates and standard errors were adjusted for clustering by school. The accuracy of working memory was poorer, reaction time for a simple learning task shorter, associative learning response time shorter and accuracy poorer in children reporting more mobile phone voice calls. There were no significant relationships between exposure and signal detection, movement monitoring or estimation. The completion time for Stroop word naming tasks was longer for those reporting more mobile phone voice calls. The findings were similar for total short message service (SMS, also known as text) messages per week, suggesting these cognitive changes were unlikely due

to radiofrequency (RF) exposure. Overall, mobile phone use was associated with faster and less accurate responding to higher level cognitive tasks. These behaviours may have been learned through frequent use of a mobile phone.

(NE) Ahlers MT, Ammermüller J. No influence of acute RF exposure (GSM-900, GSM-1800, and UMTS) on mouse retinal ganglion cell responses under constant temperature conditions. Bioelectromagnetics. 2013 Sep 21. doi: 10.1002/bem.21811. [Epub ahead of print] (CS, CC)

Possible non-thermal effects of radio frequency electromagnetic fields (RF-EMF) on retinal ganglion cells were studied in vitro under conditions of constant temperature. Isolated mouse retinæ were exposed to GSM-900, GSM-1800, and universal mobile telecommunication system (UMTS) RF-EMF applying specific absorption rates (SAR) of 0 (sham), 0.02, 0.2, 2, and 20 W/kg. Temperature was kept constant within ± 0.5 to 1°C for GSM-900 and $\pm 0.5^\circ\text{C}$ for GSM-1800 and UMTS. Responses of retinal ganglion cells to light stimuli of three intensities (0.5, 16, and 445 lx) were recorded before, during, and up to 35 min after exposure. Experiments were performed under double-blind conditions. Changes in light responses during and after exposure were determined for each condition (RF-EMF; SAR value; light intensity) with respect to the responses before exposure, respectively. Changes were calculated using the Euclidian distance of the n-dimensional response vectors, respectively. Some changes already occurred during sham (0 W/kg) exposure, reflecting the intrinsic variability in retinal ganglion cell responses. Comparison of the distance values from sham exposure with those from actual exposure yielded no significant differences. In addition, linear regression analysis of the distance values versus SAR values yielded no consistent dependence of light response changes. From these results we conclude that RF-EMF exposure at three mobile phone frequencies (GSM-900, GSM-1800, UMTS) and SARs up to 20 W/kg has no acute effects on retinal ganglion cell responses under constant temperature conditions.

(NE) Aït-Aïssa S, de Gannes FP, Taxile M, Billaudel B, Hurtier A, Haro E, Ruffié G, Athané A, Veyret B, Lagroye I. In Situ Expression of Heat-Shock Proteins and 3-Nitrotyrosine in Brains of Young Rats Exposed to a WiFi Signal In Utero and In Early Life. Radiat Res. 2013 May 10. [Epub ahead of print] (AS, CE, CH, DE, OX)

The bioeffects of exposure to Wireless High-Fidelity (WiFi) signals on the developing nervous systems of young rodents was investigated by assessing the in vivo and in situ expression levels of three stress markers: 3-Nitrotyrosine (3-NT), an oxidative stress marker and two heat-shock proteins (Hsp25 and Hsp70). These biomarkers were measured in the brains of young rats exposed to a 2450 MHz WiFi signal by immunohistochemistry. Pregnant rats were first exposed or sham exposed to WiFi from day 6 to day 21 of gestation. In addition three newborns per litter were further exposed up to 5 weeks old. Daily 2-h exposures were performed blind in a reverberation chamber and whole-body specific absorption rate levels were 0, 0.08, 0.4 and 4 W/kg. 3-NT and stress protein expression was assayed in different areas of the hippocampus and cortex. No significant difference was observed among exposed and sham-exposed groups.

These results suggest that repeated exposure to WiFi during gestation and early life has no deleterious effects on the brains of young rats.

(E) Akbari A, Jelodar G, Nazifi S. Vitamin C protects rat cerebellum and encephalon from oxidative stress following exposure to radiofrequency wave generated by a BTS antenna model. Toxicol Mech Methods. 24(5):347-352, 2014. (AS, CE, CH, OX, IA)

Radio frequency wave (RFW) generated by base transceiver station has been reported to produce deleterious effects on the central nervous system function, possibly through oxidative stress. This study was conducted to evaluate the effect of RFW-induced oxidative stress in the cerebellum and encephalon and the prophylactic effect of vitamin C on these tissues by measuring the antioxidant enzymes activity, including: glutathione peroxidase, superoxide dismutase, catalase, and malondialdehyde (MDA). Thirty-two adult male Sprague-Dawley rats were randomly divided into four equal groups. The control group; the control-vitamin C group received L-ascorbic acid (200 mg/kg of body weight/day by gavage) for 45 days. The RFW group was exposed to RFW and the RFW+ vitamin C group was exposed to RFW and received vitamin C. At the end of the experiment, all groups were killed and encephalon and cerebellum of all rats were removed and stored at -70 °C for measurement of antioxidant enzymes activity and MDA. The results indicate that exposure to RFW in the test group decreased antioxidant enzymes activity and increased MDA compared with the control groups ($p < 0.05$). The protective role of vitamin C in the treated group improved antioxidant enzymes activity and reduced MDA compared with the test group ($p < 0.05$). It can be concluded that RFW causes oxidative stress in the brain and vitamin C improves the antioxidant enzymes activity and decreases MDA.

(E) Aldad TS, Gan G, Gao XB, Taylor HS. Fetal radiofrequency radiation exposure from 800-1900 MHz-rated cellular telephones affects neurodevelopment and behavior in mice. Sci Rep. 2:312, 2012. (AS, CS, DE, BE, CE, CC)

Neurobehavioral disorders are increasingly prevalent in children, however their etiology is not well understood. An association between prenatal cellular telephone use and hyperactivity in children has been postulated, yet the direct effects of radiofrequency radiation exposure on neurodevelopment remain unknown. Here we used a mouse model to demonstrate that in-utero radiofrequency exposure from cellular telephones does affect adult behavior. Mice exposed in-utero were hyperactive and had impaired memory as determined using the object recognition, light/dark box and step-down assays. Whole cell patch clamp recordings of miniature excitatory postsynaptic currents (mEPSCs) revealed that these behavioral changes were due to altered neuronal developmental programming. Exposed mice had dose-responsive impaired glutamatergic synaptic transmission onto layer V pyramidal neurons of the prefrontal cortex. We present the first experimental evidence of neuropathology due to in-utero cellular telephone radiation. Further experiments are needed in humans or non-human primates to determine the risk of exposure during pregnancy.

(E) Ammari M, Brillaud E, Gamez C, Lecomte A, Sakly M, Abdelmelek H, de Seze R. Effect of a chronic GSM 900 MHz exposure on glia in the rat brain. Biomed Pharmacother. 62(4):273-281, 2008a. (AS, CE, CC)

Extension of the mobile phone technology raises concern about the health effects of 900 MHz microwaves on the central nervous system (CNS). In this study we measured GFAP expression using immunocytochemistry method, to evaluate glial evolution 10 days after a chronic exposure (5 days a week for 24 weeks) to GSM signal for 45 min/day at a brain-averaged specific absorption rate (SAR)=1.5 W/kg and for 15 min/day at a SAR=6 W/kg in the following rat brain areas: prefrontal cortex (PFCx), caudate putamen (Cpu), lateral globus pallidus of striatum (LGP), dentate gyrus of hippocampus (DG) and cerebellum cortex (CCx). In comparison to sham or cage control animals, rats exposed to chronic GSM signal at 6 W/kg have increased GFAP stained surface areas in the brain ($p<0.05$). But the chronic exposure to GSM at 1.5 W/kg did not increase GFAP expression. Our results indicated that chronic exposure to GSM 900 MHz microwaves (SAR=6 W/kg) may induce persistent astroglia activation in the rat brain (sign of a potential gliosis).

(E) Ammari M, Lecomte A, Sakly M, Abdelmelek H, de-Seze R. Exposure to GSM 900 MHz electromagnetic fields affects cerebral cytochrome c oxidase activity. Toxicology. 250(1):70-74, 2008b. (AS, CE, CH)

The world-wide and rapidly growing use of mobile phones has raised serious concerns about the biological and health-related effects of radio frequency (RF) radiation, particularly concerns about the effects of RFs upon the nervous system. The goal of this study was conducted to measure cytochrome oxidase (CO) levels using histochemical methods in order to evaluate regional brain metabolic activity in rat brain after exposure to a GSM 900 MHz signal for 45 min/day at a brain-averaged specific absorption rate (SAR) of 1.5 W/Kg or for 15 min/day at a SAR of 6 W/Kg over seven days. Compared to the sham and control cage groups, rats exposed to a GSM signal at 6 W/Kg showed decreased CO activity in some areas of the prefrontal and frontal cortex (infralimbic cortex, prelimbic cortex, primary motor cortex, secondary motor cortex, anterior cingulate cortex areas 1 and 2 (Cg1 and Cg2)), the septum (dorsal and ventral parts of the lateral septal nucleus), the hippocampus (dorsal field CA1, CA2 and CA3 of the hippocampus and dental gyrus) and the posterior cortex (retrosplenial agranular cortex, primary and secondary visual cortex, perirhinal cortex and lateral entorhinal cortex). However, the exposure to GSM at 1.5 W/Kg did not affect brain activity. Our results indicate that 6 W/Kg GSM 900 MHz microwaves may affect brain metabolism and neuronal activity in rats.

(NE) Ammari M, Jacquet A, Lecomte A, Sakly M, Abdelmelek H, de Seze R. Effect of head-only sub-chronic and chronic exposure to 900-MHz GSM electromagnetic fields on spatial memory in rats. Brain Inj. 22(13-14):1021-1029, 2008c. (AS, CE, BE)

PRIMARY OBJECTIVE: This study was carried out to investigate the behavioural effects of sub-chronic and chronic head-only exposure to 900 MHz GSM (Global System for Mobile communications) in male rats. **METHODS:** Rats were exposed for 45 minutes per day, at a

brain-averaged specific absorption rate (SAR) = 1.5 W Kg(-1) or 15 minutes per day at a SAR = 6 W Kg(-1), during 8 or 24 weeks. Then, their spatial memory was tested using the radial-arm maze. In the first phase (10 days), rats were trained to visit the eight arms of the maze without returning to an arm already visited. In the second phase (8 days), a 45-minute intra-trial delay was introduced after four visited arms. **RESULTS:** Performance of exposed rats (1.5 or 6 W Kg(-1)) was compared with that of sham, negative control and positive control rats. Scopolamine treatment in the positive control rats induced deficit in spatial memory task in the second phase of the test. However, spatial memory task was unaffected in exposed rats. **CONCLUSION:** Sub-chronic and chronic head-only exposure of rats to GSM 900 MHz signal (45-minutes, SAR = 1.5 or 15-minutes, SAR = 6 W Kg(-1)) did not induce spatial memory deficit in the radial-arm maze.

(E) Ammari M, Gamez C, Lecomte A, Sakly M, Abdelmelek H, De Seze R. GFAP expression in the rat brain following sub-chronic exposure to a 900 MHz electromagnetic field signal. Int J Radiat Biol. 86(5):367-375, 2010. (AS, CE, CC)

PURPOSE: The rapid development and expansion of mobile communications contributes to the general debate on the effects of electromagnetic fields emitted by mobile phones on the nervous system. This study aims at measuring the glial fibrillary acidic protein (GFAP) expression in 48 rat brains to evaluate reactive astrogliosis, three and 10 days after long-term head-only sub-chronic exposure to a 900 MHz electromagnetic field (EMF) signal, in male rats. **METHODS:** Sprague-Dawley rats were exposed for 45 min/day at a brain-averaged specific absorption rate (SAR) = 1.5 W/kg or 15 min/day at a SAR = 6 W/kg for five days per week during an eight-week period. GFAP expression was measured by the immunocytochemistry method in the following rat brain areas: Prefrontal cortex, cerebellar cortex, dentate gyrus of the hippocampus, lateral globus pallidus of the striatum, and the caudate putamen. **RESULTS:** Compared to the sham-treated rats, those exposed to the sub-chronic GSM (Global System for mobile communications) signal at 1.5 or 6 W/kg showed an increase in GFAP levels in the different brain areas, three and ten days after treatment. **CONCLUSION:** Our results show that sub-chronic exposures to a 900 MHz EMF signal for two months could adversely affect rat brain (sign of a potential gliosis).

(E) Arendash GW, Sanchez-Ramos J, Mori T, Mamcarz M, Lin X, Runfeldt M, Wang L, Zhang G, Sava V, Tan J, Cao C. Electromagnetic field treatment protects against and reverses cognitive impairment in Alzheimer's disease mice. J Alzheimers Dis. 19(1):191-210, 2010. (AS, CE, CH, BE, MA)

Despite numerous studies, there is no definitive evidence that high-frequency electromagnetic field (EMF) exposure is a risk to human health. To the contrary, this report presents the first evidence that long-term EMF exposure directly associated with cell phone use (918 MHz; 0.25 w/kg) provides cognitive benefits. Both cognitive-protective and cognitive-enhancing effects of EMF exposure were discovered for both normal mice and transgenic mice destined to develop Alzheimer's-like cognitive impairment. The cognitive interference task utilized in this study was designed from, and measure-for-measure analogous to, a human cognitive interference task. In

Alzheimer's disease mice, long-term EMF exposure reduced brain amyloid-beta (A β) deposition through A β anti-aggregation actions and increased brain temperature during exposure periods. Several inter-related mechanisms of EMF action are proposed, including increased A β clearance from the brains of Alzheimer's disease mice, increased neuronal activity, and increased cerebral blood flow. Although caution should be taken in extrapolating these mouse studies to humans, we conclude that EMF exposure may represent a non-invasive, non-pharmacologic therapeutic against Alzheimer's disease and an effective memory-enhancing approach in general.

(E) Arendash GW, Mori T, Dorsey M, Gonzalez R, Tajiri N, Borlongan C. Electromagnetic treatment to old Alzheimer's mice reverses β -amyloid deposition, modifies cerebral blood flow, and provides selected cognitive benefit. PLoS One. 7(4):e35751, 2012. (AS, CE, CH, BE, MA)

Few studies have investigated physiologic and cognitive effects of "long-term" electromagnetic field (EMF) exposure in humans or animals. Our recent studies have provided initial insight into the long-term impact of adulthood EMF exposure (GSM, pulsed/modulated, 918 MHz, 0.25-1.05 W/kg) by showing 6+ months of daily EMF treatment protects against or reverses cognitive impairment in Alzheimer's transgenic (Tg) mice, while even having cognitive benefit to normal mice. Mechanistically, EMF-induced cognitive benefits involve suppression of brain β -amyloid (A β) aggregation/deposition in Tg mice and brain mitochondrial enhancement in both Tg and normal mice. The present study extends this work by showing that daily EMF treatment given to very old (21-27 month) Tg mice over a 2-month period reverses their very advanced brain A β aggregation/deposition. These very old Tg mice and their normal littermates together showed an increase in general memory function in the Y-maze task, although not in more complex tasks. Measurement of both body and brain temperature at intervals during the 2-month EMF treatment, as well as in a separate group of Tg mice during a 12-day treatment period, revealed no appreciable increases in brain temperature (and no/slight increases in body temperature) during EMF "ON" periods. Thus, the neuropathologic/cognitive benefits of EMF treatment occur without brain hyperthermia. Finally, regional cerebral blood flow in cerebral cortex was determined to be reduced in both Tg and normal mice after 2 months of EMF treatment, most probably through cerebrovascular constriction induced by freed/disaggregated A β (Tg mice) and slight body hyperthermia during "ON" periods. These results demonstrate that long-term EMF treatment can provide general cognitive benefit to very old Alzheimer's Tg mice and normal mice, as well as reversal of advanced A β neuropathology in Tg mice without brain heating. Results further underscore the potential for EMF treatment against AD.

***(E) Arns M, Van Luitelaar G, Sumich A, Hamilton R, Gordon E. Electroencephalographic, personality, and executive function measures associated with frequent mobile phone use. Int J Neurosci. 117(9):1341-1360, 2007. (HU, BE) (*Effects observed probably not caused by exposure to RFR.)**

The present study employs standardized data acquired from the Brain Resource International Database to study the relationship between mobile phone usage, personality, and brain

function (n = 300). Based on the frequency and duration of mobile phone usage, three groups were formed. The findings suggest a subtle slowing of brain activity related to mobile phone use that is not explained by differences in personality. These changes are still within normal physiological ranges. Better executive function in mobile phone users may reflect more focused attention, possibly associated with a cognitive training effect (i.e., frequently making phone calls in distracting places), rather than a direct effect of mobile phone use on cognition.

(E) Bak M, Dudarewicz A, Zmyślony M, Sliwinska-Kowalska M. Effects of GSM signals during exposure to event related potentials (ERPs). Int J Occup Med Environ Health. 23(2):191-199, 2010. (HU, EE)

OBJECTIVES: The primary aim of this work was to assess the effect of electromagnetic field (EMF) from the GSM mobile phone system on human brain function. The assessment was based on the assay of event related potentials (ERPs). **MATERIAL AND METHODS:** The study group consisted of 15 volunteers, including 7 men and 8 women. The test protocol comprised determination of P300 wave in each volunteer during exposure to the EMF. To eliminate possible effects of the applied test procedure on the final result, the test was repeated without EMF exposure. P300 latency, amplitude, and latency of the N1, N2, P2 waves were analysed. **RESULTS:** The statistical analysis revealed an effect of EMF on P300 amplitude. In the experiment with EMF exposure, lower P300 amplitudes were observed only at the time in which the volunteers were exposed to EMF; when the exposure was discontinued, the values of the amplitude were the same as those observed before EMF application. No such change was observed when the experiment was repeated with sham exposure, which may be considered as an indirect proof that lower P300 amplitude values were due to EMF exposure. No statistically significant changes were noted in the latencies of the N1, N2, P2 waves that precede the P300 wave, nor in the latency of the P300 itself. **CONCLUSIONS:** The results suggest that exposure to GSM EMF exerts some effects on CNS, including effects on long latency ERPs.

(E) Banaceur S, Banasr S, Sakly M, Abdelmelek H. Whole body exposure to 2.4 GHz WIFI signals: effects on cognitive impairment in adult triple transgenic mouse models of Alzheimer's disease (3xTg-AD). Behav Brain Res. 240:197-201, 2013. (AS, CE, BE, MA)

The present investigation aimed at evaluating the effects of long-term exposure to WIFI type radiofrequency (RF) signals (2.40 GHz), two hours per day during one month at a Specific Absorption Rate (SAR) of 1.60 W/kg. The effects of RF exposure were studied on wildtype mice and triple transgenic mice (3xTg-AD) destined to develop Alzheimer's-like cognitive impairment. Mice were divided into four groups: two sham groups (WT, TG; n=7) and two exposed groups (WTS, TGS; n=7). The cognitive interference task used in this study was designed from an analogous human cognitive interference task including the Flex field activity system test, the two-compartment box test and the Barnes maze test. Our data demonstrate for the first time that RF improves cognitive behavior of 3xTg-AD mice. We conclude that RF exposure may represent an effective memory-enhancing approach in Alzheimer's disease.

(E) Barcal J, Vozech F. Effect of whole-body exposure to high-frequency electromagnetic field on the brain cortical and hippocampal activity in mouse experimental model. NeuroQuantology 5:292-302, 2007. (AS, EE)

Evaluation of the direct registration of brain cortical and hippocampal activity during a high-frequency electromagnetic field (HF-EMF) exposure was performed. Experimental procedures were done under general anesthesia (urethane, 20%, 2g/kg i.p.) in Lurcher mutant mice, wild type (healthy littermates) were used as controls. Animals were exposed to the HF-EMF with frequency corresponding to cellular phones (900 MHz). We used of gel electrodes (silicon tubes or glass microcapillary filled with agar) where the connection with classical electrodes was located out of HF-EMF space. ECoG evaluation showed a distinct shift to lower frequency components but clear effect has been observed only in wild type (healthy) mice whereas in Lurcher mutant mice only gentle differences between frequency spectra were found. Measurement of hippocampal rhythmicity showed gentle changes with increase of higher frequencies (i.e. opposite effect than in cortex) and changes in theta oscillations registered from a dentate gyrus and CA1 area in both types of animals (healthy and mutant). These findings support an idea about possible influencing the central nervous system by HF-EMF exposure and support also some recent results about possible health risks resulting from cellular phones use.

(E) Barthélémy A, Mouchard A, Bouji M, Blazy K, Puigsegur R, Villégier AS. Glial markers and emotional memory in rats following acute cerebral radiofrequency exposures. Environ Sci Pollut Res Int. 2016 Sep 30. [Epub ahead of print] (AS, BE, CE, CH)

The widespread mobile phone use raises concerns on the possible cerebral effects of radiofrequency electromagnetic fields (RF EMF). Reactive astrogliosis was reported in neuroanatomical structures of adaptive behaviors after a single RF EMF exposure at high specific absorption rate (SAR, 6 W/kg). Here, we aimed to assess if neuronal injury and functional impairments were related to high SAR-induced astrogliosis. In addition, the level of beta amyloid 1-40 (A β 1-40) peptide was explored as a possible toxicity marker. Sprague Dawley male rats were exposed for 15 min at 0, 1.5, or 6 W/kg or for 45 min at 6 W/kg. Memory, emotionality, and locomotion were tested in the fear conditioning, the elevated plus maze, and the open field. Glial fibrillary acidic protein (GFAP, total and cytosolic fractions), myelin basic protein (MBP), and A β 1-40 were quantified in six brain areas using enzyme-linked immunosorbent assay. According to our data, total GFAP was increased in the striatum (+114 %) at 1.5 W/kg. Long-term memory was reduced, and cytosolic GFAP was increased in the hippocampus (+119 %) and in the olfactory bulb (+46 %) at 6 W/kg (15 min). No MBP or A β 1-40 expression modification was shown. Our data corroborates previous studies indicating RF EMF-induced astrogliosis. This study suggests that RF EMF-induced astrogliosis had functional consequences on memory but did not demonstrate that it was secondary to neuronal damage.

(E) Bas O, Odaci E, Kaplan S, Acer N, Ucok K, Colakoglu S. 900 MHz electromagnetic field exposure affects qualitative and quantitative features of hippocampal pyramidal cells in the adult female rat. Brain Res. 1265:178-185, 2009. (AS, CE, ME)

The effects of electromagnetic fields (EMFs) emitted by mobile phones on humans hold special interest due to their use in close proximity to the brain. The current study investigated the number of pyramidal cells in the cornu ammonis (CA) of the 16-week-old female rat hippocampus following postnatal exposure to a 900 megahertz (MHz) EMF. In this study were three groups of 6 rats: control (Cont), sham exposed (Sham), and EMF exposed (EMF). EMF group rats were exposed to 900 MHz EMF (1 h/day for 28 days) in an exposure tube. Sham group was placed in the exposure tube but not exposed to EMF (1 h/day for 28 days). Cont group was not placed into the exposure tube nor were they exposed to EMF during the study period. In EMF group rats, the specific energy absorption rate (SAR) varied between 0.016 (whole body) and 2 W/kg (locally in the head). All of the rats were sacrificed at the end of the experiment and the number of pyramidal cells in the CA was estimated using the optical fractionator technique. Histopathological evaluations were made on sections of the CA region of the hippocampus. Results showed that postnatal EMF exposure caused a significant decrease of the pyramidal cell number in the CA of the EMF group ($P<0.05$). Additionally, cell loss can be seen in the CA region of EMF group even at qualitative observation. These results may encourage researchers to evaluate the chronic effects of 900 MHz EMF on teenagers' brains.

(E) Baş O, Sönmez OF, Aslan A, İkinci A, Hancı H, Yıldırım M, Kaya H, Akça M, Odacı E. Pyramidal Cell Loss in the Cornu Ammonis of 32-day-old Female Rats Following Exposure to a 900 Megahertz Electromagnetic Field During Prenatal Days 13–21. NeuroQuantology 11:591-599, 2013. (AS, CE, ME, DE)

The number of studies reporting that the electromagnetic field (EMF) emitted by mobile phones affects human health is increasing by the day. In previous studies we reported that a 900 megahertz (MHz) EMF applied throughout the prenatal period reduced the number of pyramidal cells in the cornu ammonis of rat pups in the postnatal period. In this study we investigated the effect of a 900 MHz EMF applied on days 13-21 of the prenatal period on the number of pyramidal cells in the cornu ammonis of rat pups in the postnatal period. For that purpose, pregnant rats were divided into experimental and control groups. Experimental group pregnant rats were exposed to the effect of a 900 MHz EMF on days 13-21 of pregnancy. No procedure was applied to the control group. Newborn female rat pups were added to the study, and no procedure was performed on these after birth. Five newborn female rats were obtained from the experimental group and six from the control group. All female rat pups were decapitated on the postnatal 32nd day, and histological procedures were performed on the brain tissues. Sections were stained with Cresyl fast violet. The optical disector technique was used to estimate the total number of pyramidal cells in the cornu ammonis. Sections of cornu ammonis were subjected to histopathological evaluations. Our results showed that exposure to 900 MHz EMF during prenatal days 13-21 led to a significant decrease in the number of pyramidal cells in the cornu ammonis of the experimental group female rat pups ($P<0.05$). Histopathological examination revealed picnotic cells in the cornu ammonis in experimental female rat pups. The pyramidal cell loss in the cornu ammonis may therefore be attributed to

exposure to 900 MHz EMF in days 13-21 of the prenatal period.

(E) Bodera P, Stankiewicz W, Antkowiak B, Paluch M, Kieliszek J, Sobiech J, Zdanowski R, Wojdas A, Siwicki AK, Skopińska-Różewska E. Suppressive effect of electromagnetic field on analgesic activity of tramadol in rats. Pol J Vet Sci. 15(1):95-100, 2012. (AS, PE, IA)

The electromagnetic fields (EMFs) have been shown to alter animal and human behavior, such as directional orientation, learning, pain perception (nociception or analgesia) and anxiety-related behaviors. The aim of this study was to evaluate the influence of electromagnetic fields of high-frequency microwaves on pain perception and anti-nociceptive activity of tramadol (TRAM) - analgetic effective in the treatment of moderate to severe acute and chronic pain states. Electromagnetic fields exposures of a) 1500 MHz frequency and b) modulated, 1800 MHz (which is identical to that generated by mobile phones) were applied. Paw withdrawal latency (PWL) to thermal stimulus was measured in vehicle or tramadol (TRAM) treated animals before and after 30, 60 and 90 minutes from injections. The differences in the level of pain (PWL) between control group and rats exposed to EMF alone in three measurements, were not observed. Tramadol alone significantly increased PWLs to thermal stimulus in comparison to vehicle results at 30 ($p < 0.001$) and 60 minutes ($p < 0.05$) after drug injection. EMF exposure of both frequencies transiently suppressed analgesic effect of tramadol, significantly reducing paw withdrawal latency in animals treated with this drug at 30 minutes from the drug injection.

(E) Bodera P, Stankiewicz W, Antkowiak B, Paluch M, Kieliszek J, Sobiech J, Niemcewicz M. Influence of electromagnetic field (1800 MHz) on lipid peroxidation in brain, blood, liver and kidney in rats. Int J Occup Med Environ Health. 28(4):751-759, 2015. (AS, OX)

OBJECTIVES: The aim of this study is the evaluation of the influence of repeated (5 times for 15 min) exposure to electromagnetic field (EMF) of 1800 MHz frequency on tissue lipid peroxidation (LPO) both in normal and inflammatory state, combined with analgesic treatment. **MATERIAL AND METHODS:** The concentration of malondialdehyde (MDA) as the end-product of the lipid peroxidation (LPO) was estimated in blood, liver, kidneys, and brain of Wistar rats, both healthy and those with complete Freund's adjuvant (CFA)-induced persistent paw inflammation. **RESULTS:** The slightly elevated levels of the MDA in blood, kidney, and brain were observed among healthy rats in electromagnetic field (EMF)-exposed groups, treated with tramadol (TRAM/EMF and exposed to the EMF). The malondialdehyde remained at the same level in the liver in all investigated groups: the control group (CON), the exposed group (EMF), treated with tramadol (TRAM) as well as exposed to and treated with tramadol (TRAM/EMF). In the group of animals treated with the complete Freund's adjuvant (CFA) we also observed slightly increased values of the MDA in the case of the control group (CON) and the exposed groups (EMF and TRAM/EMF). The MDA values concerning kidneys remained at the same levels in the control, exposed, and not-exposed group treated with tramadol. Results for healthy rats and animals with inflammation did not differ significantly. **CONCLUSIONS:** The electromagnetic field exposure (EMF), applied in the repeated manner together with opioid drug tramadol (TRAM), slightly enhanced lipid peroxidation level in brain, blood, and kidneys.

(E) Bouji M, Lecomte A, Hode Y, de Seze R, Villégier AS. Effects of 900 MHz radiofrequency on corticosterone, emotional memory and neuroinflammation in middle-aged rats. Exp Gerontol. 47(6):444-451, 2012. (AS, CC, BE, AD)

The widespread use of mobile phones raises the question of the effects of electromagnetic fields (EMF, 900 MHz) on the brain. Previous studies reported increased levels of the glial fibrillary acidic protein (GFAP) in the rat's brain after a single exposure to 900 MHz global system for mobile (GSM) signal, suggesting a potential inflammatory process. While this result was obtained in adult rats, no data is currently available in older animals. Since the transition from middle-age to senescence is highly dependent on environment and lifestyle, we studied the reactivity of middle-aged brains to EMF exposure. We assessed the effects of a single 15 min GSM exposure (900 MHz; specific absorption rate (SAR)=6 W/kg) on GFAP expression in young adults (6 week-old) and middle-aged rats (12 month-old). Brain interleukin (IL)-1 β and IL-6, plasmatic levels of corticosterone (CORT), and emotional memory were also assessed. Our data indicated that, in contrast to previously published work, acute GSM exposure did not induce astrocyte activation. Our results showed an IL-1 β increase in the olfactory bulb and enhanced contextual emotional memory in GSM-exposed middle-aged rats, and increased plasmatic levels of CORT in GSM-exposed young adults. Altogether, our data showed an age dependency of reactivity to GSM exposure in neuro-immunity, stress and behavioral parameters. Reproducing these effects and studying their mechanisms may allow a better understanding of mobile phone EMF effects on neurobiological parameters.

(NE) Bhagat S, Varshney S, Bist SS, Goel D, Mishra S, Jha VK. Effects on auditory function of chronic exposure to electromagnetic fields from mobile phones. Ear Nose Throat J. 95(8):E18-22, 2016. (HU, PE)

The widespread use of mobile phones has given rise to apprehension regarding the possible hazardous health effects of high-frequency electromagnetic fields (EMFs) on auditory function. We conducted a study to investigate the effects of long-term (>4 yr) exposure to EMFs emitted by mobile phones on auditory function. Our study population was made up of 40 healthy medical students-31 men and 9 women, aged 20 to 30 years (mean 22.7). Of this group, 31 subjects typically held their phone to the right ear and 9 to the left ear; the non-phone-using ear served as each subject's control ear. The phone-using subjects were also split into two groups of 20 based on the duration of their daily phone use (≤ 60 min vs. >60 min). All subjects underwent pure-tone audiometry, speech audiometry, impedance audiometry, and brainstem evoked response audiometry (BERA), and comparisons were made between the phone-using ear and the control ear and between the shorter and longer duration of daily use. We found no statistically significant differences in high-frequency pure-tone average between the phone-using ears and the control ears ($p = 0.69$) or between the shorter- and longer-duration phone-using ears ($p = 0.85$). Moreover, statistical analysis of BERA findings revealed no significant differences between the phone-using ears and the control ears in terms of wave I-III, III-V, and I-V interpeak latencies ($p = 0.59, 0.74$ and 0.44 , respectively). None of the subjects reported any subjective symptoms, such as headache, tinnitus, or sensations of burning or warmth behind, around, or on the phone-

using ear. We conclude that the long-term exposure to EMFs from mobile phones does not affect auditory function.

(E) Brillaud E, Piotrowski A, de Seze R. Effect of an acute 900 MHz GSM exposure on glia in the rat brain: a time-dependent study. Toxicology. 238(1):23-33, 2007. (AS, CC)

Because of the increasing use of mobile phones, the possible risks of radio frequency electromagnetic fields adverse effects on the human brain has to be evaluated. In this work we measured GFAP expression, to evaluate glial evolution 2, 3, 6 and 10 days after a single GSM exposure (15min, brain averaged SAR=6W/kg, 900 MHz signal) in the rat brain. A statistically significant increase of GFAP stained surface area was observed 2 days after exposure in the frontal cortex and the caudate putamen. A smaller statistically significant increase was noted 3 days after exposure in the same areas and in the cerebellum cortex. Our results confirm the Mausset-Bonnefont et al. study [Mausset-Bonnefont, A.L., Hirbec, H., Bonnefont, X., Privat, A., Vignon, J., de Seze, R., 2004. Acute exposure to GSM 900MHz electromagnetic fields induces glial reactivity and biochemical modifications in the rat brain. Neurobiol. Dis. 17, 445-454], showing the existence of glial reactivity after a 15min GSM acute exposure at a brain averaged SAR of 6W/kg. We conclude to a temporary effect, probably due to a hypertrophy of glial cells, with a temporal and a spatial modulation of the effect. Whether this effect could be harmful remains to be studied.

(E) Calabrò E, Condello S, Currò M, Ferlazzo N, Caccamo D, Magazù S, Ientile R. Modulation of heat shock protein response in SH-SY5Y by mobile phone microwaves. World J Biol Chem. 3(2):34-40, 2012. (CS, CH)

AIM: To investigate putative biological damage caused by GSM mobile phone frequencies by assessing electromagnetic fields during mobile phone working. METHODS: Neuron-like cells, obtained by retinoic-acid-induced differentiation of human neuroblastoma SH-SY5Y cells, were exposed for 2 h and 4 h to microwaves at 1800 MHz frequency bands. RESULTS: Cell stress response was evaluated by MTT assay as well as changes in the heat shock protein expression (Hsp20, Hsp27 and Hsp70) and caspase-3 activity levels, as biomarkers of apoptotic pathway. Under our experimental conditions, neither cell viability nor Hsp27 expression nor caspase-3 activity was significantly changed. Interestingly, a significant decrease in Hsp20 expression was observed at both times of exposure, whereas Hsp70 levels were significantly increased only after 4 h exposure. CONCLUSION: The modulation of the expression of Hsps in neuronal cells can be an early response to radiofrequency microwaves.

(NE) Calvente I, Pérez-Lobato R, Núñez MI, Ramos R, Guxens M, Villalba J, Olea N, Fernández MF. Does exposure to environmental radiofrequency electromagnetic fields cause cognitive and behavioral effects in 10-year-old boys? Bioelectromagnetics. 37(1):25-36, 2016. (HU, BE)

The relationship between exposure to electromagnetic fields from non-ionizing radiation and adverse human health effects remains controversial. We aimed to explore the association of environmental radiofrequency-electromagnetic fields (RF-EMFs) exposure with neurobehavioral function of children. A subsample of 123 boys belonging to the Environment

and Childhood cohort from Granada (Spain), recruited at birth from 2000 through 2002, were evaluated at the age of 9-11 years. Spot electric field measurements within the 100 kHz to 6 GHz frequency range, expressed as both root mean-square (SRMS) and maximum power density (SMAX) magnitudes, were performed in the immediate surrounds of children's dwellings. Neurocognitive and behavioral functions were assessed with a comprehensive battery of tests. Multivariate linear and logistic regression models were used, adjusting for potential confounders. All measurements were lower than reference guideline limits, with median SRMS and SMAX values of 285.94 and 2759.68 $\mu\text{W}/\text{m}^2$, respectively. Most of the cognitive and behavioral parameters did not show any effect, but children living in higher RF exposure areas (above median SRMS levels) had lower scores for verbal expression/comprehension and higher scores for internalizing and total problems, and obsessive-compulsive and post-traumatic stress disorders, in comparison to those living in areas with lower exposure. These associations were stronger when SMAX values were considered. Although some of our results may suggest that low-level environmental RF-EMF exposure has a negative impact on cognitive and/or behavior development in children; given limitations in the study design and that the majority of neurobehavioral functioning tasks were not affected, definitive conclusions cannot be drawn.

(E) Cammaerts MC, De Doncker P, Patris X, Bellens F, Rachidi Z, Cammaerts D. GSM 900 MHz radiation inhibits ants' association between food sites and encountered cues. Electromagn Biol Med. 31(2):151-165, 2012. (AS, BE)

The kinetics of the acquisition and loss of the use of olfactory and visual cues were previously obtained in six experimental colonies of the ant *Myrmica sabuleti* meinert 1861, under normal conditions. In the present work, the same experiments were conducted on six other naive identical colonies of *M. sabuleti*, under electromagnetic radiation similar to those surrounding GSM and communication masts. In this situation, no association between food and either olfactory or visual cues occurred. After a recovery period, the ants were able to make such an association but never reached the expected score. Such ants having acquired a weaker olfactory or visual score and still undergoing olfactory or visual training were again submitted to electromagnetic waves. Not only did they lose all that they had memorized, but also they lost it in a few hours instead of in a few days (as under normal conditions when no longer trained). They kept no visual memory at all (instead of keeping 10% of it as they normally do). The impact of GSM 900 MHz radiation was greater on the visual memory than on the olfactory one. These communication waves may have such a disastrous impact on a wide range of insects using olfactory and/or visual memory, i.e., on bees.

(E) Cammaerts MC, Rachidi Z, Bellens F, De Doncker P. Food collection and response to pheromones in an ant species exposed to electromagnetic radiation. Electromagn Biol Med. 2013 Jan 15. [Epub ahead of print] (AS, BE)

We used the ant species *Myrmica sabuleti* as a model to study the impact of electromagnetic waves on social insects' response to their pheromones and their food collection. We quantified *M. sabuleti* workers' response to their trail, area marking and alarm pheromone under normal

conditions. Then, we quantified the same responses while under the influence of electromagnetic waves. Under such an influence, ants followed trails for only short distances, no longer arrived at marked areas and no longer orientated themselves to a source of alarm pheromone. Also when exposed to electromagnetic waves, ants became unable to return to their nest and recruit congeners; therefore, the number of ants collecting food increases only slightly and slowly. After 180 h of exposure, their colonies deteriorated. Electromagnetic radiation obviously affects social insects' behavior and physiology.

(E) Cammaerts M-C, Vandenbosch GAE, Volski V. Effect of short-term GSM radiation at representative levels in society on a biological model: the ant *Myrmica sabuleti*. J Insect Beh. 27(4):514-526. 2014. (AS, CE, BE)

Well-controlled electromagnetic exposure conditions were set up at a representative societal GSM radiation intensity level, 1.5 V/m, which is the legally allowed level in Brussels. Two nests of the ant species *Myrmica sabuleti* were repeatedly irradiated during 10 min. before their behavior was observed, based on the analysis of the ant trajectories. Under these exposure conditions, behavioral effects were detected. The ants' locomotion slightly changed. The ants' orientation towards their attractive alarm pheromone statistically became of lower quality. The ants still presented their trail following behavior but less efficiently. In this controversial issue, ants could be considered as possible bioindicators.

(E) Carballo-Quintás M, Martínez-Silva I, Cadarso-Suárez C, Alvarez-Figueiras M, Ares-Pena FJ, López-Martín E. A study of neurotoxic biomarkers, c-fos and GFAP after acute exposure to GSM radiation at 900 MHz in the picrotoxin model of rat brains. Neurotoxicology. 32(4):478-494, 2011. (AS, CH)

The acute effects of microwave exposure from the Global System for Mobile Communication (GSM) were studied in rats, using 900 MHz radiation at an intensity similar to mobile phone emissions. Acute subconvulsive doses of picrotoxin were then administered to the rats and an experimental model of seizure-proneness was created from the data. Seventy-two adult male Sprague-Dawley rats underwent immunochemical testing of relevant anatomical areas to measure induction of the c-fos neuronal marker after 90min and 24h, and of the glial fibrillary acidic protein (GFAP) 72h after acute exposure to a 900MHz electromagnetic field (EMF). The experimental set-up facilitated measurement of absorbed power, from which the average specific absorption rate was calculated using the finite-difference time-domain (FDTD) 2h after exposure to EMF radiation at 1.45W/kg in picrotoxin-treated rats and 1.38W/kg in untreated rats. Ninety minutes after radiation high levels of c-fos expression were recorded in the neocortex and paleocortex along with low hippocampus activation in picrotoxin treated animals. Most brain areas, except the limbic cortical region, showed important increases in neuronal activation 24h after picrotoxin and radiation. Three days after picrotoxin treatment, radiation effects were still apparent in the neocortex, dentate gyrus and CA3, but a significant decrease in activity was noted in the piriform and entorhinal cortex. During this time, glial

reactivity increased with every seizure in irradiated, picrotoxin-treated brain regions. Our results reveal that c-fos and glial markers were triggered by the combined stress of non-thermal irradiation and the toxic effect of picrotoxin on cerebral tissues.

(E) Çeliker M, Özgür A, Tümkaya L, Terzi S, Yılmaz M, Kalkan Y, Erdoğan E. Effects of exposure to 2100MHz GSM-like radiofrequency electromagnetic field on auditory system of rats. Braz J Otorhinolaryngol. 2016 Nov 5. pii: S1808-8694(16)30222-1. doi: 10.1016/j.bjorl.2016.10.004. [Epub ahead of print] (AS, CE, CC, EE)

INTRODUCTION: The use of mobile phones has become widespread in recent years. Although beneficial from the communication viewpoint, the electromagnetic fields (EMF) generated by mobile phones may cause unwanted biological changes in the human body. **OBJECTIVE:** In this study, we aimed to evaluate the effects of 2100MHz Global System for Mobile communication (GSM-like) electromagnetic field (EMF), generated by an EMF generator, on the auditory system of rats by using electrophysiological, histopathologic and immunohistochemical methods. **METHODS:** Fourteen adult Wistar albino rats were included in the study. The rats were divided randomly into two groups of seven rats each. The study group was exposed continuously for 30 days to a 2100MHz EMF with a signal level (power) of 5.4dBm (3.47mW) to simulate the talk mode on a mobile phone. The control group was not exposed to the aforementioned EMF. After 30days, the Auditory Brainstem Responses (ABRs) of both groups were recorded and the rats were sacrificed. The cochlear nuclei were evaluated by histopathologic and immunohistochemical methods. **RESULTS:** The ABR records of the two groups did not differ significantly. The histopathologic analysis showed increased degeneration signs in the study group ($p=0.007$). In addition, immunohistochemical analysis revealed increased apoptotic index in the study group compared to that in the control group ($p=0.002$). **CONCLUSION:** The results support that long-term exposure to a GSM-like 2100MHz EMF causes an increase in neuronal degeneration and apoptosis in the auditory system.

(E) Cetin H, Nazıroğlu M, Celik O, Yüksel M, Pastacı N, Ozkaya MO. Liver antioxidant stores protect the brain from electromagnetic radiation (900 and 1800 MHz)-induced oxidative stress in rats during pregnancy and the development of offspring. J Matern Fetal Neonatal Med. 2014 Mar 3. [Epub ahead of print] (AS, CE, CH, OX, DE)

Objectives: The present study determined the effects of mobile phone (900 and 1800 MHz)-induced electromagnetic radiation (EMR) exposure on oxidative stress in the brain and liver as well as the element levels in growing rats from pregnancy to 6 weeks of age. **Methods:** Thirty-two rats and their offspring were equally divided into 3 different groups: the control, 900 MHz, and 1800 MHz groups. The 900 MHz and 1800 MHz groups were exposed to EMR for 60 min/day during pregnancy and neonatal development. At the 4th, 5th, and 6th weeks of the experiment, brain samples were obtained. **Results:** Brain and liver glutathione peroxidase (GSH-Px) activities, as well as liver vitamin A and β -carotene concentrations decreased in the EMR groups, although brain iron, vitamin A, and β -carotene concentrations increased in the EMR groups. In the 6th week, selenium concentrations in the brain decreased in the EMR

groups. There were no statistically significant differences in glutathione, vitamin E, chromium, copper, magnesium, manganese, and zinc concentrations between the 3 groups. Conclusion: EMR-induced oxidative stress in the brain and liver was reduced during the development of offspring. Mobile phone-induced EMR could be considered as a cause of oxidative brain and liver injury in growing rats.

(E) Chen C, Ma Q, Liu C, Deng P, Zhu G, Zhang L, He M, Lu Y, Duan W, Pei L, Li M, Yu Z, Zhou Z. Exposure to 1800 MHz radiofrequency radiation impairs neurite outgrowth of embryonic neural stem cells. Sci Rep. 2014 May 29;4:5103. doi: 10.1038/srep05103. (CS, ME, DE)

A radiofrequency electromagnetic field (RF-EMF) of 1800 MHz is widely used in mobile communications. However, the effects of RF-EMFs on cell biology are unclear. Embryonic neural stem cells (eNSCs) play a critical role in brain development. Thus, detecting the effects of RF-EMF on eNSCs is important for exploring the effects of RF-EMF on brain development. Here, we exposed eNSCs to 1800 MHz RF-EMF at specific absorption rate (SAR) values of 1, 2, and 4 W/kg for 1, 2, and 3 days. We found that 1800 MHz RF-EMF exposure did not influence eNSC apoptosis, proliferation, cell cycle or the mRNA expressions of related genes. RF-EMF exposure also did not alter the ratio of eNSC differentiated neurons and astrocytes. However, neurite outgrowth of eNSC differentiated neurons was inhibited after 4 W/kg RF-EMF exposure for 3 days. Additionally, the mRNA and protein expression of the proneural genes Ngn1 and NeuroD, which are crucial for neurite outgrowth, were decreased after RF-EMF exposure. The expression of their inhibitor Hes1 was upregulated by RF-EMF exposure. These results together suggested that 1800 MHz RF-EMF exposure impairs neurite outgrowth of eNSCs. More attention should be given to the potential adverse effects of RF-EMF exposure on brain development.

(E) Choi Y-J, Choi Y-S. Effects of Electromagnetic Radiation from Smartphones on Learning Ability and Hippocampal Progenitor Cell Proliferation in Mice. Osong Public Health and Research Perspectives. 7(1):12-17, 2016. (AS, CE, CC, BE)

Objectives Nonionizing radiation is emitted from electronic devices, such as smartphones. In this study, we intended to elucidate the effect of electromagnetic radiation from smartphones on spatial working memory and progenitor cell proliferation in the hippocampus. Methods Both male and female mice were randomly separated into two groups (radiated and control) and the radiated group was exposed to electromagnetic radiation for 9 weeks and 11 weeks for male and female mice, respectively. Spatial working memory was examined with a Y maze, and proliferation of hippocampal progenitor cells were examined by 5-bromo-2'-deoxyuridine administration and immunohistochemical detection. Results When spatial working memory on a Y maze was examined in the 9th week, there was no significant difference in the spontaneous alternation score on the Y maze between the two groups. In addition, there was no significant difference in hippocampal progenitor cell proliferation. However, immunoreactivity to glial fibrillary acidic protein was increased in exposed animals. Next, to test the effect of recovery following chronic radiation exposure, the remaining female mice were further exposed to

electromagnetic radiation for 2 more weeks (total 11 weeks), and spontaneous alternation was tested 4 weeks later. In this experiment, although there was no significant difference in the spontaneous alternation scores, the number of arm entry was significantly increased.

Conclusion These data indicate that although chronic electromagnetic radiation does not affect spatial working memory and hippocampal progenitor cell proliferation it can mediate astrocyte activation in the hippocampus and delayed hyperactivity-like behavior.

(NE) Cinel C, Boldini A, Russo R, Fox E. Effects of mobile phone electromagnetic fields on an auditory order threshold task. Bioelectromagnetics. 28(6):493-496, 2007. (HU, BE)

The effect of acute exposure to radio frequency electromagnetic fields (RF EMF) generated by mobile phones on an auditory threshold task was investigated. 168 participants performed the task while exposed to RF EMF in one testing session (either global system for mobile communication (GSM) or unmodulated signals) while in a separate session participants were exposed to sham signals. Lateralization effects were tested by exposing participants either on the left side or on the right side of the head. No significant effect of exposure to RF EMF was detected, suggesting that acute exposure to RF EMFs does not affect performance in the order threshold task.

(NE) Cinel C, Russo R, Boldini A, Fox E. Exposure to mobile phone electromagnetic fields and subjective symptoms: a double-blind study. Psychosom Med. 70(3):345-348, 2008. (HU, BE)

OBJECTIVES: The objective of this study was to examine whether acute exposure to radio frequency electromagnetic fields (REFs) emitted by mobile phone may affect subjective symptoms. METHODS: Three large groups of volunteers (total 496) were exposed to REFs emitted by mobile phones in one session and sham signals in a different session. REF and sham exposure sessions were counterbalanced and double blinded. Participants were exposed to either Global System for Mobile Communication (GSM) or unmodulated signals, and the mobile phone was positioned either on the left or on the right side of the head. Before and after REF and sham exposure participants completed a questionnaire to rate five symptoms. Any changes in the severity of the symptoms after REF exposure were compared with changes after sham exposure. RESULTS: For one group of participants (N = 160), it was found that dizziness was affected by GSM exposure, but this was not consistently found with the other two groups of participants. No other significant effects were found. CONCLUSIONS: We did not find consistent evidence suggesting that exposure to mobile phone REFs affect subjective symptoms. Even though we acknowledge that more research is needed, we believe that our results give an important contribution to the research on mobile phone use and subjective symptoms.

(E) Croft RJ, Hamblin DL, Spong J, Wood AW, McKenzie RJ, Stough C. The effect of mobile phone electromagnetic fields on the alpha rhythm of human electroencephalogram. Bioelectromagnetics. 29(1):1-10, 2008. (HU, EE)

Mobile phones (MP) emit low-level electromagnetic fields that have been reported to affect neural function in humans; however, demonstrations of such effects have not been conclusive. The purpose of the present study was to test one of the strongest findings in the literature; that of increased "alpha" power in response to MP-type radiation. Healthy participants (N = 120) were tested using a double-blind counterbalanced crossover design, with each receiving a 30-min Active and a 30-min Sham Exposure 1 week apart, while electroencephalogram (EEG) data were recorded. Resting alpha power (8-12 Hz) was then derived as a function of time, for periods both during and following exposure. Non-parametric analyses were employed as data could not be normalized. Previous reports of an overall alpha power enhancement during the MP exposure were confirmed (relative to Sham), with this effect larger at ipsilateral than contralateral sites over posterior regions. No overall change to alpha power was observed following exposure cessation; however, there was less alpha power contralateral to the exposure source during this period (relative to ipsilateral). Employing a strong methodology, the current findings support previous research that has reported an effect of MP exposure on EEG alpha power.

(E) Croft RJ, Leung S, McKenzie RJ, Loughran SP, Iskra S, Hamblin DL, Cooper NR. Effects of 2G and 3G mobile phones on human alpha rhythms: Resting EEG in adolescents, young adults, and the elderly. Bioelectromagnetics. 31(6):434-444, 2010. (HU, EE, AD, WS)

The present study was conducted to determine whether adolescents and/or the elderly are more sensitive to mobile phone (MP)-related bioeffects than young adults, and to determine this for both 2nd generation (2G) GSM, and 3rd generation (3G) W-CDMA exposures. To test this, resting alpha activity (8-12 Hz band of the electroencephalogram) was assessed because numerous studies have now reported it to be enhanced by MP exposure. Forty-one 13-15 year olds, forty-two 19-40 year olds, and twenty 55-70 year olds were tested using a double-blind crossover design, where each participant received Sham, 2G and 3G exposures, separated by at least 4 days. Alpha activity, during exposure relative to baseline, was recorded and compared between conditions. Consistent with previous research, the young adults' alpha was greater in the 2G compared to Sham condition, however, no effect was seen in the adolescent or the elderly groups, and no effect of 3G exposures was found in any group. The results provide further support for an effect of 2G exposures on resting alpha activity in young adults, but fail to support a similar enhancement in adolescents or the elderly, or in any age group as a function of 3G exposure.

(NE) Curcio G, Valentini E, Moroni F, Ferrara M, De Gennaro L, Bertini M. Psychomotor performance is not influenced by brief repeated exposures to mobile phones. Bioelectromagnetics. 29(3):237-241, 2008. (HU, BE)

The present study investigated the presence of a cumulative effect of brief and repeated exposures to a GSM mobile phone (902.40 MHz, 217 Hz modulated; peak power of 2 W; average power of 0.25 W; SAR = 0.5 W/kg) on psychomotor functions. To this end, after each of 3 15-min exposures, both an acoustic simple reaction time task (SRTT) and a sequential finger tapping task (SFTT) were administered to 24 subjects. The present study was unable to detect

the cumulative effects of brief and repeated EMF exposure on human psychomotor performance, although there was a non-statistical trend to shorter reaction times. In summary, these data show an absence of effects with these particular exposure conditions; however, possible cognitive effects induced by different signal characteristics cannot be excluded.

(E) Curcio G, Ferrara M, Limongi T, Tempesta D, Di Sante G, De Gennaro L, Quaresima V, Ferrari M. Acute mobile phones exposure affects frontal cortex hemodynamics as evidenced by functional near-infrared spectroscopy. J Cereb Blood Flow Metab. 29(5):903-910, 2009. (HU, PE)

This study aimed to evaluate by functional near-infrared spectroscopy (fNIRS), the effects induced by an acute exposure (40 mins) to a GSM (Global System for Mobile Communications) signal emitted by a mobile phone (MP) on the oxygenation of the frontal cortex. Eleven healthy volunteers underwent two sessions (Real and Sham exposure) after a crossover, randomized, double-blind paradigm. The whole procedure lasted 60 mins: 10-mins baseline (Bsl), 40-mins (Exposure), and 10-mins recovery (Post-Exp). Together with frontal hemodynamics, heart rate, objective and subjective vigilance, and self-evaluation of subjective symptoms were also assessed. The fNIRS results showed a slight influence of the GSM signal on frontal cortex, with a linear increase in [HHb] as a function of time in the Real exposure condition ($F(4,40)=2.67$; $P=0.04$). No other measure showed any GSM exposure-dependent changes. These results suggest that fNIRS is a convenient tool for safely and noninvasively investigating the cortical activation in MP exposure experimental settings. Given the short-term effects observed in this study, the results should be confirmed on a larger sample size and using a multichannel instrument that allows the investigation of a wider portion of the frontal cortex.

(NE) Curcio G, Nardo D, Perrucci MG, Pasqualetti P, Chen TL, Del Gratta C, Romani GL, Rossini PM. Effects of mobile phone signals over BOLD response while performing a cognitive task. Clin Neurophysiol. 123(1):129-136, 2012. (HU, BE, PE)

OBJECTIVE: The aim of this study was to investigate the effects induced by an exposure to a GSM signal (Global System for Mobile Communication) on brain BOLD (blood-oxygen-level dependent) response, as well as its time course while performing a Go-NoGo task. **METHODS:** Participants were tested twice, once in presence of a "real" exposure to GSM radiofrequency signal and once under a "sham" exposure (placebo condition). BOLD response of active brain areas and reaction times (RTs) while performing the task were measured both before and after the exposure. **RESULTS:** RTs to the somatosensory task did not change as a function of exposure (real vs sham) to GSM signal. BOLD results revealed significant activations in inferior parietal lobule, insula, precentral and postcentral gyri associated with Go responses after both "real" and "sham" exposure, whereas no significant effects were observed in the ROI analysis. **CONCLUSIONS:** The present fMRI study did not detect any brain activity changes by mobile phones. Also RTs in a somatosensory task resulted unaffected. **SIGNIFICANCE:** No changes in BOLD response have been observed as a consequence of RF-EMFs exposure.

(NE) Curcio G, Mazzucchi E, Marca GD, Vollono C, Rossini PM. Electromagnetic fields and EEG spiking rate in patients with focal epilepsy. Clin Neurophysiol. 2014 Aug 11. pii: S1388-2457(14)00404-0. doi: 10.1016/j.clinph.2014.07.013. [Epub ahead of print] (HU, EE)

OBJECTIVE: Despite the increase in mobile telephone technology use and possible effects on brain excitability, no studies have investigated the impact of GSM like (Global System for Mobile Communications) signal on the ongoing spiking activity in human epileptic patients. **METHODS:** Brain electrical (electroencephalogram, EEG) activity of 12 patients with focal epilepsy has been recorded under both Real and Sham exposure following a double-blind, crossover, counterbalanced design: before the exposure (pre-exposure/baseline session), during the Real or Sham 45min exposure (during-exposure session), and after the exposure (post-exposure session). As dependent variables both spiking activity (spikes count) and EEG quantitative indices (spectral power and coherence data) have been considered. **RESULTS:** Spiking activity tended to be lower under Real than under Sham exposure. EEG spectral content analysis indicated a significant increase of Gamma band under Real exposure, mainly evident in Parieto-occipital and Temporal areas. Connectivity data indicated increased interhemispheric (left temporal to right frontal Regions of Interest, ROIs) instantaneous coherence, in the Beta frequency band during-exposure with respect to baseline session. No significant modification of lagged coherence was observed. **CONCLUSIONS:** Acute GSM exposure in epileptic patients slightly influences their EEG properties, without reaching any clinical relevance. **SIGNIFICANCE:** No signs were found of an increased risk of incoming seizures for these patients as a consequence of using mobile phones.

(E) Daniels WM, Pitout IL, Afullo TJ, Mabandla MV. The effect of electromagnetic radiation in the mobile phone range on the behaviour of the rat. Metab Brain Dis. 24(4):629-641, 2009. (AS, ME, BE)

Electromagnetic radiation (EMR) is emitted from electromagnetic fields that surround power lines, household appliances and mobile phones. Research has shown that there are connections between EMR exposure and cancer and also that exposure to EMR may result in structural damage to neurons. In a study by Salford et al. (Environ Health Perspect 111:881-883, 2003) the authors demonstrated the presence of strongly stained areas in the brains of rats that were exposed to mobile phone EMR. These darker neurons were particularly prevalent in the hippocampal area of the brain. The aim of our study was to further investigate the effects of EMR. Since the hippocampus is involved in learning and memory and emotional states, we hypothesised that EMR will have a negative impact on the subject's mood and ability to learn. We subsequently performed behavioural, histological and biochemical tests on exposed and unexposed male and female rats to determine the effects of EMR on learning and memory, emotional states and corticosterone levels. We found no significant differences in the spatial memory test, and morphological assessment of the brain also yielded non-significant differences between the groups. However, in some exposed animals there were decreased locomotor activity, increased grooming and a tendency of increased basal corticosterone levels. These findings suggested that EMR exposure may lead to abnormal brain functioning.

***(NE) Danker-Hopfe H, Dorn H, Bornkessel C, Sauter C. Do mobile phone base stations affect sleep of residents? Results from an experimental double-blind sham-controlled field study. Am J Hum Biol. 22(5):613-618, 2010. (HU, BE, LI, SL) (*Effects observed probably not caused by exposure to RFR.)**

OBJECTIVES: The aim of the present double-blind, sham-controlled, balanced randomized cross-over study was to disentangle effects of electromagnetic fields (EMF) and non-EMF effects of mobile phone base stations on objective and subjective sleep quality. METHODS: In total 397 residents aged 18-81 years (50.9% female) from 10 German sites, where no mobile phone service was available, were exposed to sham and GSM (Global System for Mobile Communications, 900 MHz and 1,800 MHz) base station signals by an experimental base station while their sleep was monitored at their homes during 12 nights. Participants were randomly exposed to real (GSM) or sham exposure for five nights each. Individual measurement of EMF exposure, questionnaires on sleep disorders, overall sleep quality, attitude towards mobile communication, and on subjective sleep quality (morning and evening protocols) as well as objective sleep data (frontal EEG and EOG recordings) were gathered. RESULTS: Analysis of the subjective and objective sleep data did not reveal any significant differences between the real and sham condition. During sham exposure nights, objective and subjective sleep efficiency, wake after sleep onset, and subjective sleep latency were significantly worse in participants with concerns about possible health risks resulting from base stations than in participants who were not concerned. CONCLUSIONS: The study did not provide any evidence for short-term physiological effects of EMF emitted by mobile phone base stations on objective and subjective sleep quality. However, the results indicate that mobile phone base stations as such (not the electromagnetic fields) may have a significant negative impact on sleep quality.

(NE) Danker-Hopfe H, Dorn H, Bahr A, Anderer P, Sauter C. Effects of electromagnetic fields emitted by mobile phones (GSM 900 and WCDMA/UMTS) on the macrostructure of sleep. J Sleep Res. 20(1 Pt 1):73-81, 2011. (HU, BE, SL)

In the present double-blind, randomized, sham-controlled cross-over study, possible effects of electromagnetic fields emitted by Global System for Mobile Communications (GSM) 900 and Wideband Code-Division Multiple Access (WCDMA)/Universal Mobile Telecommunications System (UMTS) cell-phones on the macrostructure of sleep were investigated in a laboratory environment. An adaptation night, which served as screening night for sleep disorders and as an adjustment night to the laboratory environment, was followed by 9 study nights (separated by a 2-week interval) in which subjects were exposed to three exposure conditions (sham, GSM 900 and WCDMA/UMTS). The sample comprised 30 healthy male subjects within the age range 18-30 years (mean \pm standard deviation: 25.3 ± 2.6 years). A cell-phone usage at maximum radio frequency (RF) output power was simulated and the transmitted power was adjusted in order to approach, but not to exceed, the specific absorption rate (SAR) limits of the International Commission on Non-Ionizing Radiation Protection (ICNIRP) guidelines for general public exposure ($SAR(10g) = 2.0 \text{ W kg}^{-1}$). In this study, possible effects of long-term (8 h) continuous RF exposure on the central nervous system were analysed during sleep, because sleep is a state in which many confounding intrinsic and extrinsic factors (e.g. motivation,

personality, attitude) are eliminated or controlled. Thirteen of 177 variables characterizing the initiation and maintenance of sleep in the GSM 900 and three in the WCDMA exposure condition differed from the sham condition. The few significant results are not indicative of a negative impact on sleep architecture. From the present results there is no evidence for a sleep-disturbing effect of GSM 900 and WCDMA exposure.

(E) Danker-Hopfe H, Dorn H, Bolz T, Peter A, Hansen ML, Eggert T, Sauter C. Effects of mobile phone exposure (GSM 900 and WCDMA/UMTS) on polysomnography based sleep quality: An intra- and inter-individual perspective. Environ Res. 145:50-60, 2015. (HU, SL)

BACKGROUND: Studies on effects of radio frequency-electromagnetic fields (RF-EMF) on the macrostructure of sleep so far yielded inconsistent results. This study investigated whether possible effects of RF-EMF exposure differ between individuals. OBJECTIVE: In a double-blind, randomized, sham-controlled cross-over study possible effects of electromagnetic fields emitted by pulsed Global System for Mobile Communications (GSM) 900 and Wideband Code-Division Multiple Access (WCDMA)/Universal Mobile Telecommunications System (WCDMA/UMTS) devices on sleep were analysed. METHODS: Thirty healthy young men (range 18-30 years) were exposed three times per exposure condition while their sleep was recorded. Sleep was evaluated according to the American Academy of Sleep Medicine standard and eight basic sleep variables were considered. RESULTS: Data analyses at the individual level indicate that RF-EMF effects are observed in 90% of the individuals and that all sleep variables are affected in at least four subjects. While sleep of participants was affected in various numbers, combinations of sleep variables and in different directions, showing improvements but also deteriorations, the only consistent finding was an increase of stage R sleep under GSM 900MHz exposure (9 of 30 subjects) as well as under WCDMA/UMTS exposure (10 of 30 subjects). CONCLUSIONS: The results underline that sleep of individuals can be affected differently. The observations found here may indicate an underlying thermal mechanism of RF-EMF on human REM sleep. Nevertheless, the effect of an increase in stage R sleep in one third of the individuals does not necessarily indicate a disturbance of sleep.

(E) Dasdag S, Akdag MZ, Ulukaya E, Uzunlar AK, Ocak AR. Effect of mobile phone exposure on apoptotic glial cells and status of oxidative stress in rat brain. Electromagn Biol Med. 28(4):342-354, 2009. (AS, CE, CC, OX)

The aim of this study was to investigate the effects of mobile phone exposure on glial cells in brain. The study carried out on 31 Wistar Albino adult male rats. The rat heads in a carousel exposed to 900 MHz microwave. For the study group (n:14), rats exposed to the radiation 2 h per day (7 days in a week) for 10 months. For the sham group (n:7), rats were placed into the carousel and the same procedure was applied except that the generator was turned off. For the cage control (n:10), nothing applied to rats in this group. In this study, rats were euthanized after 10 months of exposure periods and brains were removed. Brain tissues were

immunohistochemically stained for the active (cleaved) caspase-3, which is a well-known apoptosis marker, and p53. The expression of the proteins was evaluated by a semi-quantitative scoring system. However, total antioxidative capacity (TAC), catalase, total oxidant status (TOS), and oxidative stress index were measured in rat brain. Final score for apoptosis in the exposed group was significantly lower than the sham ($p < 0.001$) and the cage control groups ($p < 0.01$). p53 was not significantly changed by the exposure ($p > 0.05$). The total antioxidant capacity and catalase in the experimental group was found higher than that in the sham group ($p < 0.001$, $p < 0.05$). In terms of the TOS and oxidative stress index, there was no statistically significant difference between exposure and sham groups ($p > 0.05$). In conclusion, the final score for apoptosis, total antioxidant capacity and catalase in rat brain might be altered by 900 MHz radiation produced by a generator to represent exposure of global systems for mobile communication (GSM) cellular phones.

(E) Dasdag S, Akdag MZ, Kizil G, Kizil M, Cakir DU, Yokus B. Effect of 900 MHz radio frequency radiation on beta amyloid protein, protein carbonyl, and malondialdehyde in the brain. Electromagn Biol Med. 31(1):67-74, 2012. (AS, CE, CH, OX)

Recently, many studies have been carried out in relation to 900 MHz radiofrequency radiation (RF) emitted from a mobile phone on the brain. However, there is little data concerning possible mechanisms between long-term exposure of RF radiation and biomolecules in brain. Therefore, we aimed to investigate long-term effects of 900 MHz radiofrequency radiation on beta amyloid protein, protein carbonyl, and malondialdehyde in the rat brain. The study was carried out on 17 Wistar Albino adult male rats. The rat heads in a carousel were exposed to 900 MHz radiofrequency radiation emitted from a generator, simulating mobile phones. For the study group (n: 10), rats were exposed to the radiation 2 h per day (7 days a week) for 10 months. For the sham group (n: 7), rats were placed into the carousel and the same procedure was applied except that the generator was turned off. In this study, rats were euthanized after 10 months of exposure and their brains were removed. Beta amyloid protein, protein carbonyl, and malondialdehyde levels were found to be higher in the brain of rats exposed to 900 MHz radiofrequency radiation. However, only the increase of protein carbonyl in the brain of rats exposed to 900 MHz radiofrequency radiation was found to be statistically significant ($p < 0.001$). In conclusion, 900 MHz radiation emitted from mobile/cellular phones can be an agent to alter some biomolecules such as protein. However, further studies are necessary.

(NE) de Gannes FP, Billaudel B, Taxile M, Haro E, Ruffié G, Lévêque P, Veyret B, Lagroye I. Effects of head-only exposure of rats to GSM-900 on blood-brain barrier permeability and neuronal degeneration. Radiat Res. 172(3):359-367, 2009. (AS, CE, ME, CC)

Salford et al. reported in 2003 that a single 2-h exposure to GSM-900 mobile telephony signals induced brain damage (increased permeability of the blood-brain barrier and presence of dark neurons) 50 days after exposure. In our study, 16 Fischer 344 rats (14 weeks old) were exposed head-only to the GSM-900 signal for 2 h at various brain-averaged SARs (0, 0.14 and 2.0 W/kg) or were used as cage or positive controls. Albumin leakage and neuron degeneration were evaluated 14 and 50 days after exposure. No apoptotic neurons were found 14 days after the

last exposure using the TUNEL method. No statistically significant albumin leakage was observed. Neuronal degeneration, assessed using cresyl violet or the more specific marker Fluoro-Jade B, was not significantly different among the tested groups. No apoptotic neurons were detected. The findings of our study did not confirm the previous results of Salford et al.

(E) de Tommaso M, Rossi P, Falsaperla R, Francesco Vde V, Santoro R, Federici A. Mobile phones exposure induces changes of contingent negative variation in humans. Neurosci Lett. 464(2):79-83, 2009. (HU, EE)

Event-related potentials have been largely employed to test effects of GSM emissions on human brain. The aim of the present study was the evaluation of initial contingent negative variation (iCNV) changes, induced by 900 MHz GSM exposure, in a double blind design in healthy volunteers, subjected to a threefold experimental condition, EXPOSED (A), a real GSM phone emitting electromagnetic power, SHAM (B), a real phone where the electromagnetic power was dissipated on an internal load and OFF (C), a phone completely switched-off. Ten healthy right-handed volunteers were evaluated. The CNV was recorded during a 10 min time interval in each of the three experimental conditions A, B, and C, in order to assess the iCNV amplitude and habituation. The iCNV amplitude decreased and habituation increased during both A and B conditions, compared with condition C. This effect was diffuse over the scalp, and there was no significant prevalence of iCNV amplitude reduction on the left side, where the phones were located. Mobile Phones exposures A and B seemed to act on brain electrical activity, reducing the arousal and expectation of warning stimulus. This evidence, limited by the low number of subjects investigated, could be explained in terms of an effect induced by both the GSM signal and the extremely low frequency magnetic field produced by battery and internal circuits.

(E) Del Vecchio G, Giuliani A, Fernandez M, Mesirca P, Bersani F, Pinto R, Ardoino L, Lovisolo GA, Giardino L, Calzà L. Effect of radiofrequency electromagnetic field exposure on in vitro models of neurodegenerative disease. Bioelectromagnetics. 30(7):564-572, 2009. (CS, CE, IA, OX)

In this work we tested viability, proliferation, and vulnerability of neural cells, after continuous radiofrequency (RF) electromagnetic fields exposure (global system for mobile telecommunications (GSM) modulated 900 MHz signal at a specific absorption rate (SAR) of 1 W/kg and maximum duration 144 h) generated by transverse electromagnetic cells. We used two cellular systems, SN56 cholinergic for example, SN56 cholinergic cell line and rat primary cortical neurons, and well-known neurotoxic challenges, such as glutamate, 25-35AA beta-amyloid, and hydrogen peroxide. Exposure to RF did not change viability/proliferation rate of the SN56 cholinergic cells or viability of cortical neurons. Co-exposure to RF exacerbated neurotoxic effect of hydrogen peroxide in SN56, but not in primary cortical neurons, whereas no cooperative effects of RF with glutamate and 25-35AA beta-amyloid were found. These data suggest that only under particular circumstances exposure to GSM modulated, 900 MHz signal act as a co-stressor for oxidative damage of neural cells.

(E) Del Vecchio G, Giuliani A, Fernandez M, Mesirca P, Bersani F, Pinto R, Ardoino L, Lovisolo GA, Giardino L, Calzà L. Continuous exposure to 900MHz GSM-modulated EMF alters morphological maturation of neural cells. Neurosci Lett. 455(3):173-177, 2009. (CS, ME, DE)

The effects of radiofrequency electromagnetic field (RF-EMF) exposure on neuronal phenotype maturation have been studied in two different in vitro models: murine SN56 cholinergic cell line and rat primary cortical neurons. The samples were exposed at a dose of 1W/kg at 900 MHz GSM modulated. The phenotype analysis was carried out at 48 and 72 h (24 and 48 h of SN56 cell line differentiation) or at 24, 72, 120 h (2, 4 and 6 days in vitro for cortical neurons) of exposure, on live and immunolabeled neurons, and included the morphological study of neurite emission, outgrowth and branching. Moreover, cortical neurons were studied to detect alterations in the expression pattern of cytoskeleton regulating factors, e.g. beta-thymosin, and of early genes, e.g. c-Fos and c-Jun through real-time PCR on mRNA extracted after 24h exposure to EMF. We found that RF-EMF exposure reduced the number of neurites generated by both cell systems, and this alteration correlates to increased expression of beta-thymosin mRNA.

(E) Deniz OG, Kaplan S, Selcuk MB, Terzi M, Altun, Yurt KK, Aslan K, Davis D. Effects of short and long term electromagnetic fields exposure on the human hippocampus. J Micros Ultrastru (2017, In press) (HU, ME, BE)

The increasing use of mobile phones may have a number of physiological and psychological effects on human health. Many animal and human studies have reported various effects on the central nervous system and cognitive performance from exposure to electromagnetic fields (EMF) emitted by mobile phones. The aim of the present study was to evaluate the effects of mobile phones on the morphology of the human brain and on cognitive performance using stereological and spectroscopic methods and neurocognitive tests. Sixty healthy female medical school students aged 18–25 years were divided into a low exposure group (30 subjects, <30 min daily use by the head) and high exposure group (30 subjects, >90 min daily use by the head). Magnetic resonance images (MRI) of the brain analysed on OsiriX 3.2.1 workstation. Neuropsychological tests were performed for each subject. In addition, three dominant specific metabolites were analysed, choline at 3.21 ppm, creatine at 3.04 ppm and N-acetyl aspartate at 2.02 ppm. Analysis of the spectroscopic results revealed no significant difference in specific metabolites between the groups ($p > 0.05$). There was also no significant difference in terms of hippocampal volume between the groups ($p > 0.05$). In contrast, the results of the stroop and digit span (backward) neurocognitive tests of high exposure group for evaluating attention were significantly poorer from low exposure group ($p < 0.05$). Based on these results, we conclude that a lack of attention and concentration may occur in subjects who talk on mobile phones for longer times, compared to those who use phones relatively less.

(E) Deshmukh PS, Banerjee BD, Abegaonkar MP, Megha K, Ahmed RS, Tripathi AK, Mediratta PK. Effect of low level microwave radiation exposure on cognitive function and oxidative stress in rats. Indian J Biochem Biophys. 50(2):114-119, 2013a. (AS, LI, CE, BE, OX)

Use of wireless communicating devices is increasing at an exponential rate in present time and is raising serious concerns about possible adverse effects of microwave (MW) radiation emitted from these devices on human health. The present study aimed to evaluate the effects of 900 MHz MW radiation exposure on cognitive function and oxidative stress in blood of Fischer rats. Animals were divided into two groups (6 animals/group): Group I (MW-exposed) and Group II (Sham-exposed). Animals were subjected to MW exposure (Frequency 900 MHz; specific absorption rate 8.4738×10^{-5} W/kg) in Gigahertz transverse electromagnetic cell (GTEM) for 30 days (2 h/day, 5 days/week). Subsequently, cognitive function and oxidative stress parameters were examined for each group. Results showed significant impairment in cognitive function and increase in oxidative stress, as evidenced by the increase in levels of MDA (a marker of lipid peroxidation) and protein carbonyl (a marker of protein oxidation) and unaltered GSH content in blood. Thus, the study demonstrated that low level MW radiation had significant effect on cognitive function and was also capable of leading to oxidative stress.

(E) Deshmukh PS, Megha K, Banerjee BD, Ahmed RS, Chandna S, Abegaonkar MP, Tripathi AK. Detection of Low Level Microwave Radiation Induced Deoxyribonucleic Acid Damage Vis-à-vis Genotoxicity in Brain of Fischer Rats. Toxicol Int. 20(1):19-24, 2013b. (AS, LI, CE, CH)

BACKGROUND: Non-ionizing radiofrequency radiation has been increasingly used in industry, commerce, medicine and especially in mobile phone technology and has become a matter of serious concern in present time. OBJECTIVE: The present study was designed to investigate the possible deoxyribonucleic acid (DNA) damaging effects of low-level microwave radiation in brain of Fischer rats. MATERIALS AND METHODS: Experiments were performed on male Fischer rats exposed to microwave radiation for 30 days at three different frequencies: 900, 1800 and **2450 MHz**. Animals were divided into 4 groups: Group I (Sham exposed): Animals not exposed to microwave radiation but kept under same conditions as that of other groups, Group II: Animals exposed to microwave radiation at frequency 900 **MHz** at specific absorption rate (SAR) 5.953×10^{-4} W/kg, Group III: Animals exposed to 1800 **MHz** at SAR 5.835×10^{-4} W/kg and Group IV: Animals exposed to **2450 MHz** at SAR 6.672×10^{-4} W/kg. At the end of the exposure period animals were sacrificed immediately and DNA damage in brain tissue was assessed using alkaline comet assay. RESULTS: In the present study, we demonstrated DNA damaging effects of low level microwave radiation in brain. CONCLUSION: We concluded that low SAR microwave radiation exposure at these frequencies may induce DNA strand breaks in brain tissue.

(E) Deshmukh PS, Nasare N, Megha K, Banerjee BD, Ahmed RS, Singh D, Abegaonkar MP, Tripathi AK, Mediratta PK. Cognitive Impairment and Neurogenotoxic Effects in Rats Exposed to Low-Intensity Microwave Radiation. Int J Toxicol. 2015 Mar 5. pii: 1091581815574348. [Epub ahead of print] (AS, CE, LI, BE, CH)

The health hazard of microwave radiation (MWR) has become a recent subject of interest as a result of the enormous increase in mobile phone usage. The present study aimed to investigate the effects of chronic low-intensity microwave exposure on cognitive function, heat shock

protein 70 (HSP70), and DNA damage in rat brain. Experiments were performed on male Fischer rats exposed to MWR for 180 days at 3 different frequencies, namely, 900, 1800 MHz, and 2450 MHz. Animals were divided into 4 groups: group I: sham exposed; group II: exposed to MWR at 900 MHz, specific absorption rate (SAR) 5.953×10^{-4} W/kg; group III: exposed to 1800 MHz, SAR 5.835×10^{-4} W/kg; and group IV: exposed to 2450 MHz, SAR 6.672×10^{-4} W/kg. All the rats were tested for cognitive function at the end of the exposure period and were subsequently sacrificed to collect brain. Level of HSP70 was estimated by enzyme-linked immunotarget assay and DNA damage was assessed using alkaline comet assay in all the groups. The results showed declined cognitive function, elevated HSP70 level, and DNA damage in the brain of microwave-exposed animals. The results indicated that, chronic low-intensity microwave exposure in the frequency range of 900 to 2450 MHz may cause hazardous effects on the brain.

(E) Deshmukh PS, Megha K, Nasare N, Banerjee BD, Ahmed RS, Abegaonkar MP, Tripathi AK, Mediratta PK. Effect of Low Level Subchronic Microwave Radiation on Rat Brain. Biomed Environ Sci. 29(12):858-867, 2016. (AS, LI, CE, BE, CC)

OBJECTIVE: The present study was designed to investigate the effects of subchronic low level microwave radiation (MWR) on cognitive function, heat shock protein 70 (HSP70) level and DNA damage in brain of Fischer rats. **METHODS:** Experiments were performed on male Fischer rats exposed to microwave radiation for 90 days at three different frequencies: 900, 1800, and 2450 MHz. Animals were divided into 4 groups: Group I: Sham exposed, Group II: animals exposed to microwave radiation at 900 MHz and specific absorption rate (SAR) 5.953×10^{-4} W/kg, Group III: animals exposed to 1800 MHz at SAR 5.835×10^{-4} W/kg and Group IV: animals exposed to 2450 MHz at SAR 6.672×10^{-4} W/kg. All the animals were tested for cognitive function using elevated plus maze and Morris water maze at the end of the exposure period and subsequently sacrificed to collect brain tissues. HSP70 levels were estimated by ELISA and DNA damage was assessed using alkaline comet assay. **RESULTS:** Microwave exposure at 900-2450 MHz with SAR values as mentioned above lead to decline in cognitive function, increase in HSP70 level and DNA damage in brain. **CONCLUSION:** The results of the present study suggest that low level microwave exposure at frequencies 900, 1800, and 2450 MHz may lead to hazardous effects on brain.

(E) Divan HA, Kheifets L, Obel C, Olsen J. Prenatal and postnatal exposure to cell phone use and behavioral problems in children. Epidemiology. 19(4):523-529, 2008. (HU, DE, BE)

BACKGROUND: The World Health Organization has emphasized the need for research into the possible effects of radiofrequency fields in children. We examined the association between prenatal and postnatal exposure to cell phones and behavioral problems in young children. **METHODS:** Mothers were recruited to the Danish National Birth Cohort early in pregnancy. When the children of those pregnancies reached 7 years of age in 2005 and 2006, mothers were asked to complete a questionnaire regarding the current health and behavioral status of children, as well as past exposure to cell phone use. Mothers evaluated the child's behavior problems using the Strength and Difficulties Questionnaire. **RESULTS:** Mothers of 13,159

children completed the follow-up questionnaire reporting their use of cell phones during pregnancy as well as current cell phone use by the child. Greater odds ratios for behavioral problems were observed for children who had possible prenatal or postnatal exposure to cell phone use. After adjustment for potential confounders, the odds ratio for a higher overall behavioral problems score was 1.80 (95% confidence interval = 1.45-2.23) in children with both prenatal and postnatal exposure to cell phones. **CONCLUSIONS:** Exposure to cell phones prenatally-and, to a lesser degree, postnatally-was associated with behavioral difficulties such as emotional and hyperactivity problems around the age of school entry. These associations may be noncausal and may be due to unmeasured confounding. If real, they would be of public health concern given the widespread use of this technology.

(NE) Divan HA, Kheifets L, Olsen J. Prenatal cell phone use and developmental milestone delays among infants. Scand J Work Environ Health. 37(4):341-348, 2011. (HU, DE, BE)

OBJECTIVE: The aim of this study was to examine if prenatal use of cell phones by pregnant mothers is associated with developmental milestones delays among offspring up to 18 months of age. **METHODS:** Our work is based upon the Danish National Birth Cohort (DNBC), which recruited pregnant mothers from 1996-2002, and was initiated to collect a variety of detailed information regarding in utero exposures and various health outcomes. At the end of 2008, over 41,000 singleton, live births had been followed with the Age-7 questionnaire, which collected cell phone use exposure for mothers during pregnancy. Outcomes for developmental milestones were obtained from telephone interviews completed by mothers at age 6 and 18 months postpartum. **RESULTS:** A logistic regression model estimated the odds ratios (OR) for developmental milestone delays, adjusted for potential confounders. Less than 5% of children at age 6 and 18 months had cognitive/language or motor developmental delays. At 6 months, the adjusted OR was 0.8 [95% confidence interval (95% CI) 0.7-1.0] for cognitive/language delay and 0.9 (95% CI 0.8-1.1) for motor development delay. At 18 months, the adjusted OR were 1.1 (95% CI 0.9-1.3) and 0.9 (95% CI 0.8-1.0) for cognitive/language and motor development delay, respectively. **CONCLUSIONS:** No evidence of an association between prenatal cell phone use and motor or cognitive/language developmental delays among infants at 6 and 18 months of age was observed. Even when considering dose-response associations for cell phone, associations were null.

(E) Divan HA, Kheifets L, Obel C, Olsen J. Cell phone use and behavioural problems in young children. J Epidemiol Community Health. 66(6):524-529, 2012. (HU, DE, BE)

BACKGROUND: Potential health effects of cell phone use in children have not been adequately examined. As children are using cell phones at earlier ages, research among this group has been identified as the highest priority by both national and international organisations. The authors previously reported results from the Danish National Birth Cohort (DNBC), which looked at prenatal and postnatal exposure to cell phone use and behavioural problems at age 7 years. Exposure to cell phones prenatally, and to a lesser degree postnatally, was associated with more behavioural difficulties. The original analysis included nearly 13 000 children who reached age 7 years by November 2006. **METHODS:** To see if a larger, separate group of DNBC children

would produce similar results after considering additional confounders, children of mothers who might better represent current users of cell phones were analysed. This 'new' dataset consisted of 28 745 children with completed Age-7 Questionnaires to December 2008.

RESULTS: The highest OR for behavioural problems were for children who had both prenatal and postnatal exposure to cell phones compared with children not exposed during either time period. The adjusted effect estimate was 1.5 (95% CI 1.4 to 1.7). **CONCLUSIONS:** The findings of the previous publication were replicated in this separate group of participants demonstrating that cell phone use was associated with behavioural problems at age 7 years in children, and this association was not limited to early users of the technology. Although weaker in the new dataset, even with further control for an extended set of potential confounders, the associations remained.

(NE) Dogan M, Turtay MG, Oguzturk H, Samdanci E, Turkoz Y, Tasdemir S, Alkan A, Bakir S. Effects of electromagnetic radiation produced by 3G mobile phones on rat brains: magnetic resonance spectroscopy, biochemical, and histopathological evaluation. Hum Exp Toxicol. 31(6):557-564, 2012. (AS, CE, OX, CC, CH)

Objective: The effects of electromagnetic radiation (EMR) produced by a third-generation (3G) mobile phone (MP) on rat brain tissues were investigated in terms of magnetic resonance spectroscopy (MRS), biochemistry, and histopathological evaluations. Methods: The rats were randomly assigned to two groups: Group 1 is composed of 3G-EMR-exposed rats (n = 9) and Group 2 is the control group (n = 9). The first group was subjected to EMR for 20 days. The control group was not exposed to EMR. Choline (Cho), creatinin (Cr), and N-acetylaspartate (NAA) levels were evaluated by MRS. Catalase (CAT) and glutathione peroxidase (GSH-Px) enzyme activities were measured by spectrophotometric method. Histopathological analyses were carried out to evaluate apoptosis in the brain tissues of both groups. Results: In MRS, NAA/Cr, Cho/Cr, and NAA/Cho ratios were not significantly different between Groups 1 and 2. Neither the oxidative stress parameters, CAT and GSH-Px, nor the number of apoptotic cells were significantly different between Groups 1 and 2. Conclusions: Usage of short-term 3G MP does not seem to have a harmful effect on rat brain tissue.

(E) Dragicevic N, Bradshaw PC, Mamcarz M, Lin X, Wang L, Cao C, Arendash GW. Long-term electromagnetic field treatment enhances brain mitochondrial function of both Alzheimer's transgenic mice and normal mice: a mechanism for electromagnetic field-induced cognitive benefit? Neuroscience 185:135-149, 2011. (AS, CE, CC, OX, MA)

We have recently reported that long-term exposure to high frequency electromagnetic field (EMF) treatment not only prevents or reverses cognitive impairment in Alzheimer's transgenic (Tg) mice, but also improves memory in normal mice. To elucidate the possible mechanism(s) for these EMF-induced cognitive benefits, brain mitochondrial function was evaluated in aged Tg mice and non-transgenic (NT) littermates following 1 month of daily EMF exposure. In Tg mice, EMF treatment enhanced brain mitochondrial function by 50-150% across six established measures, being greatest in cognitively-important brain areas (e.g. cerebral cortex and hippocampus). EMF treatment also increased brain mitochondrial function in normal aged

mice, although the enhancement was not as robust and less widespread compared to that of Tg mice. The EMF-induced enhancement of brain mitochondrial function in Tg mice was accompanied by 5-10 fold increases in soluble A β 1-40 within the same mitochondrial preparations. These increases in mitochondrial soluble amyloid- β peptide (A β) were apparently due to the ability of EMF treatment to disaggregate A β oligomers, which are believed to be the form of A β causative to mitochondrial dysfunction in Alzheimer's disease (AD). Finally, the EMF-induced mitochondrial enhancement in both Tg and normal mice occurred through non-thermal effects because brain temperatures were either stable or decreased during/after EMF treatment. These results collectively suggest that brain mitochondrial enhancement may be a primary mechanism through which EMF treatment provides cognitive benefit to both Tg and NT mice. Especially in the context that mitochondrial dysfunction is an early and prominent characteristic of Alzheimer's pathogenesis, EMF treatment could have profound value in the disease's prevention and treatment through intervention at the mitochondrial level.

(E) Eberhardt JL, Persson BR, Brun AE, Salford LG, Malmgren LO. Blood-brain barrier permeability and nerve cell damage in rat brain 14 and 28 days after exposure to microwaves from GSM mobile phones. Electromagn Biol Med. 27(3):215-229, 2008. (AS, ME, CC, LI)

We investigated the effects of global system for mobile communication (GSM) microwave exposure on the permeability of the blood-brain barrier and signs of neuronal damage in rats using a real GSM programmable mobile phone in the 900 MHz band. Ninety-six non-anaesthetized rats were either exposed to microwaves or sham exposed in TEM-cells for 2 h at specific absorption rates of average whole-body Specific Absorption Rates (SAR) of 0.12, 1.2, 12, or 120 mW/kg. The rats were sacrificed after a recovery time of either 14 or 28 d, following exposure and the extravasation of albumin, its uptake into neurons, and occurrence of damaged neurons was assessed. Albumin extravasation and also its uptake into neurons was seen to be enhanced after 14 d (Kruskal Wallis test: $p = 0.02$ and 0.002 , respectively), but not after a 28 d recovery period. The occurrence of dark neurons in the rat brains, on the other hand, was enhanced later, after 28 d ($p = 0.02$). Furthermore, in the 28-d brain samples, neuronal albumin uptake was significantly correlated to occurrence of damaged neurons (Spearman $r = 0.41$; $p < 0.01$).

(NE) Eltiti S, Wallace D, Ridgewell A, Zougkou K, Russo R, Sepulveda F, Fox E. Short-term exposure to mobile phone base station signals does not affect cognitive functioning or physiological measures in individuals who report sensitivity to electromagnetic fields and controls. Bioelectromagnetics. 30(7):556-563, 2009. (HU, BE, LI)

Individuals who report sensitivity to electromagnetic fields often report cognitive impairments that they believe are due to exposure to mobile phone technology. Previous research in this area has revealed mixed results, however, with the majority of research only testing control individuals. Two studies using control and self-reported sensitive participants found inconsistent effects of mobile phone base stations on cognitive functioning. The aim of the present study was to clarify whether short-term (50 min) exposure at 10 mW/m(2) to typical Global System for Mobile Communication (GSM) and Universal Mobile Telecommunications

System (UMTS) base station signals affects attention, memory, and physiological endpoints in sensitive and control participants. Data from 44 sensitive and 44 matched-control participants who performed the digit symbol substitution task (DSST), digit span task (DS), and a mental arithmetic task (MA), while being exposed to GSM, UMTS, and sham signals under double-blind conditions were analyzed. Overall, cognitive functioning was not affected by short-term exposure to either GSM or UMTS signals in the current study. Nor did exposure affect the physiological measurements of blood volume pulse (BVP), heart rate (HR), and skin conductance (SC) that were taken while participants performed the cognitive tasks.

(E) Erdem Koç G, Kaplan S, Altun G, Gümüş H, Gülsüm Deniz Ö, Aydın I, Emin Onger M, Altunkaynak Z. Neuroprotective effects of melatonin and omega-3 on hippocampal cells prenatally exposed to 900 MHz electromagnetic fields. Int J Radiat Biol. 2016 Jul 21:1-6. [Epub ahead of print] (AS, CE, DE, CC, IA)

PURPOSE: Adverse effects on human health caused by electromagnetic fields (EMF) associated with the use of mobile phones, particularly among young people, are increasing all the time. The potential deleterious effects of EMF exposure resulting from mobile phones being used in close proximity to the brain require particular evaluation. However, only a limited number of studies have investigated the effects of prenatal exposure to EMF in the development of the pyramidal cells using melatonin (MEL) and omega-3 (ω -3). **MATERIALS AND METHODS:** We established seven groups of pregnant rats consisting of three animals each; control (CONT), SHAM, EMF, EMF + MEL, MEL, EMF + ω -3 and ω -3 alone. The rats in the EMF, EMF + MEL, EMF + ω -3 groups were exposed to 900 MHz EMF for 60 min/day in an exposure tube during the gestation period. The CONT, MEL and ω -3 group rats were not placed inside the exposure tube or exposed to EMF during the study period. After delivery, only spontaneously delivered male rat pups were selected for the establishment of further groups. Each group of offspring consisted of six animals. The optical fractionator technique was used to determine total pyramidal neuron numbers in the rat hippocampal region. **RESULTS:** The total number of pyramidal cells in the cornu ammonis (CA) in the EMF group was significantly lower than in the CONT, SHAM, EMF + MEL, and EMF + ω -3 groups. No significant difference was observed between the EMF, MEL and ω -3 groups. No difference was also observed between any groups in terms of rats' body or brain weights. **CONCLUSION:** MEL and ω -3 can protect the cell against neuronal damage in the hippocampus induced by 900 MHz EMF. However, further studies are now needed to evaluate the chronic effects of 900 MHz EMF on the brain in the prenatal period.

(E) Eser O, Songur A, Aktas C, Karavelioglu E, Caglar V, Aylak F, Ozguner F, Kanter M. The effect of electromagnetic radiation on the rat brain: an experimental study. Turk Neurosurg. 23(6):707-715, 2013. (AS, CE, OX, ME)

AIM: The aim of this study is to determine the structural changes of electromagnetic waves in the frontal cortex, brain stem and cerebellum. **MATERIAL and METHODS:** 24 Wistar Albino adult male rats were randomly divided into four groups: group I consisted of control rats, and groups II-IV comprised electromagnetically irradiated (EMR) with 900, 1800 and 2450 MHz. The heads of the rats were exposed to 900, 1800 and 2450 MHz microwaves irradiation for 1h per day for 2 months. **RESULTS:** While the histopathological changes in the frontal cortex and brain stem

were normal in the control group, there were severe degenerative changes, shrunken cytoplasm and extensively dark pyknotic nuclei in the EMR groups. Biochemical analysis demonstrated that the Total Antioxidative Capacity level was significantly decreased in the EMR groups and also Total Oxidative Capacity and Oxidative Stress Index levels were significantly increased in the frontal cortex, brain stem and cerebellum. IL-1 β level was significantly increased in the EMR groups in the brain stem. CONCLUSION: EMR causes to structural changes in the frontal cortex, brain stem and cerebellum and impair the oxidative stress and inflammatory cytokine system. This deterioration can cause to disease including loss of these areas function and cancer development.

(NE) Fasseas MK, Fragopoulou AF, Manta AK, Skouroliaou A, Vekrellis K, Margaritis LH, Syntichaki P. Response of *Caenorhabditis elegans* to wireless devices radiation exposure. Int J Radiat Biol. 2014 Dec 9:1-34. [Epub ahead of print] (AS, CE, BE, OX)

Purpose: The aim of this study was to examine the impact of electromagnetic radiation, produced by GSM (Global System for Mobile communications) mobile phones, Wi-Fi (Wireless-Fidelity) routers and wireless DECT (Digital Enhanced Cordless Telecommunications) phones, on the nematode *C. elegans*. Materials and methods: We exposed synchronized populations, of different developmental stages, to these wireless devices at E-field levels below ICNIRP's (International Commission on Non-Ionizing Radiation Protection) guidelines for various lengths of time. WT (wild-type) and aging- or stress-sensitive mutant worms were examined for changes in growth, fertility, lifespan, chemotaxis, short-term memory, increased ROS (Reactive Oxygen Species) production and apoptosis by using fluorescent marker genes or qRT-PCR (quantitative Reverse Transcription-Polymerase Chain Reaction). Results: No statistically significant differences were found between the exposed and the sham/control animals in any of the experiments concerning lifespan, fertility, growth, memory, ROS, apoptosis or gene expression. Conclusions: The worm appears to be robust to this form of (pulsed) radiation, at least under the exposure conditions used.

(E) Favre D. Mobile phone-induced honeybee worker piping *Apidologie* 42:270–279, 2011. (AS, BE)

The worldwide maintenance of the honeybee has major ecological, economic, and political implications. In the present study, electromagnetic waves originating from mobile phones were tested for potential effects on honeybee behavior. Mobile phone handsets were placed in the close vicinity of honeybees. The sound made by the bees was recorded and analyzed. The audiograms and spectrograms revealed that active mobile phone handsets have a dramatic impact on the behavior of the bees, namely by inducing the worker piping signal. In natural conditions, worker piping either announces the swarming process of the bee colony or is a signal of a disturbed bee colony.

(NE) Finnie JW, Blumbergs PC, Cai Z, Manavis J. Expression of the water channel protein, aquaporin-4, in mouse brains exposed to mobile telephone radiofrequency fields. Pathology. 41(5):473-475, 2009a. (AS, CE, CC)

AIM: To determine whether exposure to mobile telephone radiofrequency (RF) fields, either acutely or long-term, produces up-regulation of the water channel protein, aquaporin-4 (AQP-4). **METHODS:** Using a purpose-designed exposure system at 900 MHz, mice were given a single, far-field whole body exposure at a specific absorption rate of 4 W/kg for 60 minutes or a similar exposure on 5 successive days/week for 104 weeks. Control mice were sham-exposed or freely mobile in a cage to control for any stress caused by restraint in the exposure module. A positive control group was given a clostridial toxin known to cause microvascular endothelial injury, severe vasogenic oedema and upregulation of AQP-4. Brains were perfusion fixed with 4% paraformaldehyde, coronal sections cut from six levels, and immunostained for the principal water channel protein in brain, AQP-4. **RESULTS:** There was no increase in AQP-4 expression in brains exposed to mobile phone microwaves compared to control (sham exposed and freely moving caged mice) brains after short or protracted exposure, while AQP-4 was substantially upregulated in the brains of mice given the clostridial toxin. **CONCLUSION:** Brains exposed to mobile telephone RF fields for a short (60 minutes) or long (2 years) duration did not show any immunohistochemically detectable up-regulation of the water channel protein, AQP-4, suggesting that there was no significant increase in blood-brain barrier permeability.

(NE) Finnie JW, Chidlow G, Blumbergs PC, Manavis J, Cai Z. Heat shock protein induction in fetal mouse brain as a measure of stress after whole of gestation exposure to mobile telephony radiofrequency fields. Pathology. 41(3):276-279, 2009b. (AS, LE, CC, DE)

AIM: To determine whether whole of gestation exposure of fetal mouse brain to mobile telephone radiofrequency fields produces a stress response detectable by induction of heat shock proteins (HSPs). **METHODS:** Using a purpose-designed exposure system at 900 MHz, pregnant mice were given a single, far-field, whole body exposure at a specific absorption rate of 4 W/kg for 60 min/day from day 1 to day 19 of gestation. Control mice were sham-exposed or freely mobile in a cage to control for any stress caused by restraint in the exposure module. Immediately prior to parturition on day 19, fetal brains were collected, fixed in 4% paraformaldehyde and paraffin-embedded. Three coronal sections encompassing a wide range of anatomical regions were cut from each brain and any stress response detected by immunostaining for HSP25, 32 and 70. **RESULTS:** There was no induction of HSP32 or 70 in any brains, while HSP25 expression was limited to two brainstem nuclei and occurred consistently in exposed and non-exposed brains. **CONCLUSION:** Whole of gestation exposure of fetal mouse brains to mobile phone radiofrequency fields did not produce any stress response using HSPs as an immunohistochemical marker.

(NE) Finnie JW, Cai Z, Manavis J, Helps S, Blumbergs PC. Microglial activation as a measure of stress in mouse brains exposed acutely (60 minutes) and long-term (2 years) to mobile telephone radiofrequency fields. Pathology. 42(2):151-154, 2010. (AS, CE, CC)

AIM: To determine whether acute or long-term exposure of the brain to mobile telephone radiofrequency (RF) fields produces activation of microglia, which normally respond rapidly to any change in their microenvironment. **METHODS:** Using a purpose designed exposure system at 900 MHz, mice were given a single, far-field whole body exposure at a specific absorption rate (SAR) of 4 W/kg for 60 min (acute) or on five successive days per week for 104 weeks (long-term). Control mice were sham-exposed or freely mobile in a cage to control for any stress caused by immobilisation in the exposure module. Positive control brains subjected to a stab wound were also included to confirm the ability of microglia to react to any neural stress. Brains were perfusion-fixed with 4% paraformaldehyde and representative regions of the cerebral cortex and hippocampus immunostained for ionised calcium binding adaptor molecule (Iba1), a specific microglial marker. **RESULTS:** There was no increase in microglial Iba1 expression in brains short or long-term exposed to mobile telephony microwaves compared to control (sham-exposed or freely moving caged mice) brains, while substantial microglial activation occurred in damaged positive control neural tissue. **CONCLUSION:** Acute (60 minutes) or longer duration (2 years) exposure of murine brains to mobile telephone RF fields did not produce any microglial activation detectable by Iba1 immunostaining.

(E) Fragopoulou AF, Miltiadous P, Stamatakis A, Stylianopoulou F, Koussoulakos SL, Margaritis LH. Whole body exposure with GSM 900MHz affects spatial memory in mice. Pathophysiology. 17(3):179-187, 2010. (AS, BE)

Extended work has been performed worldwide on the effects of mobile phone radiation upon rats' cognitive functions, however there is great controversy to the existence or not of deficits. The present work has been designed in order to test the effects of mobile phone radiation on spatial learning and memory in mice *Mus musculus* Balb/c using the Morris water maze (a hippocampal-dependent spatial memory task), since there is just one other study on mice with very low SAR level (0.05W/kg) showing no effects. We have applied a 2h daily dose of pulsed GSM 900MHz radiation from commercially available mobile phone for 4 days at SAR values ranging from 0.41 to 0.98W/kg. Statistical analysis revealed that during learning, exposed animals showed a deficit in transferring the acquired spatial information across training days (increased escape latency and distance swam, compared to the sham-exposed animals, on the first trial of training days 2-4). Moreover, during the memory probe-trial sham-exposed animals showed the expected preference for the target quadrant, while the exposed animals showed no preference, indicating that the exposed mice had deficits in consolidation and/or retrieval of the learned spatial information. Our results provide a basis for more thorough investigations considering reports on non-thermal effects of electromagnetic fields (EMFs).

(E) Fragopoulou AF, Samara A, Antonelou MH, Xanthopoulou A, Papadopoulou A, Vougas K, Koutsogiannopoulou E, Anastasiadou E, Stravopodis DJ, Tsangaris GT, Margaritis LH. Brain proteome response following whole body exposure of mice to mobile phone or wireless DECT base radiation. Electromagn Biol Med. 31(4):250-274, 2012. (AS, CE, CH, LI)

The objective of this study was to investigate the effects of two sources of electromagnetic fields (EMFs) on the proteome of cerebellum, hippocampus, and frontal lobe in Balb/c mice

following long-term whole body irradiation. Three equally divided groups of animals (6 animals/group) were used; the first group was exposed to a typical mobile phone, at a SAR level range of 0.17-0.37 W/kg for 3 h daily for 8 months, the second group was exposed to a wireless DECT base (Digital Enhanced Cordless Telecommunications/Telephone) at a SAR level range of 0.012-0.028 W/kg for 8 h/day also for 8 months and the third group comprised the sham-exposed animals. Comparative proteomics analysis revealed that long-term irradiation from both EMF sources altered significantly ($p < 0.05$) the expression of 143 proteins in total (as low as 0.003 fold downregulation up to 114 fold overexpression). Several neural function related proteins (i.e., Glial Fibrillary Acidic Protein (GFAP), Alpha-synuclein, Glia Maturation Factor beta (GMF), and apolipoprotein E (apoE)), heat shock proteins, and cytoskeletal proteins (i.e., Neurofilaments and tropomodulin) are included in this list as well as proteins of the brain metabolism (i.e., Aspartate aminotransferase, Glutamate dehydrogenase) to nearly all brain regions studied. Western blot analysis on selected proteins confirmed the proteomics data. The observed protein expression changes may be related to brain plasticity alterations, indicative of oxidative stress in the nervous system or involved in apoptosis and might potentially explain human health hazards reported so far, such as headaches, sleep disturbance, fatigue, memory deficits, and brain tumor long-term induction under similar exposure conditions.

(NE) Fritzer G, Göder R, Friege L, Wachter J, Hansen V, Hinze-Selch D, Aldenhoff JB. Effects of short- and long-term pulsed radiofrequency electromagnetic fields on night sleep and cognitive functions in healthy subjects. Bioelectromagnetics. 28(4):316-325, 2007. (HU, BE, EE, SL)

There has been wide public discussion on whether the electromagnetic fields of mobile telephones and their base stations affect human sleep or cognitive functioning. As there is evidence for learning and memory-consolidating effects of sleep and particularly of REM sleep, disturbance of sleep by radiofrequency electromagnetic fields might also impair cognitive functions. Previously realized sleep studies yielded inconsistent results regarding short-term exposure. Moreover, data are lacking on the effect that short- and long-term exposure might have on sleep as well as on cognitive functions. Therefore, 10 healthy young male subjects were included and nocturnal sleep was recorded during eight consecutive nights. In the second, third, and last night, we investigated polysomnographic night sleep and cognitive functions. After the adaptation and baseline nights, the participants were exposed to a defined radiofrequency electromagnetic field during the following six nights. We analyzed polysomnographic night sleep according to Rechtschaffen and Kales [1968, Manual of Standardized Terminology, Techniques and Scoring System for Sleep of Human Subjects] as well as by power spectra and correlation dimension. Cognitive functions were investigated by an array of neuropsychological tests. Data analysis was done by comparing the baseline night with the first and last exposure night and the first two sleep cycles of the respective nights. We did not find significant effects, either on conventional sleep parameters or on power spectra and correlation dimension, nor were there any significant effects on cognitive functions. With our results, we are unable to reveal either short-term or cumulative long-term effects of radiofrequency electromagnetic fields on night sleep and cognitive functions in healthy young male subjects.

(E) Gao X, Luo R, Ma B, Wang H, Liu T, Zhang J, Lian Z, Cui X. [Interference of vitamin E on the brain tissue damage by electromagnetic radiation of cell phone in pregnant and fetal rats]. Wei Sheng Yan Jiu. 42(4):642-646, 2013.[Article in Chinese] (AS, CE, ME, OX, DE)

OBJECTIVE: To investigate the interference of vitamin E on brain tissue damage by electromagnetic radiation of cell phone in pregnant and fetal rats. **METHODS:** 40 pregnant rats were randomly divided into five groups (positive control, negative control, low, middle and high dosage of vitamin E groups). The low, middle and high dosage of vitamin E groups were supplemented with 5, 15 and 30 mg/ml vitamin E respectively since the first day of pregnancy. And the negative control group and the positive control group were given peanut oil without vitamin E. All groups except for the negative control group were exposed to 900MHz intensity of cell phone radiation for one hour each time, three times per day for 21 days. After accouchement, the right hippocampus tissue of fetal rats in each group was taken and observed under electron microscope. The vitality of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), and the content of malondialdehyde (MDA) in pregnant and fetal rats' brain tissue were tested. **RESULTS:** Compared with the negative control group, the chondriosomes in neuron and neuroglia of brain tissues was swelling, mild edema was found around the capillary, chromatin was concentrated and collected, and bubbles were formed in vascular endothelial cells (VEC) in the positive fetal rat control group, whereas the above phenomenon was un-conspicuous in the middle and high dosage of vitamin E groups. We can see uniform chromatin, abundant mitochondrion, rough endoplasmic reticulum and free ribosomes in the high dosage group. The apoptosis has not found in all groups' sections. In the antioxidant activity analysis, compared with the negative control group, the vitality of SOD and GSH-Px significantly decreased and the content of MDA significantly increased both in the pregnant and fetal rats positive control group ($P < 0.05$). In fetal rats, the vitality of SOD and GSH-Px significantly increased in the brain tissues of all three different vitamin E dosages groups when compared with the positive control group, and the content of MDA was found significantly decreased in both middle and high dosage of vitamin E groups ($P < 0.05$). The same results have also been found in high dosage pregnant rat group, but in middle dosage group only SOD activity was found increased with significance ($P < 0.05$). With the dosage increase of vitamin E, the vitality of SOD and GSH-Px was increasing and the content of MDA was decreasing. **CONCLUSION:** Under the experimental dosage, vitamin E has certain interference on damage of antioxidant capacity and energy metabolism induced by electromagnetic radiation of cell phone in pregnant rats and fetal rats.

(E) Ghazizadeh V, Nazıroğlu M. Electromagnetic radiation (Wi-Fi) and epilepsy induce calcium entry and apoptosis through activation of TRPV1 channel in hippocampus and dorsal root ganglion of rats. Metab Brain Dis. 2014 May 3. [Epub ahead of print] (AS, CC, CH, OX)

Incidence rates of epilepsy and use of Wi-Fi worldwide have been increasing. TRPV1 is a Ca^{2+} permeable and non-selective channel, gated by noxious heat, oxidative stress and capsaicin (CAP). The hyperthermia and oxidant effects of Wi-Fi may induce apoptosis and Ca^{2+} entry through activation of TRPV1 channel in epilepsy. Therefore, we tested the effects of Wi-Fi

(2.45 GHz) exposure on Ca^{2+} influx, oxidative stress and apoptosis through TRPV1 channel in the murine dorsal root ganglion (DRG) and hippocampus of pentylenetetrazol (PTZ)-induced epileptic rats. Rats in the present study were divided into two groups as controls and PTZ. The PTZ groups were divided into two subgroups namely PTZ + Wi-Fi and PTZ + Wi-Fi + capsazepine (CPZ). The hippocampal and DRG neurons were freshly isolated from the rats. The DRG and hippocampus in PTZ + Wi-Fi and PTZ + Wi-Fi + CPZ groups were exposed to Wi-Fi for 1 hour before CAP stimulation. The cytosolic free Ca^{2+} , reactive oxygen species production, apoptosis, mitochondrial membrane depolarization, caspase-3 and -9 values in hippocampus were higher in the PTZ group than in the control although cell viability values decreased. The Wi-Fi exposure induced additional effects on the cytosolic Ca^{2+} increase. However, pretreatment of the neurons with CPZ, results in a protection against epilepsy-induced Ca^{2+} influx, apoptosis and oxidative damages. In results of whole cell patch-clamp experiments, treatment of DRG with Ca^{2+} channel antagonists [thapsigargin, verapamil + diltiazem, 2-APB, MK-801] indicated that Wi-Fi exposure induced Ca^{2+} influx via the TRPV1 channels. In conclusion, epilepsy and Wi-Fi in our experimental model is involved in Ca^{2+} influx and oxidative stress-induced hippocampal and DRG death through activation of TRPV1 channels, and negative modulation of this channel activity by CPZ pretreatment may account for the neuroprotective activity against oxidative stress.

(E) Ghosn R, Yahia-Cherif L, Hugueville L, Ducorps A, Lemaréchal JD, Thuróczy G, de Seze R, Selmaoui B. Radiofrequency signal affects alpha band in resting electroencephalogram. J Neurophysiol. 113(7):2753-2759, 2015. (HU, EE)

The aim of the present work was to investigate the effects of the radiofrequency (RF) electromagnetic fields (EMFs) on human resting EEG with a control of some parameters that are known to affect alpha band, such as electrode impedance, salivary cortisol, and caffeine. Eyes-open and eyes-closed resting EEG data were recorded in 26 healthy young subjects under two conditions: sham exposure and real exposure in double-blind, counterbalanced, crossover design. Spectral power of EEG rhythms was calculated for the alpha band (8-12 Hz). Saliva samples were collected before and after the study. Salivary cortisol and caffeine were assessed by ELISA and HPLC, respectively. The electrode impedance was recorded at the beginning of each run. Compared with the sham session, the exposure session showed a statistically significant ($P < 0.0001$) decrease of the alpha band spectral power during closed-eyes condition. This effect persisted in the postexposure session ($P < 0.0001$). No significant changes were detected in electrode impedance, salivary cortisol, and caffeine in the sham session compared with the exposure one. These results suggest that GSM-EMFs of a mobile phone affect the alpha band within spectral power of resting human EEG.

(E) Gökçek-Saraç Ç, Er H, Kencebay Manas C, Kantar Gok D, Özen Ş, Derin N. Effects of acute and chronic exposure to both 900 MHz and 2100 MHz electromagnetic radiation on glutamate receptor signaling pathway. Int J Radiat Biol. 93(9):980-989, 2017. (AC, CE, CC, CH)

PURPOSE: To demonstrate the molecular effects of acute and chronic exposure to both 900 and 2100 MHz radiofrequency electromagnetic radiation (RF-EMR) on the

hippocampal level/activity of some of the enzymes - including PKA, CaMKII α , CREB, and p44/42 MAPK - from N-methyl-D-aspartate receptor (NMDAR)-related signaling pathways. **MATERIALS AND METHODS:** Rats were divided into the following groups: sham rats, and rats exposed to 900 and 2100 MHz RF-EMR for 2 h/day for acute (1 week) or chronic (10 weeks), respectively. Western blotting and activity measurement assays were used to assess the level/activity of the selected enzymes. **RESULTS:** The obtained results revealed that the hippocampal level/activity of selected enzymes was significantly higher in the chronic groups as compared to the acute groups at both 900 and 2100 MHz RF-EMR exposure. In addition, hippocampal level/activity of selected enzymes was significantly higher at 2100 MHz RF-EMR than 900 MHz RF-EMR in both acute and chronic groups. **CONCLUSIONS:** The present study provides experimental evidence that both exposure duration (1 week versus 10 weeks) and different carrier frequencies (900 vs. 2100 MHz) had different effects on the protein expression of hippocampus in Wistar rats, which might encourage further research on protection against RF-EMR exposure.

(NE) Grafström G, Nittby H, Brun A, Malmgren L, Persson BR, Salford LG, Eberhardt J. Histopathological examinations of rat brains after long-term exposure to GSM-900 mobile phone radiation. Brain Res Bull. 77(5):257-263, 2008. (AS, CE, ME, CH, LI)

In order to mimic the real life situation, with often life-long exposure to the electromagnetic fields emitted by mobile phones, we have investigated in a rat model the effects of repeated exposures under a long period to Global System for Mobile Communication-900 MHz (GSM-900) radiation. Out of a total of 56 rats, 32 were exposed once weekly in a 2-h period, for totally 55 weeks, at different average whole-body specific absorption rates (SAR) (of in average 0.6 and 60 mW/kg at the initiation of the experimental period). The animals were exposed in a transverse electromagnetic transmission line chamber (TEM-cell) to radiation emitted by a GSM-900 test phone. Sixteen animals were sham exposed and eight animals were cage controls, which never left the animal house. After behavioural tests, 5-7 weeks after the last exposure, the brains were evaluated for histopathological alterations such as albumin extravasation, dark neurons, lipofuscin aggregation and signs of cytoskeletal and neuritic neuronal changes of the type seen in human ageing. In this study, no significant alteration of any these histopathological parameters was found, when comparing the GSM exposed animals to the sham exposed controls.

(NE) Gupta N, Goyal D, Sharma R, Arora KS. Effect of Prolonged Use of Mobile Phone on Brainstem Auditory Evoked Potentials. J Clin Diagn Res. 2015 May;9(5):CC07-9. (HU, CE, EE)

OBJECTIVES: Mobile phones are being widely used throughout the world. Electromagnetic waves generated from mobile phones have raised concerns as these may have adverse effects on human auditory system owing to the daily use of mobile phones. The purpose of current study was to evaluate the effects of long term mobile phone usage on auditory brainstem evoked responses (ABR). **MATERIALS AND METHODS:** A retrospective, cross-sectional, case control study was carried out in a tertiary care hospital. Total 100 healthy subjects aged 18 to

30 years of both the genders were selected, out of which 67 subjects were long-term GSM mobile phone users (using mobile phone for more than 1 year) and 33 were controls who were mobile phone non users. Both the groups were investigated for ABR and changes were studied in both the ears of cases and controls to ascertain the effects of electromagnetic exposure.

RESULTS: No significant difference ($p>0.05$) was found in latencies, interpeak latencies and amplitudes of ABR waves between cases and controls. CONCLUSION: Our study shows that long term usage of mobile phones does not affect propagation of electrical stimuli along the auditory nerve to auditory brainstem centres.

(NE) Guxens M, van Eijsden M, Vermeulen R, Loomans E, Vrijkotte TG, Komhout H, van Strien RT, Huss A. Maternal cell phone and cordless phone use during pregnancy and behaviour problems in 5-year-old children. J Epidemiol Community Health. 2013 Feb 5. [Epub ahead of print] (HU, DE, BE)

BACKGROUND: A previous study found an association between maternal cell phone use during pregnancy and maternal-reported child behaviour problems at age 7. Together with cell phones, cordless phones represent the main exposure source of radiofrequency-electromagnetic fields to the head. Therefore, we assessed the association between maternal cell phone and cordless phone use during pregnancy and teacher-reported and maternal-reported child behaviour problems at age 5. **METHODS:** The study was embedded in the Amsterdam Born Children and their Development study, a population-based birth cohort study in Amsterdam, the Netherlands (2003-2004). Teachers and mothers reported child behaviour problems using the Strength and Difficulties Questionnaire at age 5. Maternal cell phone and cordless phone use during pregnancy was asked when children were 7 years old. **RESULTS:** A total of 2618 children were included. As compared to non-users, those exposed to prenatal cell phone use showed an increased but non-significant association of having teacher-reported overall behaviour problems, although without dose-response relationship with the number of calls (OR=2.12 (95% CI 0.95 to 4.74) for <1 call/day, OR=1.58 (95% CI 0.69 to 3.60) for 1-4 calls/day and OR=2.04 (95% CI 0.86 to 4.80) for ≥ 5 calls/day). ORs for having teacher-reported overall behaviour problems across categories of cordless phone use were below 1 or close to unity. Associations of maternal cell phone and cordless phone use with maternal-reported overall behaviour problems remained non-significant. Non-significant associations were found for the specific behaviour problem subscales. **CONCLUSION:** Our results do not suggest that maternal cell phone or cordless phone use during pregnancy increases the odds of behaviour problems in their children.

(NE) Haarala C, Takio F, Rintee T, Laine M, Koivisto M, Revonsuo A, Hämäläinen H. Pulsed and continuous wave mobile phone exposure over left versus right hemisphere: effects on human cognitive function. Bioelectromagnetics. 28(4):289-295, 2007. (HU, BE)

The possible effects of continuous wave (CW) and pulse modulated (PM) electromagnetic field (EMF) on human cognition was studied in 36 healthy male subjects. They performed cognitive tasks while exposed to CW, PM, and sham EMF. The subjects performed the same tasks twice

during each session; once with left-sided and once with right-sided exposure. The EMF conditions were spread across three testing sessions, each session separated by 1 week. The exposed hemisphere, EMF condition, and test order were counterbalanced over all subjects. We employed a double-blind design: both the subject and the experimenter were unaware of the EMF condition. The EMF was created with a signal generator connected via amplifier to a dummy phone antenna, creating a power output distribution similar to the original commercial mobile phone. The EMF had either a continuous power output of 0.25 W (CW) or pulsed power output with a mean of 0.25 W. An additional control group of 16 healthy male volunteers performed the same tasks without any exposure equipment to see if mere presence of the equipment could have affected the subjects' performance. No effects were found between the different EMF conditions, separate hemisphere exposures, or between the control and experimental group. In conclusion, the current results indicate that normal mobile phones have no discernible effect on human cognitive function as measured by behavioral tests.

(E) Haghani M, Shabani M, Moazzami K. Maternal mobile phone exposure adversely affects the electrophysiological properties of Purkinje neurons in rat offspring. Neuroscience. 2013 Jul 29. pii: S0306-4522(13)00643-X. doi: 10.1016/j.neuroscience.2013.07.049. [Epub ahead of print] (AS, CE, EE, CC, DE) no behavioral effect.

Electromagnetic field (EMF) radiations emitted from mobile phones may cause structural damage to neurons. With the increased usage of mobile phones worldwide, concerns about their possible effects on the nervous system are rising. In the present study, we aimed to elucidate the possible effects of prenatal EMF exposure on the cerebellum of offspring Wistar rats. Rats in EMF group were exposed to 900 MHz Pulse-EMF irradiation for six hours per day during all gestation period. Ten offspring's per each group were evaluated for behavioral and electrophysiological evaluations. Cerebellum - related behavioral dysfunctions were analyzed using motor learning and cerebellum-dependent functional tasks (Accelerated Rotarod, Hanging and Open field tests). Whole cell- patch clamp recordings were used for electrophysiological evaluations. The results of the present study failed to show any behavioral abnormalities in rats exposed to chronic EMF radiation. However, whole cell patch clamp recordings revealed decreased neuronal excitability of Purkinje cells in rats exposed to EMF. The most prominent changes included afterhyperpolarization amplitude, spike frequency, half width and first spike latency. In conclusion, the results of the present study show that prenatal EMF exposure results in altered electrophysiological properties of Purkinje neurons. However, these changes may not be severe enough to alter the cerebellum-dependent functional tasks.

(E) Hao D, Yang L, Chen S, Tong J, Tian Y, Su B, Wu S, Zeng Y. Effects of long-term electromagnetic field exposure on spatial learning and memory in rats. Neurol Sci. 2012 Feb 24. [Epub ahead of print] (AS, CE, BE, CC, EE)

With the development of communications industry, mobile phone plays an important role in daily life. Whether or not the electromagnetic radiation emitted by mobile phone causes any adverse effects on brain function has become of a great concern. This paper investigated the

effect of electromagnetic field on spatial learning and memory in rats. 32 trained Wistar rats were divided into two groups: exposure group and control group. The exposure group was exposed to 916 MHz, 10w/m² mobile phone electromagnetic field (EMF) 6 h a day, 5 days a week, 10 weeks. The completion time, number of total errors and the neuron discharge signals were recorded while the rats were searching for food in an eight-arm radial maze at every weekend. The neuron signals of one exposed rat and one control rat in the maze were obtained by the implanted microelectrode arrays in their hippocampal regions. It can be seen that during the weeks 4-5 of the experiment, the average completion time and error rate of the exposure group were longer and larger than that of control group ($p < 0.05$). During the weeks 1-3 and 6-9, they were close to each other. The hippocampal neurons showed irregular firing patterns and more spikes with shorter interspike interval during the whole experiment period. It indicates that the 916 MHz EMF influence learning and memory in rats to some extent in a period during exposure, and the rats can adapt to long-term EMF exposure.

(E) Hao Y, Yang X, Chen C, Yuan-Wang, Wang X, Li M, Yu Z. STAT3 signalling pathway is involved in the activation of microglia induced by 2.45 GHz electromagnetic fields. Int J Radiat Biol. 86(1):27-36, 2010. (CS, CH, OX)

PURPOSE: Microglia activation plays a pivotal role in the initiation and progression of central nervous system (CNS) insult. The aim of the present work was to investigate the activation of microglia and involvement of signal transducer and activator of transcription 3 (STAT3) in microglia activation after 2.45 GHz electromagnetic fields (EMF) exposure. **MATERIALS AND METHODS:** In this study, murine N9 microglial cells were exposed to 2.45 GHz EMF, the protein expressions of STAT3, Janus Tyrosine kinase 1 and 2 (JAK1 and JAK2), phosphor-(Try705)STAT3 and DNA binding activity of STAT3 were examined by Western blot analysis and electrophoresis mobility shift assay (EMSA). Levels of the nitric oxide (NO) derivative nitrite were determined in the culture medium by the Griess reaction. The mRNA expression of tumour necrosis factor alpha (TNF-alpha) and inducible nitric oxide synthase (iNOS) were detected by reverse transcription and polymerase chain reaction (RT-PCR). **RESULTS:** A significant increase of STAT3 DNA-binding ability was noted after exposure. Consistent with this, EMF rapidly induced phosphorylation of STAT3 and activated JAK1 and JAK2. In addition, EMF exposure increased transcription levels of the inflammation-associated genes, iNOS and TNF-alpha, which are reported to contain STAT-binding elements in their promoter region. P6, a JAK inhibitor, reduced induction of iNOS and TNF-alpha, nuclear factor binding activity, and activation of STAT3 in EMF-stimulated microglia. **CONCLUSION:** These results provide evidence that EMF exposure can initiate the activation of microglia cells and STAT3 signalling involves in EMF-induced microglial activation.

(E) Hardell L, Söderqvist F, Carlberg M, Zetterberg H, Mild KH. Exposure to wireless phone emissions and serum beta-trace protein. Int J Mol Med. 26(2):301-306, 2010. (HU, CH, SL)

The lipocalin type of prostaglandin D synthase or beta-trace protein is synthesized in the choroid plexus, lepto-meninges and oligodendrocytes of the central nervous system and is

secreted into the cerebrospinal fluid. beta-trace protein is the key enzyme in the synthesis of prostaglandin D2, an endogenous sleep-promoting neurohormone in the brain.

Electromagnetic fields (EMF) in the radio frequency (RF) range have in some studies been associated with disturbed sleep. We studied the concentration of beta-trace protein in blood in relation to emissions from wireless phones. This study included 62 persons aged 18-30 years. The concentration of beta-trace protein decreased with increasing number of years of use of a wireless phone yielding a negative beta coefficient = -0.32, 95% confidence interval -0.60 to -0.04. Also cumulative use in hours gave a negative beta coefficient, although not statistically significant. Of the 62 persons, 40 participated in an experimental study with 30 min exposure to an 890-MHz GSM signal. No statistically significant change of beta-trace protein was found. In a similar study of the remaining 22 participants with no exposure, beta-trace protein increased significantly over time, probably due to a relaxed situation. EMF emissions may down-regulate the synthesis of beta-trace protein. This mechanism might be involved in sleep disturbances reported in persons exposed to RF fields. The results must be interpreted with caution since use of mobile and cordless phones were self-reported. Awareness of exposure condition in the experimental study may have influenced beta-trace protein concentrations.

(NE) Hareuveny R, Eliyahu I, Luria R, Meiran N, Margaliot M. Cognitive effects of cellular phones: a possible role of non-radiofrequency radiation factors. Bioelectromagnetics. 32(7):585-588, 2011. (See also: Luria et al., 2009) (HU, BE)

Some studies found that cognitive functions of human beings may be altered while exposed to radiofrequency radiation (RFR) emitted by cellular phones. In two recent studies, we have found that experiment duration and exposure side (i.e., phone's location--right or left) may have a major influence on the detection of such effects. In this brief follow-up experiment, 29 right-handed male subjects were divided into two groups. Each subject had two standard cellular phones attached to both sides of his head. The subjects performed a spatial working memory task that required either a left-hand or a right-hand response under one of the two exposure conditions: left side of the head or right side. Contrary to our previous studies, in this work external antennas located far away from the subjects were connected to the cellular phones. This setup prevents any emission of RFR from the internal antenna, thus drastically reducing RFR exposure. Despite that, the results remain similar to those obtained in our previous work. These results indicate that some of the effects previously attributed to RFR can be the result of some confounders.

(E) Hassanshahi A, Shafeie SA, Fatemi I, Hassanshahi E, Allahtavakoli M, Shabani M, Roohbakhsh A, Shamsizadeh A. The effect of Wi-Fi electromagnetic waves in unimodal and multimodal object recognition tasks in male rats. Neurol Sci. 2017 Mar 22. doi: 10.1007/s10072-017-2920-y. [Epub ahead of print] (AS, CE, BE, CC)

Wireless internet (Wi-Fi) electromagnetic waves (2.45 GHz) have widespread usage almost everywhere, especially in our homes. Considering the recent reports about some hazardous effects of Wi-Fi signals on the nervous system, this study aimed to

investigate the effect of 2.4 GHz Wi-Fi radiation on multisensory integration in rats. This experimental study was done on 80 male Wistar rats that were allocated into exposure and sham groups. Wi-Fi exposure to 2.4 GHz microwaves [in Service Set Identifier mode (23.6 dBm and 3% for power and duty cycle, respectively)] was done for 30 days (12 h/day). Cross-modal visual-tactile object recognition (CMOR) task was performed by four variations of spontaneous object recognition (SOR) test including standard SOR, tactile SOR, visual SOR, and CMOR tests. A discrimination ratio was calculated to assess the preference of animal to the novel object. The expression levels of M1 and GAT1 mRNA in the hippocampus were assessed by quantitative real-time RT-PCR. Results demonstrated that rats in Wi-Fi exposure groups could not discriminate significantly between the novel and familiar objects in any of the standard SOR, tactile SOR, visual SOR, and CMOR tests. The expression of M1 receptors increased following Wi-Fi exposure. In conclusion, results of this study showed that chronic exposure to Wi-Fi electromagnetic waves might impair both unimodal and cross-modal encoding of information.

(E) He GL, Luo Z, Shen TT, Li P, Yang J, Luo X, Chen CH, Gao P, Yang XS. Inhibition of STAT3- and MAPK-dependent PGE₂ synthesis ameliorates phagocytosis of fibrillar β -amyloid peptide (1-42) via EP2 receptor in EMF-stimulated N9 microglial cells. J Neuroinflammation. 13(1):296, 2016. (CS, CH)

BACKGROUND: Prostaglandin E₂ (PGE₂)-involved neuroinflammatory processes are prevalent in several neurological conditions and diseases. Amyloid burden is correlated with the activation of E-prostanoid (EP) 2 receptors by PGE₂ in Alzheimer's disease. We previously demonstrated that electromagnetic field (EMF) exposure can induce pro-inflammatory responses and the depression of phagocytosis in microglial cells, but the signaling pathways involved in phagocytosis of fibrillar β -amyloid (fA β) in microglial cells exposed to EMF are poorly understood. Given the important role of PGE₂ in neural physiopathological processes, we investigated the PGE₂-related signaling mechanism in the immunomodulatory phagocytosis of EMF-stimulated N9 microglial cells (N9 cells).

METHODS: N9 cells were exposed to EMF with or without pretreatment with the selective inhibitors of cyclooxygenase-2 (COX-2), Janus kinase 2 (JAK2), signal transducer and activator of transcription 3 (STAT3), and mitogen-activated protein kinases (MAPKs) and antagonists of PG receptors EP1-4. The production of endogenous PGE₂ was quantified by enzyme immunoassays. The phagocytic ability of N9 cells was evaluated based on the fluorescence intensity of the engulfed fluorescent-labeled fibrillar β -amyloid peptide (1-42) (fA β ₄₂) measured using a flow cytometer and a fluorescence microscope. The effects of pharmacological agents on EMF-activated microglia were investigated based on the expressions of JAK2, STAT3, p38/ERK/JNK MAPKs, COX-2, microsomal prostaglandin E synthase-1 (mPGES-1), and EP2 using real-time PCR and/or western blotting. **RESULTS:** EMF exposure significantly increased the production of PGE₂ and decreased the phagocytosis of fluorescent-labeled fA β ₄₂ by N9 cells. The selective inhibitors of COX-2, JAK2, STAT3, and MAPKs clearly depressed PGE₂ release and ameliorated microglial phagocytosis after EMF

exposure. Pharmacological agents suppressed the phosphorylation of JAK2-STAT3 and MAPKs, leading to the amelioration of the phagocytic ability of EMF-stimulated N9 cells. Antagonist studies of EP1-4 receptors showed that EMF depressed the phagocytosis of $\text{fA}\beta_{42}$ through the PGE_2 system, which is linked to EP2 receptors. **CONCLUSIONS:** This study indicates that EMF exposure could induce phagocytic depression via JAK2-STAT3- and MAPK-dependent PGE_2 -EP2 receptor signaling pathways in microglia. Therefore, pharmacological inhibition of PGE_2 synthesis and EP2 receptors may be a potential therapeutic strategy to combat the neurobiological deterioration that follows EMF exposure.

(NE) Heinrich S, Thomas S, Heumann C, von Kries R, Radon K. Association between exposure to radiofrequency electromagnetic fields assessed by dosimetry and acute symptoms in children and adolescents: a population based cross-sectional study. *Environ Health*. 9:75, 2010. **(HU, BE)**

BACKGROUND: The increase in numbers of mobile phone users was accompanied by some concern that exposure to radiofrequency electromagnetic fields (RF EMF) might adversely affect acute health especially in children and adolescents. The authors investigated this potential association using personal dosimeters. **METHODS:** A 24-hour exposure profile of 1484 children and 1508 adolescents was generated in a population-based cross-sectional study in Germany between 2006 and 2008 (participation 52%). Personal interview data on socio-demographic characteristics, self-reported exposure and potential confounders were collected. Acute symptoms were assessed twice during the study day using a symptom diary. **RESULTS:** Only few of the large number of investigated associations were found to be statistically significant. At noon, adolescents with a measured exposure in the highest quartile during morning hours reported a statistically significant higher intensity of headache (Odd Ratio: 1.50; 95% confidence interval: 1.03, 2.19). At bedtime, adolescents with a measured exposure in the highest quartile during afternoon hours reported a statistically significant higher intensity of irritation in the evening (4th quartile 1.79; 1.23, 2.61), while children reported a statistically significant higher intensity of concentration problems (4th quartile 1.55; 1.02, 2.33). **CONCLUSIONS:** We observed few statistically significant results which are not consistent over the two time points. Furthermore, when the 10% of the participants with the highest exposure are taken into consideration the significant results of the main analysis could not be confirmed. Based on the pattern of these results, we assume that the few observed significant associations are not causal but rather occurred by chance.

(E) Hidisoglu E, Kantar Gok D, Er H, Akpinar D, Uysal F, Akkoyunlu G, Ozen S, Agar A, Yargicoglu P. 2100-MHz electromagnetic fields have different effects on visual evoked potentials and oxidant/antioxidant status depending on exposure duration. *Brain Res*. 2016 Jan 14. pii: S0006-8993(16)00031-7. doi: 10.1016/j.brainres.2016.01.018. [Epub ahead of print] **(AS, CE, EE, OX)**

The purpose of the present study was to investigate the duration effects of 2100-MHz electromagnetic field (EMF) on visual evoked potentials (VEPs) and to assess lipid peroxidation (LPO), nitric oxide (NO) production and antioxidant status of EMF exposed rats. Rats were

randomized to following groups: Sham rats (S1 and S10) and rats exposed to 2100-MHz EMF (E1 and E10) for 2h/day for 1 or 10 weeks, respectively. At the end of experimental periods, VEPs were recorded under anesthesia. Brain thiobarbituric acid reactive substances (TBARS) and 4-hydroxy-2-nonenal (4-HNE) levels were significantly decreased in the E1 whereas increased in the E10 compared with their control groups. While brain catalase (CAT), glutathione peroxidase (GSH-Px) activities and NO and glutathione (GSH) levels were significantly increased in the E1, reduction of superoxide dismutase (SOD) activity was detected in the same group compared with the S1. Conversely, decreased CAT, GSH-Px activities and NO levels were observed in the E10 compared with the S10. Latencies of all VEP components were shortened in the E1 compared with the S1, whereas latencies of all VEP components, except P1, were prolonged in the E10 compared with the S10. There was a positive correlation between all VEP latencies and brain TBARS and 4-HNE values. Consequently, it could be concluded that different effects of EMFs on VEPs depend on exposure duration. Additionally, our results indicated that short-term EMF could provide protective effects, while long-term EMF could have an adverse effect on VEPs and oxidant/antioxidant status.

(NE) Hirose H, Sakuma N, Kaji N, Nakayama K, Inoue K, Sekijima M, Nojima T, Miyakoshi J. Mobile phone base station-emitted radiation does not induce phosphorylation of Hsp27. Bioelectromagnetics. 28(2):99-108, 2007. (CS, CH, LI)

An in vitro study focusing on the effects of low-level radiofrequency (RF) fields from mobile radio base stations employing the International Mobile Telecommunication 2000 (IMT-2000) cellular system was conducted to test the hypothesis that modulated RF fields act to induce phosphorylation and overexpression of heat shock protein hsp27. First, we evaluated the responses of human cells to microwave exposure at a specific absorption rate (SAR) of 80 mW/kg, which corresponds to the limit of the average whole-body SAR for general public exposure defined as a basic restriction in the International Commission on Non-Ionizing Radiation Protection (ICNIRP) guidelines. Second, we investigated whether continuous wave (CW) and Wideband Code Division Multiple Access (W-CDMA) modulated signal RF fields at 2.1425 GHz induced activation or gene expression of hsp27 and other heat shock proteins (hsps). Human glioblastoma A172 cells were exposed to W-CDMA radiation at SARs of 80 and 800 mW/kg for 2-48 h, and CW radiation at 80 mW/kg for 24 h. Human IMR-90 fibroblasts from fetal lungs were exposed to W-CDMA at 80 and 800 mW/kg for 2 or 28 h, and CW at 80 mW/kg for 28 h. Under the RF field exposure conditions described above, no significant differences in the expression levels of phosphorylated hsp27 at serine 82 (hsp27[pS82]) were observed between the test groups exposed to W-CDMA or CW signal and the sham-exposed negative controls, as evaluated immediately after the exposure periods by bead-based multiplex assays. Moreover, no noticeable differences in the gene expression of hsps were observed between the test groups and the negative controls by DNA Chip analysis. Our results confirm that exposure to low-level RF field up to 800 mW/kg does not induce phosphorylation of hsp27 or expression of hsp gene family.

(NE) Hirose H, Sasaki A, Ishii N, Sekijima M, Iyama T, Nojima T, Ugawa Y. 1950 MHz IMT-2000 field does not activate microglial cells in vitro. Bioelectromagnetics. 31(2):104-112, 2010. (CS, CC)

Given the widespread use of the cellular phone today, investigation of potential biological effects of radiofrequency (RF) fields has become increasingly important. In particular, much research has been conducted on RF effects on brain function. To examine any biological effects on the central nervous system (CNS) induced by 1950 MHz modulation signals, which are controlled by the International Mobile Telecommunication-2000 (IMT-2000) cellular system, we investigated the effect of RF fields on microglial cells in the brain. We assessed functional changes in microglial cells by examining changes in immune reaction-related molecule expression and cytokine production after exposure to a 1950 MHz Wideband Code Division Multiple Access (W-CDMA) RF field, at specific absorption rates (SARs) of 0.2, 0.8, and 2.0 W/kg. Primary microglial cell cultures prepared from neonatal rats were subjected to an RF or sham field for 2 h. Assay samples obtained 24 and 72 h after exposure were processed in a blind manner. Results showed that the percentage of cells positive for major histocompatibility complex (MHC) class II, which is the most common marker for activated microglial cells, was similar between cells exposed to W-CDMA radiation and sham-exposed controls. No statistically significant differences were observed between any of the RF field exposure groups and the sham-exposed controls in percentage of MHC class II positive cells. Further, no remarkable differences in the production of tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta), and interleukin-6 (IL-6) were observed between the test groups exposed to W-CDMA signal and the sham-exposed negative controls. These findings suggest that exposure to RF fields up to 2 W/kg does not activate microglial cells in vitro.

(E) Hountala CD, Maganioti AE, Papageorgiou CC, Nanou ED, Kyprianou MA, Tsiafakis VG, Rabavilas AD, Capsalis CN. The spectral power coherence of the EEG under different EMF conditions. Neurosci Lett. 441(2):188-192, 2008. (HU, EE)

The present study introduces the concept of spectral power coherence (SPC), which reflects the pattern of coordination of the four basic EEG bands (delta, theta, alpha, and beta) at a specific location of the brain. The SPC was calculated for the pre-stimulus EEG signal during an auditory memory task under different electromagnetic field (EMF) conditions (900 MHz and 1800 MHz). The results showed that delta rhythm is less consequential in the overall cooperation between the bands than the higher frequency theta, alpha and beta rhythms. Additionally, it has been shown that the radiation effect on SPC is different for the two genders. In the absence of radiation males exhibit higher overall SPC than females. These differences disappear in the presence of 900 MHz and are reversed in the presence of 1800 MHz.

(E) Hu S, Peng R, Wang C, Wang S, Gao Y, Dong J, Zhou H, Su Z, Qiao S, Zhang S, Wang L, Wen X. Neuroprotective effects of dietary supplement Kang-fu-ling against high-power microwave through antioxidant action. Food Funct. 2014 Jul 24. [Epub ahead of print] (AS, CE, CE, BE, ME, OX, IA)

Kang-fu-ling (KFL) is a polybotanical dietary supplement with antioxidant properties. This study aimed to evaluate the potential protective effects of KFL on cognitive deficit induced by high-power microwave (HPM) and the underlying mechanism for this neuroprotection. The electron spin resonance technique was employed to evaluate the free radical scavenging activity of KFL in vitro and KFL exhibited scavenging hydroxyl radical activity. KFL at doses of 0.75, 1.5 and 3 g kg⁻¹ and vehicle were administered orally once daily for 14 days to male Wistar rats after being exposed to 30 mW cm⁻² HPM for 15 minutes. KFL reversed HPM-induced memory loss and the histopathological changes in hippocampus of rats. In addition, KFL displayed a protective effect against HPM-induced oxidative stress and activated the nuclear factor-E2-related factor 2 (Nrf2) and its target genes in the hippocampus of rats. The Nrf2-antioxidant response element (ARE) signaling pathway may be involved in the neuroprotective effects of KFL against HPM-induced oxidative stress. In summary, the dietary supplement KFL is a promising natural complex, which ameliorates oxidative stress, with neuroprotective effects against HPM.

(E) Hung CS, Anderson C, Horne JA, McEvoy P. Mobile phone 'talk-mode' signal delays EEG-determined sleep onset. *Neurosci Lett.* 421(1):82-86, 2007. (HU, EE, BE, WS, SL)

Mobile phones signals are pulse-modulated microwaves, and EEG studies suggest that the extremely low-frequency (ELF) pulse modulation has sleep effects. However, 'talk', 'listen' and 'standby' modes differ in the ELF (2, 8, and 217Hz) spectral components and specific absorption rates, but no sleep study has differentiated these modes. We used a GSM900 mobile phone controlled by a base-station simulator and a test SIM card to simulate these three specific modes, transmitted at 12.5% (23dBm) of maximum power. At weekly intervals, 10 healthy young adults, sleep restricted to 6h, were randomly and single-blind exposed to one of: talk, listen, standby and sham (nil signal) modes, for 30 min, at 13:30 h, whilst lying in a sound-proof, lit bedroom, with a thermally insulated silent phone beside the right ear. Bipolar EEGs were recorded continuously, and subjective ratings of sleepiness obtained every 3 min (before, during and after exposure). After exposure the phone and base-station were switched off, the bedroom darkened, and a 90 min sleep opportunity followed. We report on sleep onset using: (i) visually scored latency to onset of stage 2 sleep, (ii) EEG power spectral analysis. There was no condition effect for subjective sleepiness. Post-exposure, sleep latency after talk mode was markedly and significantly delayed beyond listen and sham modes. This condition effect over time was also quite evident in 1-4Hz EEG frontal power, which is a frequency range particularly sensitive to sleep onset. It is possible that 2, 8, 217Hz modulation may differentially affect sleep onset.

(E) İkinci A, Odacı E, Yıldırım M, Kaya H, Akça M, Hancı H, Aslan A, Sönmez OF, Baş O. The Effects of Prenatal Exposure to a 900 Megahertz Electromagnetic Field on Hippocampus Morphology and Learning Behavior in Rat Pups. *NeuroQuantology.* 11(4):582-590, 2013. (AS, BE, ME, CE, DE)

The purpose of this study was to examine the effect on hippocampus morphology and learning behavior in rat pups following prenatal exposure to a 900 megahertz (MHz) electromagnetic field (EMF). Female Sprague Dawley rats weighing 180-250 g were left to mate with males. The following day, pregnant rats identified as such by the vaginal smear test were divided into two groups, control (n=3) and EMF (n=3). No procedures were performed on the control group. The rats in the EMF group were exposed to 900 MHz EMF on days 13 to 21 of pregnancy, for 1 h a day. Female rat pups were removed from their mothers at 22 days old. We then established two newborn rat groups, a 13 member control group and a 10 member EMF group. Radial arm maze and passive avoidance tests were used to measure rat pups' learning and memory performance. All rats were decapitated on the postnatal 32nd day. Routine histological procedures were performed on the brain tissues, and sections were stained with Cresyl fast violet. The radial arm maze ($p=0.007$) and passive avoidance ($p=0.032$) tests were administered to both groups under identical conditions, and compromised learning behavior was determined in the EMF group rats. Morphological compromise was also determined in the EMF group sections. Our results show that the application of a 900 MHz EMF in the prenatal period adversely affected female pups' learning behavior and also resulted in histopathological changes appearing in the hippocampus.

E) İkinci A, Mercantepe T, Unal D, Erol HS, Şahin A, Aslan A, Baş O, Erdem H, Sönmez OF, Kaya H, Odacı E. Morphological and antioxidant impairments in the spinal cord of male offspring rats following exposure to a continuous 900MHz electromagnetic field during early and mid-adolescence. 75(Pt B):99-104, 2016. (AS, CE, CH, OX)

The effects of devices emitting electromagnetic field (EMF) on human health have become the subject of intense research among scientists due to the rapid increase in their use. Children and adolescents are particularly attracted to the use of devices emitting EMF, such as mobile phones. The aim of this study was therefore to investigate changes in the spinal cords of male rat pups exposed to the effect of 900MHz EMF. The study began with 24 Sprague-Dawley male rats aged 3 weeks. Three groups containing equal numbers of rats were established-control group (CG), sham group (SG) and EMF group (EMFG). EMFG rats were placed inside an EMF cage every day between postnatal days (PD) 21 and 46 and exposed to the effect of 900MHz EMF for 1h. SG rats were kept in the EMF cage for 1h without being exposed to the effect of EMF. At the end of the study, the spinal cords in the upper thoracic region of all rats were removed. Tissues were collected for biochemistry, light microscopy (LM) and transmission electron microscopic (TEM) examination. Biochemistry results revealed significantly increased malondialdehyde and glutathione levels in EMFG compared to CG and SG, while SG and EMFG catalase and superoxide dismutase levels were significantly higher than those in CG. In EMFG, LM revealed atrophy in the spinal cord, vacuolization, myelin thickening and irregularities in the perikarya. TEM revealed marked loss of myelin sheath integrity and invagination into the axon and broad vacuoles in axoplasm. The study results show that biochemical alterations and pathological

changes may occur in the spinal cords of male rats following exposure to 900MHz EMF for 1h a day on PD 21-46.

(E) Imge EB, Kiliçoğlu B, Devrim E, Cetin R, Durak I. Effects of mobile phone use on brain tissue from the rat and a possible protective role of vitamin C - a preliminary study. Int J Radiat Biol. 86(12):1044-1049, 2010. (AS, CE, CH, OX)

PURPOSE: To evaluate effects of mobile phone use on brain tissue and a possible protective role of vitamin C. **MATERIALS AND METHODS:** Forty female rats were divided into four groups randomly (Control, mobile phone, mobile phone plus vitamin C and, vitamin C alone). The mobile phone group was exposed to a mobile phone signal (900 MHz), the mobile phone plus vitamin C group was exposed to a mobile phone signal (900 MHz) and treated with vitamin C administered orally (per os). The vitamin C group was also treated with vitamin C per os for four weeks. Then, the animals were sacrificed and brain tissues were dissected to be used in the analyses of malondialdehyde (MDA), antioxidant potential (AOP), superoxide dismutase, catalase (CAT), glutathione peroxidase (GSH-Px), xanthine oxidase, adenosine deaminase (ADA) and 5'nucleotidase (5'-NT). **RESULTS:** Mobile phone use caused an inhibition in 5'-NT and CAT activities as compared to the control group. GSH-Px activity and the MDA level were also found to be reduced in the mobile phone group but not significantly. Vitamin C caused a significant increase in the activity of GSH-Px and non-significant increase in the activities of 5'-NT, ADA and CAT enzymes. **CONCLUSION:** Our results suggest that vitamin C may play a protective role against detrimental effects of mobile phone radiation in brain tissue.

(NE) Inomata-Terada S, Okabe S, Arai N, Hanajima R, Terao Y, Frubayashi T, Ugawa Y. Effects of high frequency electromagnetic field (EMF) emitted by mobile phones on the human motor cortex. Bioelectromagnetics. 28(7):553-561, 2007. (HU, EE)

We investigated whether the pulsed high frequency electromagnetic field (EMF) emitted by a mobile phone has short term effects on the human motor cortex. We measured motor evoked potentials (MEPs) elicited by single pulse transcranial magnetic stimulation (TMS), before and after mobile phone exposure (active and sham) in 10 normal volunteers. Three sites were stimulated (motor cortex (CTX), brainstem (BST) and spinal nerve (Sp)). The short interval intracortical inhibition (SICI) of the motor cortex reflecting GABAergic interneuronal function was also studied by paired pulse TMS method. MEPs to single pulse TMS were also recorded in two patients with multiple sclerosis showing temperature dependent neurological symptoms (hot bath effect). Neither MEPs to single pulse TMS nor the SICI was affected by 30 min of EMF exposure from mobile phones or sham exposure. In two MS patients, mobile phone exposure had no effect on any parameters of MEPs even though conduction block occurred at the corticospinal tracts after taking a bath. As far as available methods are concerned, we did not detect any short-term effects of 30 min mobile phone exposure on the human motor cortical output neurons or interneurons even though we can not exclude the possibility that we failed to detect some mild effects due to a small sample size in the present study. This is the first study of MEPs after electromagnetic exposure from a mobile phone in neurological patients.

(NE) Irlenbusch L, Bartsch B, Cooper J, Herget I, Marx B, Raczek J, Thoss F. Influence of a 902.4 MHz GSM signal on the human visual system: investigation of the discrimination threshold. Bioelectromagnetics. 28(8):648-654, 2007. (HU, EE, LI)

The proximity of a mobile phone to the human eye raises the question as to whether radiofrequency (RF) electromagnetic fields (EMF) affect the visual system. A basic characteristic of the human eye is its light sensitivity, making the visual discrimination threshold (VDThr) a suitable parameter for the investigation of potential effects of RF exposure on the eye. The VDThr was measured for 33 subjects under standardized conditions. Each subject took part in two experiments (RF-exposure and sham-exposure experiment) on different days. In each experiment, the VDThr was measured continuously in time intervals of about 10 s for two periods of 30 min, having a break of 5 min in between. The sequence of the two experiments was randomized, and the study was single blinded. During the RF exposure, a GSM signal of 902.4 MHz (pulsed with 217 Hz) was applied to the subjects. The power flux density of the electromagnetic field at the subject location (in the absence of the subject) was 1 W/m², and numerical dosimetry calculations determined corresponding maximum local averaged specific absorption rate (SAR) values in the retina of SAR(1 g) = 0.007 W/kg and SAR(10 g) = 0.003 W/kg. No statistically significant differences in the VDThr were found in comparing the data obtained for RF exposure with those for sham exposure.

(E) Jing J, Yuhua Z, Xiao-qian Y, Rongping J, Dong-mei G, Xi C. The influence of microwave radiation from cellular phone on fetal rat brain. Electromagn Biol Med. 31(1):57-66, 2012. (AS, CE, CH, OX, DE)

The increasing use of cellular phones in our society has brought focus on the potential detrimental effects to human health by microwave radiation. The aim of our study was to evaluate the intensity of oxidative stress and the level of neurotransmitters in the brains of fetal rats chronically exposed to cellular phones. The experiment was performed on pregnant rats exposed to different intensities of microwave radiation from cellular phones. Thirty-two pregnant rats were randomly divided into four groups: CG, GL, GM, and GH. CG accepted no microwave radiation, GL group radiated 10 min each time, GM group radiated 30 min, and GH group radiated 60 min. The 3 experimental groups were radiated 3 times a day from the first pregnant day for consecutively 20 days, and on the 21st day, the fetal rats were taken and then the contents of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), malondialdehyde (MDA), noradrenaline (NE), dopamine (DA), and 5-hydroxyindole acetic acid (5-HT) in the brain were assayed. Compared with CG, there were significant differences ($P < 0.05$) found in the contents of SOD, GSH-Px, and MDA in GM and GH; the contents of SOD and GSH-Px decreased and the content of MDA increased. The significant content differences of NE and DA were found in fetal rat brains in GL and GH groups, with the GL group increased and the GH group decreased. Through this study, we concluded that receiving a certain period of microwave radiation from cellular phones during pregnancy has certain harm on fetal rat brains.

(E) Jorge-Mora T, Folgueiras MA, Leiro-Vidal JM, Jorge-Barreiro FJ, Ares-Pena FJ, López-Martin E. Exposure to 2.45 GHz Microwave Radiation Provokes Cerebral Changes in Induction of Hsp-90 α/β Heat Shock Protein in Rat. Prog Electromagn Res, 100:351-379, 2010. (AS, CC, CH)

Physical agents such as non-ionizing continuous-wave 2.45 GHz radiation may cause damage that alters cellular homeostasis and may trigger activation of the genes that encode heat shock proteins (HSP). We used Enzyme-Linked ImmunoSorbent Assay (ELISA) and immunohistochemistry to analyze the changes in levels of HSP-90 and its distribution in the brain of Sprague-Dawley rats, ninety minutes and twenty-four hours after acute (30min) continuous exposure to 2.45 GHz radiation in a the Gigahertz Transverse Electromagnetic (GTEM cell). In addition, we studied further indicators of neuronal insult: dark neurons, chromatin condensation and nucleus fragmentation, which were observed under optical conventional or fluorescence microscopy after DAPI staining. The cellular distribution of protein HSP-90 in the brain increased with each corresponding SAR (0.034 ± 3.10^{-3} , 0.069 ± 5.10^{-3} , 0.27 ± 21.10^{-3} W/kg), in hypothalamic nuclei, limbic cortex and somatosensorial cortex after exposure to the radiation. At twenty-four hours post-irradiation, levels of HSP-90 protein remained high in all hypothalamic nuclei for all SARs, and in the parietal cortex, except the limbic system, HSP-90 levels were lower than in non-irradiated rats, almost half the levels in rats exposed to the highest power radiation. Non-apoptotic cellular nuclei and some dark neurons were found ninety minutes and twenty-four hours after maximal SAR exposure. The results suggest that acute exposure to electromagnetic fields triggered an imbalance in anatomical HSP- 90 levels but the anti-apoptotic mechanism is probably sufficient to compensate the non-ionizing stimulus. Further studies are required to determine the regional effects of chronic electromagnetic pollution on heat shock proteins and their involvement in neurological processes and neuronal damage.

(NE) Joubert V, Leveque P, Cueille M, Bourthoumieu S, Yardin C. No apoptosis is induced in rat cortical neurons exposed to GSM phone fields. Bioelectromagnetics. 28(2):115-121, 2007. (CS, CC)

The aim of this study was to investigate the radiofrequency (RF) electromagnetic fields (EMF) effects on neuronal apoptosis in vitro. Primary cultured neurons from cortices of embryonic Wistar rats were exposed to a 900-MHz global system for mobile communication (GSM) RF field for 24 h in a wire-patch cell. The average-specific absorption rate (SAR) used was 0.25 W/kg. Apoptosis rate was assessed immediately or 24 h after exposure using three methods: (i) DAPI staining; (ii) flow cytometry using double staining with TdT-mediated dUTP nick-end labeling (TUNEL) and propidium iodide (PI); and (iii) measurement of caspase-3 activity by fluorimetry. No statistically significant difference in the apoptosis rate was observed between controls and 24 h GSM-exposed neurons, either 0 h or 24 h post-exposure. All three methods used to assess apoptosis were concordant. These results showed that, under the conditions of experiment used, GSM-exposure does not significantly increase the apoptosis rate in rat primary neuronal cultures. This work is in accordance with other studies performed on cell lines and, to our knowledge, is the first one performed on cultured cortical neurons.

**** (E) Joubert, V., Bourthoumieu, S., Leveque, P. and Yardin, C. Apoptosis is Induced by Radiofrequency Fields through the Caspase-Independent Mitochondrial Pathway in Cortical Neurons. Radiat. Res. 169, 38-45, 2008. (CS, CC)**

In the present study, we investigated whether continuous-wave (CW) radiofrequency (RF) fields induce neuron apoptosis in vitro. Rat primary neuronal cultures were exposed to a CW 900 MHz RF field with a specific absorption rate (SAR) of 2 W/kg for 24 h. During exposure, an increase of 2 degrees C was measured in the medium; control experiments with neurons exposed to 39 degrees C were then performed. Apoptosis was assessed by condensation of nuclei with 4',6-diamino-2-phenylindole (DAPI) staining observed with an epifluorescence microscope and fragmentation of DNA with TdT-mediated dUTP nick-end labeling (TUNEL) analyzed by flow cytometry. A statistically significant difference in the rate of apoptosis was found in the RF-field-exposed neurons compared to the sham-, 37 degrees C- and 39 degrees C-exposed neurons either 0 or 24 h after exposure using both methods. To assess whether the observed apoptosis was caspase-dependent or -independent, assays measuring caspase 3 activity and apoptosis-inducing factor (AIF) labeling were performed. No increase in the caspase 3 activity was found, whereas the percentage of AIF-positive nuclei in RF-field-exposed neurons was increased by three- to sevenfold compared to other conditions. Our results show that, under the experimental conditions used, exposure of primary rat neurons to CW RF fields may induce a caspase-independent pathway to apoptosis that involves AIF.

(E) Jung IS, Kim HJ, Noh R, Kim SC, Kim CW. Effects of extremely low frequency magnetic fields on NGF induced neuronal differentiation of PC12 cells. Bioelectromagnetics. 2014 Aug 26. doi: 10.1002/bem.21861. [Epub ahead of print] (CS, CE, CC, MA)

Extremely low-frequency magnetic fields (ELF-MFs) affect various cellular processes and systems, such as cell proliferation, differentiation and metabolic pathways. The present study investigated ELF-MFs effect on nerve growth factor (NGF) induced neuronal differentiation of PC12 cells using proteomic applications to understand its role in the enhancement of neuronal differentiation. After 50 Hz, 1 mT ELF-MFs 5-day exposure on NGF induced PC12 cells, it was observed to increase neurite length as well as an increase in the number of neurite bearing cells. It was also discovered that there was a decrease in proliferation activity, which is associated with an increase in differentiated cells. Neuronal differentiation related mRNA levels and protein levels were increased in NGF induced PC12 cells. Compared with NGF induced group, ELF-MFs stimulated PC12 cells had different protein expression as measured with two-dimensional electrophoresis (2-DE) gels. Consequently six differentially expressed spots were detected between the 2-DE maps, which were identified by electrospray ionization quadrupole time-of-flight tandem mass spectrometry (ESI-Q-TOF LC/MS/MS) as: peripherin, neurosecretory protein nerve growth factor inducible (VGF8a) precursor, dnaK-type molecular chaperone sp72-ps1 (HSP72-ps1), low molecular weight (Mr) phosphotyrosine protein phosphatase isoenzyme AcP1 (LMW-PTP/ACP1), Tubulin alpha-1A (TUBA1A) chain, outcome predictor in acute leukemia 1 homolog (OPA1L). The identification of these proteins provides clues to the mechanism of

ELF-MFs stimulation on NGF induced PC12 cells that occur during neuronal differentiation and may contribute to the development novel treatments for neurodegenerative diseases

(E) Júnior LC, Guimarães ED, Musso CM, Stabler CT, Garcia RM, Mourão-Júnior CA, Andreazzi AE. Behavior and memory evaluation of Wistar rats exposed to 1.8 GHz radiofrequency electromagnetic radiation. Neurol Res. 2014 Jan 27:1743132813Y0000000276. [Epub ahead of print] (AS, CE, BE)

Background: The development of communication systems has brought great social and economic benefits to society. As mobile phone use has become widespread, concerns have emerged regarding the potential adverse effects of radiofrequency electromagnetic radiation (RF-EMR) used by these devices. Objective: To verify potential effects of mobile phone radiation on the central nervous system (CNS) in an animal model. Methods: Male Wistar rats (60 days old) were exposed to RF-EMR from a Global System for Mobile (GSM) cell phone (1.8 GHz) for 3 days. At the end of the exposure, the following behavioral tests were performed: open field and object recognition. Results: Our results showed that exposed animals did not present anxiety patterns or working memory impairment, but stress behavior actions were observe. Conclusion: Given the results of the present study, we speculate that RF-EMR does not promote CNS impairment, but suggest that it may lead to stressful behavioral patterns.

(NE) Kang KA, Lee HC, Lee JJ, Hong MN, Park MJ, Lee YS, Choi HD, Kim N, Ko YK, Lee JS. Effects of combined radiofrequency radiation exposure on levels of reactive oxygen species in neuronal cells. J Radiat Res. 2013 Oct 8. [Epub ahead of print] (CS, OX, IA)

The objective of this study was to investigate the effects of the combined RF radiation (837 MHz CDMA plus 1950 MHz WCDMA) signal on levels of intracellular reactive oxygen species (ROS) in neuronal cells. Exposure of the combined RF signal was conducted at specific absorption rate values of 2 W/kg of CDMA plus 2 W/kg of WCDMA for 2 h. Co-exposure to combined RF radiation with either H₂O₂ or menadione was also performed. The experimental exposure groups were incubator control, sham-exposed, combined RF radiation-exposed with or without either H₂O₂ or menadione groups. The intracellular ROS level was measured by flow cytometry using the fluorescent probe dichlorofluorescein diacetate. Intracellular ROS levels were not consistently affected by combined RF radiation exposure alone in a time-dependent manner in U87, PC12 or SH-SY5Y cells. In neuronal cells exposed to combined RF radiation with either H₂O₂ or menadione, intracellular ROS levels showed no statically significant alteration compared with exposure to menadione or H₂O₂ alone. These findings indicate that neither combined RF radiation alone nor combined RF radiation with menadione or H₂O₂ influences the intracellular ROS level in neuronal cells such as U87, PC12 or SH-SY5Y.

(E) Kaprana AE, Chimona TS, Papadakis CE, Velegrakis SG, Vardiambasis IO, Adamidis G, Velegrakis GA. Auditory brainstem response changes during exposure to GSM-900 radiation: an experimental study. Audiol Neurotol. 16(4):270-276, 2011. (HU, EE)

The objective of the present study was to investigate the possible electrophysiological time-related changes in auditory pathway during mobile phone electromagnetic field exposure. Thirty healthy rabbits were enrolled in an experimental study of exposure to GSM-900 radiation for 60 min and auditory brainstem responses (ABRs) were recorded at regular time-intervals during exposure. The study subjects were radiated via an adjustable power and frequency radio transmitter for GSM-900 mobile phone emission simulation, designed and manufactured according to the needs of the experiment. The mean absolute latency of waves III-V showed a statistically significant delay ($p < 0.05$) after 60, 45 and 15 min of exposure to electromagnetic radiation of 900 MHz, respectively. Interwave latency I-III was found to be prolonged after 60 min of radiation exposure in correspondence to wave III absolute latency delay. Interwave latencies I-V and III-V were found with a statistically significant delay ($p < 0.05$) after 30 min of radiation. No statistically significant delay was found for the same ABR parameters in recordings from the ear contralateral to the radiation source at 60 min radiation exposure compared with baseline ABR. The ABR measurements returned to baseline recordings 24 h after the exposure to electromagnetic radiation of 900 MHz. The prolongation of interval latencies I-V and III-V indicates that exposure to electromagnetic fields emitted by mobile phone can affect the normal electrophysiological activity of the auditory system, and these findings fit the pattern of general responses to a stressor.

(E) Karaca E, Durmaz B, Aktug H, Yildiz T, Guducu C, Irgi M, Koksai MG, Ozkinay F, Gunduz C, Cogulu O. The genotoxic effect of radiofrequency waves on mouse brain. J Neurooncol. 106(1):53-58, 2012. (CS, CH)

Concerns about the health effects of radiofrequency (RF) waves have been raised because of the gradual increase in usage of cell phones, and there are scientific questions and debates about the safety of those instruments in daily life. The aim of this study is to evaluate the genotoxic effects of RF waves in an experimental brain cell culture model. Brain cell cultures of the mice were exposed to 10.715 GHz with specific absorption rate (SAR) 0.725 W/kg signals for 6 h in 3 days at 25°C to check for the changes in the micronucleus (MNi) assay and in the expression of 11 proapoptotic and antiapoptotic genes. It was found that MNi rate increased 11-fold and STAT3 expression decreased 7-fold in the cell cultures which were exposed to RF. Cell phones which spread RF may damage DNA and change gene expression in brain cells.

(E) Kesari KK, Kumar S, Behari J. 900-MHz microwave radiation promotes oxidation in rat brain. Electromagn Biol Med. 30(4):219-234, 2011. (AS, CE, CH, OX)

Recently, there have been several reports referring to detrimental effects due to radio frequency electromagnetic fields (RF-EMF) exposure. Special attention was given to investigate the effect of mobile phone exposure on the rat brain. Since the integrative mechanism of the entire body lies in the brain, it is suggestive to analyze its biochemical aspects. For this, 35-day

old Wistar rats were exposed to a mobile phone for 2 h per day for a duration of 45 days where specific absorption rate (SAR) was 0.9 W/Kg. Animals were divided in two groups: sham exposed (n = 6) and exposed group (n = 6). Our observations indicate a significant decrease ($P < 0.05$) in the level of glutathione peroxidase, superoxide dismutase, and an increase in catalase activity. Moreover, protein kinase shows a significant decrease in exposed group ($P < 0.05$) of hippocampus and whole brain. Also, a significant decrease ($P < 0.05$) in the level of pineal melatonin and a significant increase ($P < 0.05$) in creatine kinase and caspase 3 was observed in exposed group of whole brain as compared with sham exposed. Finally, a significant increase in the level of ROS (reactive oxygen species) ($P < 0.05$) was also recorded. The study concludes that a reduction or an increase in antioxidative enzyme activities, protein kinase C, melatonin, caspase 3, and creatine kinase are related to overproduction of reactive oxygen species (ROS) in animals under mobile phone radiation exposure. Our findings on these biomarkers are clear indications of possible health implications.

(E) Kesari KK, Meena R, Nirala J, Kumar J, Verma HN. Effect of 3G cell phone exposure with computer controlled 2-D stepper motor on non-thermal activation of the hsp27/p38MAPK stress pathway in rat brain. Cell Biochem Biophys. 68(2):347-358, 2014. (AS, CE, CH)

Cell phone radiation exposure and its biological interaction is the present concern of debate. Present study aimed to investigate the effect of 3G cell phone exposure with computer controlled 2-D stepper motor on 45-day-old male Wistar rat brain. Animals were exposed for 2 h a day for 60 days by using mobile phone with angular movement up to zero to 30°. The variation of the motor is restricted to 90° with respect to the horizontal plane, moving at a pre-determined rate of 2° per minute. Immediately after 60 days of exposure, animals were scarified and numbers of parameters (DNA double-strand break, micronuclei, caspase 3, apoptosis, DNA fragmentation, expression of stress-responsive genes) were performed. Result shows that microwave radiation emitted from 3G mobile phone significantly induced DNA strand breaks in brain. Meanwhile a significant increase in micronuclei, caspase 3 and apoptosis were also observed in exposed group ($P < 0.05$). Western blotting result shows that 3G mobile phone exposure causes a transient increase in phosphorylation of hsp27, hsp70, and p38 mitogen-activated protein kinase (p38MAPK), which leads to mitochondrial dysfunction-mediated cytochrome c release and subsequent activation of caspases, involved in the process of radiation-induced apoptotic cell death. Study shows that the oxidative stress is the main factor which activates a variety of cellular signal transduction pathways, among them the hsp27/p38MAPK is the pathway of principle stress response. Results conclude that 3G mobile phone radiations affect the brain function and cause several neurological disorders.

(E) Khullar S1, Sood A2, Sood S3. Auditory Brainstem Responses and EMFs Generated by Mobile Phones. Indian J Otolaryngol Head Neck Surg. 65(Suppl 3):645-649, 2013. (HU, EE)

There has been a manifold increase in the number of mobile phone users throughout the world with the current number of users exceeding 2 billion. However this advancement in technology like many others is accompanied by a progressive increase in the frequency and intensity of electromagnetic waves without consideration of the health consequences. The aim of our study

was to advance our understanding of the potential adverse effects of GSM mobile phones on auditory brainstem responses (ABRs). 60 subjects were selected for the study and divided into three groups of 20 each based on their usage of mobile phones. Their ABRs were recorded and analysed for latency of waves I-V as well as interpeak latencies I-III, I-V and III-V (in ms). Results revealed no significant difference in the ABR parameters between group A (control group) and group B (subjects using mobile phones for maximum 30 min/day for 5 years). However the latency of waves was significantly prolonged in group C (subjects using mobile phones for 10 years for a maximum of 30 min/day) as compared to the control group. Based on our findings we concluded that long term exposure to mobile phones may affect conduction in the peripheral portion of the auditory pathway. However more research needs to be done to study the long term effects of mobile phones particularly of newer technologies like smart phones and 3G.

(NE) Kim HS, An YS, Paik MJ, Lee YS, Choi HD, Kim BC, Pack JK, Kim N, Ahn YH. The effects of exposure to 915 MHz radiofrequency identification on cerebral glucose metabolism in rat: A [F-18] FDG micro-PET study. Int J Radiat Biol. 2013 May 7. [Epub ahead of print] (AS, CE, CC, CH)

Purpose: We investigated the effect of whole-body exposure to 915-MHz radiofrequency identification (RFID) on rat cortical glucose metabolism by using ¹⁸F-deoxyglucose positron emission tomography (FDG-PET). Materials and methods: Male Sprague-Dawley rats were divided into three groups: Cage-control, sham-exposed and RFID-exposed groups. Rats were exposed to the 915-MHz RFID for 8 h daily, 5 days per week, for 2 or 16 weeks. The whole-body average specific absorption rate (SAR) was 4 W/kg for the field of the 915 MHz RFID signal. FDG-PET images were obtained the day after RFID exposure, using micro-PET with a FDG tracer. With a Xeleris functional imaging workstation, absolute values in regions of interest (ROI) in the frontal, temporal and parietal cortexes and cerebellum were measured. Cortical ROI values were normalized to the cerebellar value and compared. Results: The data showed that the relative cerebral glucose metabolic rate was unchanged in the frontal, temporal and parietal cortexes of the 915 MHz RFID-exposed rats, compared with rats in cage-control and sham-exposed groups. Conclusion: Our results suggest that 915 MHz RFID radiation exposure did not cause a significant long lasting effect on glucose metabolism in the rat brain.

(NE) Kim HS, Kim YJ, Lee YH, Lee YS, Choi HD, Pack JK, Kim N, Ahn YH. Effect of whole-body exposure to the 848.5-MHz code division multiple access (CDMA) electromagnetic field on adult neurogenesis in the young, healthy rat brain. Int J Radiat Biol. 2014 Dec 15:1-15. [Epub ahead of print] (AS, CE, CC)

Introduction: Whether exposure to the 848.5-MHz code division multiple access (CDMA) signal affects adult neurogenesis is unclear. Materials and methods: An animal experiment was performed with a reverberation chamber designed as a whole-body CDMA exposure system. Male Sprague-Dawley rats were assigned to three groups (n = 6 per group): cage-control, sham-exposed, and CDMA-exposed groups. Rats in the CDMA-exposed group were exposed to the

CDMA signal at a 2 W/kg whole-body specific absorption rate (SAR) for 1 or 8 h daily, 5 days per week, for 2 weeks. Rats received a single intraperitoneal injection of Bromodeoxyuridine (BrdU) to label proliferative cells daily for the last five consecutive days of CDMA signal exposure. An unbiased stereological method was used to estimate the number of BrdU⁺ cells in the subventricular zone (SVZ) and dentate gyrus (DG). Results: We found no significant changes in the number of BrdU⁺ cells in the SVZ or DG in the CDMA-exposed rats, compared with rats in the cage-control and sham-exposed groups ($p > 0.05$). Conclusion: Our results suggest that exposure to the CDMA signal does not affect neurogenesis in the adult rat brain, at least under our experimental conditions.

(E) Kim JH, Yu DH, Huh YH, Lee EH, Kim HG, Kim HR. Long-term exposure to 835 MHz RF-EMF induces hyperactivity, autophagy and demyelination in the cortical neurons of mice. Sci Rep. 7:41129, 2017. (AS, CE, BE, CC)

Radiofrequency electromagnetic field (RF-EMF) is used globally in conjunction with mobile communications. There are public concerns of the perceived deleterious biological consequences of RF-EMF exposure. This study assessed neuronal effects of RF-EMF on the cerebral cortex of the mouse brain as a proxy for cranial exposure during mobile phone use. C57BL/6 mice were exposed to 835 MHz RF-EMF at a specific absorption rate (SAR) of 4.0 W/kg for 5 hours/day during 12 weeks. The aim was to examine activation of autophagy pathway in the cerebral cortex, a brain region that is located relatively externally. Induction of autophagy genes and production of proteins including LC3B-II and Beclin1 were increased and accumulation of autolysosome was observed in neuronal cell bodies. However, proapoptotic factor Bax was down-regulated in the cerebral cortex. Importantly, we found that RF-EMF exposure led to myelin sheath damage and mice displayed hyperactivity-like behaviour. The data suggest that autophagy may act as a protective pathway for the neuronal cell bodies in the cerebral cortex during radiofrequency exposure. The observations that neuronal cell bodies remained structurally stable but demyelination was induced in cortical neurons following prolonged RF-EMF suggests a potential cause of neurological or neurobehavioural disorders.

(E) Kim JY, Kim HJ, Kim N, Kwon JH, Park MJ. Effects of radiofrequency field exposure on glutamate-induced oxidative stress in mouse hippocampal HT22 cells. Int J Radiat Biol. 2016 Sep 20:1-22. [Epub ahead of print] (CS, CC, OX, IA)

PURPOSE: To define the impact of radiofrequency (RF) under in vitro experimental Alzheimer's disease conditions, we investigated the effect of RF radiation on glutamate-induced oxidative stress in mouse hippocampal neuronal HT22 cells. MATERIALS AND METHODS: Cell survival rate was measured by MTT and trypan blue exclusion assays. Cell cycle distribution, cell death, and ROS production were analyzed using flow cytometry. Expression of proteins was analyzed by Western blot. RESULTS: RF exposure alone had a marginal impact on cell proliferation, however significantly enhanced glutamate-induced cytotoxicity in HT22 cells. Glutamate augmented the subG1 fraction of cell cycle, annexin/propidium iodide positive cell population, and expression of cleaved poly (ADP ribose) polymerase, which were further increased by RF exposure. Glutamate induced reactive oxygen species (ROS) generation and RF exposure

further upregulated it. N-acetylcysteine (NAC) treatment completely abrogated glutamate- and RF-induced ROS production followed by cell death and restored cell proliferation in HT22 cells. Finally, glutamate phosphorylated c-Jun N-terminal kinase (JNK) and RF increased this event further. Treatment with NAC and inhibitor of JNK decreased JNK phosphorylation and restored cell proliferation, respectively. CONCLUSIONS: Our results demonstrate that RF exposure enhanced glutamate-induced cytotoxicity by further increase of ROS production in HT22 cells.

(NE) Kim TH, Huang TQ, Jang JJ, Kim MH, Kim HJ, Lee JS, Pack JK, Seo JS, Park WY. Local exposure of 849 MHz and 1763 MHz radiofrequency radiation to mouse heads does not induce cell death or cell proliferation in brain. Exp Mol Med. 40(3):294-303, 2008. (AS, CE, CC) Erratum in: Exp Mol Med. 2008 Aug 31;40(4):477. Kim, Tae-Hyoung [corrected to Kim, Tae-Hyung].

Even though there is no direct evidence to prove the cellular and molecular changes induced by radiofrequency (RF) radiation itself, we cannot completely exclude the possibility of any biological effect of mobile phone frequency radiation. We established a carousel-type exposure chamber for 849 MHz or 1763 MHz of mobile phone RF radiation to expose RF to the heads of C57BL mice. In this chamber, animals were irradiated intermittently at 7.8 W/kg for a maximum of 12 months. During this period, the body weights of 3 groups-sham, 849 MHz RF, and 1763 MHz RF-did not show any differences between groups. The brain tissues were obtained from 3 groups at 6 months and 12 months to examine the differences in histology and cell proliferation between control and RF exposure groups, but we could not find any change upon RF radiation. Likewise, we could not find changes in the expression and distribution of NeuN and GFAP in hippocampus and cerebellum, or in cell death by TUNEL assay in RF exposure groups. From these data, we conclude that the chronic exposure to 849 MHz and 1763 MHz RF radiation at a 7.8 W/kg specific absorption rate (SAR) could not induce cellular alterations such as proliferation, death, and reactive gliosis.

(NE) Kleinlogel H, Dierks T, Koenig T, Lehmann H, Minder A, Berz R. Effects of weak mobile phone - electromagnetic fields (GSM, UMTS) on well-being and resting EEG. Bioelectromagnetics. 29(6):479-487, 2008a. (HU, BE, EE)

Modern mobile phones emit electromagnetic fields (EMFs) ranging from 900 to 2000 MHz which are suggested to have an influence on well-being, attention and neurological parameters in mobile phone users. To date most studies have investigated Global System for Mobile Communications (GSM)-EMF and only very few studies were concerned with Universal Mobile Telecommunications System (UMTS)-EMF. Consequently, we tested the effects of both types of EMF, 1950 MHz UMTS (SAR 0.1 and 1 W/kg) and pulsed 900 MHz GSM (1 W/kg), on well-being and vigilance-controlled resting electroencephalogram (eyes closed) in 15 healthy, right-handed subjects. A double-blind, randomised, crossover application of the test procedure was used. Neither the UMTS- nor the GSM-EMF produced any significant changes in the measured parameters compared to sham exposure. The results do not give any evidence for a deleterious effect of the EMF on normal healthy mobile phone users.

(NE) Kleinlogel H, Dierks T, Koenig T, Lehmann H, Minder A, Berz R. Effects of weak mobile phone - electromagnetic fields (GSM, UMTS) on event related potentials and cognitive functions. Bioelectromagnetics. 29(6):488-497, 2008b. (HU, EE, BE)

Modern mobile phones emit electromagnetic fields (EMF) ranging from 900 to 2000 MHz which are suggested to have an influence on well-being, attention and neurological parameters in mobile phone users. Until now most studies have investigated Global System for Mobile Communications (GSM)-EMF and only very few studies have focused on Universal Mobile Telecommunications System (UMTS)-EMF. Therefore, we tested the effects of both types of unilaterally presented EMF, 1950 UMTS (0.1 and 1 W/kg) and pulsed 900 MHz GSM (1 W/kg), on visually evoked occipital P100, the P300 of a continuous performance test, auditory evoked central N100 and the P300 during an oddball task as well as on the respective behavioral parameters, reaction time and false reactions, in 15 healthy, right handed subjects. A double-blind, randomized, crossover application of the test procedure was used. Neither the UMTS- nor the GSM-EMF produced any significant changes in the measured parameters compared to sham exposure. The results do not give any evidence for a deleterious effect of the EMF on normal healthy mobile phone users.

(NE) Klose M, Grote K, Spathmann O, Streckert J, Clemens M, Hansen VW, Lerchl A. Effects of early-onset radiofrequency electromagnetic field exposure (GSM 900 MHz) on behavior and memory in rats. Radiat Res. 182(4):435-447, 2014. (AS, CE, BE)

Female Wistar rats, from an age of 14 days to 19 months, were exposed in the head region for 2 h per day, 5 days per week, to a GSM-modulated 900 MHz radiofrequency electromagnetic field (RF-EMF). The average specific absorption rates (SAR) in the brain were 0 (sham), 0.7, 2.5 and 10 W/kg. To ensure a primary exposure of the head region, rats were fixed in restraining tubes of different sizes according to their increasing body weight. During the experiment, a set of 4 behavioral and learning tests (rotarod, Morris water maze, 8-arm radial maze, open field) were performed 3 times in juvenile, adult and presenile rats. In these **tests, no profound differences could be identified between the groups. Only presenile rats of the cage control group showed a lower activity in two of these tests compared to the other groups** presumably due to the lack of daily handling. The rotarod data revealed on some testing days significantly longer holding times for the sham-exposed rat vs. the exposed rat, but these findings were not consistent. During the first year, body weights of sham-exposed and exposed rats were not different from those of the cage controls, and thereafter only marginally lower, so that the effect of stress as confounder was probably negligible. The results of this study do not indicate harmful effects of long-term RF-EMF exposure even when begun at an early age on subsequent development, learning skills and behavior in rats, even at relatively high SAR values.

(E) Köktürk S, Yardimoglu M, Celikozlu SD, Dolanbay EG, Cimbiz A. Effect of Lycopersicon esculentum extract on apoptosis in the rat cerebellum, following prenatal and postnatal exposure to an electromagnetic field. Exp Ther Med. 6(1):52-56, 2013. (AS, CE, DE, CC)

The expansion of mobile phone technology has raised concerns regarding the effect of 900-MHz electromagnetic field (EMF) exposure on the central nervous system. At present, the developing human brain is regularly exposed to mobile telephones, pre- and postnatally. Several studies have demonstrated the acute effects of EMF exposure during pre- or postnatal periods; however, the chronic effects of EMF exposure are less understood. Thus, the aim of the present study was to determine the chronic effects of EMF on the pre- and postnatal rat cerebellum. The control group was maintained in the same conditions as the experimental groups, without the exposure to EMF. In the EMF1 group, the rats were exposed to EMF during pre- and postnatal periods (until postnatal day 80). In the EMF2 group, the rats were also exposed to EMF pre- and postnatally; in addition, however, they were provided with a daily oral supplementation of *Lycopersicon esculentum* extract (~2 g/kg). The number of caspase-3-labeled Purkinje neurons and granule cells present in the rats in the control and experimental groups were then counted. The neurodegenerative changes were studied using cresyl violet staining, and these changes were evaluated. In comparison with the control animals, the EMF1 group demonstrated a significant increase in the number of caspase-3-labeled Purkinje neurons and granule cells present in the cerebellum ($P < 0.001$). However, in comparison with the EMF1 group, the EMF2 group exhibited significantly fewer caspase-3-labeled Purkinje neurons and granule cells in the cerebellum. In the EMF1 group, the Purkinje neurons were revealed to have undergone dark neuron degenerative changes. However, the presence of dark Purkinje neurons was reduced in the EMF2 group, compared with the EMF1 group. The results indicated that apoptosis and neurodegeneration in rats exposed to EMF during pre- and postnatal periods may be reduced with *Lycopersicon esculentum* extract therapy.

(NE) Krause CM, Pesonen M, Haarala Björnberg C, Hämäläinen H. Effects of pulsed and continuous wave 902 MHz mobile phone exposure on brain oscillatory activity during cognitive processing. Bioelectromagnetics. 28(4):296-308, 2007. (HU, EE)

The aim of the current double-blind studies was to partially replicate the studies by Krause et al. [2000ab, 2004] and to further investigate the possible effects of electromagnetic fields (EMF) emitted by mobile phones (MP) on the event-related desynchronisation/synchronisation (ERD/ERS) EEG (electroencephalogram) responses during cognitive processing. Two groups, both consisting of 36 male participants, were recruited. One group performed an auditory memory task and the other performed a visual working memory task in six exposure conditions: SHAM (no EMF), CW (continuous wave EMF) and PM (pulse modulated EMF) during both left- and right-side exposure, while the EEG was recorded. In line with our previous studies, we observed that the exposure to EMF had modest effects on brain oscillatory responses in the alpha frequency range (approximately 8-12 Hz) and had no effects on the behavioural measures. The effects on the EEG were, however, varying, unsystematic and inconsistent with previous reports. We conclude that the effects of EMF on brain oscillatory responses may be subtle, variable and difficult to replicate for unknown reasons.

(E) Kumar RS, Sareesh NN, Nayak S, Mailankot M. Hypoactivity of Wistar rats exposed to mobile phone on elevated plus maze. Indian J Physiol Pharmacol. 53(3):283-286, 2009. (AS, BE)

No abstract available. From discussion section: "In conclusion, our preliminary results indicate mobile phone exposure induced behavioral changes in rats, expressed as deficit in open arm exploration on elevated plus-maze."

(E) Kumlin T, Iivonen H, Miettinen P, Juvonen A, van Groen T, Puranen L, Pitkääho R, Juutilainen J, Tanila H. Mobile phone radiation and the developing brain: behavioral and morphological effects in juvenile rats. Radiat Res. 168(4):471-479, 2007. (AS, CE, ME, BE)

The increasing use of mobile phones by children and teenagers has raised concerns about their safety. Addressing such concerns is difficult, because no data are available on possible effects from long-term exposure to radiofrequency (RF) fields during the development of the nervous system. Possible morphological and functional changes were evaluated in the central nervous system of young male Wistar rats exposed to 900 MHz mobile phone signal for 2 h/day on 5 days/week. After 5 weeks of exposure at whole-body average specific energy absorption rates of 0.3 or 3.0 W/kg or sham exposure, six rats per group were examined histologically, and the remaining 18 rats per group were subjected to behavioral tests. No degenerative changes, dying neurons, or effects on the leakage of the blood-brain barrier were detected. No group differences were observed in the open-field test, plus maze test or acoustic startle response tests. In the water maze test, however, significantly improved learning (P = 0.012) and memory (P = 0.01) were detected in rats exposed to RF fields. The results do not indicate a serious threat to the developing brain from mobile phone radiation at intensities relevant to human exposure. However, the interesting finding of improved learning and memory warrants further studies.

(NE) Kwon MS, Jääskeläinen SK, Toivo T, Hämäläinen H. No effects of mobile phone electromagnetic field on auditory brainstem response. Bioelectromagnetics. 31(1):48-55, 2010a. (HU, EE)

The present study investigated the possible effects of the electromagnetic field (EMF) emitted by an ordinary GSM mobile phone (902.4 MHz pulsed at 217 Hz) on brainstem auditory processing. Auditory brainstem responses (ABR) were recorded in 17 healthy young adults, without a mobile phone at baseline, and then with a mobile phone on the ear under EMF-off and EMF-on conditions. The amplitudes, latencies, and interwave intervals of the main ABR components (waves I, III, V) were compared among the three conditions. ABR waveforms showed no significant differences due to exposure, suggesting that short-term exposure to mobile phone EMF did not affect the transmission of sensory stimuli from the cochlea up to the midbrain along the auditory nerve and brainstem auditory pathways.

(NE) Kwon MS, Huutilainen M, Shestakova A, Kujala T, Näätänen R, Hämäläinen H. No effects of mobile phone use on cortical auditory change-detection in children: an ERP study. Bioelectromagnetics. 31(3):191-199, 2010b. (HU, EE)

We investigated the effect of mobile phone use on the auditory sensory memory in children. Auditory event-related potentials (ERPs), P1, N2, mismatch negativity (MMN), and P3a, were recorded from 17 children, aged 11-12 years, in the recently developed multi-feature paradigm. This paradigm allows one to determine the neural change-detection profile consisting of several different types of acoustic changes. During the recording, an ordinary GSM (Global System for Mobile Communications) mobile phone emitting 902 MHz (pulsed at 217 Hz) electromagnetic field (EMF) was placed on the ear, over the left or right temporal area ($SAR(1g) = 1.14 \text{ W/kg}$, $SAR(10g) = 0.82 \text{ W/kg}$, peak value = 1.21 W/kg). The EMF was either on or off in a single-blind manner. We found that a short exposure (two 6 min blocks for each side) to mobile phone EMF has no statistically significant effects on the neural change-detection profile measured with the MMN. Furthermore, the multi-feature paradigm was shown to be well suited for studies of perception accuracy and sensory memory in children. However, it should be noted that the present study only had sufficient statistical power to detect a large effect size.

(NE) Kwon MS, Vorobyev V, Kännälä S, Laine M, Rinne JO, Toivonen T, Johansson J, Teräs M, Joutsa J, Tuominen L, Lindholm H, Alanko T, Hämäläinen H. No effects of short-term GSM mobile phone radiation on cerebral blood flow measured using positron emission tomography. Bioelectromagnetics. 33(3):247-256, 2012. (HU, PE)

The present study investigated the effects of 902.4 MHz global system for mobile communications (GSM) mobile phone radiation on cerebral blood flow using positron emission tomography (PET) with the $(15)\text{O}$ -water tracer. Fifteen young, healthy, right-handed male subjects were exposed to phone radiation from three different locations (left ear, right ear, forehead) and to sham exposure to test for possible exposure effects on brain regions close to the exposure source. Whole-brain $[^{15}\text{O}]\text{H}_2\text{O}$ -PET images were acquired 12 times, 3 for each condition, in a counterbalanced order. Subjects were exposed for 5 min in each scan while performing a simple visual vigilance task. Temperature was also measured in the head region (forehead, eyes, cheeks, ear canals) during exposure. The exposure induced a slight temperature rise in the ear canals but did not affect brain hemodynamics and task performance. The results provided no evidence for acute effects of short-term mobile phone radiation on cerebral blood flow.

(E) Kwon MS, Vorobyev V, Kännälä S, Laine M, Rinne JO, Toivonen T, Johansson J, Teräs M, Lindholm H, Alanko T, Hämäläinen H. GSM mobile phone radiation suppresses brain glucose metabolism. J Cereb Blood Flow Metab. 31(12):2293-2301, 2011. (HU, PE)

We investigated the effects of mobile phone radiation on cerebral glucose metabolism using high-resolution positron emission tomography (PET) with the $(18)\text{F}$ -deoxyglucose (FDG) tracer. A long half-life (109 minutes) of the $(18)\text{F}$ isotope allowed a long, natural exposure condition outside the PET scanner. Thirteen young right-handed male subjects were exposed to a pulse-modulated 902.4 MHz Global System for Mobile Communications signal for 33 minutes, while performing a simple visual vigilance task. Temperature was also measured in the head region (forehead, eyes, cheeks, ear canals) during exposure. $(18)\text{F}$ -deoxyglucose PET images acquired after the exposure showed that relative cerebral metabolic rate of glucose was significantly

reduced in the temporoparietal junction and anterior temporal lobe of the right hemisphere ipsilateral to the exposure. Temperature rise was also observed on the exposed side of the head, but the magnitude was very small. The exposure did not affect task performance (reaction time, error rate). Our results show that short-term mobile phone exposure can locally suppress brain energy metabolism in humans.

(NE) Kwon MS, Kujala T, Huotilainen M, Shestakova A, Näätänen R, Hämäläinen H. Preattentive auditory information processing under exposure to the 902 MHz GSM mobile phone electromagnetic field: a mismatch negativity (MMN) study. Bioelectromagnetics. 30(3):241-248, 2009. (HU, EE)

Previous studies on the effects of the mobile phone electromagnetic field (EMF) on various event-related potential (ERP) components have yielded inconsistent and even contradictory results, and often failed in replication. The mismatch negativity (MMN) is an auditory ERP component elicited by infrequent (deviant) stimuli differing in some physical features from the repetitive frequent (standard) stimuli in a sound sequence. The MMN provides a sensitive measure for cortical auditory stimulus feature discrimination, regardless of attention and other contaminating factors. In this study, MMN responses to duration, intensity, frequency, and gap changes were recorded in healthy young adults ($n = 17$), using a multifeature paradigm including several types of auditory change in the same stimulus sequence, while a GSM mobile phone was placed on either ear with the EMF (902 MHz pulsed at 217 Hz; SAR(1g) = 1.14 W/kg, SAR(10g) = 0.82 W/kg, peak value = 1.21 W/kg, measured with an SAM phantom) on or off. An MMN was elicited by all deviant types, while its amplitude and latency showed no significant differences due to EMF exposure for any deviant types. In the present study, we found no conclusive evidence that acute exposure to GSM mobile phone EMF affects cortical auditory change detection processing reflected by the MMN.

(E) Lee D, Lee J, Lee I. Cell Phone Generated Radio Frequency Electromagnetic Field Effects on the Locomotor Behaviors of the Fishes *Poecilia reticulata* and *Danio rerio*. Int J Radiat Biol. 2015 Jun 15:1-20. [Epub ahead of print] (AS, BE)

PURPOSE: The locomotor behavior of small fish was characterized under a cell phone generated radio frequency electromagnetic field (RF EMF). **MATERIALS AND METHODS:** The trajectory of movement of 10 pairs of *poecilia reticulata* and 15 pairs of *danio rerio* in a fish tank was recorded and tracked under the presence of a cell phone generated RF EMF. The measures were based on spatial and temporal distributions. A time-series trajectory was utilized to emphasize the dynamic nature of locomotor behavior. Fish movement was recorded in real-time. Their spatial, velocity, turning angle and sinuosity distribution were analyzed in terms of $F(v,x)$, $P[n(x,t)]$, $P(v)$, $F(\Theta)$ and $F(s)$, respectively. In addition, potential temperature elevation caused by a cellular phone was also examined. **RESULTS:** We demonstrated that a cellular phone induced temperature elevation was not relevant, and that our measurements reflected RF EMF-induced effects on the locomotor behavior of *poecilia reticulata* and *danio rerio*. Fish

locomotion was observed under normal conditions, in the visual presence of a cell phone, after feeding, and under starvation. Fish locomotor behavior was random both in normal conditions and in the presence of an off-signaled cell phone. However, there were significant changes in the locomotion of the fish after feeding under the RF EMF. CONCLUSIONS: The locomotion of the fed fish was affected in terms of changes in population and velocity distributions under the presence of the RF EMF emitted by the cell phone. There was, however, no significant difference in angular distribution.

(E) Lee KS, Choi JS, Hong SY, Son TH, Yu K. Mobile phone electromagnetic radiation activates MAPK signaling and regulates viability in *Drosophila*. Bioelectromagnetics. 29(5):371-379, 2008. (AS, CC)

Mobile phones are widely used in the modern world. However, biological effects of electromagnetic radiation produced by mobile phones are largely unknown. In this report, we show biological effects of the mobile phone 835 MHz electromagnetic field (EMF) in the *Drosophila* model system. When flies were exposed to the specific absorption rate (SAR) 1.6 W/kg, which is the proposed exposure limit by the American National Standards Institute (ANSI), more than 90% of the flies were viable even after the 30 h exposure. However, in the SAR 4.0 W/kg strong EMF exposure, viability dropped from the 12 h exposure. These EMF exposures triggered stress response and increased the production of reactive oxygen species. The EMF exposures also activated extracellular signal regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) signaling, but not p38 kinase signaling. Interestingly, SAR 1.6 W/kg activated mainly ERK signaling and expression of an anti-apoptotic gene, whereas SAR 4.0 W/kg strongly activated JNK signaling and expression of apoptotic genes. In addition, SAR 4.0 W/kg amplified the number of apoptotic cells in the fly brain. These findings demonstrate that the exposure limit on electromagnetic radiation proposed by ANSI triggered ERK-survival signaling but the strong electromagnetic radiation activated JNK-apoptotic signaling in *Drosophila*.

(E) Lee W, Yang KL. Using medaka embryos as a model system to study biological effects of the electromagnetic fields on development and behavior. Ecotoxicol Environ Saf. 2014 Jul 29;108C:187-194. doi: 10.1016/j.ecoenv.2014.06.035. [Epub ahead of print]. (AS, CE, BE, DE, ME)

The electromagnetic fields (EMFs) of anthropogenic origin are ubiquitous in our environments. The health hazard of extremely low frequency and radiofrequency EMFs has been investigated for decades, but evidence remains inconclusive, and animal studies are urgently needed to resolve the controversies regarding developmental toxicity of EMFs. Furthermore, as undersea cables and technological devices are increasingly used, the lack of information regarding the health risk of EMFs to aquatic organisms needs to be addressed. Medaka embryos (*Oryzias*

latipes) have been a useful tool to study developmental toxicity in vivo due to their optical transparency. Here we explored the feasibility of using medaka embryos as a model system to study biological effects of EMFs on development. We also used a white preference test to investigate behavioral consequences of the EMF developmental toxicity. Newly fertilized embryos were randomly assigned to four groups that were exposed to an EMF with 3.2 kHz at the intensity of 0.12, 15, 25, or 60 μ T. The group exposed to the background 0.12 μ T served as the control. The embryos were exposed continually until hatch. They were observed daily, and the images were recorded for analysis of several developmental endpoints. Four days after hatching, the hatchlings were tested with the white preference test for their anxiety-like behavior. The results showed that embryos exposed to all three levels of the EMF developed significantly faster. The endpoints affected included the number of somites, eye width and length, eye pigmentation density, midbrain width, head growth, and the day to hatch. In addition, the group exposed to the EMF at 60 μ T exhibited significantly higher levels of anxiety-like behavior than the other groups did. In conclusion, the EMF tested in this study accelerated embryonic development and heightened anxiety-like behavior. Our results also demonstrate that the medaka embryo is a sensitive and cost-efficient in vivo model system to study developmental toxicity of EMFs.

(E) Leung S, Croft RJ, McKenzie RJ, Iskra S, Silber B, Cooper NR, O'Neill B, Cropley V, Diaz-Trujillo A, Hamblin D, Simpson D. Effects of 2G and 3G mobile phones on performance and electrophysiology in adolescents, young adults and older adults. Clin Neurophysiol. 122(11):2203-2216, 2011. (HU, AD, BE, EE)

OBJECTIVE: This study examined sensory and cognitive processing in adolescents, young adults and older adults, when exposed to 2nd (2G) and 3rd (3G) generation mobile phone signals. **METHODS:** Tests employed were the auditory 3-stimulus oddball and the N-back. Forty-one 13-15 year olds, forty-two 19-40 year olds and twenty 55-70 year olds were tested using a double-blind cross-over design, where each participant received Sham, 2G and 3G exposures, separated by at least 4 days. **RESULTS:** 3-Stimulus oddball task: Behavioural: accuracy and reaction time of responses to targets were not affected by exposure. Electrophysiological: augmented N1 was found in the 2G condition (independent of age group). N-back task: Behavioural: the combined groups performed less accurately during the 3G exposure (compared to Sham), with post hoc tests finding this effect separately in the adolescents only. Electrophysiological: delayed ERD/ERS responses of the alpha power were found in both 3G and 2G conditions (compared to Sham; independent of age group). **CONCLUSION:** Employing tasks tailored to each individual's ability level, this study provides support for an effect of acute 2G and 3G exposure on human cognitive function. **SIGNIFICANCE:** The subtlety of mobile phone effect on cognition in our study suggests that it is important to account for individual differences in future mobile phone research.

(E) Li H, Peng R, Wang C, Qiao S, Yong-Zou, Gao Y, Xu X, Wang S, Dong J, Zuo H, Li-Zhao, Zhou H, Wang L, Hu X. Alterations of cognitive function and 5-HT system in rats after long term microwave exposure. *Physiol Behav.* 2014 Dec 24. pii: S0031-9384(14)00663-5. doi: 10.1016/j.physbeh.2014.12.039. [Epub ahead of print] (AS, CE, BE, CC, CH, EE, ME)

The increased use of microwaves raises concerns about its impact on health including cognitive function in which neurotransmitter system plays an important role. In this study, we focused on the serotonergic system and evaluated the long term effects of chronic microwave radiation on cognition and correlated items. Wistar rats were exposed or sham exposed to 2.856GHz microwaves with the average power density of 5, 10, 20 or 30mW/cm² respectively for 6min three times a week up to 6weeks. At different time points after the last exposure, spatial learning and memory function, morphology structure of the hippocampus, electroencephalogram (EEG) and neurotransmitter content (amino acid and monoamine) of rats were tested. Above results raised our interest in serotonin system. Tryptophan hydroxylase 1 (TPH1) and monoamine oxidase (MAO), two important rate-limiting enzymes in serotonin synthesis and metabolic process respectively, were detected. Expressions of serotonin receptors including 5-HT_{1A}, 2A, 2C receptors were measured. We demonstrated that chronic exposure to microwave (2.856GHz, with the average power density of 5, 10, 20 and 30mW/cm²) could induce dose-dependent deficit of spatial learning and memory in rats accompanied with inhibition of brain electrical activity, the degeneration of hippocampus neurons, and the disturbance of neurotransmitters, among which the increase of 5-HT occurred as the main long-term change that the decrease of its metabolism partly contributed to. Besides, the variations of 5-HT_{1A}R and 5-HT_{2C}R expressions were also indicated. The results suggested that in the long-term way, chronic microwave exposure could induce cognitive deficit and 5-HT system may be involved in it.

(E) Li Y, Shi C, Lu G, Xu Q, Liu S. Effects of electromagnetic radiation on spatial memory and synapses in rat hippocampal CA1. *Neural Regen Res.* 7(16):1248-1255, 2012. (AS, CE, BE, ME)

In this study, we investigated the effects of mobile phone radiation on spatial learning, reference memory, and morphology in related brain regions. After the near-field radiation (0.52-1.08 W/kg) was delivered to 8-week-old Wistar rats 2 hours per day for 1 month, behavioral changes were examined using the Morris water maze. Compared with the sham-irradiated rats, the irradiated rats exhibited impaired performance. Morphological changes were investigated by examining synaptic ultrastructural changes in the hippocampus. Using the physical dissector technique, the number of pyramidal neurons, the synaptic profiles, and the length of postsynaptic densities in the CA1 region were quantified stereologically. The morphological changes included mitochondrial degenerations, fewer synapses, and shorter postsynaptic densities in the radiated rats. These findings indicate that mobile phone radiation can significantly impair spatial learning and reference memory and induce morphological changes in the hippocampal CA1 region.

(NE) Lipping T, Rorarius M, Jäntti V, Annala K, Mennander A, Ferenets R, Toivonen T, Toivo T, Värri A, Korpinen L. Using the nonlinear control of anaesthesia-induced hypersensitivity of EEG at burst suppression level to test the effects of radiofrequency radiation on brain function. *Nonlinear Biomed Phys.* 3(1):5, 2009. **(AS, IA, EE)**

BACKGROUND: In this study, investigating the effects of mobile phone radiation on test animals, eleven pigs were anaesthetised to the level where burst-suppression pattern appears in the electroencephalogram (EEG). At this level of anaesthesia both human subjects and animals show high sensitivity to external stimuli which produce EEG bursts during suppression. The burst-suppression phenomenon represents a nonlinear control system, where low-amplitude EEG abruptly switches to very high amplitude bursts. This switching can be triggered by very minor stimuli and the phenomenon has been described as hypersensitivity. To test if also radio frequency (RF) stimulation can trigger this nonlinear control, the animals were exposed to pulse modulated signal of a GSM mobile phone at 890 MHz. In the first phase of the experiment electromagnetic field (EMF) stimulation was randomly switched on and off and the relation between EEG bursts and EMF stimulation onsets and endpoints were studied. In the second phase a continuous RF stimulation at 31 W/kg was applied for 10 minutes. The ECG, the EEG, and the subcutaneous temperature were recorded. **RESULTS:** No correlation between the exposure and the EEG burst occurrences was observed in phase I measurements. No significant changes were observed in the EEG activity of the pigs during phase II measurements although several EEG signal analysis methods were applied. The temperature measured subcutaneously from the pigs' head increased by 1.6 degrees C and the heart rate by 14.2 bpm on the average during the 10 min exposure periods. **CONCLUSION:** The hypothesis that RF radiation would produce sensory stimulation of somatosensory, auditory or visual system or directly affect the brain so as to produce EEG bursts during suppression was not confirmed.

(E) Liu ML, Wen JQ, Fan YB. Potential protection of green tea polyphenols against 1800 MHz electromagnetic radiation-induced injury on rat cortical neurons. *Neurotox Res.* 20(3):270-276, 2011. **(CS, IA, CC, OX)**

Radiofrequency electromagnetic fields (EMF) are harmful to public health, but the certain anti-irradiation mechanism is not clear yet. The present study was performed to investigate the possible protective effects of green tea polyphenols against electromagnetic radiation-induced injury in the cultured rat cortical neurons. In this study, green tea polyphenols were used in the cultured cortical neurons exposed to 1800 MHz EMFs by the mobile phone. We found that the mobile phone irradiation for 24 h induced marked neuronal cell death in the MTT (3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl-tetrazolium bromide) and TUNEL (TdT mediated biotin-dUTP nicked-end labeling) assay, and protective effects of green tea polyphenols on the injured cortical neurons were demonstrated by testing the content of Bcl-2 Associated X protein (Bax) in the immunoprecipitation assay and Western blot assay. In our study results, the mobile phone irradiation-induced increases in the content of active Bax were inhibited significantly by green tea polyphenols, while the contents of total Bax had no marked changes after the treatment of green tea polyphenols. Our results suggested a neuroprotective effect of green

tea polyphenols against the mobile phone irradiation-induced injury on the cultured rat cortical neurons.

(E) Liu YX, Tai JL, Li GQ, Zhang ZW, Xue JH, Liu HS, Zhu H, Cheng JD, Liu YL, Li AM, Zhang Y. Exposure to 1950-MHz TD-SCDMA Electromagnetic Fields Affects the Apoptosis of Astrocytes via Caspase-3-Dependent Pathway. PLoS One. 7(8):e42332, 2012. (CS, CC)

The usage of mobile phone increases globally. However, there is still a paucity of data about the impact of electromagnetic fields (EMF) on human health. This study investigated whether EMF radiation would alter the biology of glial cells and act as a tumor-promoting agent. We exposed rat astrocytes and C6 glioma cells to 1950-MHz TD-SCDMA for 12, 24 and 48 h respectively, and found that EMF exposure had differential effects on rat astrocytes and C6 glioma cells. A 48 h of exposure damaged the mitochondria and induced significant apoptosis of astrocytes. Moreover, caspase-3, a hallmark of apoptosis, was highlighted in astrocytes after 48 h of EMF exposure, accompanied by a significantly increased expression of bax and reduced level of bcl-2. The tumorigenicity assays demonstrated that astrocytes did not form tumors in both control and exposure groups. In contrast, the unexposed and exposed C6 glioma cells show no significant differences in both biological feature and tumor formation ability. Therefore, our results implied that exposure to the EMF of 1950-MHz TD-SCDMA may not promote the tumor formation, but continuous exposure damaged the mitochondria of astrocytes and induce apoptosis through a caspase-3-dependent pathway with the involvement of bax and bcl-2.

(E) López-Martín E, Bregains J, Relova-Quinteiro JL, Cadarso-Suárez C, Jorge-Barreiro FJ, Ares-Pena FJ. The action of pulse-modulated GSM radiation increases regional changes in brain activity and c-Fos expression in cortical and subcortical areas in a rat model of picrotoxin-induced seizure proneness. J Neurosci Res. 87(6):1484-1499, 2009. (AS, CC, WS)

The action of the pulse-modulated GSM radiofrequency of mobile phones has been suggested as a physical phenomenon that might have biological effects on the mammalian central nervous system. In the present study, GSM-exposed picrotoxin-pretreated rats showed differences in clinical and EEG signs, and in c-Fos expression in the brain, with respect to picrotoxin-treated rats exposed to an equivalent dose of unmodulated radiation. Neither radiation treatment caused tissue heating, so thermal effects can be ruled out. The most marked effects of GSM radiation on c-Fos expression in picrotoxin-treated rats were observed in limbic structures, olfactory cortex areas and subcortical areas, the dentate gyrus, and the central lateral nucleus of the thalamic intralaminar nucleus group. Nonpicrotoxin-treated animals exposed to unmodulated radiation showed the highest levels of neuronal c-Fos expression in cortical areas. These results suggest a specific effect of the pulse modulation of GSM radiation on brain activity of a picrotoxin-induced seizure-proneness rat model and indicate that this mobile-phone-type radiation might induce regional changes in previous preexcitability conditions of neuronal activation.

(E) Loughran SP, McKenzie RJ, Jackson ML, Howard ME, Croft RJ. Individual differences in the effects of mobile phone exposure on human sleep: rethinking the problem. Bioelectromagnetics. 33(1):86-93, 2012. (HU, EE, SL)

Mobile phone exposure-related effects on the human electroencephalogram (EEG) have been shown during both waking and sleep states, albeit with slight differences in the frequency affected. This discrepancy, combined with studies that failed to find effects, has led many to conclude that no consistent effects exist. We hypothesised that these differences might partly be due to individual variability in response, and that mobile phone emissions may in fact have large but differential effects on human brain activity. Twenty volunteers from our previous study underwent an adaptation night followed by two experimental nights in which they were randomly exposed to two conditions (Active and Sham), followed by a full-night sleep episode. The EEG spectral power was increased in the sleep spindle frequency range in the first 30 min of non-rapid eye movement (non-REM) sleep following Active exposure. This increase was more prominent in the participants that showed an increase in the original study. These results confirm previous findings of mobile phone-like emissions affecting the EEG during non-REM sleep. Importantly, this low-level effect was also shown to be sensitive to individual variability. Furthermore, this indicates that previous negative results are not strong evidence for a lack of an effect and, given the far-reaching implications of mobile phone research, we may need to rethink the interpretation of results and the manner in which research is conducted in this field.

(NE) Loughran SP, Benz DC, Schmid MR, Murbach M, Kuster N, Achermann P. No increased sensitivity in brain activity of adolescents exposed to mobile phone-like emissions. Clin Neurophysiol. 124(7):1303-1308, 2013. (HU, BE, EE, AD)

OBJECTIVE: To examine the potential sensitivity of adolescents to radiofrequency electromagnetic field (RF EMF) exposures, such as those emitted by mobile phones. **METHODS:** In a double-blind, randomized, crossover design, 22 adolescents aged 11-13years (12 males) underwent three experimental sessions in which they were exposed to mobile phone-like RF EMF signals at two different intensities, and a sham session. During exposure cognitive tasks were performed and waking EEG was recorded at three time-points subsequent to exposure (0, 30 and 60min). **RESULTS:** No clear significant effects of RF EMF exposure were found on the waking EEG or cognitive performance. **CONCLUSIONS:** Overall, the current study was unable to demonstrate exposure-related effects previously observed on the waking EEG in adults, and also provides further support for a lack of an influence of mobile phone-like exposure on cognitive performance. **SIGNIFICANCE:** Adolescents do not appear to be more sensitive than adults to mobile phone RF EMF emissions.

(E) Lowden A, Akerstedt T, Ingre M, Wiholm C, Hillert L, Kuster N, Nilsson JP, Arnetz B. Sleep after mobile phone exposure in subjects with mobile phone-related symptoms. Bioelectromagnetics. 32(1):4-14, 2011. (HU, EE, SL)

Several studies show increases in activity for certain frequency bands (10-14 Hz) and visually scored parameters during sleep after exposure to radiofrequency electromagnetic fields. A

shortened REM latency has also been reported. We investigated the effects of a double-blind radiofrequency exposure (884 MHz, GSM signaling standard including non-DTX and DTX mode, time-averaged 10 g psSAR of 1.4 W/kg) on self-evaluated sleepiness and objective EEG measures during sleep. Forty-eight subjects (mean age 28 years) underwent 3 h of controlled exposure (7:30-10:30 PM; active or sham) prior to sleep, followed by a full-night polysomnographic recording in a sleep laboratory. The results demonstrated that following exposure, time in Stages 3 and 4 sleep (SWS, slow-wave sleep) decreased by 9.5 min (12%) out of a total of 78.6 min, and time in Stage 2 sleep increased by 8.3 min (4%) out of a total of 196.3 min compared to sham. The latency to Stage 3 sleep was also prolonged by 4.8 min after exposure. Power density analysis indicated an enhanced activation in the frequency ranges 0.5-1.5 and 5.75-10.5 Hz during the first 30 min of Stage 2 sleep, with 7.5-11.75 Hz being elevated within the first hour of Stage 2 sleep, and bands 4.75-8.25 Hz elevated during the second hour of Stage 2 sleep. No pronounced power changes were observed in SWS or for the third hour of scored Stage 2 sleep. No differences were found between controls and subjects with prior complaints of mobile phone-related symptoms. The results confirm previous findings that RF exposure increased the EEG alpha range in the sleep EEG, and indicated moderate impairment of SWS. Furthermore, reported differences in sensitivity to mobile phone use were not reflected in sleep parameters.

(E) Lu Y, Xu S, He M, Chen C, Zhang L, Liu C, Chu F, Yu Z, Zhou Z, Zhong M. Glucose administration attenuates spatial memory deficits induced by chronic low-power-density microwave exposure. *Physiol Behav.* 106(5):631-637, 2012. (AS, CE, BE)

Extensive evidence indicates that glucose administration attenuates memory deficits in rodents and humans, and cognitive impairment has been associated with reduced glucose metabolism and uptake in certain brain regions including the hippocampus. In the present study, we investigated whether glucose treatment attenuated memory deficits caused by chronic low-power-density microwave (MW) exposure, and the effect of MW exposure on hippocampal glucose uptake. We exposed Wistar rats to 2.45 GHz pulsed MW irradiation at a power density of 1 mW/cm² for 3 h/day, for up to 30 days. MW exposure induced spatial learning and memory impairments in rats. Hippocampal glucose uptake was also reduced by MW exposure in the absence or presence of insulin, but the levels of blood glucose and insulin were not affected. However, these spatial memory deficits were reversed by systemic glucose treatment. Our results indicate that glucose administration attenuates the spatial memory deficits induced by chronic low-power-density MW exposure, and reduced hippocampal glucose uptake may be associated with cognitive impairment caused by MW exposure.

(E) Lu Y, He M, Zhang Y, Xu S, Zhang L, He Y, Chen C, Liu C, Pi H, Yu Z, Zhou Z. Differential Pro-Inflammatory Responses of Astrocytes and Microglia Involve STAT3 Activation in Response to 1800 MHz Radiofrequency Fields. *PLoS One.* 2014 Oct 2;9(9):e108318. doi: 10.1371/journal.pone.0108318. (CS, CH)

Microglia and astrocytes play important role in maintaining the homeostasis of central nervous system (CNS). Several CNS impacts have been postulated to be associated with radiofrequency (RF) electromagnetic fields exposure. Given the important role of inflammation in neural physiopathologic processes, we investigated the pro-inflammatory responses of microglia and astrocytes and the involved mechanism in response to RF fields. Microglial N9 and astroglial C8-D1A cells were exposed to 1800 MHz RF for different time with or without pretreatment with STAT3 inhibitor. Microglia and astrocytes were activated by RF exposure indicated by up-regulated CD11b and glial fibrillary acidic protein (GFAP). However, RF exposure induced differential pro-inflammatory responses in astrocytes and microglia, characterized by different expression and release profiles of IL-1 β , TNF- α , IL-6, PGE2, nitric oxide (NO), inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2). Moreover, the RF exposure activated STAT3 in microglia but not in astrocytes. Furthermore, the STAT3 inhibitor Stattic ameliorated the RF-induced release of pro-inflammatory cytokines in microglia but not in astrocytes. Our results demonstrated that RF exposure differentially induced pro-inflammatory responses in microglia and astrocytes, which involved differential activation of STAT3 in microglia and astrocytes. Our data provide novel insights into the potential mechanisms of the reported CNS impacts associated with mobile phone use and present STAT3 as a promising target to protect humans against increasing RF exposure.

(E) Luria R, Eliyahu I, Hareuveny R, Margaliot M, Meiran N. Cognitive effects of radiation emitted by cellular phones: the influence of exposure side and time. Bioelectromagnetics. 30(3):198-204, 2009. (See also Hareuveny et al., 2011) (HU, BE)

This study examined the time dependence effects of exposure to radiofrequency radiation (RFR) emitted by standard GSM cellular phones on the cognitive functions of humans. A total of 48 healthy right-handed male subjects performed a spatial working memory task (that required either a left-hand or a right-hand response) while being exposed to one of two GSM phones placed at both sides of the head. The subjects were randomly divided into three groups. Each group was exposed to one of three exposure conditions: left-side of the head, right-side, or sham-exposure. The experiment consisted of 12 blocks of trials. Response times (RTs) and accuracy of the responses were recorded. It was found that the average RT of the right-hand responses under left-side exposure condition was significantly longer than those of the right-side and sham-exposure groups averaged together during the first two time blocks. These results confirmed the existence of an effect of exposure on RT, as well as the fact that exposure duration (together with the responding hand and the side of exposure) may play an important role in producing detectable RFR effects on performance. Differences in these parameters might be the reason for the failure of certain studies to detect or replicate RFR effects.

(E) Lustenberger C, Murbach M, Durr R, Schmid MR, Kuster N, Achermann P, Huber R. Stimulation of the brain with radiofrequency electromagnetic field pulses affects sleep-dependent performance improvement. Brain Stimul 6(5):805-811, 2013. (HU, BE, EE, SL)

Background: Sleep-dependent performance improvements seem to be closely related to sleep spindles (12–15 Hz) and sleep slow-wave activity (SWA, 0.75–4.5 Hz). Pulse-modulated

radiofrequency electromagnetic fields (RF EMF, carrier frequency 900 MHz) are capable to modulate these electroencephalographic (EEG) characteristics of sleep. Objective: The aim of our study was to explore possible mechanisms how RF EMF affects cortical activity during sleep and to test whether such effects on cortical activity during sleep interact with sleep-dependent performance changes. Methods: Sixteen male subjects underwent 2 experimental nights, one of them with all-night 0.25–0.8 Hz pulsed RF EMF exposure. All-night EEG was recorded. To investigate RF EMF induced changes in overnight performance improvement, subjects were trained for both nights on a motor task in the evening and the morning. Results: We obtained good sleep quality in all subjects under both conditions (mean sleep efficiency > 90%). After pulsed RF EMF we found increased SWA during exposure to pulse-modulated RF EMF compared to sham exposure ($P < 0.05$) toward the end of the sleep period. Spindle activity was not affected. Moreover, subjects showed an increased RF EMF burst-related response in the SWA range, indicated by an increase in event-related EEG spectral power and phase changes in the SWA range. Notably, during exposure, sleep-dependent performance improvement in the motor sequence task was reduced compared to the sham condition (–20.1%, $P = 0.03$). Conclusion: The changes in the time course of SWA during the exposure night may reflect an interaction of RF EMF with the renormalization of cortical excitability during sleep, with a negative impact on sleep-dependent performance improvement.

(E) Lustenberger, C., Murbach, M., Tüshaus, L., Wehrle, F., Kuster, N., Achermann, P. and Huber, R., Inter-individual and intra-individual variation of the effects of pulsed RF EMF exposure on the human sleep EEG. *Bioelectromagnetics*. 36(3) 169, 2015. (HU, EE)

Pulse-modulated radiofrequency electromagnetic fields (RF EMF) can alter brain activity during sleep; increases of electroencephalographic (EEG) power in the sleep spindle (13.75–15.25 Hz) and delta-theta (1.25–9 Hz) frequency range have been reported. These field effects show striking inter-individual differences. However, it is still unknown whether individual subjects react in a similar way when repeatedly exposed. Thus, our study aimed to investigate inter-individual variation and intra-individual stability of field effects. To do so, we exposed 20 young male subjects twice for 30 min prior to sleep to the same amplitude modulated 900 MHz (2 Hz pulse, 20 Hz Gaussian low-pass filter and a ratio of peak-to-average of 4) RF EMF (spatial peak absorption of 2 W/kg averaged over 10 g) 2 weeks apart. The topographical analysis of EEG power during all-night non-rapid eye movement sleep revealed: (1) exposure-related increases in delta-theta frequency range in several fronto-central electrodes; and (2) no differences in spindle frequency range. We did not observe reproducible within-subject RF EMF effects on sleep spindle and delta-theta activity in the sleep EEG and it remains unclear whether a biological trait of how the subjects' brains react to RF EMF exists.

(E) Lv B, Chen Z, Wu T, Shao Q, Yan D, Ma L, Lu K, Xie Y. The alteration of spontaneous low frequency oscillations caused by acute electromagnetic fields exposure. *Clin Neurophysiol*.

2013 Sep 4. pii: S1388-2457(13)00976-0. doi: 10.1016/j.clinph.2013.07.018. [Epub ahead of print] (HU, EE, PE)

OBJECTIVE: The motivation of this study is to evaluate the possible alteration of regional resting state brain activity induced by the acute radiofrequency **electromagnetic** field (RF-EMF) exposure (30min) of Long Term Evolution (LTE) signal. **METHODS:** We designed a controllable near-field LTE RF-EMF exposure environment. Eighteen subjects participated in a double-blind, crossover, randomized and counterbalanced experiment including two sessions (real and sham exposure). The radiation source was close to the right ear. Then the resting state fMRI signals of human brain were collected before and after the exposure in both sessions. We measured the amplitude of low frequency fluctuation (ALFF) and fractional ALFF (fALFF) to characterize the spontaneous brain activity. **RESULTS:** We found the decreased ALFF value around in left superior temporal gyrus, left middle temporal gyrus, right superior temporal gyrus, right medial frontal gyrus and right paracentral lobule after the real exposure. And the decreased fALFF value was also detected in right medial frontal gyrus and right paracentral lobule. **CONCLUSIONS:** The study provided the evidences that 30min LTE RF-EMF exposure modulated the spontaneous low frequency fluctuations in some brain regions. **SIGNIFICANCE:** With resting state fMRI, we found the alteration of spontaneous low frequency fluctuations induced by the acute LTE RF-EMF exposure.

(E) Lv B, Su C, Yang L, Xie Y, Wu T. Whole brain EEG synchronization likelihood modulated by long term evolution electromagnetic fields exposure. Conf Proc IEEE Eng Med Biol Soc. 2014:986-989, 2014. (HU, EE)

In this paper, we aimed to investigate the possible interactions between human brain and radiofrequency electromagnetic fields (EMF) with electroencephalogram (EEG) technique. Unlike the previous studies which mainly focused on EMF effect on local brain activities, we attempted to evaluate whether the EMF emitted from Long Term Evolution (LTE) devices can modulate the functional connectivity of brain electrical activities. Ten subjects were recruited to participate in a crossover, double-blind exposure experiment which included two sessions (real and sham exposure). In each session, LTE EMF exposure (power on or off) lasted for 30 min and the EEG signals were collected with 32 channels throughout the experiment. Then we applied the synchronization likelihood method to quantify the neural synchronization over the whole brain in different frequency bands and in different EEG record periods. Our results illustrated that the short-term LTE EMF exposure would modulate the synchronization patterns of EEG activation across the whole brain.

(E) Maaroufi K, Had-Aissouni L, Melon C, Sakly M, Abdelmelek H, Poucet B, Save E. Spatial learning, monoamines and oxidative stress in rats exposed to 900MHz electromagnetic field in combination with iron overload. Behav Brain Res. 2013 Oct 18. pii: S0166-4328(13)00624-4. doi: 10.1016/j.bbr.2013.10.016. [Epub ahead of print] (AS, CE, BE, CH)

The increasing use of mobile phone technology over the last decade raises concerns about the impact of high frequency electromagnetic fields (EMF) on health. More recently, a link between EMF, iron overload in the brain and neurodegenerative disorders including Parkinson's and Alzheimer's diseases has been suggested. Co-exposure to EMF and brain iron overload may have a greater impact on brain tissues and cognitive processes than each treatment by itself. To examine this hypothesis, Long-Evans rats submitted to 900MHz exposure or combined 900MHz EMF and iron overload treatments were tested in various spatial learning tasks (navigation task in the Morris water maze, working memory task in the radial-arm maze, and object exploration task involving spatial and non spatial processing). Biogenic monoamines and metabolites (dopamine, serotonin) and oxidative stress were measured. Rats exposed to EMF were impaired in the object exploration task but not in the navigation and working memory tasks. They also showed alterations of monoamine content in several brain areas but mainly in the hippocampus. Rats that received combined treatment did not show greater behavioral and neurochemical deficits than EMF-exposed rats. None of the two treatments produced global oxidative stress. These results show that there is an impact of EMF on the brain and cognitive processes but this impact is revealed only in a task exploiting spontaneous exploratory activity. In contrast, there are no synergistic effects between EMF and a high content of iron in the brain.

(E) Maganioti AE, Hountala CD, Papageorgiou CC, Kyprianou MA, Rabavilas AD, Capsalis CN. Principal component analysis of the P600 waveform: RF and gender effects. Neurosci Lett. 478(1):19-23, 2010. (HU, EE)

The aim of the present study was to examine the patterns of activation of the P600 waveform of the event-related potentials (ERP), applying principal component analysis (PCA) and repeated measures ANOVA, and whether these patterns are RF and gender dependent. The ERPs of thirty-nine healthy subjects (20 male and 19 female) were recorded during an auditory memory task in the presence and absence of RF, similar to that emitted by mobile phones. Both PCA and ANOVA produced congruent results, showing that activation of the P600 component occurs early and more intensely in the region of the posterior electrodes and in a less intense manner in the central electrodes. Conversely, the activation at the anterior electrodes arises later with a considerably reduced intensity. In the absence of RF female subjects exhibited significantly lower amplitudes at anterior electrodes and earlier latencies at central electrodes than male subjects. These differences disappear in the presence of RF. Consequently, the P600 component follows distinct patterns of activation in the anterior, central and posterior brain areas and gender differences are observed simultaneously at several electrodes within these areas. Finally, the gender-related functional architecture with regard the P600 component appears to be RF sensitive. In conclusion, the application of the PCA procedure provides an adequate model of the spatially distributed event-related dynamics that correspond to the P600 waveform.

(NE) Malek F, Rani KA, Rahim HA, Omar MH. Effect of Short-Term Mobile Phone Base Station Exposure on Cognitive Performance, Body Temperature, Heart Rate and Blood Pressure of Malaysians. Sci Rep. 5:13206, 2015. (HU, BE)

Individuals who report their sensitivity to electromagnetic fields often undergo cognitive impairments that they believe are due to the exposure of mobile phone technology. The aim of this study is to clarify whether short-term exposure at 1 V/m to the typical Global System for Mobile Communication and Universal Mobile Telecommunications System (UMTS) affects cognitive performance and physiological parameters (body temperature, blood pressure and heart rate). This study applies counterbalanced randomizing single blind tests to determine if sensitive individuals experience more negative health effects when they are exposed to base station signals compared with sham (control) individuals. The sample size is 200 subjects with 50.0% Idiopathic Environmental Intolerance attributed to electromagnetic fields (IEI-EMF) also known as sensitive and 50.0% (non-IEI-EMF). The computer-administered Cambridge Neuropsychological Test Automated Battery (CANTAB eclipse(TM)) is used to examine cognitive performance. Four tests are chosen to evaluate Cognitive performance in CANTAB: Reaction Time (RTI), Rapid Visual Processing (RVP), Paired Associates Learning (PAL) and Spatial Span (SSP). Paired sample t-test on the other hand, is used to examine the physiological parameters. Generally, in both groups, there is no statistical significant difference between the exposure and sham exposure towards cognitive performance and physiological effects (P's > 0.05).

(E) Mandalà M, Colletti V, Sacchetto L, Manganotti P, Ramat S, Marcocci A, Colletti L. Effect of Bluetooth headset and mobile phone electromagnetic fields on the human auditory nerve. Laryngoscope. 2013 Apr 25. doi: 10.1002/lary.24103. [Epub ahead of print] (HU, EE)

OBJECTIVES/HYPOTHESIS: The possibility that long-term mobile phone use increases the incidence of astrocytoma, glioma and acoustic neuroma has been investigated in several studies. Recently, our group showed that direct exposure (in a surgical setting) to cell phone electromagnetic fields (EMFs) induces deterioration of auditory evoked cochlear nerve compound action potential (CNAP) in humans. To verify whether the use of Bluetooth devices reduces these effects, we conducted the present study with the same experimental protocol. STUDY DESIGN: Randomized trial. METHODS: Twelve patients underwent retrosigmoid vestibular neurectomy to treat definite unilateral Ménière's disease while being monitored with acoustically evoked CNAPs to assess direct mobile phone exposure or alternatively the EMF effects of Bluetooth headsets. RESULTS: We found no short-term effects of Bluetooth EMFs on the auditory nervous structures, whereas direct mobile phone EMF exposure confirmed a significant decrease in CNAPs amplitude and an increase in latency in all subjects. CONCLUSIONS: The outcomes of the present study show that, contrary to the finding that the latency and amplitude of CNAPs are very sensitive to EMFs produced by the tested mobile phone, the EMFs produced by a common Bluetooth device do not induce any significant change in cochlear nerve activity. The conditions of exposure, therefore, differ from those of everyday life, in which various biological tissues may reduce the EMF affecting the cochlear nerve. Nevertheless, these novel findings may have important safety implications.

(E) Maskey D, Kim M, Aryal B, Pradhan J, Choi IY, Park KS, Son T, Hong SY, Kim SB, Kim HG, Kim MJ. Effect of 835 MHz radiofrequency radiation exposure on calcium binding proteins in the hippocampus of the mouse brain. Brain Res. 1313:232-241, 2010a. (AS, CE, ME, CH)

Worldwide expansion of mobile phones and electromagnetic field (EMF) exposure has raised question of their possible biological effects on the brain and nervous system. Radiofrequency (RF) radiation might alter intracellular signaling pathways through changes in calcium (Ca^{2+}) permeability across cell membranes. Changes in the expression of calcium binding proteins (CaBP) like calbindin D28-k (CB) and calretinin (CR) could indicate impaired Ca^{2+} homeostasis due to EMF exposure. CB and CR expression were measured with immunohistochemistry in the hippocampus of mice after EMF exposure at 835 MHz for different exposure times and absorption rates, 1 h/day for 5 days at a specific absorption rate (SAR)=1.6 W/kg, 1 h/day for 5 days at SAR=4.0 W/kg, 5 h/day for 1 day at SAR=1.6 W/kg, 5 h/day for 1 day at SAR=4.0 W/kg, daily exposure for 1 month at SAR=1.6 W/kg. Body weights did not change significantly. CB immunoreactivity (IR) displayed moderate staining of cells in the cornu ammonis (CA) areas and prominently stained granule cells. CR IR revealed prominently stained pyramidal cells with dendrites running perpendicularly in the CA area. Exposure for 1 month produced almost complete loss of pyramidal cells in the CA1 area. CaBP differences could cause changes in cellular Ca^{2+} levels, which could have deleterious effect on normal hippocampal functions concerned with neuronal connectivity and integration.

(E) Maskey D, Pradhan J, Aryal B, Lee CM, Choi IY, Park KS, Kim SB, Kim HG, Kim MJ. Chronic 835-MHz radiofrequency exposure to mice hippocampus alters the distribution of calbindin and GFAP immunoreactivity. Brain Res. 1346:237-246, 2010b. (AS, CE, ME, CH)

Exponential interindividual handling in wireless communication system has raised possible doubts in the biological aspects of radiofrequency (RF) exposure on human brain owing to its close proximity to the mobile phone. In the nervous system, calcium (Ca^{2+}) plays a critical role in releasing neurotransmitters, generating action potential and membrane integrity. Alterations in intracellular Ca^{2+} concentration trigger aberrant synaptic action or cause neuronal apoptosis, which may exert an influence on the cellular pathology for learning and memory in the hippocampus. Calcium binding proteins like calbindin D28-K (CB) is responsible for the maintaining and controlling Ca^{2+} homeostasis. Therefore, in the present study, we investigated the effect of RF exposure on rat hippocampus at 835 MHz with low energy (specific absorption rate: SAR=1.6 W/kg) for 3 months by using both CB and glial fibrillary acidic protein (GFAP) specific antibodies by immunohistochemical method. Decrease in CB immunoreactivity (IR) was noted in exposed (E1.6) group with loss of interneurons and pyramidal cells in CA1 area and loss of granule cells. Also, an overall increase in GFAP IR was observed in the hippocampus of E1.6. By TUNEL assay, apoptotic cells were detected in the CA1, CA3 areas and dentate gyrus of hippocampus, which reflects that chronic RF exposure may affect the cell viability. In addition, the increase of GFAP IR due to RF exposure could be well suited with the feature of reactive astrogliosis, which is an abnormal increase in the number of astrocytes due to the loss of nearby neurons. Chronic RF exposure to the rat brain suggested that the decrease of CB IR

accompanying apoptosis and increase of GFAP IR might be morphological parameters in the hippocampus damages.

(E) Maskey D, Kim HJ, Kim HG, Kim MJ. Calcium-binding proteins and GFAP immunoreactivity alterations in murine hippocampus after 1 month of exposure to 835 MHz radiofrequency at SAR values of 1.6 and 4.0 W/kg. Neurosci Lett. 506(2):292-296, 2012. (AS, CE, ME, CH)

Widespread use of wireless mobile communication has raised concerns of adverse effect to the brain owing to the proximity during use due to the electromagnetic field emitted by mobile phones. Changes in calcium ion concentrations via binding proteins can disturb calcium homeostasis; however, the correlation between calcium-binding protein (CaBP) immunoreactivity (IR) and glial cells has not been determined with different SAR values. Different SAR values [1.6 (E1.6 group) and 4.0 (E4 group) W/kg] were applied to determine the distribution of calbindin D28-k (CB), calretinin (CR), and glial fibrillary acidic protein (GFAP) IR in murine hippocampus. Compared with sham control group, decreased CB and CR IRs, loss of CB and CR immunoreactive cells and increased GFAP IR exhibiting hypertrophic cytoplasmic processes were noted in both experimental groups. E4 group showed a prominent decrement in CB and CR IR than the E1.6 group due to down-regulation of CaBP proteins and neuronal loss. GFAP IR was more prominent in the E4 group than the E1.6 group. Decrement in the CaBPs can affect the calcium-buffering capacity leading to cell death, while increased GFAP IR and changes in astrocyte morphology, may mediate brain injury due to radiofrequency exposure.

(E) Maskey D, Kim MJ. Immunohistochemical Localization of Brain-derived Neurotrophic Factor and Glial Cell Line-derived Neurotrophic Factor in the Superior Olivary Complex of Mice after Radiofrequency Exposure. Neuroscience Letters. 564:78-82, 2014. (AS, CE, CH)

Raising health concerns about the biological effects from radiofrequency exposure, even with conflicting results, has prompted calls for formulation of a guideline of the biological safety level. Given the close proximity between a mobile phone and the ear, it has been suggested that the central auditory system may be detrimentally influenced by radiofrequency exposure. In the auditory system, neurotrophins are important in the regulation of neuron survival, especially mammalian cochlear neurons. Neurotrophic factors like brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF) present in the auditory system are responsible for the maintenance of auditory neurons. BDNF and GDNF may protect against acoustic trauma and prevent from hearing defect. The present study applied radiofrequency at a specific absorption rate (SAR) of 1.6 W/kg (E1.6) or 0 W/kg group to determine the distribution of BDNF and GDNF in the nuclei of superior olivary complex (SOC). In the E1.6 group, significant decrements of BDNF immunoreactivity (IR) were noted in the lateral superior olive, medial superior olive, superior paraolivary nucleus and medial nucleus of the trapezoid body. GDNF IR was also significantly decreased ($p < 0.001$) in all SOC nuclei of the E1.6 group. The decrease in the IR of these neurotrophic factors in the SOC of the E1.6 group suggests a detrimental effect of RF exposure in the auditory nuclei.

(E) Masuda H, Hirata A, Kawai H, Wake K, Watanabe S, Arima T, Poullietier de Gannes F, Lagroye I, Veyret B. Local exposure of the rat cortex to radiofrequency electromagnetic fields increases local cerebral blood flow along with temperature. J Appl Physiol. 110(1):142-148, 2011. (AS, PE)

Few studies have shown that local exposure to radiofrequency electromagnetic fields (RF) induces intensity-dependent physiological changes, especially in the brain. The aim of the present study was to detect reproducible responses to local RF exposure in the parietal cortex of anesthetized rats and to determine their dependence on RF intensity. The target cortex tissue was locally exposed to 2-GHz RF using a figure-eight loop antenna within a range of averaged specific absorption rates (10.5, 40.3, 130, and 263 W/kg averaged over 4.04 mg) in the target area. Local cerebral blood flow (CBF) and temperatures in three regions (target area, rectum, and calf hypodermis) were measured using optical fiber blood flow meters and thermometers during RF exposure. All parameters except for the calf hypodermis temperature increased significantly in exposed animals compared with sham-exposed ones during 18-min exposures. Dependence of parameter values on exposure intensity was analyzed using linear regression models. The elevation of local CBF was correlated with temperature rise in both target and rectum at the end of RF exposure. However, the local CBF elevation seemed to be elevated by the rise in target temperature, but not by that of the rectal temperature, in the early part of RF exposure or at low-intensity RF exposure. These findings suggest that local RF exposure of the rat cortex drives a regulation of CBF accompanied by a local temperature rise, and our findings may be helpful for discussing physiological changes in the local cortex region, which is locally exposed to RF.

(E) Mathur R. Effect of chronic intermittent exposure to AM radiofrequency field on responses to various types of noxious stimuli in growing rats. Electromagn Biol Med. 27(3):266-276, 2008. (AS, CE, BE)

There are several reports of altered pain sensation after exposure (from a few minutes to hours in single or repeated doses for 2-3 weeks) to electromagnetic fields (EMF) in adults. The commonly utilized noxious stimulus is radiant heat. The nociceptive responses are known to be influenced by characteristics of stimulus, organism, and environment. We studied the pattern of nociceptive responses to various noxious stimuli in growing rats exposed to radiofrequency field (73.5 MHz amplitude modulated, 16 Hz power density 1.33 mw/cm², SAR = 0.4 w/kg) for 45 d (2 h/d). Threshold current for stimulation of nociceptive afferents to mediate motor response of tail (TF), vocalization during stimulus (VD), and vocalization after discharge (VA); the withdrawal latency of tail (TFL) and hind paw (HPL) to thermal noxious stimulus and tonic pain responses were recorded in every rat. The TFL was not affected, HPL was decreased ($p < 0.01$), and the thresholds of TF and VD were not affected, while, that of VA was significantly decreased. The tonic pain rating was decreased ($p < 0.01$). A decrease in the threshold of VA ($p < 0.01$) is indicative of an increase in the emotional component of the response to the phasic pain, whereas a decrease in the pain rating indicates analgesia in response to the tonic pain. The results of our study suggest that chronic (45 d), intermittent (2 h/d) amplitude modulated RF field exposure to the peripubertal rat increases the emotional component of phasic pain

over a basal euanalgesic state, while late response to tonic pain is decreased. The data suggest that amplitude modulated RF field differentially affects the mechanisms involved in the processing of various noxious stimuli.

(E) Megha K, Deshmukh PS, Banerjee BD, Tripathi AK, Abegaonkar MP. Microwave radiation induced oxidative stress, cognitive impairment and inflammation in brain of Fischer rats. Indian J Exp Biol. 50(12):889-896, 2012. (AS, LI, CE, BE, OX, CH)

Public concerns over possible adverse effects of microwave radiation emitted by mobile phones on health are increasing. To evaluate the intensity of oxidative stress, cognitive impairment and inflammation in brain of Fischer rats exposed to microwave radiation, male Fischer-344 rats were exposed to 900 MHz microwave radiation ($SAR = 5.953 \times 10^{-4}$ W/kg) and 1800 MHz microwave radiation ($SAR = 5.835 \times 10^{-4}$ W/kg) for 30 days (2 h/day). Significant impairment in cognitive function and induction of oxidative stress in brain tissues of microwave exposed rats were observed in comparison with sham exposed groups. Further, significant increase in level of cytokines (IL-6 and TNF-alpha) was also observed following microwave exposure. Results of the present study indicated that increased oxidative stress due to microwave exposure may contribute to cognitive impairment and inflammation in brain.

(E) Megha K, Deshmukh PS, Ravi AK, Tripathi AK, Abegaonkar MP, Banerjee BD. Effect of Low-Intensity Microwave Radiation on Monoamine Neurotransmitters and Their Key Regulating Enzymes in Rat Brain. Cell Biochem Biophys. 2015 Feb 12. [Epub ahead of print] (AS, LI, CE, CH)

The increasing use of wireless communication devices has raised major concerns towards deleterious effects of microwave radiation on human health. The aim of the study was to demonstrate the effect of low-intensity microwave radiation on levels of monoamine neurotransmitters and gene expression of their key regulating enzymes in brain of Fischer rats. Animals were exposed to 900 MHz and 1800 MHz microwave radiation for 30 days (2 h/day, 5 days/week) with respective specific absorption rates as 5.953×10^{-4} and 5.835×10^{-4} W/kg. The levels of monoamine neurotransmitters viz. dopamine (DA), norepinephrine (NE), epinephrine (E) and serotonin (5-HT) were detected using LC-MS/MS in hippocampus of all experimental animals. In addition, mRNA expression of key regulating enzymes for these neurotransmitters viz. tyrosine hydroxylase (TH) (for DA, NE and E) and tryptophan hydroxylase (TPH1 and TPH2) (for serotonin) was also estimated. Results showed significant reduction in levels of DA, NE, E and 5-HT in hippocampus of microwave-exposed animals in comparison with sham-exposed (control) animals. In addition, significant downregulation in mRNA expression of TH, TPH1 and TPH2 was also observed in microwave-exposed animals ($p < 0.05$). In conclusion, the results indicate that low-intensity microwave radiation may cause learning and memory disturbances by altering levels of brain monoamine neurotransmitters at mRNA and protein levels.

(E) Meral I, Mert H, Mert N, Deger Y, Yoruk I, Yetkin A, Keskin S. Effects of 900-MHz electromagnetic field emitted from cellular phone on brain oxidative stress and some vitamin levels of guinea pigs. Brain Res. 1169:120-124, 2007. (AS, CE, OX)

This study was designed to demonstrate the effects of 900-MHz electromagnetic field (EMF) emitted from cellular phone on brain tissue and also blood malondialdehyde (MDA), glutathione (GSH), retinol (vitamin A), vitamin D(3) and tocopherol (vitamin E) levels, and catalase (CAT) enzyme activity of guinea pigs. Fourteen male guinea pigs, weighing 500-800 g were randomly divided into one of two experimental groups: control and treatment (EMF-exposed), each containing seven animals. Animals in treatment group were exposed to 890- to 915-MHz EMF (217-Hz pulse rate, 2-W maximum peak power, SAR 0.95 w/kg) of a cellular phone for 12 h/day (11-h 45-min stand-by and 15-min spiking mode) for 30 days. Control guinea pigs were housed in a separate room without exposing EMF of a cellular phone. Blood samples were collected through a cardiac puncture and brains were removed after decapitation for the biochemical analysis at the end of the 30 days of experimental period. It was found that the MDA level increased ($P<0.05$), GSH level and CAT enzyme activity decreased ($P<0.05$), and vitamins A, E and D(3) levels did not change ($P>0.05$) in the brain tissues of EMF-exposed guinea pigs. In addition, MDA, vitamins A, D(3) and E levels, and CAT enzyme activity increased ($P<0.05$), and GSH level decreased ($P<0.05$) in the blood of EMF-exposed guinea pigs. It was concluded that electromagnetic field emitted from cellular phone might produce oxidative stress in brain tissue of guinea pigs. However, more studies are needed to demonstrate whether these effects are harmful or/and affect the neural functions.

(NE) Mohler E, Frei P, Braun-Fahrlander C, Fröhlich J, Neubauer G, Röösli M; Qualifex Team. Effects of everyday radiofrequency electromagnetic-field exposure on sleep quality: a cross-sectional study. Radiat Res. 174(3):347-356, 2010. (HU, SL)

The aim of this cross-sectional study was to investigate the association between exposure to various sources of radiofrequency electromagnetic fields (RF EMFs) in the everyday environment and sleep quality, which is a common public health concern. We assessed self-reported sleep disturbances and daytime sleepiness in a random population sample of 1,375 inhabitants from the area of Basel, Switzerland. Exposure to environmental far-field RF EMFs was predicted for each individual using a prediction model that had been developed and validated previously. Self-reported cordless and mobile phone use as well as objective mobile phone operator data for the previous 6 months were also considered in the analyses. In multivariable regression models, adjusted for relevant confounders, no associations between environmental far-field RF EMF exposure and sleep disturbances or excessive daytime sleepiness were observed. The 10% most exposed participants had an estimated risk for sleep disturbances of 1.11 (95% CI: 0.50 to 2.44) and for excessive daytime sleepiness of 0.58 (95% CI: 0.31 to 1.05). Neither mobile phone use nor cordless phone use was associated with decreased sleep quality. The results of this large cross-sectional study did not indicate an impairment of subjective sleep quality due to exposure from various sources of RF EMFs in everyday life.

(NE) Mohler E, Frei P, Fröhlich J, Braun-Fahrländer C, Rösli M; QUALIFEX-team. Exposure to radiofrequency electromagnetic fields and sleep quality: a prospective cohort study. PLoS One. 7(5):e37455, 2012. (HU, SL)

BACKGROUND: There is persistent public concern about sleep disturbances due to radiofrequency electromagnetic field (RF-EMF) exposure. The aim of this prospective cohort study was to investigate whether sleep quality is affected by mobile phone use or by other RF-EMF sources in the everyday environment. **METHODS:** We conducted a prospective cohort study with 955 study participants aged between 30 and 60 years. Sleep quality and daytime sleepiness was assessed by means of standardized questionnaires in May 2008 (baseline) and May 2009 (follow-up). We also asked about mobile and cordless phone use and asked study participants for consent to obtain their mobile phone connection data from the mobile phone operators. Exposure to environmental RF-EMF was computed for each study participant using a previously developed and validated prediction model. In a nested sample of 119 study participants, RF-EMF exposure was measured in the bedroom and data on sleep behavior was collected by means of actigraphy during two weeks. Data were analyzed using multivariable regression models adjusted for relevant confounders. **RESULTS:** In the longitudinal analyses neither operator-recorded nor self-reported mobile phone use was associated with sleep disturbances or daytime sleepiness. Also, exposure to environmental RF-EMF did not affect self-reported sleep quality. The results from the longitudinal analyses were confirmed in the nested sleep study with objectively recorded exposure and measured sleep behavior data. **CONCLUSIONS:** We did not find evidence for adverse effects on sleep quality from RF-EMF exposure in our everyday environment.

(E) Mohammed HS, Fahmy HM, Radwah NM, Elsayed AA. Non-thermal continuous and modulated electromagnetic radiation fields effects on sleep EEG of rats. J Adv Res 4(2) 181-187, 2013. (AS, CE, EE, SL, WS)

In the present study, the alteration in the sleep EEG in rats due to chronic exposure to low-level non-thermal electromagnetic radiation was investigated. Two types of radiation fields were used; 900 MHz *unmodulated* wave and 900 MHz *modulated* at 8 and 16 Hz waves. Animals has exposed to radiation fields for 1 month (1 h/day). EEG power spectral analyses of exposed and control animals during slow wave sleep (SWS) and rapid eye movement sleep (REM sleep) revealed that the REM sleep is more susceptible to modulated radiofrequency radiation fields (RFR) than the SWS. The latency of REM sleep increased due to radiation exposure indicating a change in the ultradian rhythm of normal sleep cycles. The cumulative and irreversible effect of radiation exposure was proposed and the interaction of the extremely low frequency radiation with the similar EEG frequencies was suggested.

(E) Moretti D, Garenne A, Haro E, Poullietier de Gannes F, Lagroye I, Lévêque P, Veyret B, Lewis N. In-vitro exposure of neuronal networks to the GSM-1800 signal. Bioelectromagnetics. 34(8):571-578, 2013. (CS, EE)

The central nervous system is the most likely target of mobile telephony radiofrequency (RF) field exposure in terms of biological effects. Several electroencephalography (EEG) studies have reported variations in the alpha-band power spectrum during and/or after RF exposure, in resting EEG and during sleep. In this context, the observation of the spontaneous electrical activity of neuronal networks under RF exposure can be an efficient tool to detect the occurrence of low-level RF effects on the nervous system. Our research group has developed a dedicated experimental setup in the GHz range for the simultaneous exposure of neuronal networks and monitoring of electrical activity. A transverse electromagnetic (TEM) cell was used to expose the neuronal networks to GSM-1800 signals at a SAR level of 3.2 W/kg. Recording of the neuronal electrical activity and detection of the extracellular spikes and bursts under exposure were performed using microelectrode arrays (MEAs). This work provides the proof of feasibility and preliminary results of the integrated investigation regarding exposure setup, culture of the neuronal network, recording of the electrical activity, and analysis of the signals obtained under RF exposure. In this pilot study on 16 cultures, there was a 30% reversible decrease in firing rate (FR) and bursting rate (BR) during a 3 min exposure to RF. Additional experiments are needed to further characterize this effect.

(E) Mortazavi SM, Rouintan MS, Taeb S, Dehghan N, Ghaffarpanah AA, Sadeghi Z, Ghafouri F. Human short-term exposure to electromagnetic fields emitted by mobile phones decreases computer-assisted visual reaction time. Acta Neurol Belg. 112(2):171-175, 2012. (HU, BE)

The worldwide dramatic increase in mobile phone use has generated great concerns about the detrimental effects of microwave radiations emitted by these communication devices. Reaction time plays a critical role in performing tasks necessary to avoid hazards. As far as we know, this study is the first survey that reports decreased reaction time after exposure to electromagnetic fields generated by a high specific absorption rate mobile phone. It is also the first study in which previous history of mobile phone use is taken into account. The aim of this study was to assess both the acute and chronic effects of electromagnetic fields emitted by mobile phones on reaction time in university students. Visual reaction time (VRT) of young university students was recorded with a simple blind computer-assisted-VRT test, before and after a 10 min real/sham exposure to electromagnetic fields of mobile phones. Participants were 160 right-handed university students aged 18-31. To assess the effect of chronic exposures, the reaction time in sham-exposed phases were compared among low level, moderate and frequent users of mobile phones. The mean \pm SD reaction time after real exposure and sham exposure were 286.78 ± 31.35 ms and 295.86 ± 32.17 ms ($P < 0.001$), respectively. The age of students did not significantly alter the reaction time either in talk or in standby mode. The reaction time either in talk or in standby mode was shorter in male students. The students' VRT was significantly affected by exposure to electromagnetic fields emitted by a mobile phone. It can be concluded

that these exposures cause decreased reaction time, which may lead to a better response to different hazards. In this light, this phenomenon might decrease the chances of human errors and fatal accidents.

(E) Mortazavi SM, Taeb S, Dehghan N. Alterations of visual reaction time and short term memory in military radar personnel. Iran J Public Health. 42(4):428-435, 2013. (HU, BE)

BACKGROUND: Radar transmitters emit high-power radiofrequency radiation by creation of a high-voltage and high-frequency alternating electrical current. METHODS: Health effects of occupational exposure to military radar were investigated. Visual reaction time was recorded with a simple blind computer-assisted-visual reaction time test. To assess the short-term memory, modified Wechsler Memory Scale test was performed. RESULTS: The mean \pm SD reaction time in radar works (N=100) and the control group (N=57) were 238.58 \pm 23.47 milliseconds and 291.86 \pm 28.26 milliseconds ($P < 0.0001$), respectively. The scores of forward digit span in radar works and the control group were 3.56 \pm 0.77 and 4.29 \pm 1.06 ($P < 0.0001$), while the scores of backward digit span in radar works and the control group were 2.70 \pm 0.69 and 3.62 \pm 0.95 ($P < 0.0001$). The scores of word recognition in radar works and the control group were 3.37 \pm 1.13 and 5.86 \pm 1.11 ($P < 0.0001$). Finally, the scores of paired words in radar works and the control group were 13.56 \pm 1.78 and 15.21 \pm 2.20 ($P < 0.0001$). It can be concluded that occupational exposures to radar radiations decreases reaction time, which may lead to a better response to different hazards. CONCLUSION: To the best of our knowledge, this is the first study to show that occupational exposure to radar microwave radiation leads to decreased reaction time and the lower performance of short-term memory. Altogether, these results indicate that occupational exposure to radar microwave radiations may be linked to some non-detrimental and detrimental health effects.

(E) Motawi TK, Darwish HA, Moustafa YM, Labib MM. Biochemical Modifications and Neuronal Damage in Brain of Young and Adult Rats After Long-Term Exposure to Mobile Phone Radiations. Cell Biochem Biophys. 2014 May 7. [Epub ahead of print] (AS, CE, CH, CC, OX)

This study investigated the effect of exposure to mobile phone radiations on oxidative stress and apoptosis in brain of rats. Rats were allocated into six groups (three young and three adult). Groups 1 and 4 were not subjected to the radiation source and served as control groups. In groups 2 and 5, the mobile phones were only connected to the global system for mobile communication, while in groups 3 and 6, the option of calling was in use. Microwaves were generated by a mobile test phone (SAR = 1.13 W/kg) during 60 days (2 h/day). Significant increments in conjugated dienes, protein carbonyls, total oxidant status, and oxidative stress index along with a significant reduction of total antioxidant capacity levels were evident after exposure. Bax/Bcl-2 ratio, caspase-3 activity, and tumor necrosis factor- α level were enhanced, whereas no DNA fragmentation was detected. The relative brain weight of young

rats was greatly affected, and histopathological examination reinforced the neuronal damage. The study highlights the detrimental effects of mobile phone radiations on brain during young and adult ages. The interaction of these radiations with brain is via dissipating its antioxidant status and/or triggering apoptotic cell death.

(E) Movvahedi MM, Tavakkoli-Golpayegani A, Mortazavi SA, Haghani M, Razi Z, Shojaie-Fard MB, Zare M, Mina E, Mansourabadi L, Nazari-Jahromi, Safari A, Shokrpour N, Mortazavi SM. Does exposure to GSM 900 MHz mobile phone radiation affect short-term memory of elementary school students? J Pediatr Neurosci. 9(2):121-124, 2014. (HU, BE)

BACKGROUND: Now-a-days, children are exposed to mobile phone radiation at a very early age. We have previously shown that a large proportion of children in the city of Shiraz, Iran use mobile phones. Furthermore, we have indicated that the visual reaction time (VRT) of university students was significantly affected by a 10 min real/sham exposure to electromagnetic fields emitted by mobile phone. We found that these exposures decreased the reaction time which might lead to a better response to different hazards. We have also revealed that occupational exposures to radar radiations decreased the reaction time in radar workers. The purpose of this study was to investigate whether short-term exposure of elementary school students to radiofrequency (RF) radiation leads to changes in their reaction time and short-term memory. MATERIALS AND METHODS: A total of 60 elementary school children ages ranging from 8 to 10 years studying at a public elementary school in Shiraz, Iran were enrolled in this study. Standardized computer-based tests of VRT and short-term memory (modified for children) were administered. The students were asked to perform some preliminary tests for orientation with the VRT test. After orientation, to reduce the random variation of measurements, each test was repeated ten times in both real and sham exposure phases. The time interval between the two subsequent sham and real exposure phases was 30 min. RESULTS: The mean \pm standard deviation reaction times after a 10 min talk period and after a 10 min sham exposure (switched off mobile) period were 249.0 ± 82.3 ms and 252.9 ± 68.2 ms ($P = 0.629$), respectively. On the other hand, the mean short-term memory scores after the talk and sham exposure periods were 1062.60 ± 305.39 , and 1003.84 ± 339.68 ($P = 0.030$), respectively. Conclusion: To the best of our knowledge, this is the first study to show that short-term exposure of elementary school students to RF radiation leads to the better performance of their short-term memory.

(E) Mugunthan N, Shanmugasamy K, Anbalagan J, Rajanarayanan S, Meenachi S. Effects of Long Term Exposure of 900-1800 MHz Radiation Emitted from 2G Mobile Phone on Mice Hippocampus- A Histomorphometric Study. J Clin Diagn Res. 10(8):AF01-6, 2016. (AS, CE, CC)

INTRODUCTION: The advancement in the telecommunications technology with multi-functional added features in mobile phone, attracts more users of all age group. It is alarming to note that, the mobile phone use has increased amongst children and they are exposed to potentially harmful radiofrequency radiation in their lifetime. AIM: To investigate the long term exposure of 900 to 1800 MHz radiations emitted from 2G mobile phone in mice hippocampus at

histomorphometric level. MATERIALS AND METHODS: With due approval from institutional animal ethics committee, 36 mice were exposed to 2G mobile phone radiation, 48 minutes per day for a period of 30-180 days. The control group was kept under similar conditions without 2G exposure. Mice were sacrificed and the brain was removed from the first month to six months period. Brain was removed from the cranial cavity and hippocampus region was dissected out carefully and processed for routine histological study. Random serial sections were analysed under microscope for histomorphometric changes. For statistical analysis, independent t-test was used for comparing control and 2G exposed groups. RESULTS: The mean density of neurons in the hippocampus regions CA1, CA2 and DGDB from first to sixth month was significantly lower in the 2G exposed groups; however, in CA3 and DGVB, the 2G exposed mice showed significantly higher density of neurons. The mean nuclear diameter of neurons in the hippocampus region of CA1, CA2, CA3, DGDB and DGVB from first to sixth months showed lower nuclear diameter in 2G exposed mice. CONCLUSION: The long term exposure to 900-1800 MHz frequency radiations emitted from 2G mobile phone could cause significantly reduced neuron density and decreased nuclear diameter in the hippocampus neurons of mice.

(NE) Nakatani-Enomoto S, Furubayashi T, Ushiyama A, Groiss SJ, Ueshima K, Sokejima S, Simba AY, Wake K, Watanabe SI, Nishikawa M, Miyawaki K, Taki M, Ugawa Y. Effects of electromagnetic fields emitted from W-CDMA-like mobile phones on sleep in humans. Bioelectromagnetics. 2013 Aug 22. doi: 10.1002/bem.21809. [Epub ahead of print] (HU, EE, SL)

In this study, we investigated subjective and objective effects of mobile phones using a Wideband Code Division Multiple Access (W-CDMA)-like system on human sleep. Subjects were 19 volunteers. Real or sham electromagnetic field (EMF) exposures for 3 h were performed before their usual sleep time on 3 consecutive days. They were exposed to real EMF on the second or third experimental day in a double-blind design. Sleepiness and sleep insufficiency were evaluated the next morning. Polysomnograms were recorded for analyses of the sleep variables and power spectra of electroencephalograms (EEG). No significant differences were observed between the two conditions in subjective feelings. Sleep parameters including sleep stage percentages and EEG power spectra did not differ significantly between real and sham exposures. We conclude that continuous wave EMF exposure for 3 h from a W-CDMA-like system has no detectable effects on human sleep.

(E) Narayanan SN, Kumar RS, Potu BK, Nayak S, Mailankot M. Spatial memory performance of Wistar rats exposed to mobile phone. Clinics (Sao Paulo). 64(3):231-234, 2009. (AS, CE, BE)

INTRODUCTION: With the tremendous increase in number of mobile phone users world wide, the possible risks of this technology have become a serious concern. OBJECTIVE: We tested the effects of mobile phone exposure on spatial memory performance. MATERIALS AND METHODS: Male Wistar rats (10-12 weeks old) were exposed to 50 missed calls/day for 4 weeks from a GSM (900/1800 MHz) mobile phone in vibratory mode (no ring tone). After the experimental

period, the animals were tested for spatial memory performance using the Morris water maze test. RESULTS: Both phone exposed and control animals showed a significant decrease in escape time with training. Phone exposed animals had significantly (approximately 3 times) higher mean latency to reach the target quadrant and spent significantly (approximately 2 times) less time in the target quadrant than age- and sex-matched controls. CONCLUSION: Mobile phone exposure affected the acquisition of learned responses in Wistar rats. This in turn points to the poor spatial navigation and the object place configurations of the phone-exposed animals.

(E) Narayanan SN, Kumar RS, Potu BK, Nayak S, Bhat PG, Mailankot M. Effect of radio-frequency electromagnetic radiations (RF-EMR) on passive avoidance behaviour and hippocampal morphology in Wistar rats. Ups J Med Sci. 115(2):91-96, 2010. (AS, CE, ME, BE)

INTRODUCTION: The interaction of mobile phone radio-frequency electromagnetic radiation (RF-EMR) with the brain is a serious concern of our society. **OBJECTIVE:** We evaluated the effect of RF-EMR from mobile phones on passive avoidance behaviour and hippocampal morphology in rats. **MATERIALS AND METHODS:** Healthy male albino Wistar rats were exposed to RF-EMR by giving 50 missed calls (within 1 hour) per day for 4 weeks, keeping a GSM (0.9 GHz/1.8 GHz) mobile phone in vibratory mode (no ring tone) in the cage. After the experimental period, passive avoidance behaviour and hippocampal morphology were studied. **RESULTS:** Passive avoidance behaviour was significantly affected in mobile phone RF-EMR-exposed rats demonstrated as shorter entrance latency to the dark compartment when compared to the control rats. Marked morphological changes were also observed in the CA(3) region of the hippocampus of the mobile phone-exposed rats in comparison to the control rats. **CONCLUSION:** Mobile phone RF-EMR exposure significantly altered the passive avoidance behaviour and hippocampal morphology in rats.

(E) Narayanan SN, Kumar RS, Paval J, Kedage V, Bhat MS, Nayak S, Bhat PG. Analysis of emotionality and locomotion in radio-frequency electromagnetic radiation exposed rats. Neurol Sci. 34(7):1117-1124, 2013. (AS, CE, BE)

In the current study the modulatory role of mobile phone radio-frequency electromagnetic radiation (RF-EMR) on emotionality and locomotion was evaluated in adolescent rats. Male albino Wistar rats (6-8 weeks old) were randomly assigned into the following groups having 12 animals in each group. Group I (Control): they remained in the home cage throughout the experimental period. Group II (Sham exposed): they were exposed to mobile phone in switch-off mode for 28 days, and Group III (RF-EMR exposed): they were exposed to RF-EMR (900 MHz) from an active GSM (Global system for mobile communications) mobile phone with a peak power density of 146.60 $\mu\text{W}/\text{cm}^2$ for 28 days. On 29th day, the animals were tested for emotionality and locomotion. Elevated plus maze (EPM) test revealed that, percentage of entries into the open arm, percentage of time spent on the open arm and distance travelled on the open arm were significantly reduced in the RF-EMR exposed rats. Rearing frequency and grooming frequency were also decreased in the RF-EMR exposed rats. Defecation boli count during the EPM test was more with the RF-EMR group. No statistically significant difference was

found in total distance travelled, total arm entries, percentage of closed arm entries and parallelism index in the RF-EMR exposed rats compared to controls. Results indicate that mobile phone radiation could affect the emotionality of rats without affecting the general locomotion.

(E) Narayanan SN, Kumar RS, Kedage V, Nalini K, Nayak S, Bhat PG. Evaluation of oxidant stress and antioxidant defense in discrete brain regions of rats exposed to 900 MHz radiation. Bratisl Lek Listy. 115(5):260-266, 2014. (AS, CE, CH, OX)

AIM: In the current study, the effects of 900 MHz radio-frequency electromagnetic radiation (RF-EMR) on levels of thiobarbituric acid-reactive substances (TBARS), total antioxidants (TA), and glutathione S-transferase (GST) activity in discrete brain regions were studied in adolescent rats. MATERIALS AND METHODS: Thirty-six male Wistar rats (6-8 weeks old) were allotted into three groups (n = 12 in each group). Control group (1) remained undisturbed in their home cage; sham group (2) was exposed to mobile phone in switch off mode for four weeks; RF-EMR-exposed group (3) was exposed to 900 MHz of RF-EMR (1 hr/day with peak power density of 146.60 $\mu\text{W}/\text{cm}^2$) from an activated Global System for Mobile communication (GSM) mobile phone (kept in silent mode; no ring tone and no vibration) for four weeks. On 29th day, behavioral analysis was done. Followed by this, six animals from each group were sacrificed and biochemical parameters were studied in amygdala, hippocampus, frontal cortex, and cerebellum. RESULTS: Altered behavioral performances were found in RF-EMR-exposed rats. Additionally, elevated TBARS level was found with all brain regions studied. RF-EMR exposure significantly decreased TA in the amygdala and cerebellum but its level was not significantly changed in other brain regions. GST activity was significantly decreased in the hippocampus but, its activity was unaltered in other brain regions studied. CONCLUSION: RF-EMR exposure for a month induced oxidative stress in rat brain, but its magnitude was different in different regions studied. RF-EMR-induced oxidative stress could be one of the underlying causes for the behavioral deficits seen in rats after RF-EMR exposure (Fig. 5, Ref. 37).

(E) Narayanan SN, Kumar RS, Karun KM, Nayak SB, Bhat PG. Possible cause for altered spatial cognition of prepubescent rats exposed to chronic radiofrequency electromagnetic radiation. Metab Brain Dis. 2015 Jun 3. [Epub ahead of print] (AS, CE, BE, ME)

The effects of chronic and repeated radiofrequency electromagnetic radiation (RFEMR) exposure on spatial cognition and hippocampal architecture were investigated in prepubescent rats. Four weeks old male Wistar rats were exposed to RF-EMR (900 MHz; SAR-1.15 W/kg with peak power density of 146.60 $\mu\text{W}/\text{cm}^2$) for 1 h/day, for 28 days. Followed by this, spatial cognition was evaluated by Morris water maze test. To evaluate the hippocampal morphology; H&E staining, cresyl violet staining, and Golgi-Cox staining were performed on hippocampal sections. CA3 pyramidal neuron morphology and surviving neuron count (in CA3 region) were

studied using H&E and cresyl violet stained sections. Dendritic arborization pattern of CA3 pyramidal neuron was investigated by concentric circle method. Progressive learning abilities were found to be decreased in RF-EMR exposed rats. Memory retention test performed 24 h after the last training revealed minor spatial memory deficit in RF-EMR exposed group. However, RF-EMR exposed rats exhibited poor spatial memory retention when tested 48 h after the final trial. Hirano bodies and Granulovacuolar bodies were absent in the CA3 pyramidal neurons of different groups studied. Nevertheless, RF-EMR exposure affected the viable cell count in dorsal hippocampal CA3 region. RF-EMR exposure influenced dendritic arborization pattern of both apical and basal dendritic trees in RF-EMR exposed rats. Structural changes found in the hippocampus of RF-EMR exposed rats could be one of the possible reasons for altered cognition.

(E) Nazıroğlu M, Gümral N. Modulator effects of L-carnitine and selenium on wireless devices (2.45 GHz)-induced oxidative stress and electroencephalography records in brain of rat. Int J Radiat Biol. 85(8):680-689, 2009. (AS, CE, CH, EE, OX)

PURPOSE: Electromagnetic radiation (EMR) from wireless devices may affect biological systems by increasing free radicals. The present study was designed to determine the effects of 2.45 GHz EMR on the brain antioxidant redox system and electroencephalography (EEG) records in rat. The possible protective effects of selenium and L-carnitine were also tested and compared to untreated controls. MATERIALS AND METHODS: Thirty rats were equally divided into five different groups, namely Group A(1): Cage control, Group A(2): Sham control, group B: 2.45 GHz EMR, group C: 2.45 GHz EMR + selenium, group D: 2.45 GHz EMR + L-carnitine. Groups B, C and D were exposed to 2.45 GHz EMR during 60 min/day for 28 days. End of the experiments, EEG records and the brain cortex samples were taken. RESULTS: The cortex brain vitamin A ($p < 0.05$), vitamin C ($p < 0.01$) and vitamin E ($p < 0.05$) concentrations values were lower in group B than in group A1 and A2 although their concentrations were increased by selenium and L-carnitine supplementation. Lipid peroxidation, levels were lower in group C ($p < 0.05$) and D ($p < 0.01$) than in group B where as reduced glutathione levels were higher in group C ($p < 0.05$) than in group A1, A2 and B. However, B-carotene levels did not change in the five groups. CONCLUSIONS: L-carnitine and selenium seem to have protective effects on the 2.45 GHz-induced decrease of the vitamins by supporting antioxidant redox system. L-carnitine on the vitamin concentrations seems to more protective affect than in selenium.

(E) Nazıroğlu M, Çelik Ö, Özgül C, Çiğ B, Doğan S, Bal R, Gümral N, Rodríguez AB, Pariente JA. Melatonin modulates wireless (2.45 GHz)-induced oxidative injury through TRPM2 and voltage gated Ca(2+) channels in brain and dorsal root ganglion in rat. Physiol Behav. 105(3):683-692, 2012. (AS, CE, CH, EE, OX)

We aimed to investigate the protective effects of melatonin and 2.45 GHz electromagnetic radiation (EMR) on brain and dorsal root ganglion (DRG) neuron antioxidant redox system,

Ca(2+) influx, cell viability and electroencephalography (EEG) records in the rat. Thirty two rats were equally divided into four different groups namely group A1: Cage control, group A2: Sham control, group B: 2.45 GHz EMR, group C: 2.45 GHz EMR+melatonin. Groups B and C were exposed to 2.45 GHz EMR during 60 min/day for 30 days. End of the experiments, EEG records and the brain cortex and DRG samples were taken. Lipid peroxidation (LP), cell viability and cytosolic Ca(2+) values in DRG neurons were higher in group B than in groups A1 and A2 although their concentrations were increased by melatonin, 2-aminoethyldiphenyl borinate (2-APB), diltiazem and verapamil supplementation. Spike numbers of EEG records in group C were lower than in group B. Brain cortex vitamin E concentration was higher in group C than in group B. In conclusion, Melatonin supplementation in DRG neurons and brain seems to have protective effects on the 2.45 GHz-induced increase Ca(2+) influx, EEG records and cell viability of the hormone through TRPM2 and voltage gated Ca(2+) channels.

(NE) Nazıroğlu M, Ozkan FF, Hapil SR, Ghazizadeh V, Cığ B. Epilepsy But Not Mobile Phone Frequency (900 MHz) Induces Apoptosis and Calcium Entry in Hippocampus of Epileptic Rat: Involvement of TRPV1 Channels. J Membr Biol. 2014 Nov 9. [Epub ahead of print] (CS, CC, IA)

Electromagnetic radiation (EMR) and epilepsy are reported to mediate the regulation of apoptosis and oxidative stress through Ca²⁺ influx. Results of recent reports indicated that EMR can increase temperature and oxidative stress of body cells, and TRPV1 channel is activated by noxious heat, oxidative stress, and capsaicin (CAP). We investigated the effects of mobile phone (900 MHz) EMR exposure on Ca²⁺ influx, apoptosis, oxidative stress, and TRPV1 channel activations in the hippocampus of pentylenetetrazol (PTZ)-induced epileptic rats. Freshly isolated hippocampal neurons of twenty-one rats were used in study within three groups namely control, PTZ, and PTZ + EMR. The neurons in the three groups were stimulated by CAP. Epilepsy was induced by PTZ administration. The neurons in PTZ + EMR group were exposed to the 900 MHz EMR for 1 h. The apoptosis, mitochondrial membrane depolarization, intracellular reactive oxygen species (ROS), and caspase-3 and caspase-9 values were higher in PTZ and PTZ + EMR groups than in control. However, EMR did not add additional increase effects on the values in the hippocampal neurons. Intracellular-free Ca²⁺ concentrations in fura-2 analyses were also higher in PTZ + CAP group than in control although their concentrations were decreased by TRPV1 channel blocker, capsazepine. However, there were no statistical changes on the Ca²⁺ concentrations between epilepsy and EMR groups. In conclusion, apoptosis, mitochondrial, ROS, and Ca²⁺ influx via TRPV1 channel were increased in the hippocampal neurons by epilepsy induction although the mobile phone did not change the values. The results indicated that TRPV1 channels in hippocampus may possibly be a novel target for effective target of epilepsy.

(E) Ning W, Xu SJ, Chiang H, Xu ZP, Zhou SY, Yang W, Luo JH. Effects of GSM 1800 MHz on dendritic development of cultured hippocampal neurons. Acta Pharmacol Sin. 28(12):1873-1880, 2007. (CS, CE, DE, ME)

AIM: To evaluate the effects of global system for mobile communications (GSM) 1800 MHz microwaves on dendritic filopodia, dendritic arborization, and spine maturation during

development in cultured hippocampal neurons in rats. **METHODS:** The cultured hippocampal neurons were exposed to GSM 1800 MHz microwaves with 2.4 and 0.8 W/kg, respectively, for 15 min each day from 6 days in vitro (DIV6) to DIV14. The subtle structures of dendrites were displayed by transfection with farnesylated enhanced green fluorescent protein (F-GFP) and GFP-actin on DIV5 into the hippocampal neurons. **RESULTS:** There was a significant decrease in the density and mobility of dendritic filopodia at DIV8 and in the density of mature spines at DIV14 in the neurons exposed to GSM 1800 MHz microwaves with 2.4 W/kg. In addition, the average length of dendrites per neuron at DIV10 and DIV14 was decreased, while the dendritic arborization was unaltered in these neurons. However, there were no significant changes found in the neurons exposed to the GSM 1800 MHz microwaves with 0.8 W/kg. **CONCLUSION:** These data indicate that the chronic exposure to 2.4 W/kg GSM 1800 MHz microwaves during the early developmental stage may affect dendritic development and the formation of excitatory synapses of hippocampal neurons in culture.

(E) Nirwane A, Sridhar V, Majumdar A. Neurobehavioural Changes and Brain Oxidative Stress Induced by Acute Exposure to GSM 900 Mobile Phone Radiations in Zebrafish (Danio rerio). Toxicol Res. 32(2):123-132 (2016). (AS, CE, BE, OX)

The impact of mobile phone (MP) radiation on the brain is of specific interest to the scientific community and warrants investigations, as MP is held close to the head. Studies on humans and rodents revealed hazards MP radiation associated such as brain tumors, impairment in cognition, hearing etc. Melatonin (MT) is an important modulator of CNS functioning and is a neural antioxidant hormone. Zebrafish has emerged as a popular model organism for CNS studies. Herein, we evaluated the impact of GSM900MP (GSM900MP) radiation exposure daily for 1 hr for 14 days with the SAR of 1.34W/Kg on neurobehavioral and oxidative stress parameters in zebrafish. Our study revealed that, GSM900MP radiation exposure, significantly decreased time spent near social stimulus zone and increased total distance travelled, in social interaction test. In the novel tank dive test, the GSM900MP radiation exposure elicited anxiety as revealed by significantly increased time spent in bottom half; freezing bouts and duration and decreased distance travelled, average velocity, and number of entries to upper half of the tank. Exposed zebrafish spent less time in the novel arm of the Y-Maze, corroborating significant impairment in learning as compared to the control group. Exposure decreased superoxide dismutase (SOD), catalase (CAT) activities whereas, increased levels of reduced glutathione (GSH) and lipid peroxidation (LPO) was encountered showing compromised antioxidant defense. Treatment with MT significantly reversed the above neurobehavioral and oxidative derangements induced by GSM900MP radiation exposure. This study traced GSM900MP radiation exposure induced neurobehavioral aberrations and alterations in brain oxidative status. Furthermore, MT proved to be a promising therapeutic candidate in ameliorating such outcomes in zebrafish.

(E) Nittby H, Widegren B, Krogh M, Grafström G, Berlin H, Rehn G, Eberhardt JL, Malmgren L, Persson BRR, Salford L. Exposure to radiation from global system for mobile

communications at 1,800 MHz significantly changes gene expression in rat hippocampus and cortex. *Environmentalist* 28(4), 458-465, 2008. (AS, CH, LI)

We have earlier shown that radio frequency electromagnetic fields can cause significant leakage of albumin through the blood–brain barrier of exposed rats as compared to non-exposed rats, and also significant neuronal damage in rat brains several weeks after a 2 h exposure to a mobile phone, at 915 MHz with a global system for mobile communications (GSM) frequency modulation, at whole-body specific absorption rate values (SAR) of 200, 20, 2, and 0.2 mW/kg. We have now studied whether 6 h of exposure to the radiation from a GSM mobile test phone at 1,800 MHz (at a whole-body SAR-value of 13 mW/kg, corresponding to a brain SAR-value of 30 mW/kg) has an effect upon the gene expression pattern in rat brain cortex and hippocampus—areas where we have observed albumin leakage from capillaries into neurons and neuronal damage. Microarray analysis of 31,099 rat genes, including splicing variants, was performed in cortex and hippocampus of 8 Fischer 344 rats, 4 animals exposed to global system for mobile communications electromagnetic fields for 6 h in an anechoic chamber, one rat at a time, and 4 controls kept as long in the same anechoic chamber without exposure, also in this case one rat at a time. Gene ontology analysis (using the gene ontology categories biological processes, molecular functions, and cell components) of the differentially expressed genes of the exposed animals versus the control group revealed the following highly significant altered gene categories in both cortex and hippocampus: extracellular region, signal transducer activity, intrinsic to membrane, and integral to membrane. The fact that most of these categories are connected with membrane functions may have a relation to our earlier observation of albumin transport through brain capillaries.

(E) Nittby H, Grafström G, Tian DP, Malmgren L, Brun A, Persson BR, Salford LG, Eberhardt J. Cognitive impairment in rats after long-term exposure to GSM-900 mobile phone radiation. *Bioelectromagnetics*. 29(3):219-232, 2008. (AS, CE, BE, LI)

Considering the frequent use of mobile phones, we have directed attention to possible implications on cognitive functions. In this study we investigated in a rat model the long-term effects of protracted exposure to Global System for Mobile Communication-900 MHz (GSM-900) radiation. Out of a total of 56 rats, 32 were exposed for 2 h each week for 55 weeks to radio-frequency electromagnetic radiation at different SAR levels (0.6 and 60 mW/kg at the initiation of the experimental period) emitted by a (GSM-900) test phone. Sixteen animals were sham exposed and eight animals were cage controls, which never left the animal house. After this protracted exposure, GSM-900 exposed rats were compared to sham exposed controls. Effects on exploratory behaviour were evaluated in the open-field test, in which no difference was seen. Effects on cognitive functions were evaluated in the episodic-like memory test. In our study, GSM exposed rats had impaired memory for objects and their temporal order of presentation, compared to sham exposed controls ($P = 0.02$). Detecting the place in which an object was presented was not affected by GSM exposure. Our results suggest significantly reduced memory functions in rats after GSM microwave exposure ($P = 0.02$).

(E) Nittby H, Brun A, Eberhardt J, Malmgren L, Persson BR, Salford LG. Increased blood-brain barrier permeability in mammalian brain 7 days after exposure to the radiation from a GSM-900 mobile phone. Pathophysiology. 16(2-3):103-112, 2009. (AS, ME, LI)

Microwaves were for the first time produced by humans in 1886 when radio waves were broadcasted and received. Until then microwaves had only existed as a part of the cosmic background radiation since the birth of universe. By the following utilization of microwaves in telegraph communication, radars, television and above all, in the modern mobile phone technology, mankind is today exposed to microwaves at a level up to 10(20) times the original background radiation since the birth of universe. Our group has earlier shown that the electromagnetic radiation emitted by mobile phones alters the permeability of the blood-brain barrier (BBB), resulting in albumin extravasation immediately and 14 days after 2h of exposure. In the background section of this report, we present a thorough review of the literature on the demonstrated effects (or lack of effects) of microwave exposure upon the BBB. Furthermore, we have continued our own studies by investigating the effects of GSM mobile phone radiation upon the blood-brain barrier permeability of rats 7 days after one occasion of 2h of exposure. Forty-eight rats were exposed in TEM-cells for 2h at non-thermal specific absorption rates (SARs) of 0mW/kg, 0.12mW/kg, 1.2mW/kg, 12mW/kg and 120mW/kg. Albumin extravasation over the BBB, neuronal albumin uptake and neuronal damage were assessed. Albumin extravasation was enhanced in the mobile phone exposed rats as compared to sham controls after this 7-day recovery period (Fisher's exact probability test, $p=0.04$ and Kruskal-Wallis, $p=0.012$), at the SAR-value of 12mW/kg (Mann-Whitney, $p=0.007$) and with a trend of increased albumin extravasation also at the SAR-values of 0.12mW/kg and 120mW/kg. There was a low, but significant correlation between the exposure level (SAR-value) and occurrence of focal albumin extravasation ($r(s)=0.33$; $p=0.04$). The present findings are in agreement with our earlier studies where we have seen increased BBB permeability immediately and 14 days after exposure. We here discuss the present findings as well as the previous results of altered BBB permeability from our and other laboratories.

(E) Nittby H, Moghadam MK, Sun W, Malmgren L, Eberhardt J, Persson BR, Salford LG. Analgetic effects of non-thermal GSM-1900 radiofrequency electromagnetic fields in the land snail *Helix pomatia*. Int J Radiat Biol. 88(3):245-252, 2012. (AS, BE, MA, LI)

PURPOSE: To investigate whether mobile phone radiation might affect snail nociception, employing radiofrequency (RF) electromagnetic fields (EMF) which, to our knowledge, have hitherto not been studied in a snail model. Exposure to extremely low frequency (ELF) magnetic fields has however been shown to significantly affect nociceptive responses. **MATERIALS AND METHODS:** In the present study, we exposed 29 land snails of the strain *Helix pomatia* to global system for mobile communications (GSM) EMF at 1900 MHz at the non-thermal level 48 mW/kg for 1 hour each and 29 snails were sham controls. The experiments took place during the onset of summer, with all snails being well out of hibernation. Before and after GSM or sham exposure, the snails were subjected to thermal pain by being placed on a hot plate. The reaction time for retraction from the hot plate was measured by two blinded observers. **RESULTS:** Comparing the reaction pattern of each snail before and after exposure, the GSM-

exposed snails were less sensitive to thermal pain as compared to the sham controls, indicating that RF exposure induces a significant analgesia (Mann-Whitney $p < 0.001$). CONCLUSION: This study might support earlier findings, describing beneficial effects of EMF exposure upon nociception.

(E) Noor NA, Mohammed HS, Ahmed NA, Radwan NM. Variations in amino acid neurotransmitters in some brain areas of adult and young male albino rats due to exposure to mobile phone radiation. Eur Rev Med Pharmacol Sci. 15(7):729-742, 2011. (AS, CE, CH, AD)

BACKGROUND AND OBJECTIVES: Mobile phone radiation and health concerns have been raised, especially following the enormous increase in the use of wireless mobile telephony throughout the world. The present study aims to investigate the effect of one hour daily exposure to electromagnetic radiation (EMR) with frequency of 900 Mz (SAR 1.165 w/kg, power density 0.02 mW/cm²) on the levels of amino acid neurotransmitters in the midbrain, cerebellum and medulla of adult and young male albino rats. **MATERIALS AND METHODS:** Adult and young rats were divided into two main groups (treated and control). The treated group of both adult and young rats was exposed to EMR for 1 hour daily. The other group of both adult and young animals was served as control. The determination of amino acid levels was carried out after 1 hour, 1 month, 2 months and 4 months of EMR exposure as well as after stopping radiation. **RESULTS:** Data of the present study showed a significant increase in both excitatory and inhibitory amino acids in the cerebellum of adult and young rats and midbrain of adult animals after 1 hour of EMR exposure. In the midbrain of adult animals, there was a significant increase in glycine level after 1 month followed by significant increase in GABA after 4 months. Young rats showed significant decreases in the midbrain excitatory amino acids. In the medulla, the equilibrium ratio percent (ER%) calculations showed a state of neurochemical inhibition after 4 months in case of adult animals, whereas in young animals, the neurochemical inhibitory state was observed after 1 month of exposure due to significant decrease in glutamate and aspartate levels. This state was converted to excitation after 4 months due to the increase in glutamate level. **CONCLUSION:** The present changes in amino acid concentrations may underlie the reported adverse effects of using mobile phones.

(E) Ntzouni MP, Stamatakis A, Stylianopoulou F, Margaritis LH. Short-term memory in mice is affected by mobile phone radiation. Pathophysiology. 18(3):193-199, 2011. (AS, CE, BE)

The effects of mobile phone electromagnetic fields (EMFs) were studied on a non-spatial memory task (Object Recognition Task - ORT) that requires entorhinal cortex function. The task was applied to three groups of mice *Mus musculus* C57BL/6 (exposed, sham-exposed and control) combined with 3 different radiation exposure protocols. In the first protocol designated "acute exposure", mice 45 days old (PND45 - postnatal day 45) were exposed to mobile phone (MP) radiation (SAR value 0.22W/kg) during the habituation, the training and the test sessions of the ORT, but not during the 10min inter-trial interval (ITI) where consolidation of stored object information takes place. On the second protocol designated "chronic exposure-I", the same mice were exposed for 17 days for 90min/per day starting at PND55 to the same MP radiation. ORT recognition memory was performed at PND72 with radiation present only

during the ITI phase. In the third protocol designated "chronic exposure-II", mice continued to be exposed daily under the same conditions up to PND86 having received radiation for 31 days. One day later the ORT test was performed without irradiation present in any of the sessions. The ORT-derived discrimination indices in all three exposure protocols revealed a major effect on the "chronic exposure-I" suggesting a possible severe interaction of EMF with the consolidation phase of recognition memory processes. This may imply that the primary EMF target may be the information transfer pathway connecting the entorhinal-parahippocampal regions which participate in the ORT memory task.

(E) Ntzouni MP, Skouroliaou A, Kostomitsopoulos N, Margaritis LH. Transient and cumulative memory impairments induced by GSM 1.8 GHz cell phone signal in a mouse model. Electromagn Biol Med. 2013 Jan 15. [Epub ahead of print] (AS, CE, BE)

This study was designed to investigate the transient and cumulative impairments in spatial and non-spatial memory of C57Bl/6J mice exposed to GSM 1.8 GHz signal for 90 min daily by a typical cellular (mobile) phone at a specific absorption rate value of 0.11 W/kg. Free-moving male mice 2 months old were irradiated in two experimental protocols, lasting for 66 and for 148 days respectively. Each protocol used three groups of animals (n = 8 each for exposed, sham exposed and controls) in combination with two behavioural paradigms, the object recognition task and the object location task sequentially applied at different time points. One-way analysis of variance revealed statistically significant impairments of both types of memory gradually accumulating, with more pronounced effects on the spatial memory. The impairments persisted even 2 weeks after interruption of the 8 weeks daily exposure, whereas the memory of mice as detected by both tasks showed a full recovery approximately 1 month later. Intermittent every other day exposure for 1 month had no effect on both types of memory. The data suggest that visual information processing mechanisms in hippocampus, perirhinal and entorhinal cortex are gradually malfunctioning upon long-term daily exposure, a phenotype that persists for at least 2 weeks after interruption of radiation, returning to normal memory performance levels 4 weeks later. It is postulated that cellular repair mechanisms are operating to eliminate the memory affecting molecules. The overall contribution of several possible mechanisms to the observed cumulative and transient impairments in spatial and non-spatial memory is discussed.

(NE) Nylund R, Kuster N, Leszczynski D. Analysis of proteome response to the mobile phone radiation in two types of human primary endothelial cells. Proteome Sci. 8:52, 2010. (CS, CH, WS)

BACKGROUND: Use of mobile phones has widely increased over the past decade. However, in spite of the extensive research, the question of potential health effects of the mobile phone radiation remains unanswered. We have earlier proposed, and applied, proteomics as a tool to study biological effects of the mobile phone radiation, using as a model human endothelial cell line EA.hy926. Exposure of EA.hy926 cells to 900 MHz GSM radiation has caused statistically significant changes in expression of numerous proteins. However, exposure of EA.hy926 cells to 1800 MHz GSM signal had only very small effect on cell proteome, as compared with 900 MHz

GSM exposure. In the present study, using as model human primary endothelial cells, we have examined whether exposure to 1800 MHz GSM mobile phone radiation can affect cell proteome. **RESULTS:** Primary human umbilical vein endothelial cells and primary human brain microvascular endothelial cells were exposed for 1 hour to 1800 MHz GSM mobile phone radiation at an average specific absorption rate of 2.0 W/kg. The cells were harvested immediately after the exposure and the protein expression patterns of the sham-exposed and radiation-exposed cells were examined using two dimensional difference gel electrophoresis-based proteomics (2DE-DIGE). There were observed numerous differences between the proteomes of human umbilical vein endothelial cells and human brain microvascular endothelial cells (both sham-exposed). These differences are most likely representing physiological differences between endothelia in different vascular beds. However, the exposure of both types of primary endothelial cells to mobile phone radiation did not cause any statistically significant changes in protein expression. **CONCLUSIONS:** Exposure of primary human endothelial cells to the mobile phone radiation, 1800 MHz GSM signal for 1 hour at an average specific absorption rate of 2.0 W/kg, does not affect protein expression, when the proteomes were examined immediately after the end of the exposure and when the false discovery rate correction was applied to analysis. This observation agrees with our earlier study showing that the 1800 MHz GSM radiation exposure had only very limited effect on the proteome of human endothelial cell line EA.hy926, as compared with the effect of 900 MHz GSM radiation.

(NE) O'Connor RP, Madison SD, Leveque P, Roderick HL, Bootman MD. Exposure to GSM RF fields does not affect calcium homeostasis in human endothelial cells, rat pheochromocytoma cells or rat hippocampal neurons. PLoS One. 5(7):e11828, 2010. (CS, CC, CH)

In the course of modern daily life, individuals are exposed to numerous sources of electromagnetic radiation that are not present in the natural environment. The strength of the electromagnetic fields from sources such as hairdryers, computer display units and other electrical devices is modest. However, in many home and office environments, individuals can experience perpetual exposure to an "electromagnetic smog", with occasional peaks of relatively high electromagnetic field intensity. This has led to concerns that such radiation can affect health. In particular, emissions from mobile phones or mobile phone masts have been invoked as a potential source of pathological electromagnetic radiation. Previous reports have suggested that cellular calcium (Ca²⁺) homeostasis is affected by the types of radiofrequency fields emitted by mobile phones. In the present study, we used a high-throughput imaging platform to monitor putative changes in cellular Ca²⁺ during exposure of cells to 900 MHz GSM fields of differing power (specific absorption rate 0.012-2 W/Kg), thus mimicking the type of radiation emitted by current mobile phone handsets. Data from cells experiencing the 900 Mhz GSM fields were compared with data obtained from paired experiments using continuous wave fields or no field. We employed three cell types (human endothelial cells, PC-12 neuroblastoma and primary hippocampal neurons) that have previously been suggested to be sensitive to radiofrequency fields. Experiments were designed to examine putative effects of radiofrequency fields on resting Ca²⁺, in addition to Ca²⁺ signals evoked by an InsP(3)-generating agonist. Furthermore, we examined putative effects of radiofrequency field

exposure on Ca²⁺ store emptying and store-operated Ca²⁺ entry following application of the Ca²⁺-ATPase inhibitor thapsigargin. Multiple parameters (e.g., peak amplitude, integrated Ca²⁺ signal, recovery rates) were analysed to explore potential impact of radiofrequency field exposure on Ca²⁺ signals. Our data indicate that 900 MHz GSM fields do not affect either basal Ca²⁺ homeostasis or provoked Ca²⁺ signals. Even at the highest field strengths applied, which exceed typical phone exposure levels, we did not observe any changes in cellular Ca²⁺ signals. We conclude that under the conditions employed in our experiments, and using a highly-sensitive assay, we could not detect any consequence of RF exposure.

(E) Odacı E, Bas O, Kaplan S. Effects of prenatal exposure to a 900 MHz electromagnetic field on the dentate gyrus of rats: a stereological and histopathological study. Brain Res. 1238:224-229, 2008. (AS, CE, DE, ME)

Electromagnetic fields (EMFs) inhibit the formation and differentiation of neural stem cells during embryonic development. In this study, the effects of prenatal exposure to EMF on the number of granule cells in the dentate gyrus of 4-week-old rats were investigated. This experiment used a control (Cont) group and an EMF exposed (EMF) group (three pregnant rats each group). The EMF group consisted of six offspring (n=6) of pregnant rats that were exposed to an EMF of up to 900 megahertz (MHz) for 60 min/day between the first and last days of gestation. The control group consisted of five offspring (n=5) of pregnant rats that were not treated at all. The offspring were sacrificed when they were 4 weeks old. The numbers of granule cells in the dentate gyrus were analyzed using the optical fractionator technique. The results showed that prenatal EMF exposure caused a decrease in the number of granule cells in the dentate gyrus of the rats (P<0.01). This suggests that prenatal exposure to a 900 MHz EMF affects the development of the dentate gyrus granule cells in the rat hippocampus. Cell loss might be caused by an inhibition of granule cell neurogenesis in the dentate gyrus.

(E) Odacı E, İkinci A, Yıldırım M, Kaya H, Akça M, Hancı H, Sönmez OF, Aslan A, Okuyan M, Baş O. The Effects of 900 Megahertz Electromagnetic Field Applied in the Prenatal Period on Spinal Cord Morphology and Motor Behavior in Female Rat Pups. NeuroQuantology 11:573-581, 2013. (AS, CE, DE, BE, ME)

This study investigated the effect of a 900 megahertz (MHz) electromagnetic field (EMF) applied in the prenatal period on the spinal cord and motor behavior of female rat pups. Beginning of the study, female Sprague Dawley rats (180–250 g) were left to mate with male rats. Rats identified as pregnant were then divided into control (n=3) and EMF groups (n=3). The EMF group was exposed to 1-h 900 MHz EMF daily between days 13 and 21 of pregnancy. At 21 days old, rat pups were removed from their mothers and divided into two newborn rat groups, control (n=13) and EMF (n=10). The rotarod test was applied to the rat pups to assess motor functions and the open field test to evaluate locomotor activity. On day 32 of the study, the rat pups were decapitated, and the spinal cord in the upper thoracic region was removed. Following routine histological tests, they were stained with Cresyl fast violet. Rotarod test

results revealed a significant increase in EMF group rat pups' motor functions ($p=0.037$). However, no difference was observed in the open field test results ($p>0.05$). In the EMF group' rat pups, we observed pathological changes in the spinal cord. On the basis of our results, 900 MHz EMF applied in the prenatal period affected spinal cord development. This effect was observed in the form of pathological changes in the spinal cord of rat pups, and it may be that these pathological changes led to an increase in rat pups' motor activities.

(E) Odacı E, Hancı H, İkinci A, Sönmez OF, Aslan A, Şahin A, Kaya H, Çolakoğlu S, Baş O. Maternal exposure to a continuous 900-MHz electromagnetic field provokes neuronal loss and pathological changes in cerebellum of 32-day-old female rat offspring. J Chem Neuroanat. 75(Pt B):105-110, 2016. (AS, CE, ME)

Large numbers of people are unknowingly exposed to electromagnetic fields (EMF) from wireless devices. Evidence exists for altered cerebellar development in association with prenatal exposure to EMF. However, insufficient information is still available regarding the effects of exposure to 900 megahertz (MHz) EMF during the prenatal period on subsequent postnatal cerebellar development. This study was planned to investigate the 32-day-old female rat pup cerebellum following exposure to 900MHz EMF during the prenatal period using stereological and histopathological evaluation methods. Pregnant rats were divided into control, sham and EMF groups. Pregnant EMF group (PEMFG) rats were exposed to 900MHz EMF for 1h inside an EMF cage during days 13-21 of pregnancy. Pregnant sham group (PSG) rats were also placed inside the EMF cage during days 13-21 of pregnancy for 1h, but were not exposed to any EMF. No procedure was performed on the pregnant control group (PCG) rats. Newborn control group (CG) rats were obtained from the PCG mothers, newborn sham group (SG) rats from the PSG and newborn EMF group (EMFG) rats from the PEMFG rats. The cerebellums of the newborn female rats were extracted on postnatal day 32. The number of Purkinje cells was estimated stereologically, and histopathological evaluations were also performed on cerebellar sections. Total Purkinje cell numbers calculated using stereological analysis were significantly lower in EMFG compared to CG ($p<0.05$) and SG ($p<0.05$). Additionally, some pathological changes such as pyknotic neurons with dark cytoplasm were observed in EMFG sections under light microscopy. In conclusion, our study results show that prenatal exposure to EMF affects the development of Purkinje cells in the female rat cerebellum and that the consequences of this pathological effect persist after the postnatal period.

(NE) Ogawa K, Nabae K, Wang J, Wake K, Watanabe S, Kawabe M, Fujiwara O, Takahashi S, Ichihara T, Tamano S, Shirai T. Effects of gestational exposure to 1.95-GHz W-CDMA signals for IMT-2000 cellular phones: Lack of embryotoxicity and teratogenicity in rats. Bioelectromagnetics. 30(3):205-212, 2009. (AS, CE, DE)

The present study was designed to evaluate whether gestational exposure to an EMF targeting the head region, similar to that from cellular phones, might affect embryogenesis in rats. A 1.95-GHz wide-band code division multiple access (W-CDMA) signal, which is one applied for

the International Mobile Telecommunication 2000 (IMT-2000) system and used for the freedom of mobile multimedia access (FOMA), was employed for exposure to the heads of four groups of pregnant CD(SD) IGS rats (20 per group) for gestational days 7-17. The exposure was performed for 90 min/day in the morning. The spatial average specific absorption rate (SAR) for individual brains was designed to be 0.67 and 2.0 W/kg with peak brain SARs of 3.1 and 7.0 W/kg for low (group 3) and high (group 4) exposures, respectively, and a whole-body average SAR less than 0.4 W/kg so as not to cause thermal effects due to temperature elevation. Control and sham exposure groups were also included. At gestational day 20, all dams were killed and fetuses were taken out by cesarean section. There were no differences in maternal body weight gain. No adverse effects of EMF exposure were observed on any reproductive and embryotoxic parameters such as number of live (243-271 fetuses), dead or resorbed embryos, placental weights, sex ratios, weights or external, visceral or skeletal abnormalities of live fetuses.

(NE) Okano T, Terao Y, Furubayashi T, Yugeta A, Hanajima R, Ugawa Y. The effect of electromagnetic field emitted by a mobile phone on the inhibitory control of saccades. Clin Neurophysiol. 121(4):603-611, 2010. (HU, PE)

OBJECTIVE: To investigate whether exposure to a pulsed high-frequency electromagnetic field (pulsed EMF) emitted by a mobile phone has short-term effects on the inhibitory control of saccades. METHODS: A double-blind, counterbalanced crossover study design was employed. We assessed the performance of 10 normal subjects on antisaccade (AS) and cued saccade (CUED) tasks as well as two types of overlap saccade (OL1, OL2) task before and after 30 min of exposure to EMF emitted by a mobile phone or sham exposure. RESULTS: After EMF or sham exposure, we observed a slight but significant shortening of latency in the CUED and OL2 tasks. AS amplitude decreased as well as the saccade velocities in the AS, CUED, and OL1 tasks after exposure. These changes occurred regardless of whether exposure was real or sham. The frequencies of pro-saccades in the AS task, saccades to cue in the CUED task, and prematurely initiated saccades in the overlap (OL2) task did not change significantly after real or sham EMF exposure. CONCLUSIONS: Thirty minutes of mobile phone exposure has no significant short-term effect on the inhibitory control of saccades. SIGNIFICANCE: The cortical processing responsible for saccade inhibition is not affected by exposure to EMF emitted by a mobile phone.

(E) Othman H, Ammari M, Sakly M, Abdelmelek H. Effects of prenatal exposure to WIFI signal (2.45GHz) on postnatal development and behavior in rat: Influence of maternal restraint. Behav Brain Res. 326:291-302, 2017. (AS, CE, DE, BE, OX)

The present study was carried out to investigate the potential combined influence of maternal restraint stress and 2.45GHz WiFi signal exposure on postnatal development and behavior in the offspring of exposed rats. 24 pregnant albino Wistar rats were randomly assigned to four groups: Control, WiFi-exposed, restrained and both WiFi-exposed and restrained groups. Each of WiFi exposure and restraint occurred 2h/day along gestation till parturition. The pups were evaluated for physical development and neuromotor maturation. Moreover, elevated plus maze test, open

field activity and stationary beam test were also determined on postnatal days 28, 30 and 31, respectively. After behavioral tests, the rats were anesthetized and their brains were removed for biochemical analysis. Our main findings showed no detrimental effects on gestation progress and outcomes at delivery in all groups. Subsequently, WiFi and restraint, per se and mainly in concert altered physical development of pups with slight differences between genders. Behaviorally, the gestational WiFi irradiation, restraint and especially the associated treatment affected the neuromotor maturation mainly in male progeny. At adult age, we noticed anxiety, motor deficit and exploratory behavior impairment in male offspring co-exposed to WiFi radiation and restraint, and in female progeny subjected to three treatments. The biochemical investigation showed that, all three treatments produced global oxidative stress in brain of both sexes. As for serum biochemistry, phosphorus, magnesium, glucose, triglycerides and calcium levels were disrupted. Taken together, prenatal WiFi radiation and restraint, alone and combined, provoked several behavioral and biochemical impairments at both juvenile and adult age of the offspring.

(E) Özgür A, Tümkaya L, Terzi S, Kalkan Y, Erdivanlı ÖÇ, Dursun E. Effects of chronic exposure to electromagnetic waves on the auditory system. Acta Otolaryngol. 2015 Apr 2:1-6. [Epub ahead of print] (AS, CE, ME)

OBJECTIVES: Numerous researches have been done about the risks of exposure to the electromagnetic fields that occur during the use of these devices, especially the effects on hearing. The aim of this study is to evaluate the effects of the electromagnetic waves emitted by the mobile phones through the electrophysiological and histological methods. **METHODS:** Twelve adult Wistar albino rats were included in the study. The rats were divided into two groups of six rats. The study group was exposed to the electromagnetic waves over a period of 30 days. The control group was not given any exposure to the electromagnetic fields. After the completion of the electromagnetic wave application, the auditory brainstem responses of both groups were recorded under anesthesia. The degeneration of cochlear nuclei was graded by two different histologists, both of whom were blinded to group information. **RESULTS:** The histopathologic and immunohistochemical analysis showed neuronal degeneration signs, such as increased vacuolization in the cochlear nucleus, pyknotic cell appearance, and edema in the group exposed to the electromagnetic fields compared to the control group. The average latency of wave in the ABR was similar in both groups ($p > 0.05$). **CONCLUSION:** The results support that chronic electromagnetic field exposure may cause damage by leading to neuronal degeneration of the auditory system.

(E) Panda NK, Jain R, Bakshi J, Munjal S. Audiologic disturbances in long-term mobile phone users. J Otolaryngol Head Neck Surg. 39(1):5-11, 2010. (HU, CE, PE)

INTRODUCTION: There is general concern regarding the possible hazardous health effects of exposure to radiofrequency electromagnetic radiation emitted from mobile phones. This study

aimed to assess the effects of chronic exposure to electromagnetic waves emitted from Global System for Mobile Communication (GSM) mobile phones on auditory functions. **MATERIAL AND METHODS:** A retrospective, cross-sectional, randomized, case control study was carried out in a tertiary care hospital. One hundred twelve subjects who were long-term mobile phone users (more than 1 year) and 50 controls who had never used a mobile phone underwent a battery of audiologic investigations including pure-tone audiometry (both speech and high frequency), tympanometry, distortion product otoacoustic emissions, auditory brain responses, and middle latency responses. Changes in the various parameters were studied in the mobile phone- and non-mobile phone-using ears of subjects and corresponding ears of the controls to ascertain the effects of electromagnetic exposure. **RESULTS:** There was no significant difference between users and controls for any of the audiologic parameters. However, trends for audiologic abnormalities were seen within the users. High-frequency loss and absent distortion product otoacoustic emissions were observed with an increase in the duration of mobile phone use, excessive use of mobile phones, and age more than 30 years. Additionally, users with some complaints during mobile phone use demonstrated absent distortion product otoacoustic emissions and abnormalities in auditory brainstem response. **CONCLUSION:** Long-term and intensive mobile phone use may cause inner ear damage. A large sample size would be required to reach definitive conclusions.

(E) Panda NK, Modi R, Munjal S, Virk RS. Auditory changes in mobile users: is evidence forthcoming? Otolaryngol Head Neck Surg. 144(4):581-585, 2011. (HU, CE, PE)

OBJECTIVE: Genuine concerns are being raised as to the potential health risks posed by electromagnetic frequency exposure secondary to mobile phone usage. This study was undertaken to assess and compare potential changes in hearing function at the level of the inner ear and central auditory pathway due to chronic exposure to electromagnetic waves from both global system for mobile communications (GSM) and code division multiple access (CDMA) mobile phone usage. **DESIGN:** Cohort study. **SETTING:** Tertiary referral center. **SUBJECTS AND METHODS:** One hundred twenty-five subjects who were long-term mobile phone users (more than 1 year; 63 GSM and 62 CDMA) and 58 controls who had never used mobile phones underwent audiological investigations including pure tone audiometry (250-12 kHz), tympanometry, distortion product otoacoustic emissions (DPOAE), auditory brain responses (ABR), and middle latency responses (MLRs). The changes in various parameters were studied in mobile-using and non-mobile-using ears of both GSM and CDMA subjects and corresponding ears of the controls to ascertain the effects of electromagnetic exposure. **RESULTS:** GSM and CDMA users were found to be at a significantly higher risk of having DPOAE absent as compared with controls ($P < .05$). They were found to have higher speech frequency thresholds and lower MLR wave and Na and Pa amplitudes. More than 3 years of mobile phone usage emerged as a risk factor ($P < .05$). The damage done was bilateral, with the quantum of damage being the same for both GSM and CDMA. **CONCLUSION:** Long-term and intensive GSM and CDMA mobile phone use may cause damage to cochlea as well as the auditory cortex.

(E) Papageorgiou CC, Hountala CD, Maganioti AE, Kyprianou MA, Rabavilas AD, Papadimitriou GN, Capsalis CN. Effects of wi-fi signals on the p300 component of event-related potentials during an auditory hayling task. J Integr Neurosci. 10(2):189-202, 2011 (HU, EE)

The P300 component of event-related potentials (ERPs) is believed to index attention and working memory (WM) operation of the brain. The present study focused on the possible gender-related effects of Wi-Fi (Wireless Fidelity) electromagnetic fields (EMF) on these processes. Fifteen male and fifteen female subjects, matched for age and education level, were investigated while performing a modified version of the Hayling Sentence Completion test adjusted to induce WM. ERPs were recorded at 30 scalp electrodes, both without and with the exposure to a Wi-Fi signal. P300 amplitude values at 18 electrodes were found to be significantly lower in the response inhibition condition than in the response initiation and baseline conditions. Independent of the above effect, within the response inhibition condition there was also a significant gender X radiation interaction effect manifested at 15 leads by decreased P300 amplitudes of males in comparison to female subjects only at the presence of EMF. In conclusion, the present findings suggest that Wi-Fi exposure may exert gender-related alterations on neural activity associated with the amount of attentional resources engaged during a linguistic test adjusted to induce WM.

(NE) Paparini A, Rossi P, Gianfranceschi G, Brugaletta V, Falsaperla R, De Luca P, Romano Spica V. No evidence of major transcriptional changes in the brain of mice exposed to 1800 MHz GSM signal. Bioelectromagnetics. 29(4):312-323, 2008. (AS, CH)

To analyze possible effects of microwaves on gene expression, mice were exposed to global system for mobile communication (GSM) 1800 MHz signal for 1 h at a whole body SAR of 1.1 W/kg. Gene expression was studied in the whole brain, where the average SAR was 0.2 W/kg, by expression microarrays containing over 22,600 probe sets. Comparison of data from sham and exposed animals showed no significant difference in gene expression modulation. However, when less stringent constraints were adopted to analyze microarray results, 75 genes were found to be modulated following exposure. Forty-two probes showed fold changes ranging from 1.5 to 2.8, whereas 33 were down-regulated from 0.67- to 0.29-fold changes, but these differences in gene expression were not confirmed by real-time PCR. Under these specific limited conditions, no consistent indication of gene expression modulation in whole mouse brain was found associated to GSM 1800 MHz exposure.

(E) Parazzini M, Ravazzani P, Tognola G, Thuróczy G, Molnar FB, Sacchettini A, Ardesi G, Mainardi LT. Electromagnetic fields produced by GSM cellular phones and heart rate variability. Bioelectromagnetics. 28(2):122-129, 2007. (HU, PE)

In this study, 26 healthy young volunteers were submitted to 900 MHz (2 W) GSM cellular phone exposure and to sham exposure in separate sessions. The study was designed to assess cardiac regulatory mechanism in different autonomic nervous system (ANS) states during exposure to low-intensity EMF. Rest-to-stand protocol was applied to evaluate ANS in quiet condition (rest, vagal prevalence) and after a sympathetic activation (stand). The procedure is

conducted twice in a double-blind design: once with a genuine EMF exposure and once with a sham exposure (at least 24 h apart). During each session three-leads electrocardiograms were recorded and RR series extracted off-line. Time domain and frequency domain HRV parameters were calculated in every phase of the protocol and during different exposures. The analysis of the data show there was no statistically significant effect due to EMF exposure both on main (i.e., RR mean) and most of the other HRV parameters. A weak interaction between some HRV parameters (i.e., SDNN, TINN, and triangular index in time domain and LF power in frequency domain analysis) and RF exposure was observed and this effect seems to be gathered around the sympathetic response to stand.

(NE) Parazzini M, Sibella F, Lutman ME, Mishra S, Moulin A, Sliwinska-Kowalska M, Woznicka E, Politanski P, Zmyslony M, Thuroczy G, Molnár F, Kubinyi G, Tavartkiladze G, Bronyakin S, Uloziene I, Uloza V, Gradauskiene E, Ravazzani P. Effects of UMTS cellular phones on human hearing: results of the European project EMFnEAR. Radiat Res. 172(2):244-251, 2009. (HU, PE)

The European project EMFnEAR was undertaken to assess potential changes in human auditory function after a short-term exposure to radiofrequency (RF) radiation produced by UMTS (Universal Mobile Telecommunication System) mobile phones. Participants were healthy young adults with no hearing or ear disorders. Auditory function was assessed immediately before and after exposure to radiofrequency radiation, and only the exposed ear was tested. Tests for the assessment of auditory function were hearing threshold level (HTL), distortion product otoacoustic emissions (DPOAE), contralateral suppression of transiently evoked otoacoustic emission (CAS effect on TEOAE), and auditory evoked potentials (AEP). The exposure consisted of speech at a typical conversational level delivered via an earphone to one ear, plus genuine or sham RF-radiation exposure produced by a commercial phone controlled by a personal computer. Results from 134 participants did not show any consistent pattern of effects on the auditory system after a 20-min UMTS exposure at the maximum output of the phone with 69 mW/kg SAR in the cochlea region in a double blind comparison of genuine and sham exposure. An isolated effect on the hearing threshold at high frequencies was identified, but this was statistically nonsignificant after correction for multiple comparisons. It is concluded that UMTS short-term exposure at the maximum output of consumer mobile phones does not cause measurable immediate effects on the human auditory system.

(E) Partsvania B, Sulaberidze T, Shoshiashvili L, Modebadze Z. Acute effect of exposure of mollusk single neuron to 900-MHz mobile phone radiation. Electromagn Biol Med. 30(3):170-179, 2011. (CS, EE)

The goal of the present work was to explore the influence of commercially available cell phone irradiation on the single neuron excitability and memory processes. A Transverse Electromagnetic Cell (TEM Cell) was used to expose single neurons of mollusk to the electromagnetic field. Finite-Difference Time-Domain (FDTD) method was used for modeling the TEM Cell and the electromagnetic field interactions with living nerve ganglion and neurons. Neuron electrophysiology was investigated using standard microelectrode technique. The specific absorption rate (SAR) deposited into the single neuron was calculated to be 0.63 W/kg

with a temperature increment of 0.1°C. After acute exposure, average firing threshold of the action potentials was not changed. However, the average latent period was significantly decreased. This indicates that together with latent period the threshold and the time of habituation might be altered during exposure. However, these alterations are transient and only latent period remains on the changed level.

(E) Pelletier A, Delanaud S, Décima P, Thuroczy G, de Seze R, Cerri M, Bach V, Libert JP, Loos N. Effects of chronic exposure to radiofrequency electromagnetic fields on energy balance in developing rats. Environ Sci Pollut Res Int. 2012 Nov 10. [Epub ahead of print] (AS, LI, CE, BE, PE, EE, SL)

The effects of radiofrequency electromagnetic fields (RF-EMF) on the control of body energy balance in developing organisms have not been studied, despite the involvement of energy status in vital physiological functions. We examined the effects of chronic RF-EMF exposure (900 MHz, 1 V m⁻¹) on the main functions involved in body energy homeostasis (feeding behaviour, sleep and thermoregulatory processes). Thirteen juvenile male Wistar rats were exposed to continuous RF-EMF for 5 weeks at 24 °C of air temperature (T (a)) and compared with 11 non-exposed animals. Hence, at the beginning of the 6th week of exposure, the functions were recorded at T (a) of 24 °C and then at 31 °C. We showed that the frequency of rapid eye movement sleep episodes was greater in the RF-EMF-exposed group, independently of T (a) (+42.1 % at 24 °C and +31.6 % at 31 °C). The other effects of RF-EMF exposure on several sleep parameters were dependent on T (a). At 31 °C, RF-EMF-exposed animals had a significantly lower subcutaneous tail temperature (-1.21 °C) than controls at all sleep stages; this suggested peripheral vasoconstriction, which was confirmed in an experiment with the vasodilator prazosin. Exposure to RF-EMF also increased daytime food intake (+0.22 g h⁻¹). Most of the observed effects of RF-EMF exposure were dependent on T (a). Exposure to RF-EMF appears to modify the functioning of vasomotor tone by acting peripherally through α -adrenoceptors. The elicited vasoconstriction may restrict body cooling, whereas energy intake increases. Our results show that RF-EMF exposure can induce energy-saving processes without strongly disturbing the overall sleep pattern.

(E) Pelletier A, Delanaud S, de Seze R, Bach V, Libert JP, Loos N. Does Exposure to a Radiofrequency Electromagnetic Field Modify Thermal Preference in Juvenile Rats? PLoS One. 2014 Jun 6;9(6):e99007. doi: 10.1371/journal.pone.0099007. eCollection 2014. (AS, LI, CE, BE, PE, EE, SL)

Some studies have shown that people living near a mobile phone base station may report sleep disturbances and discomfort. Using a rat model, we have previously shown that chronic exposure to a low-intensity radiofrequency electromagnetic field (RF-EMF) was associated with paradoxical sleep (PS) fragmentation and greater vasomotor tone in the tail. Here, we sought to

establish whether sleep disturbances might result from the disturbance of thermoregulatory processes by a RF-EMF. We recorded thermal preference and sleep stage distribution in 18 young male Wistar rats. Nine animals were exposed to a low-intensity RF-EMF (900 MHz, 1 V.m-1) for five weeks and nine served as non-exposed controls. Thermal preference was assessed in an experimental chamber comprising three interconnected compartments, in which the air temperatures (T_a) were set to 24°C, 28°C and 31°C. Sleep and tail skin temperature were also recorded. Our results indicated that relative to control group, exposure to RF-EMF at 31°C was associated with a significantly lower tail skin temperature (-1.6°C) which confirmed previous data. During the light period, the exposed group preferred to sleep at T_a = 31°C and the controls preferred T_a = 28°C. The mean sleep duration in exposed group was significantly greater (by 15.5%) than in control group (due in turn to a significantly greater amount of slow wave sleep (SWS, +14.6%). Similarly, frequency of SWS was greater in exposed group (by 4.9 episodes.h-1). The PS did not differ significantly between the two groups. During the dark period, there were no significant intergroup differences. We conclude that RF-EMF exposure induced a shift in thermal preference towards higher temperatures. The shift in preferred temperature might result from a cold thermal sensation. The change in sleep stage distribution may involve signals from thermoreceptors in the skin. Modulation of SWS may be a protective adaptation in response to RF-EMF exposure.

(NE) Perentos N, Croft RJ, McKenzie RJ, Cvetkovic D, Cosic I. Comparison of the effects of continuous and pulsed mobile phone like RF exposure on the human EEG. Australas Phys Eng Sci Med. 30(4):274-280, 2007. (HU, EE)

It is not clear yet whether Global System for Mobiles (GSM) mobile phone radiation has the ability to interfere with normal resting brain function. There have been reports that GSM exposure increases alpha band power, and does so only when the signal is modulated at low frequencies (Huber, R., Treyer, V., Borbely, A. A., Schuderer, J., Gottselig, J. M., Landolt, H.P., Werth, E., Berthold, T., Kuster, N., Buck, A and Achermann, P. Electromagnetic fields, such as those from mobile phones, alter regional cerebral blood flow and sleep and waking EEG. J Sleep Res 11, 289-295, 2002.) However, as that research employed exposure distributions that are not typical of normal GSM handset usage (deep brain areas were overexposed), it remains to be determined whether a similar result patterning would arise from a more representative exposure. In this fully counterbalanced cross-over design, we recruited 12 participants and tried to replicate the modulation linked post exposure alpha band power increase described above, but with an exposure source (dipole antenna) more closely resembling that of a real GSM handset. Exposures lasted for 15 minutes. No changes to alpha power were found for either modulated or unmodulated radiofrequency fields, and thus we failed to replicate the above results. Possible reasons for this failure to replicate are discussed, with the main reason argued to be the lower and more representative exposure distribution employed in the present study. In addition we investigated the possible GSM exposure related effects on the non-linear features of the resting electroencephalogram using the Approximate Entropy (ApEn) method of analysis. Again, no effect was demonstrated for either modulated or unmodulated radiofrequency exposures.

(E) Perentos N, Croft RJ, McKenzie RJ, Cosic I. The alpha band of the resting electroencephalogram under pulsed and continuous radio frequency exposures. IEEE Trans Biomed Eng. 60(6):1702-1710, 2013. (HU, EE)

The effect of GSM-like electromagnetic fields with the resting electroencephalogram (EEG) alpha band activity was investigated in a double-blind cross-over experimental paradigm, testing the hypothesis that pulsed but not continuous radio frequency (RF) exposure would affect alpha activity, and the hypothesis that GSM-like pulsed low frequency fields would affect alpha. Seventy-two healthy volunteers attended a single recording session where the eyes open resting EEG activity was recorded. Four exposure intervals were presented (sham, pulsed modulated RF, continuous RF, and pulsed low frequency) in a counterbalanced order where each exposure lasted for 20 min. Compared to sham, a suppression of the global alpha band activity was observed under the pulsed modulated RF exposure, and this did not differ from the continuous RF exposure. No effect was seen in the extremely low frequency condition. That there was an effect of pulsed RF that did not differ significantly from continuous RF exposure does not support the hypothesis that "pulsed" RF is required to produce EEG effects. The results support the view that alpha is altered by RF electromagnetic fields, but suggest that the pulsing nature of the fields is not essential for this effect to occur.

(NE) Platano D, Mesirca P, Paffi A, Pellegrino M, Liberti M, Apollonio F, Bersani F, Aicardi G. Acute exposure to low-level CW and GSM-modulated 900 MHz radiofrequency does not affect Ba²⁺ currents through voltage-gated calcium channels in rat cortical neurons. Bioelectromagnetics. 28(8):599-607, 2007. (CS, EE)

We have studied the non-thermal effects of radiofrequency (RF) electromagnetic fields (EMFs) on Ba(2+) currents (I Ba 2+) through voltage-gated calcium channels (VGCC), recorded in primary cultures of rat cortical neurons using the patch-clamp technique. To assess whether low-level acute RF field exposure could modify the amplitude and/or the voltage-dependence of I Ba 2+, Petri dishes containing cultured neurons were exposed for 1-3 periods of 90 s to 900 MHz RF-EMF continuous wave (CW) or amplitude-modulated according to global system mobile communication standard (GSM) during whole-cell recording. The specific absorption rates (SARs) were 2 W/kg for CW and 2 W/kg (time average value) for GSM-modulated signals, respectively. The results obtained indicate that single or multiple acute exposures to either CW or GSM-modulated 900 MHz RF-EMFs do not significantly alter the current amplitude or the current-voltage relationship of I Ba 2+, through VGCC.

(NE) Poulletier de Gannes F, Haro E, Hurtier A, Taxile M, Ruffié G, Billaudel B, Veyret B, Lagroye I. Effect of exposure to the edge signal on oxidative stress in brain cell models. Radiat Res. 175(2):225-230, 2011. (CS, OX)

In this study we investigated the effect of the Enhanced Data rate for GSM Evolution (EDGE) signal on cells of three human brain cell lines, SH-SY5Y, U87 and CHME5, used as models of neurons, astrocytes and microglia, respectively, as well as on primary cortical neuron cultures. SXC-1800 waveguides (IT'IS-Foundation, Zürich, Switzerland) were modified for in vitro exposure to the EDGE signal radiofrequency (RF) radiation at 1800 MHz. Four exposure conditions were tested: 2 and 10 W/kg for 1 and 24 h. The production of reactive oxygen species (ROS) was measured by flow cytometry using the dichlorofluorescein diacetate (DCFH-DA) probe at the end of the 24-h exposure or 24 h after the 1-h exposure. Rotenone treatment

was used as a positive control. All cells tested responded to rotenone treatment by increasing ROS production. These findings indicate that exposure to the EDGE signal does not induce oxidative stress under these test conditions, including 10 W/kg. Our results are in agreement with earlier findings that RF radiation alone does not increase ROS production.

(NE) Prochnow N, Gebing T, Ladage K, Krause-Finkeldey D, El Ouardi A, Bitz A, Streckert J, Hansen V, Dermietzel R. Electromagnetic field effect or simply stress? Effects of UMTS exposure on hippocampal longterm plasticity in the context of procedure related hormone release. PLoS One. 6(5):e19437, 2011. (AS, EE)

Harmful effects of electromagnetic fields (EMF) on cognitive and behavioural features of humans and rodents have been controversially discussed and raised persistent concern about adverse effects of EMF on general brain functions. In the present study we applied radio-frequency (RF) signals of the Universal Mobile Telecommunications System (UMTS) to full brain exposed male Wistar rats in order to elaborate putative influences on stress hormone release (corticosteron; CORT and adrenocorticotrophic hormone; ACTH) and on hippocampal derived synaptic long-term plasticity (LTP) and depression (LTD) as electrophysiological hallmarks for memory storage and memory consolidation. Exposure was computer controlled providing blind conditions. Nominal brain-averaged specific absorption rates (SAR) as a measure of applied mass-related dissipated RF power were 0, 2, and 10 W/kg over a period of 120 min. Comparison of cage exposed animals revealed, regardless of EMF exposure, significantly increased CORT and ACTH levels which corresponded with generally decreased field potential slopes and amplitudes in hippocampal LTP and LTD. Animals following SAR exposure of 2 W/kg (averaged over the whole brain of 2.3 g tissue mass) did not differ from the sham-exposed group in LTP and LTD experiments. In contrast, a significant reduction in LTP and LTD was observed at the high power rate of SAR (10 W/kg). The results demonstrate that a rate of 2 W/kg displays no adverse impact on LTP and LTD, while 10 W/kg leads to significant effects on the electrophysiological parameters, which can be clearly distinguished from the stress derived background. Our findings suggest that UMTS exposure with SAR in the range of 2 W/kg is not harmful to critical markers for memory storage and memory consolidation, however, an influence of UMTS at high energy absorption rates (10 W/kg) cannot be excluded.

(E) Qiao S, Peng R, Yan H, Gao Y, Wang C, Wang S, Zou Y, Xu X, Zhao L, Dong J, Su Z, Feng X, Wang L, Hu X. Reduction of Phosphorylated Synapsin I (Ser-553) Leads to Spatial Memory Impairment by Attenuating GABA Release after Microwave Exposure in Wistar Rats. PLoS One. 2014 Apr 17;9(4):e95503. doi: 10.1371/journal.pone.0095503. eCollection 2014. (AS, CS, BE, CH)

BACKGROUND: Abnormal release of neurotransmitters after microwave exposure can cause learning and memory deficits. This study investigated the mechanism of this effect by exploring the potential role of phosphorylated synapsin I (p-Syn I). METHODS: Wistar rats, rat hippocampal synaptosomes, and differentiated (neuronal) PC12 cells were exposed to microwave radiation for 5 min at a mean power density of 30 mW/cm². Sham group rats, synaptosomes, and cells were otherwise identically treated and acted as controls for all of the

following post-exposure analyses. Spatial learning and memory in rats was assessed using the Morris Water Maze (MWM) navigation task. The protein expression and presynaptic distribution of p-Syn I and neurotransmitter transporters were examined via western blotting and immunoelectron microscopy, respectively. Levels amino acid neurotransmitter release from rat hippocampal synaptosomes and PC12 cells were measured using high performance liquid chromatograph (HPLC) at 6 hours after exposure, with or without synapsin I silencing via shRNA transfection. RESULTS: In the rat experiments, there was a decrease in spatial memory performance after microwave exposure. The expression of p-Syn I (ser-553) was decreased at 3 days post-exposure and elevated at later time points. Vesicular GABA transporter (VGAT) was significantly elevated after exposure. The GABA release from synaptosomes was attenuated and p-Syn I (ser-553) and VGAT were both enriched in small clear synaptic vesicles, which abnormally assembled in the presynaptic terminal after exposure. In the PC12 cell experiments, the expression of p-Syn I (ser-553) and GABA release were both attenuated at 6 hours after exposure. Both microwave exposure and p-Syn I silencing reduced GABA release and maximal reduction was found for the combination of the two, indicating a synergetic effect. CONCLUSION: p-Syn I (ser-553) was found to play a key role in the impaired GABA release and cognitive dysfunction that was induced by microwave exposure.

(E) Qin F, Yuan H, Nie J, Cao Y, Tong J. [Effects of nano-selenium on cognition performance of mice exposed in 1800 MHz radiofrequency fields]. Wei Sheng Yan Jiu. 43(1):16-21, 2014. [Article in Chinese] (AS, CE, BE, CH, OX)

OBJECTIVE: To study the effects of nano-selenium (NSe) on cognition performance of mice exposed to 1800 MHz radiofrequency fields (RF). METHODS: Male mice were randomly divided into four groups, control and nano-Se low, middle and high dose groups (L, M, H). Each group was sub-divided into three groups, RF 0 min, RF 30 min and RF 120 min. Nano-se solution (2, 4 and 8 microg/ml) were administered to mice of L, M, H groups by intra-gastric injection respectively, 0.5 ml/d for 50 days, the control group was administered with distilled water. At the 21st day, the mice in RF subgroup were exposed to 208 microW/cm² 1800 MHz radiofrequency fields (0, 30 and 120 min/d respectively) for 30 days. The cognitive ability of the mice were tested with Y-maze. Further, the levels of MDA, GABA, Glu, Ach and the activities of CAT and GSH-Px in cerebra were measured. RESULTS: Significant impairments in learning and memory ($P < 0.05$) were observed in the RF 120 min group, and with reduction of the Ach level and the activities of CAT and GSH-Px and increase of the content of GABA, Glu and MDA in cerebrum. NSe enhanced cognitive performance of RF mice, decreased GABA, Glu and MDA levels, increased Ach levels, GSH-Px and CAT activities. CONCLUSION: NSe could improve cognitive impairments of mice exposed to RF, the mechanism of which might involve the increasing antioxidation, decreasing free radical content and the changes of cerebra neurotransmitters.

(NE) Rağbetli MC, Aydinlioğlu A, Koyun N, Rağbetli C, Karayel M. Effect of prenatal exposure to mobile phone on pyramidal cell numbers in the mouse hippocampus: a stereological study. Int J Neurosci. 119(7):1031-1041, 2009. (AS, ME, DE)

Because of the possible risk factor for the health, World Health Organization (WHO) recommended the study with animals on the developing nervous system concerning the exposure to radiofrequency (RF) field. A few studies related to hippocampal exposure are available, which indicate the impact of RF field in some parameters. The present study investigated the effect of exposure to mobile phone on developing hippocampus. Male and female Swiss albino mice were housed as control and mobile phone exposed groups. The pregnant animals in tested group were exposed to the effects of mobile phone in a room possessing the exposure system. The left hemispheres of the brains were processed by frozen microtome. The sections obtained were stained with Hematoxylin & Eosin. For cell counting by the optical fractionator method, a pilot study was first performed. Hippocampal areas were analyzed using Axiovision software running on a personal computer. The optical dissector, systematically and randomly spaced, was focused to the widest profile of the pyramidal cell nucleus. No significant difference in pyramidal cell number of total Cornu Ammonis (CA) sectors of hippocampus was found between the control and the mobile phone exposed groups ($p > .05$). It was concluded that further study is needed in this field due to popular use of mobile telephones and relatively high exposure to the developing brain.

(E) Rağbetli MC, Aydinlioğlu A, Koyun N, Rağbetli C, Bektas S, Ozdemir S. The effect of mobile phone on the number of Purkinje cells: a stereological study. Int J Radiat Biol. 86(7):548-554, 2010. (AS, ME, DE)

PURPOSE: The World Health Organisation proposed an investigation concerning the exposure of animals to radiofrequency fields because of the possible risk factor for health. At power frequencies there is evidence to associate both childhood leukaemia and brain tumours with magnetic field exposures. There is also evidence of the effect of mobile phone exposure on both cognitive functions and the cerebellum. Purkinje cells of the cerebellum are also sensitive to high dose microwave exposure in rats. The present study investigated the effect of exposure to mobile phone on the number of Purkinje and granule neurons in the developing cerebellum. **MATERIAL AND METHODS:** Male and female Swiss albino mice were housed as control and mobile phone-exposed groups. Pregnant animals in the experimental group were exposed to Global System for Mobile Communication (GSM) mobile phone radiation at 890-915 MHz at 0.95 W/Kg specific absorption rate (SAR). The cerebella were processed by frozen microtome. The sections obtained were stained with Haematoxylin-eosin and cresyl violet. For cell counting by the optical fractionator method, a pilot study was firstly performed. Cerebellar areas were analysed by using Axiovision software running on a personal computer. The optical dissectors were systematically spaced at random, and focused to the widest profile of the neuron cell nucleus. **RESULTS:** A significant decrease in the number of Purkinje cells and a tendency for granule cells to increase in cerebellum was found. **CONCLUSION:** Further studies in this area are needed due to the popular use of mobile telephones and relatively high exposure on developing brain.

(E) Razavinasab M, Moazzami K, Shabani M. Maternal mobile phone exposure alters intrinsic electrophysiological properties of CA1 pyramidal neurons in rat offspring. Toxicol Ind Health. 2014 Mar 6. [Epub ahead of print] (AS, CE, BE, DE, EE)

Some studies have shown that exposure to electromagnetic field (EMF) may result in structural damage to neurons. In this study, we have elucidated the alteration in the hippocampal function of offspring Wistar rats (n = 8 rats in each group) that were chronically exposed to mobile phones during their gestational period by applying behavioral, histological, and electrophysiological tests. Rats in the EMF group were exposed to 900 MHz pulsed-EMF irradiation for 6 h/day. Whole cell recordings in hippocampal pyramidal cells in the mobile phone groups did show a decrease in neuronal excitability. Mobile phone exposure was mostly associated with a decrease in the number of action potentials fired in spontaneous activity and in response to current injection in both male and female groups. There was an increase in the amplitude of the afterhyperpolarization (AHP) in mobile phone rats compared with the control. The results of the passive avoidance and Morris water maze assessment of learning and memory performance showed that phone exposure significantly altered learning acquisition and memory retention in male and female rats compared with the control rats. Light microscopy study of brain sections of the control and mobile phone-exposed rats showed normal morphology. Our results suggest that exposure to mobile phones adversely affects the cognitive performance of both female and male offspring rats using behavioral and electrophysiological techniques.

(E) Redmayne M, Smith E, and Abramson MJ. The relationship between adolescents' well-being and their wireless phone use: a cross-sectional study. Environmental Health 12(1):90, 2013. (HU, BE)

Background. The exposure of young people to radiofrequency electromagnetic fields (RF-EMFs) has increased rapidly in recent years with their increased use of cellphones and use of cordless phones and WiFi. We sought to ascertain associations between New Zealand early-adolescents' subjective well-being and self-reported use of, or exposure to, wireless telephone and internet technology. Methods. In this cross-sectional survey, participants completed questionnaires in class about their cellphone and cordless phone use, their self-reported well-being, and possible confounding information such as whether they had had influenza recently or had a television in the bedroom. Parental questionnaires provided data on whether they had WiFi at home and cordless phone ownership and model. Data were analysed with Ordinal Logistic Regression adjusting for common confounders. Odds ratios (OR) and 95% confidence intervals were calculated. Results. The number and duration of cellphone and cordless phone calls were associated with increased risk of headaches (>6 cellphone calls over 10 minutes weekly, adjusted OR 2.4, CI 1.2-4.8; >15 minutes cordless use daily adjusted OR 1.74, CI 1.1-2.9)). Texting and extended use of wireless phones was related to having a painful 'texting' thumb). Using a wired cellphone headset was associated with tinnitus (adjusted OR 1.8, CI 1.0-3.3), while wireless headsets were associated with headache (adjusted OR 2.2, CI 1.1-4.5), feeling down/depressed (adjusted OR 2.0, CI 1.1-3.8), and waking in the night (adjusted OR 2.4, CI 1.2-4.8). Several cordless phone frequencies bands were related to tinnitus, feeling

down/depressed and sleepiness at school, while the last of these was also related to modulation. Waking nightly was less likely for those with WiFi at home (adjusted OR 0.7, CI 0.4-0.99). Being woken at night by a cellphone was strongly related to tiredness at school (OR 4.1, CI 2.2-7.7). Conclusions . There were more statistically significant associations (36%) than could be expected by chance (5%). Several were dose-dependent relationships. To safeguard young people's well-being, we suggest limiting their use of cellphones and cordless phones to less than 15 minutes daily, and employing a speaker-phone device for longer daily use. We recommend parental measures are taken to prevent young people being woken by their cellphones.

(NE) Redmayne M, Smith CL, Benke G, Croft RJ, Dalecki A, Dimitriadis C, Kaufman J, Macleod S, Sim MR, Wolfe R, Abramson MJ. Use of mobile and cordless phones and cognition in Australian primary school children: a prospective cohort study. Environ Health. 15(1):26, 2016. (HU, CE, BE)

BACKGROUND: Use of mobile (MP) and cordless phones (CP) is common among young children, but whether the resulting radiofrequency exposure affects development of cognitive skills is not known. Small changes have been found in older children. This study focused on children's exposures to MP and CP and cognitive development. The hypothesis was that children who used these phones would display differences in cognitive function compared to those who did not. METHODS: We recruited 619 fourth-grade students (8-11 years) from 37 schools around Melbourne and Wollongong, Australia. Participants completed a short questionnaire, a computerised cognitive test battery, and the Stroop colour-word test. Parents completed exposure questionnaires on their child's behalf. Analysis used multiple linear regression. The principal exposure-metrics were the total number of reported MP and CP calls weekly categorised into no use ('None'); use less than or equal to the median amount ('Some'); and use more than the median ('More'). The median number of calls/week was 2.5 for MP and 2.0 for CP. RESULTS: MP and CP use for calls was low; and only 5 of 78 comparisons of phone use with cognitive measures were statistically significant. The reaction time to the response-inhibition task was slower in those who used an MP 'More' compared to the 'Some' use group and non-users. For CP use, the response time to the Stroop interference task was slower in the 'More' group versus the 'Some' group, and accuracy was worse in visual recognition and episodic memory tasks and the identification task. In an additional exploratory analysis, there was some evidence of a gender effect on mean reaction times. The highest users for both phone types were girls. CONCLUSIONS: Overall, there was little evidence cognitive function was associated with CP and MP use in this age group. Although there was some evidence that effects of MP and CP use on cognition may differ by gender, this needs further exploration. CP results may be

more reliable as parents estimated children's phone use and the CPs were at home; results for CP use were broadly consistent with our earlier study of older children.

(E) Regel SJ, Tinguely G, Schuderer J, Adam M, Kuster N, Landolt HP, Achermann P. Pulsed radio-frequency electromagnetic fields: dose-dependent effects on sleep, the sleep EEG and cognitive performance. J Sleep Res. 16(3):253-258, 2007. (HU, EE, BE, SL)

To establish a dose-response relationship between the strength of electromagnetic fields (EMF) and previously reported effects on the brain, we investigated the influence of EMF exposure by varying the signal intensity in three experimental sessions. The head of 15 healthy male subjects was unilaterally exposed for 30 min prior to sleep to a pulse-modulated EMF (GSM handset like signal) with a 10 g-averaged peak spatial specific absorption rate of (1) 0.2 W kg⁻¹, (2) 5 W kg⁻¹, or (3) sham exposed in a double-blind, crossover design. During exposure, subjects performed two series of three computerized cognitive tasks, each presented in a fixed order [simple reaction time task, two-choice reaction time task (CRT), 1-, 2-, 3-back task]. Immediately after exposure, night-time sleep was polysomnographically recorded for 8 h. Sleep architecture was not affected by EMF exposure. Analysis of the sleep electroencephalogram (EEG) revealed a dose-dependent increase of power in the spindle frequency range in non-REM sleep. Reaction speed decelerated with increasing field intensity in the 1-back task, while accuracy in the CRT and N-back task were not affected in a dose-dependent manner. In summary, this study reveals first indications of a dose-response relationship between EMF field intensity and its effects on brain physiology as demonstrated by changes in the sleep EEG and in cognitive performance.

(NE) Riddervold IS, Pedersen GF, Andersen NT, Pedersen AD, Andersen JB, Zachariae R, Mølhave L, Sigsgaard T, Kjaergaard SK. Cognitive function and symptoms in adults and adolescents in relation to rf radiation from UMTS base stations. Bioelectromagnetics. 29(4):257-267, 2008. (HU, BE)

There is widespread public concern about the potential adverse health effects of mobile phones in general and their associated base stations in particular. This study was designed to investigate the acute effects of radio frequency (RF) electromagnetic fields (EMF) emitted by the Universal Mobile Telecommunication System (UMTS) mobile phone base stations on human cognitive function and symptoms. Forty adolescents (15-16 years) and 40 adults (25-40 years) were exposed to four conditions: (1) sham, (2) a Continuous Wave (CW) at 2140 MHz, (3) a signal at 2140 MHz modulated as UMTS and (4) UMTS at 2140 MHz including all control features in a randomized, double blinded cross-over design. Each exposure lasted 45 min. During exposure the participants performed different cognitive tasks with the Trail Making B (TMB) test as the main outcome and completed a questionnaire measuring self reported subjective symptoms. No statistically significant differences between the UMTS and sham conditions were found for performance on TMB. For the adults, the estimated difference between UMTS and sham was -3.2% (-9.2%; 2.9%) and for the adolescents 5.5% (-1.1%; 12.2%). No significant changes were found in any of the cognitive tasks. An increase in 'headache rating' was observed when data from the adolescents and adults were combined (P = 0.027), an effect

that may be due to differences at baseline. In conclusion, the primary hypothesis that UMTS radiation reduces general performance in the TMB test was not confirmed. However, we suggest that the hypothesis of subjective symptoms and EMF exposure needs further research.

(E) Roggeveen S, van Os J, Viechtbauer W, Lousberg R. EEG Changes Due to Experimentally Induced 3G Mobile Phone Radiation. PLoS One. 2015a Jun 8;10(6):e0129496. doi: 10.1371/journal.pone.0129496. (HU, EE)

The aim of this study was to investigate whether a 15-minute placement of a 3G dialing mobile phone causes direct changes in EEG activity compared to the placement of a sham phone. Furthermore, it was investigated whether placement of the mobile phone on the ear or the heart would result in different outcomes. Thirty-one healthy females participated. All subjects were measured twice: on one of the two days the mobile phone was attached to the ear, the other day to the chest. In this single-blind, cross-over design, assessments in the sham phone condition were conducted directly preceding and following the mobile phone exposure. During each assessment, EEG activity and radiofrequency radiation were recorded jointly. Delta, theta, alpha, slow beta, fast beta, and gamma activity was computed. The association between radiation exposure and the EEG was tested using multilevel random regression analyses with radiation as predictor of main interest. Significant radiation effects were found for the alpha, slow beta, fast beta, and gamma bands. When analyzed separately, ear location of the phone was associated with significant results, while chest placement was not. The results support the notion that EEG alterations are associated with mobile phone usage and that the effect is dependent on site of placement. Further studies are required to demonstrate the physiological relevance of these findings.

(E) Roggeveen S, van Os J, Lousberg R. Does the Brain Detect 3G Mobile Phone Radiation Peaks? An Explorative In-Depth Analysis of an Experimental Study. PLoS One. 2015b May 11;10(5):e0125390. doi: 10.1371/journal.pone.0125390. eCollection 2015. (HU, EE)

This study aimed to investigate whether third generation mobile phone radiation peaks result in event related potentials. Thirty-one healthy females participated. In this single-blind, cross-over design, a 15 minute mobile phone exposure was compared to two 15 minute sham phone conditions, one preceding and one following the exposure condition. Each participant was measured on two separate days, where mobile phone placement was varied between the ear and heart. EEG activity and radiofrequency radiation were recorded jointly. Epochs of 1200ms, starting 200ms before and lasting until 1000ms after the onset of a radiation peak, were extracted from the exposure condition. Control epochs were randomly selected from the two sham phone conditions. The main a-priori hypothesis to be tested concerned an increase of the area in the 240-500ms post-stimulus interval, in the exposure session with ear-placement. Using multilevel regression analyses the placement*exposure interaction effect was significant for the frontal and central cortical regions, indicating that only in the mobile phone exposure with ear-placement an enlarged cortical reactivity was found. Post-hoc analyses based on visual inspection of the ERPs showed a second significantly increased area between 500-1000ms post-stimulus for almost every EEG location measured. It was concluded that, when a dialing mobile

phone is placed on the ear, its radiation, although unconsciously, is electrically detected by the brain. The question of whether or not this cortical reactivity results in a negative health outcome has to be answered in future longitudinal experiments.

(NE) Roser K, Schoeni A, Rösli M. Mobile phone use, behavioural problems and concentration capacity in adolescents: A prospective study. Int J Hyg Environ Health.; 219(8):759-769, 2016. (HU, BE)

The aim of this study is to prospectively investigate whether exposure to radiofrequency electromagnetic fields (RF-EMF) emitted by mobile phones and other wireless communication devices is related to behavioural problems or concentration capacity in adolescents. The HERMES (Health Effects Related to Mobile phone use in adolescentS) study sample consisted of 439 Swiss adolescents aged 12-17 years. Behavioural problems were assessed using the Strengths and Difficulties Questionnaire (SDQ), concentration capacity of the adolescents was measured by means of a standardized computerized cognitive test named FAKT. Cross-sectional and longitudinal (1 year of follow-up) analyses were performed to investigate possible associations between behavioural problems and concentration capacity and different exposure measures: self-reported and operator-recorded wireless communication device use, cumulative RF-EMF brain and whole body dose and measured personal RF-EMF exposure. In the cross-sectional analyses behavioural problems were associated with several self-reported wireless device use measures but not operator-recorded mobile phone use measures, concentration capacity was associated with several self-reported and operator-recorded exposures. The longitudinal analyses point towards absence of associations. The lack of consistent exposure-response patterns in the longitudinal analyses suggests that behavioural problems and concentration capacity are not affected by the use of wireless communication devices or RF-EMF exposure. Information bias and reverse causality are likely explanations for the observed cross-sectional findings.

(E) Şahin A, Aslan A, Baş O, İkinci A, Özyılmaz C, Fikret Sönmez O, Çolakoğlu S, Odacı E. Deleterious impacts of a 900MHz electromagnetic field on hippocampal pyramidal neurons of 8-week-old Sprague Dawley male rats. Brain Res. 2015 Jul 31. pii: S0006-8993(15)00586-7. doi: 10.1016/j.brainres.2015.07.042. [Epub ahead of print] (AS, CE, ME)

Children are at potential risk due to their intense use of mobile phones. We examined 8-week-old rats because that age is comparable with the preadolescent period in humans. The numbers of pyramidal neurons in the cornu ammonis of the Sprague Dawley male rat (8-weeks old, weighing 180-250g) hippocampus following exposure to a 900MHz (MHz) electromagnetic field (EMF) were examined. The study consisted of control (CN-G), sham exposed (SHM-EG) and EMF exposed (EMF-EG) groups, 6 rats in each. The EMF-EG rats were exposed to 900MHz EMF (1h/day for 30 days) in an EMF jar. The SHM-EG rats were placed in the EMF jar but not exposed to EMF (1h/day for 30 days). The CN-G rats were not placed into the exposure jar and were not exposed to EMF during the study period. All animals were sacrificed at the end of the experiment, and their brains were removed for histopathological and stereological analysis. The number of pyramidal neurons in the cornu ammonis of the hippocampus was estimated on Cresyl violet stained sections of the brain using the optical dissector counting technique.

Histopathological evaluations were also performed on these sections. Histopathological observation showed abundant cells with abnormal, black or dark blue cytoplasm and shrunken morphology among the normal pyramidal neurons. The largest lateral ventricles were observed in the EMF-EG sections compared to those from the other groups. Stereological analyses showed that the total number of pyramidal neurons in the cornu ammonis of the EMF-EG rats was significantly lower than those in CN-G ($p < 0.05$) and SHM-EG ($p < 0.05$). In conclusion, our results suggest that pyramidal neuron loss and histopathological changes in the cornu ammonis of 8-week-old male rats may be due to 900MHz EMF exposure.

(E) Saikhedkar N, Bhatnagar M, Jain A, Sukhwai P, Sharma C, Jaiswal N. Effects of mobile phone radiation (900 MHz radiofrequency) on structure and functions of rat brain. Neurol Res. 2014 May 26:1743132814Y0000000392. [Epub ahead of print] (AS, CE, BE, CC, OX)

Objectives: The goals of this study were: (1) to obtain basic information about the effects of long-term use of mobile phone on cytological makeup of the hippocampus in rat brain (2) to evaluate the effects on antioxidant status, and (3) to evaluate the effects on cognitive behavior particularly on learning and memory. Methods: Rats (age 30 days, 120 ± 5 g) were exposed to 900 MHz radio waves by means of a mobile hand set for 4 hours per day for 15 days. Effects on anxiety, spatial learning, and memory were studied using open field test, elevated plus maze, Morris water maze (MWM), and classic maze test. Effects on brain antioxidant status were also studied. Cresyl violet staining was done to assess the neuronal damage. Result: A significant change in behavior, i.e., more anxiety and poor learning was shown by test animals as compared to controls and sham group. A significant change in level of antioxidant enzymes and non-enzymatic antioxidants, and increase in lipid peroxidation were observed in test rats. Histological examination showed neurodegenerative cells in hippocampal sub regions and cerebral cortex. Discussion: Thus our findings indicate extensive neurodegeneration on exposure to radio waves. Increased production of reactive oxygen species due to exhaustion of enzymatic and non-enzymatic antioxidants and increased lipid peroxidation are indicating extensive neurodegeneration in selective areas of CA1, CA3, DG, and cerebral cortex. This extensive neuronal damage results in alterations in behavior related to memory and learning.

(NE) Sakurai T, Kiyokawa T, Narita E, Suzuki Y, Taki M, Miyakoshi J. Analysis of gene expression in a human-derived glial cell line exposed to 2.45 GHz continuous radiofrequency electromagnetic fields. J Radiat Res. 52(2):185-192, 2011. (CS, CH)

The increasing use of mobile phones has aroused public concern regarding the potential health risks of radiofrequency (RF) fields. We investigated the effects of exposure to RF fields (2.45 GHz, continuous wave) at specific absorption rate (SAR) of 1, 5, and 10 W/kg for 1, 4, and 24 h on gene expression in a normal human glial cell line, SVGp12, using DNA microarray. Microarray analysis revealed 23 assigned gene spots and 5 non-assigned gene spots as prospective altered gene spots. Twenty-two genes out of the 23 assigned gene spots were further analyzed by reverse transcription-polymerase chain reaction to validate the results of microarray, and no significant alterations in gene expression were observed. Under the experimental conditions

used in this study, we found no evidence that exposure to RF fields affected gene expression in SVGp12 cells.

(NE) Salunke BP, Umathe SN, Chavan JG. Behavioral in-effectiveness of high frequency electromagnetic field in mice. *Physiol Behav.* 140:32-37, 2015. (AS, CE, BE)

The present investigation was carried out with an objective to study the influence of high frequency electromagnetic field (HF-EMF) on anxiety, obsessive compulsive disorder (OCD) and depression-like behavior. For exposure to HF-EMF, non-magnetic material was used to fabricate the housing. Mice were exposed to HF-EMF (2.45 GHz), 60 min/day for 7 or 30 or 60 or 90 or 120 days. The exposure was carried out by switching-on inbuilt class-I BLUETOOTH device that operates on 2.45 GHz frequency in file transfer mode at a peak density of 100mW. Mice were subjected to the assessment of anxiety, OCD and depression-like behavior for 7 or 30 or 60 or 90 or 120days of exposure. The anxiety-like behavior was assessed by elevated plus maze, open field test and social interaction test. OCD-like behavior was assessed by marble burying behavior, whereas depression-like behavior was assessed by forced swim test and tail suspension test. The present experiment demonstrates that up to 120days of exposure to HF-EMF does not produce anxiety, OCD and depression-like behavior in mice.

(E) Sarapultseva EI, Igolkina JV, Tikhonov VN, Dubrova YE. THE IN VIVO EFFECTS OF LOW-INTENSITY RADIOFREQUENCY FIELDS ON THE MOTOR ACTIVITY OF PROTOZOA. *Int J Radiat Biol.* 2013 Nov 25. [Epub ahead of print] (AS, BE, LI)

Purpose: To analyze the direct and transgenerational effects of exposure to low-dose 1 GHz (mobile phone/wireless telecommunication range) and 10 GHz (radar/satellite communication range) radiofrequency electromagnetic fields (RF-EMF) on the motility of ciliates *Spirostomum ambiguum*. Materials and Methods: *S. ambiguum* were exposed to 1 GHz and 10 GHz RF-EMF with power flux densities (PD) ranging from 0.05 to 0.5 W/m² over a period of time from 0.05 to 10 h. The motility of directly exposed ciliates and their non-exposed progeny across 10-15 generations was measured. Results: Exposure to 0.1 W/m² of either 1 or 10 GHz RF-EMF resulted in a significant decrease in the motility. The dose of exposure capable of altering the mobility of ciliates was inversely correlated with the flux density of RF-EMF. The motility of the non-exposed progeny of ciliates irradiated with 0.1 W/m² of 10 GHz RF-EMF remained significantly compromised, at least, across 10-15 generations, thus indicating the presence of transgenerational effects. Conclusions: The results of our study show that low-dose exposure to RF-EMF can significantly affect the motility of irradiated ciliates and their non-exposed offspring, thus providing further insights into the unknown mechanisms underlying the in vivo effects of RF-EMF.

(NE) Sauter C, Dorn H, Bahr A, Hansen ML, Peter A, Bajbouj M, Danker-Hopfe H. Effects of exposure to electromagnetic fields emitted by GSM 900 and WCDMA mobile phones on cognitive function in young male subjects. *Bioelectromagnetics.* 32(3):179-190, 2011. (HU, BE)

Results of studies on the possible effects of electromagnetic fields emitted by mobile phones on cognitive functions are contradictory, therefore, possible effects of long-term (7 h 15 min) electromagnetic field (EMF) exposure to handset-like signals of Global System for Mobile Communications (GSM) 900 and Wideband Code-Division Multiple Access (WCDMA) on attention and working memory were studied. The sample comprised 30 healthy male subjects (mean \pm SD: 25.3 \pm 2.6 years), who were tested on nine study days in which they were exposed to three exposure conditions (sham, GSM 900 and WCDMA) in a randomly assigned and balanced order. All tests were presented twice (morning and afternoon) on each study day within a fixed timeframe. Univariate comparisons revealed significant changes when subjects were exposed to GSM 900 compared to sham, only in the vigilance test. In the WCDMA exposure condition, one parameter in the vigilance and one in the test on divided attention were altered compared to sham. Performance in the selective attention test and the n-back task was not affected by GSM 900 or WCDMA exposure. Time-of-day effects were evident for the tests on divided and selective attention, as well as for working memory. After correction for multiple testing, only time-of-day effects remained significant in two tests, resulting in faster reactions in the afternoon trials. The results of the present study do not provide any evidence of an EMF effect on human cognition, but they underline the necessity to control for time of day.

(NE) Sauter C, Eggert T, Dorn H, Schmid G, Bolz T, Marasanov A, Hansen ML, Peter A, Danker-Hopfe H. Do signals of a hand-held TETRA transmitter affect cognitive performance, well-being, mood or somatic complaints in healthy young men? Results of a randomized double-blind cross-over provocation study. Environ Res. 140:85-94, 2015. (HU, BE)

BACKGROUND: TETRA (terrestrial trunked radio) is a digital radio communication standard, which has been implemented in several European countries and is used by public executives, transportation services, and by private companies. Studies on possible impacts on the users' health considering different exposure conditions are missing. OBJECTIVES: To investigate possible acute effects of electromagnetic fields (EMF) of two different levels of TETRA hand-held transmitter signals on cognitive function and well-being in healthy young males. METHODS: In the present double-blind cross-over study possible effects of short-term (2.5h) EMF exposure of handset-like signals of TETRA (385MHz) were studied in 30 healthy male participants (mean \pm SD: 25.4 \pm 2.6 years). Individuals were tested on nine study days, on which they were exposed to three different exposure conditions (Sham, TETRA 1.5W/kg and TETRA 6.0W/kg) in a randomly assigned and balanced order. Participants were tested in the afternoon at a fixed timeframe. RESULTS: Attention remained unchanged in two out of three tasks. In the working memory significant changes were observed in two out of four subtasks. Significant results were found in 5 out of 35 tested parameters, four of them led to an improvement in performance. Mood, well-being and subjective somatic complaints were not affected by TETRA exposure. CONCLUSIONS: The results of the present study do not indicate a negative impact of a short-term EMF-effect of TETRA on cognitive function and well-being in healthy young men.

(E) Schmid MR, Loughran SP, Regel SJ, Murbach M, Bratic Grunauer A, Rusterholz T, Bersagliere A, Kuster N, Achermann P. Sleep EEG alterations: effects of different pulse-modulated radio frequency electromagnetic fields. J Sleep Res. 21(1):50-58, 2012a. (HU, EE, BE, SL, WS)

Previous studies have observed increases in electroencephalographic power during sleep in the spindle frequency range (approximately 11-15 Hz) after exposure to mobile phone-like radio frequency electromagnetic fields (RF EMF). Results also suggest that pulse modulation of the signal is crucial to induce these effects. Nevertheless, it remains unclear which specific elements of the field are responsible for the observed changes. We investigated whether pulse-modulation frequency components in the range of sleep spindles may be involved in mediating these effects. Thirty young healthy men were exposed, at weekly intervals, to three different conditions for 30 min directly prior to an 8-h sleep period. Exposure consisted of a 900-MHz RF EMF, pulse modulated at 14 Hz or 217 Hz, and a sham control condition. Both active conditions had a peak spatial specific absorption rate of 2 W kg^{-1} . During exposure subjects performed three different cognitive tasks (measuring attention, reaction speed and working memory), which were presented in a fixed order. Electroencephalographic power in the spindle frequency range was increased during non-rapid eye movement sleep (2nd episode) following the 14-Hz pulse-modulated condition. A similar but non-significant increase was also observed following the 217-Hz pulse-modulated condition. Importantly, this exposure-induced effect showed considerable individual variability. Regarding cognitive performance, no clear exposure-related effects were seen. Consistent with previous findings, our results provide further evidence that pulse-modulated RF EMF alter brain physiology, although the time-course of the effect remains variable across studies. Additionally, we demonstrated that modulation frequency components within a physiological range may be sufficient to induce these effects.

(E) Schmid MR, Murbach M, Lustenberger C, Maire M, Kuster N, Achermann P, Loughran SP. Sleep EEG alterations: effects of pulsed magnetic fields versus pulse-modulated radio frequency electromagnetic fields. J Sleep Res. 21(6):620-629, 2012b. (HU, EE, SL)

Studies have repeatedly shown that electroencephalographic power during sleep is enhanced in the spindle frequency range following radio frequency electromagnetic field exposures pulse-modulated with fundamental frequency components of 2, 8, 14 or 217 Hz and combinations of these. However, signals used in previous studies also had significant harmonic components above 20 Hz. The current study aimed: (i) to determine if modulation components above 20 Hz, in combination with radio frequency, are necessary to alter the electroencephalogram; and (ii) to test the demodulation hypothesis, if the same effects occur after magnetic field exposure with the same pulse sequence used in the pulse-modulated radio frequency exposure. In a randomized double-blind crossover design, 25 young healthy men were exposed at weekly intervals to three different conditions for 30 min before sleep. Cognitive tasks were also performed during exposure. The conditions were a 2-Hz pulse-modulated radio frequency field, a 2-Hz pulsed magnetic field, and sham. Radio frequency exposure increased electroencephalogram power in the spindle frequency range. Furthermore, delta and theta activity (non-rapid eye movement sleep), and alpha and delta activity (rapid eye movement

sleep) were affected following both exposure conditions. No effect on sleep architecture and no clear impact of exposure on cognition was observed. These results demonstrate that both pulse-modulated radio frequency and pulsed magnetic fields affect brain physiology, and the presence of significant frequency components above 20 Hz are not fundamental for these effects to occur. Because responses were not identical for all exposures, the study does not support the hypothesis that effects of radio frequency exposure are based on demodulation of the signal only.

(E) Schneider J, Stangassinger M. Nonthermal Effects of Lifelong High-Frequency Electromagnetic Field Exposure on Social Memory Performance in Rats. Behav Neurosci. 2014 Jul 7. [Epub ahead of print] (AS, CE, BE, WS)

We are today surrounded almost constantly by high-frequency electromagnetic fields (EMFs) from mobile communications base stations. To date, however, there has been little concern regarding nonthermal effects of EMFs on cognition. In the present study, male and female rats were subjected to continuous far-field exposure to a frequency of 900-MHz (Global System for Mobile Communications [GSM]) or 1.966-GHz (Universal Mobile Telecommunications System [UMTS]) at 0.4 W/kg. Memory performance of adult EMF-exposed and sham-exposed female rats (at 6 months of age) and male rats (at 3 and 6 months of age) was tested using a social discrimination procedure. For this procedure, a target juvenile male was introduced to the subject's home cage for 4 min (Trial 1). After 30 min, the same target animal and a novel juvenile male were simultaneously presented to the subject for 4 min (Trial 2). Differences in sniffing duration to the familiar and novel target rats during Trial 2 were used to assess memory performance. EMF-exposed females exhibited no differences in sniffing duration compared with controls. In contrast, the sniffing durations of EMF-exposed males at 3 months of age were significantly affected. At 6 months of age, GSM-, but not UMTS-, exposed male adults showed a memory performance deficit. These findings provide new insight into the nonthermal effects of long-term high-frequency EMF exposure on memory.

(E) Schoeni A, Roser K, Rösli M. Memory performance, wireless communication and exposure to radiofrequency electromagnetic fields: A prospective cohort study in adolescents. Environ Int. 85:343-351, 2015. (HU, CE, BE)

BACKGROUND: The aim of this study is to investigate whether memory performance in adolescents is affected by radiofrequency electromagnetic fields (RF-EMF) from wireless device use or by the wireless device use itself due to non-radiation related factors in that context.

METHODS: We conducted a prospective cohort study with 439 adolescents. Verbal and figural memory tasks at baseline and after one year were completed using a standardized, computerized cognitive test battery. Use of wireless devices was inquired by questionnaire and operator recorded mobile phone use data was obtained for a subgroup of 234 adolescents. RF-EMF dose measures considering various factors affecting RF-EMF exposure were computed for the brain and the whole body. Data were analysed using a longitudinal approach, to investigate whether cumulative exposure over one year was related to changes in memory performance. All analyses were adjusted for relevant confounders.

RESULTS: The kappa coefficients between cumulative mobile phone call duration and RF-EMF brain and whole body dose were 0.62 and 0.67, respectively for the whole sample and 0.48 and 0.28, respectively for the sample with operator data. In linear exposure-response models an interquartile increase in cumulative operator recorded mobile phone call duration was associated with a decrease in figural memory performance score by -0.15 (95% CI: -0.33, 0.03) units. For cumulative RF-EMF brain and whole body dose corresponding decreases in figural memory scores were -0.26 (95% CI: -0.42, -0.10) and -0.40 (95% CI: -0.79, -0.01), respectively. No exposure-response associations were observed for sending text messages and duration of gaming, which produces tiny RF-EMF emissions.

CONCLUSIONS: A change in memory performance over one year was negatively associated with cumulative duration of wireless phone use and more strongly with RF-EMF dose. This may indicate that RF-EMF exposure affects memory performance.

(E) Seckin E, Suren Basar F, Atmaca S, Kaymaz FF, Suzer A, Akar A, Sunan E, Koyuncu M. The effect of radiofrequency radiation generated by a Global System for Mobile Communications source on cochlear development in a rat model. *J Laryngol Otol.* 2014 May 1:1-6. [Epub ahead of print] **(AS, CE, CC, DE)**

Objective: This study aimed to determine the effect of radiofrequency radiation generated by 900 and 1800 MHz Global System for Mobile Communications sources on cochlear development in the rat model. **Methods:** Eight pregnant albino Wistar rats were divided into three groups: control, 900 MHz and 1800 MHz. The latter two groups of pregnant rats were exposed to radiofrequency radiation for 1 hour per day starting on the 12th day of pregnancy until delivery. The rats in the control, 900 MHz and 1800 MHz groups gave birth to 24, 31 and 26 newborn rats respectively. Newborn rats in the 900 MHz and 1800 MHz groups were exposed to radiofrequency radiation for 1 hour per day for 21 days after delivery. Hearing evaluations of newborn rats were carried out using distortion product otoacoustic emissions testing. Eight newborn rats were randomly selected from each group for electron microscopic evaluation. **Results:** Distortion product otoacoustic emission tests revealed no significant difference among the groups, but electron microscopic evaluation revealed significant

differences among the groups with regard to the number of normal, apoptotic and necrotic cells. Conclusion: The findings indicated cellular structural damage in the cochlea caused by radiofrequency radiation exposure during cochlear development in the rat model.

(E) Sharma A, Sisodia R, Bhatnagar D, Saxena VK. Spatial memory and learning performance and its relationship to protein synthesis of Swiss albino mice exposed to 10 GHz microwaves. Int J Radiat Biol. 2013 Aug 19. [Epub ahead of print] (AS, CE, BE, CH)

Purpose: To study the possible role of microwave (MW) exposure on spatial memory of Swiss albino mice and its relationship to protein concentration in whole brain. Materials and methods: Mice were exposed to 10 GHz (Giga Hertz) microwaves with the power density of 0.25 mW/cm^2 (milliwatt per centimeter square) with average whole body specific absorption rate (SAR) 0.1790 W/kg daily for 2 hours per day (h/day) for 30 days. After exposure mice were tested for spatial memory performance using Morris water maze test (MWT). For this purpose mice (6-8 weeks old) were divided into two groups (i) sham exposed and, (ii) microwaves exposed. After initial training for two days, MWT was performed for another 6 days. Protein was estimated 48 hours after exposure and immediately after completion of MWT. Results: Both sham exposed and microwave exposed animals showed a significant decrease in escape time with training. Microwave exposed animals had statistically significant higher mean latency to reach the target quadrant compared to sham exposed. A concurrent decrease in protein levels was estimated in whole brain of the exposed mice compared to sham exposed mice. Conclusions: It can be concluded from the current study that exposure to microwave radiation caused decrements in the ability of mice to learn the special memory task, this may be due to simultaneous decrease in protein levels in the brain of mice.

(E) Sharma A, Kesari KK, Saxena VK, Sisodia R. Ten gigahertz microwave radiation impairs spatial memory, enzymes activity, and histopathology of developing mice brain. Mol Cell Biochem. 2017 May 3. doi: 10.1007/s11010-017-3051-8. [Epub ahead of print] (AS, CE, BE, ME, OX)

For decades, there has been an increasing concern about the potential hazards of non-ionizing electromagnetic fields that are present in the environment and alarming as a major pollutant or electro-pollutant for health risk and neuronal diseases. Therefore, the objective of the present study was to explore the effects of 10 GHz microwave radiation on developing mice brain. Two weeks old mice were selected and divided into two groups (i) sham-exposed and (ii) microwave-exposed groups. Animals were exposed for 2 h/day for 15 consecutive days. After the completion of exposure, within an hour, half of the animals were autopsied immediately and others were allowed to attain 6 weeks of age for the follow-up study. Thereafter results were recorded in terms of various biochemical, behavioral, and histopathological parameters. Body weight result showed significant changes immediately after treatment, whereas non-significant changes were observed in mice attaining 6 weeks of age. Several other endpoints like brain weight, lipid peroxidation, glutathione, protein, catalase, and superoxide dismutase were also found significantly ($p < 0.05$) altered in mice whole brain. These significant differences were found immediately after exposure and also in follow-up on attaining 6 weeks of age in

microwave exposure group. Moreover, statistically significant ($p < 0.001$) effect was investigated in spatial memory of the animals, in learning to locate the position of platform in Morris water maze test. Although in probe trial test, sham-exposed animals spent more time in searching for platform into the target quadrant than in opposite or other quadrants. Significant alteration in histopathological parameters (qualitative and quantitative) was also observed in CA1 region of the hippocampus, cerebral cortex, and ansiform lobule of cerebellum. Results from the present study concludes that the brain of 2 weeks aged mice was very sensitive to microwave exposure as observed immediately after exposure and during follow-up study at 6 weeks of age.

(E) Shehu A, Mohammed A, Magaji RA, Muhammad MS. Exposure to mobile phone electromagnetic field radiation, ringtone and vibration affects anxiety-like behaviour and oxidative stress biomarkers in albino wistar rats. Metab Brain Dis. 2015 Nov 7. [Epub ahead of print] (AS, CE, BE, OX)

Research on the effects of Mobile phone radio frequency emissions on biological systems has been focused on noise and vibrations as auditory stressors. This study investigated the potential effects of exposure to mobile phone electromagnetic field radiation, ringtone and vibration on anxiety-like behaviour and oxidative stress biomarkers in albino wistar rats. Twenty five male wistar rats were randomly divided into five groups of 5 animals each: group I: exposed to mobile phone in switched off mode (control), group II: exposed to mobile phone in silent mode, group III: exposed to mobile phone in vibration mode, group IV: exposed to mobile phone in ringtone mode, group V: exposed to mobile phone in vibration and ringtone mode. The animals in group II to V were exposed to 10 min call (30 missed calls for 20 s each) per day for 4 weeks. Neurobehavioural studies for assessing anxiety were carried out 24 h after the last exposure and the animals were sacrificed. Brain samples were collected for biochemical evaluation immediately. Results obtained showed a significant decrease ($P < 0.05$) in open arm duration in all the experimental groups when compared to the control. A significant decrease ($P < 0.05$) was also observed in catalase activity in group IV and V when compared to the control. In conclusion, the results of the present study indicates that 4 weeks exposure to electromagnetic radiation, vibration, ringtone or both produced a significant effect on anxiety-like behavior and oxidative stress in young wistar rats.

(NE) Shirai T, Imai N, Wang J, Takahashi S, Kawabe M, Wake K, Kawai H, Watanabe S-I, Furukawa F, Fujiwara O. Multigenerational effects of whole body exposure to 2.14 GHz W-CDMA cellular phone signals on brain function in rats. Bioelectromagnetics. 35(7):497-511, 2014. (AS, CE, BE, ME)

The present experimental study was carried out with rats to evaluate the effects of whole body exposure to 2.14 GHz band code division multiple access (W-CDMA) signals for 20 h a day, over three generations. The average specific absorption rate (SAR, in unit of W/kg) for dams was designed at three levels: high (<0.24 W/kg), low (<0.08 W/kg), and 0 (sham exposure). Pregnant mothers (4 rats/group) were exposed from gestational day (GD) 7 to weaning and then their

offspring (F₁ generation, 4 males and 4 females/dam, respectively) were continuously exposed until 6 weeks of age. The F₁ females were mated with F₁ males at 11 weeks old, and then starting from GD 7, they were exposed continuously to the electromagnetic field (EMF; one half of the F₁ offspring was used for mating, that is, two of each sex per dam and 8 males and 8 females/group, except for all offspring for the functional development tests). This protocol was repeated in the same manner on pregnant F₂ females and F₃ pups; the latter were killed at 10 weeks of age. No abnormalities were observed in the mother rats (F₀, F₁, and F₂) and in the offspring (F₁, F₂, and F₃) in any biological parameters, including neurobehavioral function. Thus, it was concluded that under the experimental conditions applied, multigenerational whole body exposure to 2.14 GHz W-CDMA signals for 20 h/day did not cause any adverse effects on the F₁, F₂, and F₃ offspring.

(E) Sirav B, Seyhan N. Blood-brain barrier disruption by continuous-wave radio frequency radiation. *Electromagn Biol Med.* 28:215-222, 2009. (AS, ME)

The increasing use of cellular phones and the increasing number of associated base stations are becoming a widespread source of non ionizing electromagnetic radiation. Some biological effects are likely to occur even at low-level EM fields. This study was designed to investigate the effects of 900 and 1,800 MHz Continuous Wave Radio Frequency Radiation (CW RFR) on the permeability of Blood Brain Barrier (BBB) of rats. Results have shown that 20 min RFR exposure of 900 and 1,800 MHz induces an effect and increases the permeability of BBB of male rats. There was no change in female rats. The scientific evidence on RFR safety or harm remains inconclusive. More studies are needed to demonstrate the effects of RFR on the permeability of BBB and the mechanisms of that breakdown.

(E) Sirav B, Seyhan N. Effects of radiofrequency radiation exposure on blood-brain barrier permeability in male and female rats. *Electromagn Biol Med.* 30(4):253-260, 2011. (AS, ME)

During the last several decades, numerous studies have been performed aiming at the question of whether or not exposure to radiofrequency radiation (RFR) influences the permeability of the blood-brain barrier (BBB). The objective of this study was to investigate the effect of RFR on the permeability of BBB in male and female Wistar albino rats. Right brain, left brain, cerebellum, and total brain were analyzed separately in the study. Rats were exposed to 0.9 and 1.8 GHz continuous-wave (CW) RFR for 20 min (at SARs of 4.26 mW/kg and 1.46 mW/kg, respectively) while under anesthesia. Control rats were sham-exposed. Disruption of BBB integrity was detected spectrophotometrically using the Evans-blue dye, which has been used as a BBB tracer and is known to be bound to serum albumin. Right brain, left brain, cerebellum, and total brain were evaluated for BBB permeability. In female rats, no albumin extravasation was found in the brain after RFR exposure. A significant increase in albumin was found in the brains of the RF-exposed male rats when compared to sham-exposed male brains. These results suggest that exposure to 0.9 and 1.8 GHz CW RFR at levels below the international limits can affect the vascular permeability in the brain of male rats. The possible risk of RFR exposure in humans is a major concern for the society. Thus, this topic should be investigated more thoroughly in the future.

(E) Sirav B, Seyhan N. Effects of GSM modulated radio-frequency electromagnetic radiation on permeability of blood-brain barrier in male & female rats. J Chem Neuroanat. 75(Pt B):123-127, 2016. (AS, ME)

With the increased use of mobile phones, their biological and health effects have become more important. Usage of mobile phones near the head increases the possibility of effects on brain tissue. This study was designed to investigate the possible effects of pulse modulated 900MHz and 1800MHz radio-frequency radiation on the permeability of blood-brain barrier of rats. Study was performed with 6 groups of young adult male and female wistar albino rats. The permeability of blood-brain barrier to intravenously injected evans blue dye was quantitatively examined for both control and radio-frequency radiation exposed groups. For male groups; Evans blue content in the whole brain was found to be $0.08 \pm 0.01 \text{ mg\%}$ in the control, $0.13 \pm 0.03 \text{ mg\%}$ in 900MHz exposed and $0.26 \pm 0.05 \text{ mg\%}$ in 1800MHz exposed animals. In both male radio-frequency radiation exposed groups, the permeability of blood-brain barrier found to be increased with respect to the controls ($p < 0.01$). 1800MHz pulse modulated radio-frequency radiation exposure was found more effective on the male animals ($p < 0.01$). For female groups; dye contents in the whole brains were $0.14 \pm 0.01 \text{ mg\%}$ in the control, $0.24 \pm 0.03 \text{ mg\%}$ in 900MHz exposed and $0.14 \pm 0.02 \text{ mg\%}$ in 1800MHz exposed animals. No statistical variance found between the control and 1800MHz exposed animals ($p > 0.01$). However 900MHz pulse modulated radio-frequency exposure was found effective on the permeability of blood-brain barrier of female animals. Results have shown that 20min pulse modulated radio-frequency radiation exposure of 900MHz and 1800MHz induces an effect and increases the permeability of blood-brain barrier of male rats. For females, 900MHz was found effective and it could be concluded that this result may due to the physiological differences between female and male animals. The results of this study suggest that mobile phone radiation could lead to increase the permeability of blood-brain barrier under non-thermal exposure levels. More studies are needed to demonstrate the mechanisms of that breakdown.

(E) Söderqvist F, Carlberg M, Hardell L. Mobile and cordless telephones, serum transthyretin and the blood-cerebrospinal fluid barrier: a cross-sectional study. Environ Health. 21; 8:19, 2009. (HU, PE)

BACKGROUND: Whether low-intensity radiofrequency radiation damages the blood-brain barrier has long been debated, but little or no consideration has been given to the blood-cerebrospinal fluid barrier. In this cross-sectional study we tested whether long-term and/or short-term use of wireless telephones was associated with changes in the serum transthyretin level, indicating altered transthyretin concentration in the cerebrospinal fluid, possibly reflecting an effect of radiation. **METHODS:** One thousand subjects, 500 of each sex aged 18-65 years, were randomly recruited using the population registry. Data on wireless telephone use were assessed by a postal questionnaire and blood samples were analyzed for serum transthyretin concentrations determined by standard immunonephelometric techniques on a BN Prospec instrument. **RESULTS:** The response rate was 31.4%. Logistic regression of dichotomized TTR serum levels with a cut-point of 0.31 g/l on wireless telephone use yielded increased odds ratios that were statistically not significant. Linear regression of time since first use overall and on the day that blood was withdrawn gave different results for males and females: for men significantly higher serum concentrations of TTR were seen the longer an analogue telephone or a mobile and cordless desktop telephone combined had been used, and in contrast, significantly lower serum levels were seen the longer an UMTS telephone had been

used. Adjustment for fractions of use of the different telephone types did not modify the effect for cumulative use or years since first use for mobile telephone and DECT, combined. For women, linear regression gave a significant association for short-term use of mobile and cordless telephones combined, indicating that the sooner blood was withdrawn after the most recent telephone call, the higher the expected transthyretin concentration. **CONCLUSION:** In this hypothesis-generating descriptive study time since first use of mobile telephones and DECT combined was significantly associated with higher TTR levels regardless of how much each telephone type had been used. Regarding short-term use, significantly higher TTR concentrations were seen in women the sooner blood was withdrawn after the most recent telephone call on that day.

(E) Söderqvist F, Carlberg M, Hansson Mild K, Hardell L. Exposure to an 890-MHz mobile phone-like signal and serum levels of S100B and transthyretin in volunteers. Toxicol Lett. 189(1):63-66, 2009. (HU, PE)

Whether low-intensity non-thermal microwave radiation alters the integrity of the blood-brain barrier has been debated since the late 1970s, yet no experimental study has been carried out on humans. The aim of this study was to test, using peripheral markers, whether exposure to a mobile phone-like signal alters the integrity of the human blood-brain and blood-cerebrospinal fluid barriers. A provocation study was carried out that exposed 41 volunteers to a 30 min GSM 890 MHz signal with an average specific energy absorption rate distribution of 1.0 W/kg in the temporal area of the head as measured over any 1g of contiguous tissue. The outcome was assessed by changes in serum concentrations of two putative markers of brain barrier integrity, S100B and transthyretin. Repeated blood sampling before and after the provocation showed no statistically significant increase in the serum levels of S100B, while for transthyretin a statistically significant increase was seen in the final blood sample 60 min after the end of the provocation as compared to the prior sample taken immediately after provocation (p=0.02). The clinical significance of this finding, if any, is unknown. Further randomized studies with use of additional more brain specific markers are needed.

(NE) Söderqvist F, Carlberg M, Hardell L. Use of wireless telephones and serum S100B levels: a descriptive cross-sectional study among healthy Swedish adults aged 18-65 years. Sci Total Environ. 407(2):798-805, 2009. (HU, PE)

BACKGROUND: Since the late 1970s, experimental animal studies have been carried out on the possible effects of low-intensive radiofrequency fields on the blood-brain barrier (BBB), but no epidemiological study has been published to date. **OBJECTIVE:** Using serum S100B as a putative marker of BBB dysfunction we performed a descriptive cross-sectional study to investigate whether protein levels were higher among frequent than non-frequent users of mobile and cordless desktop phones. **METHOD:** One thousand subjects, 500 of each sex aged 18-65 years, were randomly recruited using the population registry. Data on wireless phone use were assessed by a postal questionnaire and blood samples were analyzed for S100B. **RESULTS:** The response rate was 31.4%. The results from logistic and linear regression analyses were statistically insignificant, with one exception: the linear regression analysis of latency for UMTS

use, which after stratifying on gender remained significant only for men ($p = 0.01$; $n = 31$). A low p -value (0.052) was obtained for use of cordless phone ($n = 98$) prior to giving the blood samples indicating a weak negative association. Total use of mobile and cordless phones over time yielded odds ratio (OR) 0.8 and 95% confidence interval (CI) 0.3-2.0 and use on the same day as giving blood yielded OR=1.1, CI=0.4-2.8. **CONCLUSIONS:** This study failed to show that long- or short-term use of wireless telephones was associated with elevated levels of serum S100B as a marker of BBB integrity. The finding regarding latency of UMTS use may be interesting but it is based on small numbers. Generally, S100B levels were low and to determine whether this association - if causal - is clinically relevant, larger studies with sufficient follow-up are needed.

(E) Söderqvist F, Hardell L, Carlberg M, Mild KH. Radiofrequency fields, transthyretin, and Alzheimer's disease. J Alzheimers Dis. 20(2):599-606, 2010. (HU, PE, MA)

Radiofrequency field (RF) exposure provided cognitive benefits in an animal study. In Alzheimer's disease (AD) mice, exposure reduced brain amyloid-beta (Abeta) deposition through decreased aggregation of Abeta and increase in soluble Abeta levels. Based on our studies on humans on RF from wireless phones, we propose that transthyretin (TTR) might explain the findings. In a cross-sectional study on 313 subjects, we used serum TTR as a marker of cerebrospinal fluid TTR. We found a statistically significantly positive beta coefficient for TTR for time since first use of mobile phones and desktop cordless phones combined ($P=0.03$). The electromagnetic field parameters were similar for the phone types. In a provocation study on 41 persons exposed for 30 min to an 890-MHz GSM signal with specific absorption rate of 1.0 Watt/kg to the temporal area of the brain, we found statistically significantly increased serum TTR 60 min after exposure. In our cross-sectional study, use of oral snuff also yielded statistically significantly increased serum TTR concentrations and nicotine has been associated with decreased risk for AD and to upregulate the TTR gene in choroid plexus but not in the liver, another source of serum TTR. TTR sequesters Abeta, thereby preventing the formation of Abeta plaques in the brain. Studies have shown that patients with AD have lowered TTR concentrations in the cerebrospinal fluid and have attributed the onset of AD to insufficient sequestering of Abeta by TTR. We propose that TTR might be involved in the findings of RF exposure benefit in AD mice.

(E) Sokolovic D, Djindjic B, Nikolic J, Bjelakovic G, Pavlovic D, Kocic G, Krstic D, Cvetkovic T, Pavlovic V. Melatonin reduces oxidative stress induced by chronic exposure of microwave radiation from mobile phones in rat brain. J Radiat Res. 49(6):579-586, 2008. (AS, CE, CH, OX)

PURPOSE: The aim of the study was to evaluate the intensity of oxidative stress in the brain of animals chronically exposed to mobile phones and potential protective effects of melatonin in reducing oxidative stress and brain injury. **MATERIALS AND METHODS:** Experiments were performed on Wistar rats exposed to microwave radiation during 20, 40 and 60 days. Four groups were formed: I group (control)- animals treated by saline, intraperitoneally (i.p.) applied daily during follow up, II group (Mel)- rats treated daily with melatonin (2 mg kg⁻¹ body weight i.p.), III group (MWs)- microwave exposed rats, IV group (MWs + Mel)- MWs exposed

rats treated with melatonin (2 mg kg⁻¹ body weight i.p.). The microwave radiation was produced by a mobile test phone (SAR = 0.043-0.135 W/kg). **RESULTS:** A significant increase in the brain tissue malondialdehyde (MDA) and carbonyl group concentration was registered during exposure. Decreased activity of catalase (CAT) and increased activity of xanthine oxidase (XO) remained after 40 and 60 days of exposure to mobile phones. Melatonin treatment significantly prevented the increase in the MDA content and XO activity in the brain tissue after 40 days of exposure while it was unable to prevent the decrease of CAT activity and increase of carbonyl group contents. **CONCLUSION:** We demonstrated two important findings; that mobile phones caused oxidative damage biochemically by increasing the levels of MDA, carbonyl groups, XO activity and decreasing CAT activity; and that treatment with the melatonin significantly prevented oxidative damage in the brain.

(E) Sokolovic D, Djordjevic B, Kocic G, Babovic P, Ristic G, Stanojkovic Z, Sokolovic DM, Veljkovic A, Jankovic A, Radovanovic Z. The effect of melatonin on body mass and behaviour of rats during an exposure to microwave radiation from mobile phone. Bratisl Lek Listy. 113(5):265-269, 2012. (AS, CE, PE, BE)

BACKGROUND: Microwave radiation (MW) produced by wireless telecommunications and a number of electrical devices used in household or in healthcare institutions may cause various disorders in human organism. On the other hand, melatonin is a potent antioxidant, immunostimulator and neuromodulator. The aim of this research was to determine body mass and behaviour changes in rats after a chronic microwave exposure, as well as to determine the effects of melatonin on body mass and behaviour in irradiated rats. METHODS: Wistar rats were divided into the four experimental groups: I group (control) - rats treated with 0,9 % saline, II group (Mel) - rats treated with melatonin (2 mg/kg), III group (MW) - rats exposed to MW radiation (4 h/day), IV group (MW+Mel) - rats, which were both exposed to MW radiation and received melatonin premedication (2 mg/kg). RESULTS: A significant body mass reduction was noted in animals exposed to MW radiation when compared to controls after 20, 40 and 60 days ($p < 0.001$). Furthermore, body weight was significantly increased ($p < 0.05$) in irradiated rats, which received melatonin pretreatment (MW+Mel) in comparison to irradiated group (MW) after 20 days. Microwave radiation exposed animals showed an anxiety related behaviour (agitation, irritability) after 10 days of exposure. After the radiation source removal, changes in behaviour were less noticeable. Melatonin administration to irradiated rats caused a decrease in the stress induced behaviour. CONCLUSION: Microwave radiation causes body mass decrease and anxiety related behaviour in rats, however melatonin causes a reverse of those effects on both body weight and behaviour of irradiated animals (Fig. 2, Ref. 32).

(E) Sonmez OF, Odaci E, Bas O, Kaplan S. Purkinje cell number decreases in the adult female rat cerebellum following exposure to 900 MHz electromagnetic field. Brain Res. 1356:95-101, 2010. (AS, CE, ME)

The biological effects of electromagnetic field (EMF) exposure from mobile phones have growing concern among scientists since there are some reports showing increased risk for human health, especially in the use of mobile phones for a long duration. In the presented

study, the effects on the number of Purkinje cells in the cerebellum of 16-week (16 weeks) old female rats were investigated following exposure to 900 MHz EMF. Three groups of rats, a control group (CG), sham exposed group (SG) and an electromagnetic field exposed group (EMFG) were used in this study. While EMFG group rats were exposed to 900 MHz EMF (1h/day for 28 days) in an exposure tube, SG was placed in the exposure tube but not exposed to EMF (1h/day for 28 days). The specific energy absorption rate (SAR) varied between 0.016 (whole body) and 2 W/kg (locally in the head). The CG was not placed into the exposure tube nor was it exposed to EMF during the study period. At the end of the experiment, all of the female rats were sacrificed and the number of Purkinje cells was estimated using a stereological counting technique. Histopathological evaluations were also done on sections of the cerebellum. Results showed that the total number of Purkinje cells in the cerebellum of the EMFG was significantly lower than those of CG ($p<0.004$) and SG ($p<0.002$). In addition, there was no significant difference at the 0.05 level between the rats' body and brain weights in the EMFG and CG or SG. Therefore, it is suggested that long duration exposure to 900 MHz EMF leads to decreases of Purkinje cell numbers in the female rat cerebellum.

(E) Spichtig S, Scholkmann F, Chin L, Lehmann H, Wolf M. Assessment of intermittent UMTS electromagnetic field effects on blood circulation in the human auditory region using a near-infrared system. Bioelectromagnetics. 33(1):40-54, 2012. (HU, PE)

The aim of the present study was to assess the potential effects of intermittent Universal Mobile Telecommunications System electromagnetic fields (UMTS-EMF) on blood circulation in the human head (auditory region) using near-infrared spectroscopy (NIRS) on two different timescales: short-term (effects occurring within 80 s) and medium-term (effects occurring within 80 s to 30 min). For the first time, we measured potential immediate effects of UMTS-EMF in real-time without any interference during exposure. Three different exposures (sham, 0.18 W/kg, and 1.8 W/kg) were applied in a controlled, randomized, crossover, and double-blind paradigm on 16 healthy volunteers. In addition to oxy-, deoxy-, and total haemoglobin concentrations ([O(2) Hb], [HHb], and [tHb], respectively), the heart rate (HR), subjective well-being, tiredness, and counting speed were recorded. During exposure to 0.18 W/kg, we found a significant short-term increase in Δ [O(2) Hb] and Δ [tHb], which is small ($\approx 17\%$) compared to a functional brain activation. A significant decrease in the medium-term response of Δ [HHb] at 0.18 and 1.8 W/kg exposures was detected, which is in the range of physiological fluctuations. The medium-term Δ HR was significantly higher (+1.84 bpm) at 1.8 W/kg than for sham exposure. The other parameters showed no significant effects. Our results suggest that intermittent exposure to UMTS-EMF has small short- and medium-term effects on cerebral blood circulation and HR.

(NE) Stefanics G, Kellényi L, Molnár F, Kubinyi G, Thuróczy G, Hernádi I. Short GSM mobile phone exposure does not alter human auditory brainstem response. BMC Public Health. 7:325, 2007. (HU, EE)

BACKGROUND: There are about 1.6 billion GSM cellular phones in use throughout the world today. Numerous papers have reported various biological effects in humans exposed to

electromagnetic fields emitted by mobile phones. The aim of the present study was to advance our understanding of potential adverse effects of the GSM mobile phones on the human hearing system. **METHODS:** Auditory Brainstem Response (ABR) was recorded with three non-polarizing Ag-AgCl scalp electrodes in thirty young and healthy volunteers (age 18-26 years) with normal hearing. ABR data were collected before, and immediately after a 10 minute exposure to 900 MHz pulsed electromagnetic field (EMF) emitted by a commercial Nokia 6310 mobile phone. Fifteen subjects were exposed to genuine EMF and fifteen to sham EMF in a double blind and counterbalanced order. Possible effects of irradiation was analyzed by comparing the latency of ABR waves I, III and V before and after genuine/sham EMF exposure. **RESULTS:** Paired sample t-test was conducted for statistical analysis. Results revealed no significant differences in the latency of ABR waves I, III and V before and after 10 minutes of genuine/sham EMF exposure. **CONCLUSION:** The present results suggest that, in our experimental conditions, a single 10 minute exposure of 900 MHz EMF emitted by a commercial mobile phone does not produce measurable immediate effects in the latency of auditory brainstem waves I, III and V.

(NE) Stefanics G, Thuróczy G, Kellényi L, Hernádi I. Effects of twenty-minute 3G mobile phone irradiation on event related potential components and early gamma synchronization in auditory oddball paradigm. Neuroscience. 157(2):453-462, 2008. (HU, EE)

We investigated the potential effects of 20 min irradiation from a new generation Universal Mobile Telecommunication System (UMTS) 3G mobile phone on human event related potentials (ERPs) in an auditory oddball paradigm. In a double-blind task design, subjects were exposed to either genuine or sham irradiation in two separate sessions. Before and after irradiation subjects were presented with a random series of 50 ms tone burst (frequent standards: 1 kHz, P=0.8, rare deviants: 1.5 kHz, P=0.2) at a mean repetition rate of 1500 ms while electroencephalogram (EEG) was recorded. The subjects' task was to silently count the appearance of targets. The amplitude and latency of the N100, N200, P200 and P300 components for targets and standards were analyzed in 29 subjects. We found no significant effects of electromagnetic field (EMF) irradiation on the amplitude and latency of the above ERP components. In order to study possible effects of EMF on attentional processes, we applied a wavelet-based time-frequency method to analyze the early gamma component of brain responses to auditory stimuli. We found that the early evoked gamma activity was insensitive to UMTS RF exposition. Our results support the notion, that a single 20 min irradiation from new generation 3G mobile phones does not induce measurable changes in latency or amplitude of ERP components or in oscillatory gamma-band activity in an auditory oddball paradigm.

(NE) Stovner LJ, Oftedal G, Straume A, Johnsson A. Nocebo as headache trigger: evidence from a sham-controlled provocation study with RF fields. Acta Neurol Scand Suppl. 188:67-71, 2008. (HU, PE)

BACKGROUND: A large proportion of the population in Norway has experienced headache in connection with mobile phone use, but several double-blind provocation studies with radiofrequency (RF) and sham exposures have shown no relation between headache and

mobile phone RF fields. AIMS: To investigate the type and location of headache experienced by participants in one provocation study in order to gain insight into possible causes and mechanisms of the headaches. METHOD: Questionnaire about headache, indication on figure of location of headache after exposure, interview with neurologist about headache features to make headache diagnoses. RESULTS: The 17 participants went through 130 trials (sham or RF exposure). No significant difference existed in headache type, laterality or location between the headaches experienced with the two exposures types. In most participants, the headache was compatible with tension-type headache. DISCUSSION: As participants experienced their typical 'mobile phone headache' both with and without RF exposure, and since the experiment did not involve the stress or the arm/head position of mobile phone use, the most likely explanation is that the headache in this situation is caused by negative expectations (nocebo). CONCLUSION: This and other similar studies indicate that headache occurring in connection with mobile phone use is not related to RF fields, and that a placebo effect is important for this and possibly other headache triggers.

(E) Sudan M, Kheifets L, Arah OA, Olsen J. Cell phone exposures and hearing loss in children in the Danish National Birth Cohort. Paediatr Perinat Epidemiol. 27(3):247-257, 2013. (HU, BE)

BACKGROUND: Children today are exposed to cell phones early in life, and may be the most vulnerable if exposure is harmful to health. We investigated the association between cell phone use and hearing loss in children. METHODS: The Danish National Birth Cohort (DNBC) enrolled pregnant women between 1996 and 2002. Detailed interviews were conducted during gestation, and when the children were 6 months, 18 months and 7 years of age. We used multivariable-adjusted logistic regression, marginal structural models (MSM) with inverse-probability weighting, and doubly robust estimation (DRE) to relate hearing loss at age 18 months to cell phone use at age 7 years, and to investigate cell phone use reported at age 7 in relation to hearing loss at age 7. RESULTS: Our analyses included data from 52 680 children. We observed weak associations between cell phone use and hearing loss at age 7, with odds ratios and 95% confidence intervals from the traditional logistic regression, MSM and DRE models being 1.21 [95% confidence interval [CI] 0.99, 1.46], 1.23 [95% CI 1.01, 1.49] and 1.22 [95% CI 1.00, 1.49], respectively. CONCLUSIONS: Our findings could have been affected by various biases and are not sufficient to conclude that cell phone exposures have an effect on hearing. This is the first large-scale epidemiologic study to investigate this potentially important association among children, and replication of these findings is needed.

(E) Tang J, Zhang Y, Yang L, Chen Q, Tan L, Zuo S, Feng H, Chen Z, Zhu G. Exposure to 900 MHz electromagnetic fields activates the mmp-1/ERK pathway and causes blood-brain barrier damage and cognitive impairment in rats. Brain Res. 1601:92-101, 2015. (AS, CE, BE, ME)

With the rapid increase in the number of mobile phone users, the potential adverse effects of the electromagnetic field radiation emitted by a mobile phone has become a serious concern. This study demonstrated, for the first time, the blood-brain barrier and cognitive changes in rats exposed to 900MHz electromagnetic field (EMF) and aims to elucidate the potential molecular pathway underlying these changes. A total of 108 male Sprague-Dawley rats were

exposed to a 900MHz, 1mW/cm² EMF or sham (unexposed) for 14 or 28 days (3h per day). The specific energy absorption rate (SAR) varied between 0.016 (whole body) and 2W/kg (locally in the head). In addition, the Morris water maze test was used to examine spatial memory performance determination. Morphological changes were investigated by examining ultrastructural changes in the hippocampus and cortex, and the Evans Blue assay was used to assess blood brain barrier (BBB) damage. Immunostaining was performed to identify heme oxygenase-1 (HO-1)-positive neurons and albumin extravasation detection. Western blot was used to determine HO-1 expression, phosphorylated ERK expression and the upstream mediator, mkp-1 expression. We found that the frequency of crossing platforms and the percentage of time spent in the target quadrant were lower in rats exposed to EMF for 28 days than in rats exposed to EMF for 14 days and unexposed rats. Moreover, 28 days of EMF exposure induced cellular edema and neuronal cell organelle degeneration in the rat. In addition, damaged BBB permeability, which resulted in albumin and HO-1 extravasation were observed in the hippocampus and cortex. Thus, for the first time, we found that EMF exposure for 28 days induced the expression of mkp-1, resulting in ERK dephosphorylation. Taken together, these results demonstrated that exposure to 900MHz EMF radiation for 28 days can significantly impair spatial memory and damage BBB permeability in rat by activating the mkp-1/ERK pathway.

(NE) Terao Y, Okano T, Furubayashi T, Yugeta A, Inomata-Terada S, Ugawa Y. Effects of thirty-minute mobile phone exposure on saccades. Clin Neurophysiol. 118(7):1545-1556, 2007. (HU PE)

OBJECTIVE: To investigate whether exposure to pulsed high-frequency electromagnetic field (pulsed EMF) emitted by a mobile phone has short-term effects on saccade performances. METHODS: A double blind, counterbalanced crossover design was employed. In 10 normal subjects, we studied the performance of visually guided saccade (VGS), gap saccade (GAP), and memory guided saccade (MGS) tasks before and after exposure to EMF emitted by a mobile phone for thirty minutes or sham exposure. We also implemented a hand reaction time (RT) task in response to a visual signal. RESULTS: With the exception of VGS and MGS latencies, the parameters of VGS, GAP and MGS tasks were unchanged before and after real or sham EMF exposure. In addition, the latencies of VGS and MGS did not change differently after real and sham exposure. The hand RT shortened with the repetition of trials, but again this trend was of similar magnitude for real and sham exposures. CONCLUSIONS: Thirty minutes of mobile phone exposure has no significant short-term effect on saccade performances. SIGNIFICANCE: This is the first study to investigate saccade performance in relation to mobile phone exposure. No significant effect of mobile phone use was demonstrated on the performance of various saccade tasks, suggesting that the cortical processing for saccades and attention is not affected by exposure to EMF emitted by a mobile phone.

(NE) Thomas S, Benke G, Dimitriadis C, Inyang I, Sim MR, Wolfe R, Croft RJ, Abramson MJ. Use of mobile phones and changes in cognitive function in adolescents. Occup Environ Med. 67(12):861-866, 2010a. (HU, BE)

BACKGROUND: Several studies have investigated the impact of mobile phone exposure on cognitive function in adults. However, children and adolescents are of special interest due to their developing nervous systems. METHODS: Data were derived from the Australian Mobile Radiofrequency Phone Exposed Users' Study (MoRPhEUS) which comprised a baseline examination of year 7 students during 2005/2006 and a 1-year follow-up. Sociodemographic and exposure data were collected with a questionnaire. Cognitive functions were assessed with a computerised test battery and the Stroop Color-Word test. RESULTS: 236 students participated in both examinations. The proportion of mobile phone owners and the number of voice calls and short message services (SMS) per week increased from baseline to follow-up. Participants with more voice calls and SMS at baseline showed less reductions in response times over the 1-year period in various computerised tasks. Furthermore, those with increased voice calls and SMS exposure over the 1-year period showed changes in response time in a simple reaction and a working memory task. No associations were seen between mobile phone exposure and the Stroop test. CONCLUSIONS: We have observed that some changes in cognitive function, particularly in response time rather than accuracy, occurred with a latency period of 1 year and that some changes were associated with increased exposure. However, the increased exposure was mainly applied to those who had fewer voice calls and SMS at baseline, suggesting that these changes over time may relate to statistical regression to the mean, and not be the effect of mobile phone exposure.

(E) Thomas S, Heinrich S, von Kries R, Radon K. Exposure to radio-frequency electromagnetic fields and behavioural problems in Bavarian children and adolescents. Eur J Epidemiol. 25(2):135-141, 2010b. (HU, BE)

Only few studies have so far investigated possible health effects of radio-frequency electromagnetic fields (RF EMF) in children and adolescents, although experts discuss a potential higher vulnerability to such fields. We aimed to investigate a possible association between measured exposure to RF EMF fields and behavioural problems in children and adolescents. 1,498 children and 1,524 adolescents were randomly selected from the population registries of four Bavarian (South of Germany) cities. During an Interview data on participants' mental health, socio-demographic characteristics and potential confounders were collected. Mental health behaviour was assessed using the German version of the Strengths and Difficulties Questionnaire (SDQ). Using a personal dosimeter, we obtained radio-frequency EMF exposure profiles over 24 h. Exposure levels over waking hours were expressed as mean percentage of the reference level. Overall, exposure to radiofrequency electromagnetic fields was far below the reference level. Seven percent of the children and 5% of the adolescents showed an abnormal mental behaviour. In the multiple logistic regression analyses measured exposure to RF fields in the highest quartile was associated to overall behavioural problems for adolescents (OR 2.2; 95% CI 1.1-4.5) but not for children (1.3; 0.7-2.6). These results are mainly driven by one subscale, as the results showed an association between exposure and conduct

problems for adolescents (3.7; 1.6-8.4) and children (2.9; 1.4-5.9). As this is one of the first studies that investigated an association between exposure to mobile telecommunication networks and mental health behaviour more studies using personal dosimetry are warranted to confirm these findings.

(E) Thomée S, Härenstam A, Hagberg M. Mobile phone use and stress, sleep disturbances, and symptoms of depression among young adults--a prospective cohort study. BMC Public Health. 11:66, 2011. (HU, BE) (Effects may not be caused by RFR exposure.)

BACKGROUND: Because of the quick development and widespread use of mobile phones, and their vast effect on communication and interactions, it is important to study possible negative health effects of mobile phone exposure. The overall aim of this study was to investigate whether there are associations between psychosocial aspects of mobile phone use and mental health symptoms in a prospective cohort of young adults. METHODS: The study group consisted of young adults 20-24 years old (n = 4156), who responded to a questionnaire at baseline and 1-year follow-up. Mobile phone exposure variables included frequency of use, but also more qualitative variables: demands on availability, perceived stressfulness of accessibility, being awakened at night by the mobile phone, and personal overuse of the mobile phone. Mental health outcomes included current stress, sleep disorders, and symptoms of depression. Prevalence ratios (PRs) were calculated for cross-sectional and prospective associations between exposure variables and mental health outcomes for men and women separately. RESULTS: There were cross-sectional associations between high compared to low mobile phone use and stress, sleep disturbances, and symptoms of depression for the men and women. When excluding respondents reporting mental health symptoms at baseline, high mobile phone use was associated with sleep disturbances and symptoms of depression for the men and symptoms of depression for the women at 1-year follow-up. All qualitative variables had cross-sectional associations with mental health outcomes. In prospective analysis, overuse was associated with stress and sleep disturbances for women, and high accessibility stress was associated with stress, sleep disturbances, and symptoms of depression for both men and women. CONCLUSIONS: High frequency of mobile phone use at baseline was a risk factor for mental health outcomes at 1-year follow-up among the young adults. The risk for reporting mental health symptoms at follow-up was greatest among those who had perceived accessibility via mobile phones to be stressful. Public health prevention strategies focusing on attitudes could include information and advice, helping young adults to set limits for their own and others' accessibility.

(E) Tombini M, Pellegrino G, Pasqualetti P, Assenza G, Benvenga A, Fabrizio E, Rossini PM Mobile phone emissions modulate brain excitability in patients with focal epilepsy. Brain Stimul. 2012 Aug 9. [Epub ahead of print] (HU, EE, MA)

BACKGROUND: Electromagnetic fields (EMFs) emitted by mobile phones had been shown to increase cortical excitability in healthy subjects following 45 min of continuous exposure on the ipsilateral hemisphere. OBJECTIVE: Using Transcranial Magnetic Stimulation (TMS), the current study assessed the effects of acute exposure to mobile phone EMFs on the cortical excitability

in patients with focal epilepsy. METHODS: Ten patients with cryptogenic focal epilepsy originating outside the primary motor area (M1) were studied. Paired-pulse TMS were applied to the M1 of both the hemisphere ipsilateral (IH) and contralateral (CH) to the epileptic focus before and immediately after real/sham exposure to the GSM-EMFs (45 min). The TMS study was carried out in all subjects in three different experimental sessions (IH and CH exposure, sham), 1 week apart, according to a crossover, double-blind and counter-balanced paradigm. RESULTS: The present study clearly demonstrated that an acute and relatively prolonged exposure to GSM-EMFs modulates cortical excitability in patients affected by focal epilepsy; however, in contrast to healthy subjects, these effects were evident only after EMFs exposure over the hemisphere contralateral to the epileptic focus (CH). They were characterized by a significant cortical excitability increase in the exposed hemisphere paired with slight excitability decrease in the other one (IH). Both sham and real EMFs exposure of the IH did not affect brain excitability. CONCLUSION: Present results suggest a significant interaction between the brain excitability changes induced by EMFs and the epileptic focus, which eliminated the excitability enhancing effects of EMFs evident only in the CH.

(E) Tong J, Chen S, Liu XM, Hao DM. [Effect of electromagnetic radiation on discharge activity of neurons in the hippocampus CA1 in rats]. Zhongguo Ying Yong Sheng Li Xue Za Zhi. 29(5):423-427, 2013. [Article in Chinese] (AS, CE, EE)

OBJECTIVE: In order to explore effect of electromagnetic radiation on learning and memory ability of hippocampus neuron in rats, the changes in discharge patterns and overall electrical activity of hippocampus neuron after electromagnetic radiation were observed. METHODS: Rat neurons discharge was recorded with glass electrode extracellular recording technology and a polygraph respectively. Radiation frequency of electromagnetic wave was 900 MHZ and the power was 10 W/m². In glass electrode extracellular recording, the rats were separately irradiated for 10, 20, 30, 40, 50 and 60 min, every points repeated 10 times and updated interval of 1h, observing the changes in neuron discharge and spontaneous discharge patterns after electromagnetic radiation. In polygraph recording experiments, irradiation group rats for five days a week, 6 hours per day, repeatedly for 10 weeks, memory electrical changes in control group and irradiation group rats when they were feeding were repeatedly monitored by the implanted electrodes, observing the changes in peak electric digits and the largest amplitude in hippocampal CA1 area, and taking some electromagnetic radiation sampling sequence for correlation analysis. RESULTS: (1) Electromagnetic radiation had an inhibitory role on discharge frequency of the hippocampus CA1 region neurons. After electromagnetic radiation, discharge frequency of the hippocampus CA1 region neurons was reduced, but the changes in scale was not obvious. (2) Electromagnetic radiation might change the spontaneous discharge patterns of hippocampus CA1 region neurons, which made the explosive discharge pattern increased obviously. (3) Peak potential total number within 5 min in irradiation group was significantly reduced, the largest amplitude was less than that of control group. (4) Using mathematical method to make the correlation analysis of the electromagnetic radiation sampling sequence, that of irradiation group was less than that of control group, indicating that there was a tending to be inhibitory connection between neurons in irradiation group after

electromagnetic radiation. **CONCLUSION:** Electromagnetic radiation may cause structure and function changes of transfer synaptic in global, make hippocampal CA1 area neurons change in the overall discharge characteristic and discharge patterns, thus lead to decrease in the ability of learning and memory.

(E) Trosić I, Pavčić I, Milković-Kraus S, Mladinić M, Zeljezić D. Effect of electromagnetic radiofrequency radiation on the rats' brain, liver and kidney cells measured by comet assay. Coll Antropol. 35(4):1259-1264, 2011. (AS, CE, CH)

The goal of study was to evaluate DNA damage in rat's renal, liver and brain cells after in vivo exposure to radiofrequency/microwave (Rf/Mw) radiation of cellular phone frequencies range. To determine DNA damage, a single cell gel electrophoresis/comet assay was used. Wistar rats (male, 12 week old, approximate body weight 350 g) (N = 9) were exposed to the carrier frequency of 915 MHz with Global System Mobile signal modulation (GSM), power density of 2.4 W/m², whole body average specific absorption rate SAR of 0.6 W/kg. The animals were irradiated for one hour/day, seven days/week during two weeks period. The exposure set-up was Gigahertz Transversal Electromagnetic Mode Cell (GTEM--cell). Sham irradiated controls (N = 9) were apart of the study. The body temperature was measured before and after exposure. There were no differences in temperature in between control and treated animals. Comet assay parameters such as the tail length and tail intensity were evaluated. In comparison with tail length in controls (13.5 +/- 0.7 microm), the tail was slightly elongated in brain cells of irradiated animals (14.0 +/- 0.3 microm). The tail length obtained for liver (14.5 +/- 0.3 microm) and kidney (13.9 +/- 0.5 microm) homogenates notably differs in comparison with matched sham controls (13.6 +/- 0.3 microm) and (12.9 +/- 0.9 microm). Differences in tail intensity between control and exposed animals were not significant. The results of this study suggest that, under the experimental conditions applied, repeated 915 MHz irradiation could be a cause of DNA breaks in renal and liver cells, but not affect the cell genome at the higher extent compared to the basal damage.

(NE) Trunk A, Stefanics G, Zentai N, Kovács-Bálint Z, Thuróczy G, Hernádi I. No effects of a single 3G UMTS mobile phone exposure on spontaneous EEG activity, ERP correlates, and automatic deviance detection. Bioelectromagnetics. 34: 31-42, 2013. (HU, EE)

Potential effects of a 30 min exposure to third generation (3G) Universal Mobile Telecommunications System (UMTS) mobile phone-like electromagnetic fields (EMFs) were investigated on human brain electrical activity in two experiments. In the first experiment, spontaneous electroencephalography (sEEG) was analyzed (n = 17); in the second experiment, auditory event-related potentials (ERPs) and automatic deviance detection processes reflected by mismatch negativity (MMN) were investigated in a passive oddball paradigm (n = 26). Both sEEG and ERP experiments followed a double-blind protocol where subjects were exposed to either genuine or sham irradiation in two separate sessions. In both experiments, electroencephalograms (EEG) were recorded at midline electrode sites before and after exposure while subjects were watching a silent documentary. Spectral power of sEEG data was analyzed in the delta, theta, alpha, and beta frequency bands. In the ERP experiment, subjects

were presented with a random series of standard (90%) and frequency-deviant (10%) tones in a passive binaural oddball paradigm. The amplitude and latency of the P50, N100, P200, MMN, and P3a components were analyzed. We found no measurable effects of a 30 min 3G mobile phone irradiation on the EEG spectral power in any frequency band studied. Also, we found no significant effects of EMF irradiation on the amplitude and latency of any of the ERP components. In summary, the present results do not support the notion that a 30 min unilateral 3G EMF exposure interferes with human sEEG activity, auditory evoked potentials or automatic deviance detection indexed by MMN.

(NE) Trunk A, Stefanics G, Zentai N, Bacskay I, Felinger A, Thuróczy G, Hernádi I. Lack of interaction between concurrent caffeine and mobile phone exposure on visual target detection: An ERP study. Pharmacol Biochem Behav. 2014 Jul 26. pii: S0091-3057(14)00215-9. doi: 10.1016/j.pbb.2014.07.011. [Epub ahead of print] (HU, BE, EE, IA)

BACKGROUND: Caffeine affects information processing by acting predominantly on cortical activation, arousal and attention. Millions consume caffeine and simultaneously use their mobile phone (MP) during everyday activities. However, it is not known whether and how MP-emitted electromagnetic fields (EMFs) can modulate known psychoactive effects of caffeine. Here we investigated behavioral and neural correlates of caffeine and simultaneous MP exposure in a third generation (3G) Universal Mobile Telecommunication System (UMTS) signal modulation scheme. METHODS: We recorded electroencephalography (EEG) and event related potentials (ERP) in an oddball paradigm to frequent standard ($P=0.8$) and rare target ($P=0.2$) stimuli in a placebo controlled, double blind, within-subject protocol in four experimental sessions: 1) no caffeine and no MP, 2) caffeine only, 3) MP only, 4) caffeine and MP. The subjects' task was to discriminate between standard and target stimuli and respond to the latter by pressing a button while reaction time (RT) and EEG were recorded. To provide a complete analysis of any possible caffeine and/or MP treatment effects that may have occurred, we analyzed the P300 ERP wave using four different ERP measures: 1) peak latency, 2) peak amplitude, 3) 50% fractional area latency (FAL) and 4) area under the curve (AUC). RESULTS: Caffeine significantly shortened RT and decreased AUC of the P300 component compared to the control or the UMTS MP alone conditions. However, no effects were observed on RT or P300 in the UMTS MP exposure sessions, neither alone nor in combination with caffeine. CONCLUSION: Overall, the present results did not demonstrate any interactive or synergistic effects of caffeine and UMTS MP like EMF exposure on basic neural or cognitive measures. However, we found that caffeine consistently enhanced behavioral and ERP measures of visual target detection, showing that present results were obtained using a pharmacologically validated, consistent and replicable methodology.

(NE) Trunk A, Stefanics G, Zentai N, Bacskay I, Felinger A, Thuróczy G, Hernádi I. Effects of concurrent caffeine and mobile phone exposure on local target probability processing in the human brain. Sci Rep. 5:14434, 2015. (HU, EE, BE)

Millions of people use mobile phones (MP) while drinking coffee or other caffeine containing beverages. Little is known about the potential combined effects of MP irradiation and caffeine

on cognitive functions. Here we investigated whether caffeine intake and concurrent exposure to Universal Mobile Telecommunications System (UMTS) MP-like irradiation may interactively influence neuro-cognitive function in an active visual oddball paradigm. In a full factorial experimental design, 25 participants performed a simple visual target detection task while reaction time (RT) and electroencephalogram (EEG) was recorded. Target trials were divided into Low and High probability sets based on target-to-target distance. We analyzed single trial RT and alpha-band power (amplitude) in the pre-target interval. We found that RT was shorter in High vs. Low local probability trials, and caffeine further shortened RT in High probability trials relative to the baseline condition suggesting that caffeine improves the efficiency of implicit short-term memory. Caffeine also decreased pre-target alpha amplitude resulting in higher arousal level. Furthermore, pre-target gamma power positively correlated with RT, which may have facilitated target detection. However, in the present pharmacologically validated study UMTS exposure either alone or in combination with caffeine did not alter RT or pre-stimulus oscillatory brain activity.

(NE) Unterlechner M, Sauter C, Schmid G, Zeitlhofer J. No effect of an UMTS mobile phone-like electromagnetic field of 1.97 GHz on human attention and reaction time. Bioelectromagnetics. 29(2):145-153, 2008. (HU, BE)

Several studies in the past reported influences of electromagnetic emissions of GSM phones on reaction time in humans. However, there are currently only a few studies available dealing with possible effects of the electromagnetic fields emitted by UMTS mobile phones. In our study, 40 healthy volunteers (20 female, 20 male), aged 26.0 years (range 21-30 years) underwent four different computer tests measuring reaction time and attention under three different UMTS mobile phone-like exposure conditions (two exposure levels plus sham exposure). Exposure of the subjects was accomplished by small helical antennas operated close to the head and fed by a generic signal representing the emissions of a UMTS mobile phone under constant receiving conditions as well as under a condition of strongly varying transmit power. In the high exposure condition the resulting peak spatial average exposure of the test subjects in the cortex of the left temporal lobe of the brain was 0.63 W/kg (min. 0.25 W/kg, max. 1.49 W/kg) in terms of 1 g averaged SAR and 0.37 W/kg (min. 0.16 W/kg, max. 0.84 W/kg) in terms of 10 g averaged SAR, respectively. Low exposure condition was one-tenth of high exposure and sham was at least 50 dB below low exposure. Statistical analysis of the obtained test parameters showed that exposure to the generic UMTS signal had no statistically significant immediate effect on attention or reaction. Therefore, this study does not provide any evidence that exposure of UMTS mobiles interferes with attention under short-term exposure conditions.

(E) Vácha M, Puzová T, Kvácalová M. Radio frequency magnetic fields disrupt magnetoreception in American cockroach. J Exp Biol. 212(Pt 21):3473-3477, 2009. (AS, LI, BE)

The sense that allows birds to orient themselves by the Earth's magnetic field can be disabled by an oscillating magnetic field whose intensity is just a fraction of the geomagnetic field intensity and whose oscillations fall into the medium or high frequency radio wave bands. This remarkable phenomenon points very clearly at one of two existing alternative

magnetoreception mechanisms in terrestrial animals, i.e. the mechanism based on the radical pair reactions of specific photosensitive molecules. As the first such study in invertebrates, our work offers evidence that geomagnetic field reception in American cockroach is sensitive to a weak radio frequency field. Furthermore, we show that the 'deafening' effect at Larmor frequency 1.2 MHz is stronger than at different frequencies. The parameter studied was the rise in locomotor activity of cockroaches induced by periodic changes in the geomagnetic North positions by 60 deg. The onset of the disruptive effect of a 1.2 MHz field was found between 12 nT and 18 nT whereas the threshold of a doubled frequency field 2.4 MHz fell between 18 nT and 44 nT. A 7 MHz field showed no impact even in maximal 44 nT magnetic flux density. The results indicate resonance effects rather than non-specific bias of procedure itself and suggest that insects may be equipped with the same magnetoreception system as the birds.

(E) Vecchio F, Babiloni C, Ferreri F, Curcio G, Fini R, Del Percio C, Rossini PM. Mobile phone emission modulates interhemispheric functional coupling of EEG alpha rhythms. Eur J Neurosci. 25(6):1908-1913, 2007. (HU, EE)

We tested the working hypothesis that electromagnetic fields from mobile phones (EMFs) affect interhemispheric synchronization of cerebral rhythms, an important physiological feature of information transfer into the brain. Ten subjects underwent two electroencephalographic (EEG) recordings, separated by 1 week, following a crossover double-blind paradigm in which they were exposed to a mobile phone signal (global system for mobile communications; GSM). The mobile phone was held on the left side of the subject head by a modified helmet, and orientated in the normal position for use over the ear. The microphone was orientated towards the corner of the mouth, and the antenna was near the head in the parietotemporal area. In addition, we positioned another similar phone (but without battery) on the right side of the helmet, to balance the weight and to prevent the subject localizing the side of GSM stimulation (and consequently lateralizing attention). In one session the exposure was real (GSM) while in the other it was Sham; both sessions lasted 45 min. Functional interhemispheric connectivity was modelled using the analysis of EEG spectral coherence between frontal, central and parietal electrode pairs. Individual EEG rhythms of interest were delta (about 2-4 Hz), theta (about 4-6 Hz), alpha 1 (about 6-8 Hz), alpha 2 (about 8-10 Hz) and alpha 3 (about 10-12 Hz). Results showed that, compared to Sham stimulation, GSM stimulation modulated the interhemispheric frontal and temporal coherence at alpha 2 and alpha 3 bands. The present results suggest that prolonged mobile phone emission affects not only the cortical activity but also the spread of neural synchronization conveyed by interhemispherical functional coupling of EEG rhythms.

(E) Vecchio F, Buffo P, Sergio S, Iacoviello D, Rossini PM, Babiloni C. Mobile phone emission modulates event-related desynchronization of α rhythms and cognitive-motor performance in healthy humans. Clin Neurophysiol. 123(1):121-128, 2012a. (HU, EE, BE)

OBJECTIVES: It has been shown that electromagnetic fields of Global System for Mobile Communications phone (GSM-EMFs) affect human brain rhythms (Vecchio et al., 2007, 2010), but it is not yet clear whether these effects are related to alterations of cognitive functions.

METHODS: Eleven healthy adults underwent two electroencephalographic (EEG) sessions separated by 1 week, following a cross-over, placebo-controlled, double-blind paradigm. In both sessions, they performed a visual go/no-go task before real exposure to GSM-EMFs or after a sham condition with no EMF exposure. In the GSM real session, temporal cortex was continuously exposed to GSM-EMFs for 45 min. In the sham session, the subjects were not aware that the EMFs had been switched off for the duration of the experiment. In the go/no-go task, a central fixation stimulus was followed by a green (50% of probability) or red visual stimulus. Subjects had to press the mouse button after the green stimuli (go trials). With reference to a baseline period, power decrease of low- (about 8-10 Hz) and high-frequency (about 10-12 Hz) alpha rhythms indexed the cortical activity. **RESULTS:** It was found less power decrease of widely distributed high-frequency alpha rhythms and faster reaction time to go stimuli in the post- than pre-exposure period of the GSM session. No effect was found in the sham session. **CONCLUSIONS:** These results suggest that the peak amplitude of alpha ERD and the reaction time to the go stimuli are modulated by the effect of the GSM-EMFs on the cortical activity. **SIGNIFICANCE:** Exposure to GSM-EMFs for 45 min may enhance human cortical neural efficiency and simple cognitive-motor processes in healthy adults.

(E) Vecchio F, Tombini M, Buffo P, Assenza G, Pellegrino G, Benvenaga A, Babiloni C, Rossini PM. Mobile phone emission increases inter-hemispheric functional coupling of electroencephalographic alpha rhythms in epileptic patients. Int J Psychophysiol. 84(2):164-171, 2012b. (HU, EE, MA)

It has been reported that GSM electromagnetic fields (GSM-EMFs) of mobile phones modulate - after a prolonged exposure - inter-hemispheric synchronization of temporal and frontal resting electroencephalographic (EEG) rhythms in normal young and elderly subjects (Vecchio et al., 2007, 2010). Here we tested the hypothesis that this can be even more evident in epileptic patients, who typically suffer from abnormal mechanisms governing synchronization of rhythmic firing of cortical neurons. Eyes-closed resting EEG data were recorded in ten patients affected by focal epilepsy in real and sham exposure conditions. These data were compared with those obtained from 15 age-matched normal subjects of the previous reference studies. The GSM device was turned on (45 min) in the "GSM" condition and was turned off (45 min) in the other condition ("sham"). The mobile phone was always positioned on the left side in both patients and control subjects. Spectral coherence evaluated the inter-hemispheric synchronization of EEG rhythms at the following frequency bands: delta (about 2-4 Hz), theta (about 4-6 Hz), alpha1 (about 6-8 Hz), alpha2 (about 8-10 Hz), and alpha3 (about 10-12 Hz). The effects on the patients were investigated comparing the inter-hemispheric EEG coherence in the epileptic patients with the control group of subjects evaluated in the previous reference studies. Compared with the control subjects, epileptic patients showed a statistically significant higher inter-hemispheric coherence of temporal and frontal alpha rhythms (about 8-12 Hz) in the GSM than "Sham" condition. These results suggest that GSM-EMFs of mobile phone may affect inter-hemispheric synchronization of the dominant (alpha) EEG rhythms in epileptic patients. If confirmed by future studies on a larger group of epilepsy patients, the modulation of the inter-hemispheric alpha coherence due to the GSM-EMFs could have clinical implications and be related to changes in cognitive-motor function.

(E) Vecchio F, Babiloni C, Ferreri F, Buffo P, Cibelli G, Curcio G, van Dijkman S, Melgari JM, Giambattistelli F, Rossini PM. Mobile phone emission modulates inter-hemispheric functional coupling of EEG alpha rhythms in elderly compared to young subjects. Clin Neurophysiol. 121(2):163-171, 2010. (HU, EE, AD)

OBJECTIVE: It has been reported that GSM electromagnetic fields (GSM-EMFs) of mobile phones modulate--after a prolonged exposure--inter-hemispheric synchronization of temporal and frontal resting electroencephalographic (EEG) rhythms in normal young subjects [Vecchio et al., 2007]. Here we tested the hypothesis that this effect can vary on physiological aging as a sign of changes in the functional organization of cortical neural synchronization. **METHODS:** Eyes-closed resting EEG data were recorded in 16 healthy elderly subjects and 5 young subjects in the two conditions of the previous reference study. The GSM device was turned on (45 min) in one condition and was turned off (45 min) in the other condition. Spectral coherence evaluated the inter-hemispheric synchronization of EEG rhythms at the following bands: delta (about 2-4 Hz), theta (about 4-6 Hz), alpha 1 (about 6-8 Hz), alpha 2 (about 8-10 Hz), and alpha 3 (about 10-12 Hz). The aging effects were investigated comparing the inter-hemispheric EEG coherence in the elderly subjects vs. a young group formed by 15 young subjects (10 young subjects of the reference study; Vecchio et al., 2007). **RESULTS:** Compared with the young subjects, the elderly subjects showed a statistically significant ($p < 0.001$) increment of the inter-hemispheric coherence of frontal and temporal alpha rhythms (about 8-12 Hz) during the GSM condition. **CONCLUSIONS:** These results suggest that GSM-EMFs of a mobile phone affect inter-hemispheric synchronization of the dominant (alpha) EEG rhythms as a function of the physiological aging. **SIGNIFICANCE:** This study provides further evidence that physiological aging is related to changes in the functional organization of cortical neural synchronization.

(E) Vecsei Z, Csathó A, Thuróczy G, Hernádi I. Effect of a single 30 min UMTS mobile phone-like exposure on the thermal pain threshold of young healthy volunteers. Bioelectromagnetics. 2013 Jun 20. doi: 10.1002/bem.21801. [Epub ahead of print] (HU, BE)

One of the most frequently investigated effects of radiofrequency electromagnetic fields (RF EMFs) on the behavior of complex biological systems is pain sensitivity. Despite the growing body of evidence of EMF-induced changes in pain sensation, there is no currently accepted experimental protocol for such provocation studies for the healthy human population. In the present study, therefore, we tested the effects of third generation Universal Mobile Telecommunications System (UMTS) RF EMF exposure on the thermal pain threshold (TPT) measured on the surface of the fingers of 20 young adult volunteers. The protocol was initially validated with a topical capsaicin treatment. The exposure time was 30 min and the genuine (or sham) signal was applied to the head through a patch antenna, where RF EMF specific absorption rate (SAR) values were controlled and kept constant at a level of 1.75 W/kg. Data were obtained using randomized, placebo-controlled trials in a double-blind manner. Subjective pain ratings were tested blockwise on a visual analogue rating scale (VAS). Compared to the control and sham conditions, the results provide evidence for intact TPT but a reduced desensitization effect between repeated stimulations within the individual blocks of trials,

observable only on the contralateral side for the genuine UMTS exposure. Subjective pain perception (VAS) data indicated marginally decreased overall pain ratings in the genuine exposure condition only. The present results provide pioneering information about human pain sensation in relation to RF EMF exposure and thus may contribute to cover the existing gap between safety research and applied biomedical science targeting the potential biological effects of environmental RF EMFs.

(E) Velayutham P, Govindasamy GK, Raman R, Prepageran N, Ng KH. High-frequency hearing loss among mobile phone users. Indian J Otolaryngol Head Neck Surg. 2014 Jan;66(Suppl 1):169-72. doi: 10.1007/s12070-011-0406-4. Epub 2011 Dec 15. (HU, BE)

The objective of this study is to assess high frequency hearing (above 8 kHz) loss among prolonged mobile phone users is a tertiary Referral Center. Prospective single blinded study. This is the first study that used high-frequency audiometry. The wide usage of mobile phone is so profound that we were unable to find enough non-users as a control group. Therefore we compared the non-dominant ear to the dominant ear using audiometric measurements. The study was a blinded study wherein the audiologist did not know which was the dominant ear. A total of 100 subjects were studied. Of the subjects studied 53% were males and 47% females. Mean age was 27. The left ear was dominant in 63%, 22% were dominant in the right ear and 15% did not have a preference. This study showed that there is significant loss in the dominant ear compared to the non-dominant ear ($P < 0.05$). Chronic usage mobile phone revealed high frequency hearing loss in the dominant ear (mobile phone used) compared to the non dominant ear.

(E) Volkow ND, Tomasi D, Wang GJ, Vaska P, Fowler JS, Telang F, Alexoff D, Logan J, Wong C. Effects of cell phone radiofrequency signal exposure on brain glucose metabolism. JAMA. 305(8):808-813, 2011. (HU, PE)

CONTEXT: The dramatic increase in use of cellular telephones has generated concern about possible negative effects of radiofrequency signals delivered to the brain. However, whether acute cell phone exposure affects the human brain is unclear. **OBJECTIVE:** To evaluate if acute cell phone exposure affects brain glucose metabolism, a marker of brain activity. **DESIGN, SETTING, AND PARTICIPANTS:** Randomized crossover study conducted between January 1 and December 31, 2009, at a single US laboratory among 47 healthy participants recruited from the community. Cell phones were placed on the left and right ears and positron emission tomography with ((18)F)fluorodeoxyglucose injection was used to measure brain glucose metabolism twice, once with the right cell phone activated (sound muted) for 50 minutes ("on" condition) and once with both cell phones deactivated ("off" condition). Statistical parametric mapping was used to compare metabolism between on and off conditions using paired t tests, and Pearson linear correlations were used to verify the association of metabolism and estimated amplitude of radiofrequency-modulated electromagnetic waves emitted by the cell phone. Clusters with at least 1000 voxels (volume $>8 \text{ cm}^3$) and $P < .05$ (corrected for multiple comparisons) were considered significant. **MAIN OUTCOME MEASURE:** Brain glucose metabolism computed as absolute metabolism ($\mu\text{mol}/100 \text{ g per minute}$) and as normalized

metabolism (region/whole brain). **RESULTS:** Whole-brain metabolism did not differ between on and off conditions. In contrast, metabolism in the region closest to the antenna (orbitofrontal cortex and temporal pole) was significantly higher for on than off conditions (35.7 vs 33.3 $\mu\text{mol}/100\text{ g}$ per minute; mean difference, 2.4 [95% confidence interval, 0.67-4.2]; $P = .004$). The increases were significantly correlated with the estimated electromagnetic field amplitudes both for absolute metabolism ($R = 0.95$, $P < .001$) and normalized metabolism ($R = 0.89$; $P < .001$). **CONCLUSIONS:** In healthy participants and compared with no exposure, 50-minute cell phone exposure was associated with increased brain glucose metabolism in the region closest to the antenna. This finding is of unknown clinical significance.

(NE) Wallace D, Eltiti S, Ridgewell A, Garner K, Russo R, Sepulveda F, Walker S, Quinlan T, Dudley S, Maung S, Deeble R, Fox E. Cognitive and physiological responses in humans exposed to a TETRA base station signal in relation to perceived electromagnetic hypersensitivity. *Bioelectromagnetics*. 33(1):23-39, 2012. **(HU, BE)**

Terrestrial Trunked Radio (TETRA) technology ("Airwave") has led to public concern because of its potential interference with electrical activity in the brain. The present study is the first to examine whether acute exposure to a TETRA base station signal has an impact on cognitive functioning and physiological responses. Participants were exposed to a 420 MHz TETRA signal at a power flux density of 10 mW/m² as well as sham (no signal) under double-blind conditions. Fifty-one people who reported a perceived sensitivity to electromagnetic fields as well as 132 controls participated in a double-blind provocation study. Forty-eight sensitive and 132 control participants completed all three sessions. Measures of short-term memory, working memory, and attention were administered while physiological responses (blood volume pulse, heart rate, skin conductance) were monitored. After applying exclusion criteria based on task performance for each aforementioned cognitive measure, data were analyzed for 36, 43, and 48 sensitive participants for these respective tasks and, likewise, 107, 125, and 129 controls. We observed no differences in cognitive performance between sham and TETRA exposure in either group; physiological response also did not differ between the exposure conditions. These findings are similar to previous double-blind studies with other mobile phone signals (900-2100 MHz), which could not establish any clear evidence that mobile phone signals affect health or cognitive function.

(E) Wang H, Peng R, Zhou H, Wang S, Gao Y, Wang L, Yong Z, Zuo H, Zhao L, Dong J, Xu X, Su Z. Impairment of long-term potentiation induction is essential for the disruption of spatial memory after microwave exposure. *Int J Radiat Biol*. 2013 Jul 24. [Epub ahead of print] **(AS, BE, ME, EE)**

Purpose: To assess the impact of microwave exposure on learning and memory and to explore the underlying mechanisms. Materials and methods: 100 Wistar rats were exposed to a 2.856 GHz pulsed microwave field at average power densities of 0 mW/cm², 5 mW/cm², 10 mW/cm² and 50 mW/cm² for 6 min. The spatial memory was assessed by the Morris Water Maze (MWM) task. An in vivo study was conducted soon after microwave exposure to evaluate the

changes of population spike (PS) amplitudes of long-term potentiation (LTP) in the medial perforant path (MPP)-dentate gyrus (DG) pathway. The structure of the hippocampus was observed by the light microscopy and the transmission electron microscopy (TEM) at 7 d after microwave exposure. Results: Our results showed that the rats exposed in 10 mW/cm² and 50 mW/cm² microwave displayed significant deficits in spatial learning and memory at 6 h, 1 d and 3 d after exposure. Decreased PS amplitudes were also found after 10 mW/cm² and 50 mW/cm² microwave exposure. In addition, varying degrees of degeneration of hippocampal neurons, decreased synaptic vesicles and blurred synaptic clefts were observed in the rats exposed in 10 mW/cm² and 50 mW/cm² microwave. Compared with the sham group, the rats exposed in 5 mW/cm² microwave showed no difference in the above experiments. Conclusions: This study suggested that impairment of LTP induction and the damages of hippocampal structure, especially changes of synapses, might contribute to cognitive impairment after microwave exposure.

(E) Wang H, Peng R, Zhao L, Wang S, Gao Y, Wang L, Zuo H, Dong J, Xu X, Zhou H, Su Z. The relationship between NMDA receptors and microwave induced learning and memory impairment: a long term observation on Wistar rats. Int J Radiat Biol. 2014 Nov 26:1-25. [Epub ahead of print] (AS, BE, ME, CH)

Purpose: In the present study, we intended to investigate whether the high power microwave could cause the continuous disorders of learning and memory in Wistar rats and to explore the underlying mechanisms. Materials and methods: 80 Wistar rats were exposed to a 2.856 GHz pulsed microwave source at a power density of 0 mW/cm² and 50 mW/cm² microwave for 6 min. The spatial memory ability, the structure of the hippocampus, contents of amino acids neurotransmitters in hippocampus and the expression of N-methyl-D-aspartic acid receptors (NMDAR) subunit 1, 2A and 2B (NR1, NR2A and NR2B) were detected at 1 m, 3 m, 6 m, 9 m, 12 m and 18 m after microwave exposure. Results: Our results showed that the microwave exposed rats showed consistent deficiencies in spatial learning and memory. The level of amino acid neurotransmitters also decreased after microwave radiation. The ratio of glutamate (Glu) and gamma-aminobutyric acid (GABA) significantly decreased at 6 m. Besides, the hippocampus showed varying degrees of degeneration of neurons, increased postsynaptic density and blurred synaptic clefts in the exposure group. The NR1 and NR2B expression showed a significant decrease, especially the NR2B expression. Conclusions: This study indicated that the content of amino acids neurotransmitters, the expression of NMDAR subunits and the variation of hippocampal structure might contribute to the long term cognitive impairment after microwave exposure.

(E) Wang H, Tan S, Xu X, Zhao L, Zhang J, Yao B, Gao Y, Zhou H, Peng R. Long term impairment of cognitive functions and alterations of NMDAR subunits after continuous microwave exposure. Physiol Behav. 181:1-9, 2017. (AS, CE, BE, ME, EE)

OBJECTIVE: The long term effects of continuous microwave exposure cannot be ignored for the simulation of the real environment and increasing concerns about the negative cognitive effects of microwave exposure. METHODS: In this study, 220 male Wistar rats were exposed by

a 2.856GHz radiation source with the average power density of 0, 2.5, 5 and 10mW/cm² for 6min/day, 5days/week and up to 6weeks. The MWM task, the EEG analysis, the hippocampus structure observation and the western blot were applied until the 12months after microwave exposure to detect the spatial learning and memory abilities, the cortical electrical activity, changes of hippocampal structure and the NMDAR subunits expressions. RESULTS: Results found that the rats in the 10mW/cm² group showed the decline of spatial learning and memory abilities and EEG disorders (the decrease of EEG frequencies, and increase of EEG amplitudes and delta wave powers). Moreover, changes of basic structure and ultrastructure of hippocampus also found in the 10 and 5mW/cm² groups. The decrease of NR 2A, 2B and p-NR2B might contribute to the impairment of cognitive functions. CONCLUSIONS: Our findings suggested that the continuous microwave exposure could cause the dose-dependent long term impairment of spatial learning and memory, the abnormalities of EEG and the hippocampal structure injuries. The decrease of NMDAR key subunits and phosphorylation of NR 2B might contribute to the cognitive impairment.

(E) Wang K, Lu JM, Xing ZH, Zhao QR, Hu LQ, Xue L, Zhang J, Mei YA. Effect of 1.8 GHz radiofrequency electromagnetic radiation on novel object associative recognition memory in mice. Sci Rep. 2017 Mar 17;7:44521. doi: 10.1038/srep44521. (AS, BE, CC, ME)

Mounting evidence suggests that exposure to radiofrequency electromagnetic radiation (RF-EMR) can influence learning and memory in rodents. In this study, we examined the effects of single exposure to 1.8 GHz RF-EMR for 30 min on subsequent recognition memory in mice, using the novel object recognition task (NORT). RF-EMR exposure at an intensity of >2.2 W/kg specific absorption rate (SAR) power density induced a significant density-dependent increase in NORT index with no corresponding changes in spontaneous locomotor activity. RF-EMR exposure increased dendritic-spine density and length in hippocampal and prefrontal cortical neurons, as shown by Golgi staining. Whole-cell recordings in acute hippocampal and medial prefrontal cortical slices showed that RF-EMR exposure significantly altered the resting membrane potential and action potential frequency, and reduced the action potential half-width, threshold, and onset delay in pyramidal neurons. These results demonstrate that exposure to 1.8 GHz RF-EMR for 30 min can significantly increase recognition memory in mice, and can change dendritic-spine morphology and neuronal excitability in the hippocampus and prefrontal cortex. The SAR in this study (3.3 W/kg) was outside the range encountered in normal daily life, and its relevance as a potential therapeutic approach for disorders associated with recognition memory deficits remains to be clarified.

(E) Wang LF, Li X, Gao YB, Wang SM, Zhao L, Dong J, Yao BW, Xu XP, Chang GM, Zhou HM, Hu XJ, Peng RY. Activation of VEGF/Flk-1-ERK Pathway Induced Blood-Brain Barrier Injury After Microwave Exposure. Mol Neurobiol. 2014 Sep 9. [Epub ahead of print] (CS, ME, CH)

Microwaves have been suggested to induce neuronal injury and increase permeability of the blood-brain barrier (BBB), but the mechanism remains unknown. The role of the vascular endothelial growth factor (VEGF)/Flk-1-Raf/MAPK kinase (MEK)/extracellular-regulated protein kinase (ERK) pathway in structural and functional injury of the blood-brain barrier (BBB)

following microwave exposure was examined. An in vitro BBB model composed of the ECV304 cell line and primary rat cerebral astrocytes was exposed to microwave radiation (50 mW/cm², 5 min). The structure was observed by scanning electron microscopy (SEM) and the permeability was assessed by measuring transendothelial electrical resistance (TEER) and horseradish peroxidase (HRP) transmission. Activity and expression of VEGF/Flk-1-ERK pathway components and occludin also were examined. Our results showed that microwave radiation caused intercellular tight junctions to broaden and fracture with decreased TEER values and increased HRP permeability. After microwave exposure, activation of the VEGF/Flk-1-ERK pathway and Tyr phosphorylation of occludin were observed, along with down-regulated expression and interaction of occludin with zonula occludens-1 (ZO-1). After Flk-1 (SU5416) and MEK1/2 (U0126) inhibitors were used, the structure and function of the BBB were recovered. The increase in expression of ERK signal transduction molecules was muted, while the expression and the activity of occludin were accelerated, as well as the interactions of occludin with p-ERK and ZO-1 following microwave radiation. Thus, microwave radiation may induce BBB damage by activating the VEGF/Flk-1-ERK pathway, enhancing Tyr phosphorylation of occludin, while partially inhibiting expression and interaction of occludin with ZO-1.

(E) Wang LF, Tian DW, Li HJ, Gao YB, Wang CZ, Zhao L, Zuo HY, Dong J, Qiao SM, Zou Y, Xiong L, Zhou HM, Yang YF, Peng RY, Hu XJ. Identification of a Novel Rat NR2B Subunit Gene Promoter Region Variant and Its Association with Microwave-Induced Neuron Impairment. Mol Neurobiol. 53(4):2100-2111, 2016. (AS, CE, CH, BE)

Microwave radiation has been implicated in cognitive dysfunction and neuronal injury in animal models and in human investigations; however, the mechanism of these effects is unclear. In this study, single nucleotide polymorphism (SNP) sites in the rat GRIN2B promoter region were screened. The associations of these SNPs with microwave-induced rat brain dysfunction and with rat pheochromocytoma-12 (PC12) cell function were investigated. Wistar rats (n = 160) were exposed to microwave radiation (30 mW/cm²) for 5 min/day, 5 days/week, over a period of 2 months). Screening of the GRIN2B promoter region revealed a stable C-to-T variant at nucleotide position -217 that was not induced by microwave exposure. The learning and memory ability, amino acid contents in the hippocampus and cerebrospinal fluid, and NR2B expression were then investigated in the different genotypes. Following microwave exposure, NR2B protein expression decreased, while the Glu contents in the hippocampus and CSF increased, and memory impairment was observed in the TT genotype but not the CC and CT genotypes. In PC12 cells, the effects of the T allele were more pronounced than those of the C allele on transcription factor binding ability, transcriptional activity, NR2B mRNA, and protein expression. These effects may be related to the detrimental role of the T allele and the protective role of the C allele in rat brain function and PC12 cells exposed to microwave radiation.

(NE) Watilliaux A, Edeline JM, L  v  que P, Jay TM, Mallat M. Effect of exposure to 1,800 MHz electromagnetic fields on heat shock proteins and glial cells in the brain of developing rats. Neurotox Res. 20(2):109-119, 2011. (AS, DE, CC)

The increasing use of mobile phones by children raise issues about the effects of electromagnetic fields (EMF) on the immature Central Nervous System (CNS). In the present study, we quantified cell stress and glial responses in the brain of developing rats one day after a single exposure of 2 h to a GSM 1,800 MHz signal at a brain average Specific Absorption Rate (SAR) in the range of 1.7 to 2.5 W/kg. Young rats, exposed to EMF on postnatal days (P) 5 (n = 6), 15 (n = 5) or 35 (n = 6), were compared to pseudo-exposed littermate rats (n = 6 at all ages). We used western blotting to detect heat shock proteins (HSPs) and cytoskeleton- or neurotransmission-related proteins in the developing astroglia. The GSM signal had no significant effect on the abundance of HSP60, HSC70 or HSP90, of serine racemase, glutamate transporters including GLT1 and GLAST, or of glial fibrillary acid protein (GFAP) in either total or soluble tissue extracts. Immunohistochemical detection of CD68 antigen in brain sections from pseudo-exposed and exposed animals did not reveal any differences in the morphology or distribution of microglial cells. These results provide no evidence for acute cell stress or glial reactions indicative of early neural cell damage, in developing brains exposed to 1,800 MHz signals in the range of SAR used in our study.

(E) Wiholm C, Lowden A, Kuster N, Hillert L, Arnetz BB, Akerstedt T, Moffat SD. Mobile phone exposure and spatial memory. Bioelectromagnetics. 30(1):59-65, 2009. (HU, BE)

Radiofrequency (RF) emission during mobile phone use has been suggested to impair cognitive functions, that is, working memory. This study investigated the effects of a 2 1/2 h RF exposure (884 MHz) on spatial memory and learning, using a double-blind repeated measures design. The exposure was designed to mimic that experienced during a real-life mobile phone conversation. The design maximized the exposure to the left hemisphere. The average exposure was peak spatial specific absorption rate (psSAR10g) of 1.4 W/kg. The primary outcome measure was a "virtual" spatial navigation task modeled after the commonly used and validated Morris Water Maze. The distance traveled on each trial and the amount of improvement across trials (i.e., learning) were used as dependent variables. The participants were daily mobile phone users, with and without symptoms attributed to regular mobile phone use. Results revealed a main effect of RF exposure and a significant RF exposure by group effect on distance traveled during the trials. The symptomatic group improved their performance during RF exposure while there was no such effect in the non-symptomatic group. Until this new finding is further investigated, we can only speculate about the cause.

(E) Xiong L, Sun CF, Zhang J, Gao YB, Wang LF, Zuo HY, Wang SM, Zhou HM, Xu XP, Dong J, Yao BW, Zhao L, Peng RY. Microwave Exposure Impairs Synaptic Plasticity in the Rat Hippocampus and PC12 Cells through Over-activation of the NMDA Receptor Signaling Pathway. Biomed Environ Sci. 28(1):13-24, 2015. (AS, CE, ME, CH)

OBJECTIVE: The aim of this study is to investigate whether microwave exposure would affect the N-methyl-D-aspartate receptor (NMDAR) signaling pathway to establish whether this plays a role in synaptic plasticity impairment. **METHODS:** 48 male Wistar rats were exposed to 30 mW/cm² microwave for 10 min every other day for three times. Hippocampal structure was observed through H&E staining and transmission electron microscope. PC12 cells were exposed to 30 mW/cm² microwave for 5 min and the synapse morphology was visualized with scanning electron microscope and atomic force microscope. The release of amino acid neurotransmitters and calcium influx were detected. The expressions of several key NMDAR signaling molecules were evaluated. **RESULTS:** Microwave exposure caused injury in rat hippocampal structure and PC12 cells, especially the structure and quantity of synapses. The ratio of glutamic acid and gamma-aminobutyric acid neurotransmitters was increased and the intracellular calcium level was elevated in PC12 cells. A significant change in NMDAR subunits (NR1, NR2A, and NR2B) and related signaling molecules (Ca²⁺/calmodulin-dependent kinase II gamma and phosphorylated cAMP-response element binding protein) were examined. **CONCLUSION:** 30 mW/cm² microwave exposure resulted in alterations of synaptic structure, amino acid neurotransmitter release and calcium influx. NMDAR signaling molecules were closely associated with impaired synaptic plasticity.

(E) Xu F, Bai Q, Zhou K, Ma L, Duan J, Zhuang F, Xie C, Li W, Zou P, Zhu C. Age-dependent acute interference with stem and progenitor cell proliferation in the hippocampus after exposure to 1800 MHz electromagnetic radiation. Electromagn Biol Med. 36(2):158-166, 2017. (AS, CE, CC, AD)

To investigate the effects of exposure to an 1800 MHz electromagnetic field on cell death and cell proliferation in the developing brain, postnatal day 7 (P7) and P21 healthy Kunming mice were randomly assigned into the experimental and control groups. The experimental groups were exposed to an 1800 MHz electromagnetic field for 8 h daily for three consecutive days. The thymidine analog 5-bromo-2-deoxyuridine (BrdU) was injected intraperitoneally 1 h before each exposure session, and all animals were sacrificed 24 h after the last exposure. Cell death and proliferation markers were detected by immunohistochemistry in the dentate gyrus of the hippocampus. Electromagnetic exposure has no influence on cell death in the dentate gyrus of the hippocampus in P7 and P21 mice as indicated by active caspase-3 immunostaining and Fluoro-Jade labeling. The basal cell proliferation in the hippocampus was higher in P7 than in P21 mice as indicated by the number of cells labeled with BrdU and by immunohistochemical staining for phosphor-histone H3 (PHH3) and brain lipid-binding protein (BLBP). Electromagnetic exposure stimulated DNA synthesis in P7 neural stem and progenitor cells, but reduced cell division and the total number of stem cells in the hippocampus as indicated by increased BrdU labeling and reduced PHH3 and BLBP labeling compared to P7 control mice. There were no significant changes in cell proliferation in P21 mice after exposure to the electromagnetic field. These results indicate that interference with stem cell proliferation upon short-term exposure to an 1800 MHz electromagnetic field depends on the developmental stage of the brain.

(E) Xu S, Zhou Z, Zhang L, Yu Z, Zhang W, Wang Y, Wang X, Li M, Chen Y, Chen C, He M, Zhang G, Zhong M. Exposure to 1800 MHz radiofrequency radiation induces oxidative damage to mitochondrial DNA in primary cultured neurons. Brain Res. 1311:189-196, 2010. (CS, CH, OX)

Increasing evidence indicates that oxidative stress may be involved in the adverse effects of radiofrequency (RF) radiation on the brain. Because mitochondrial DNA (mtDNA) defects are closely associated with various nervous system diseases and mtDNA is particularly susceptible to oxidative stress, the purpose of this study was to determine whether radiofrequency radiation can cause oxidative damage to mtDNA. In this study, we exposed primary cultured cortical neurons to pulsed RF electromagnetic fields at a frequency of 1800 MHz modulated by 217 Hz at an average specific absorption rate (SAR) of 2 W/kg. At 24 h after exposure, we found that RF radiation induced a significant increase in the levels of 8-hydroxyguanine (8-OHdG), a common biomarker of DNA oxidative damage, in the mitochondria of neurons. Concomitant with this finding, the copy number of mtDNA and the levels of mitochondrial RNA (mtRNA) transcripts showed an obvious reduction after RF exposure. Each of these mtDNA disturbances could be reversed by pretreatment with melatonin, which is known to be an efficient antioxidant in the brain. Together, these results suggested that 1800 MHz RF radiation could cause oxidative damage to mtDNA in primary cultured neurons. Oxidative damage to mtDNA may account for the neurotoxicity of RF radiation in the brain.

(E) Yan JG, Agresti M, Zhang LL, Yan Y, Matloub HS. Upregulation of specific mRNA levels in rat brain after cell phone exposure. Electromagn Biol Med. 27(2):147-154, 2008. (AS, CE, CH)

Adult Sprague-Dawley rats were exposed to regular cell phones for 6 h per day for 126 days (18 weeks). RT-PCR was used to investigate the changes in levels of mRNA synthesis of several injury-associated proteins. Calcium ATPase, Neural Cell Adhesion Molecule, Neural Growth Factor, and Vascular Endothelial Growth Factor were evaluated. The results showed statistically significant mRNA up-regulation of these proteins in the brains of rats exposed to cell phone radiation. These results indicate that relative chronic exposure to cell phone microwave radiation may result in cumulative injuries that could eventually lead to clinically significant neurological damage.

(E) Yang L, Chen Q, Lv B, Wu T. Long-Term Evolution Electromagnetic Fields Exposure Modulates the Resting State EEG on Alpha and Beta Bands. Clin EEG Neurosci. 2016 Apr 25. pii: 1550059416644887. [Epub ahead of print] (HU, EE)

Long-term evolution (LTE) wireless telecommunication systems are widely used globally, which has raised a concern that exposure to electromagnetic fields (EMF) emitted from LTE devices can change human neural function. To date, few studies have been conducted on the effect of exposure to LTE EMF. Here, we evaluated the changes in electroencephalogram (EEG) due to LTE EMF exposure. An LTE EMF exposure system with a stable power emission, which was equivalent to the maximum emission from an LTE mobile phone, was used to radiate the subjects. Numerical simulations were conducted to ensure that the specific absorption rate in

the subject's head was below the safety limits. Exposure to LTE EMF reduced the spectral power and the interhemispheric coherence in the alpha and beta bands of the frontal and temporal brain regions. No significant change was observed in the spectral power and the interhemispheric coherence in different timeslots during and after the exposure. These findings also corroborated those of our previous study using functional magnetic resonant imaging.

(E) Yang XS, He GL, Hao YT, Xiao Y, Chen CH, Zhang GB, Yu ZP. Exposure to 2.45 GHz electromagnetic fields elicits an HSP-related stress response in rat hippocampus. Brain Res Bull. 88(4):371-378, 2012. (AS, CH)

The issue of possible neurobiological effects of the electromagnetic field (EMF) exposure is highly controversial. To determine whether electromagnetic field exposure could act as an environmental stimulus capable of producing stress responses, we employed the hippocampus, a sensitive target of electromagnetic radiation, to assess the changes in its stress-related gene and protein expression after EMF exposure. Adult male Sprague-Dawley rats with body restrained were exposed to a 2.45 GHz EMF at a specific absorption rate (SAR) of 6 W/kg or sham conditions. cDNA microarray was performed to examine the changes of gene expression involved in the biological effects of electromagnetic radiation. Of 2048 candidate genes, 23 upregulated and 18 downregulated genes were identified. Of these differential expression genes, two heat shock proteins (HSP), HSP27 and HSP70, are notable because expression levels of both proteins are increased in the rat hippocampus. Result from immunocytochemistry revealed that EMF caused intensive staining for HSP27 and HSP70 in the hippocampus, especially in the pyramidal neurons of cornu ammonis 3 (CA3) and granular cells of dentate gyrus (DG). The gene and protein expression profiles of HSP27 and HSP70 were further confirmed by reverse transcription polymerase chain reaction (RT-PCR) and Western blot. Our data provide direct evidence that exposure to electromagnetic fields elicits a stress response in the rat hippocampus.

(E) Yang X, He G, Hao Y, Chen C, Li M, Wang Y, Zhang G, Yu Z. The role of the JAK2-STAT3 pathway in pro-inflammatory responses of EMF-stimulated N9 microglial cells. J Neuroinflammation. 7:54, 2010. (CS, CH)

BACKGROUND: In several neuropathological conditions, microglia can become overactivated and cause neurotoxicity by initiating neuronal damage in response to pro-inflammatory stimuli. Our previous studies have shown that exposure to electromagnetic fields (EMF) activates cultured microglia to produce tumor necrosis factor (TNF)- α and nitric oxide (NO) through signal transduction involving the activator of transcription STAT3. Here, we investigated the role of STAT3 signaling in EMF-induced microglial activation and pro-inflammatory responses in more detail than the previous study. **METHODS:** N9 microglial cells were treated with EMF exposure or a sham treatment, with or without pretreatment with an inhibitor (Pyridone 6, P6) of the Janus family of tyrosine kinases (JAK). The activation state of microglia was assessed via immunoreaction using the microglial marker CD11b. Levels of inducible nitric oxide synthase (iNOS), TNF- α and NO were measured using real-time reverse transcription-polymerase chain reaction (RT-PCR), enzyme-linked immunosorbent assay (ELISA) and the nitrate reductase

method. Activation of JAKs and STAT3 proteins was evaluated by western blotting for specific tyrosine phosphorylation. The ability of STAT3 to bind to DNA was detected with an electrophoresis mobility shift assay (EMSA). **RESULTS:** EMF was found to significantly induce phosphorylation of JAK2 and STAT3, and DNA-binding ability of STAT3 in N9 microglia. In addition, EMF dramatically increased the expression of CD11b, TNF- α and iNOS, and the production of NO. P6 strongly suppressed the phosphorylation of JAK2 and STAT3 and diminished STAT3 activity in EMF-stimulated microglia. Interestingly, expression of CD11b as well as gene expression and production of TNF- α and iNOS were suppressed by P6 at 12 h, but not at 3 h, after EMF exposure. **CONCLUSIONS:** EMF exposure directly triggers initial activation of microglia and produces a significant pro-inflammatory response. Our findings confirm that the JAK2-STAT3 pathway may not mediate this initial microglial activation but does promote pro-inflammatory responses in EMF-stimulated microglial cells. Thus, the JAK2-STAT3 pathway might be a therapeutic target for reducing pro-inflammatory responses in EMF-activated microglia.

(NE) Yilmaz F, Dasdag S, Akdag MZ, Kilinc N. Whole-body exposure of radiation emitted from 900 MHz mobile phones does not seem to affect the levels of anti-apoptotic bcl-2 protein. Electromagn Biol Med. 27(1):65-72, 2008. (AS, CH)

The purpose of the present study was to investigate the anti-apoptotic bcl-2 protein in rat brain and testes after whole-body exposure to radiation emitted from 900 MHz cellular phones. Two groups (sham and experimental) of Sprague-Dawley rats of eight rats each were used in the study. Exposure began approximately 10 min after transferring into the exposure cages, a period of time when rats settled down to a prone position and selected a fixed location inside the cage spontaneously. For the experimental group, the phones were in the speech condition for 20 min per day for 1 month. The same procedure was applied to the sham group rats, but the phones were turned off. Immunohistochemical staining of bcl-2 was performed according to the standardized avidin-biotin complex method. The results of this study showed that 20 min of the radiation emitted from 900 MHz cellular phones did not alter anti-apoptotic bcl-2 protein in the brain and testes of rats. We speculate that bcl-2 may not be involved in the effects of radiation on the brain and testes of rats.

(E) Yilmaz A, Yilmaz N, Serarslan Y, Aras M, Altas M, Ozgür T, Sefil F. The effects of mobile phones on apoptosis in cerebral tissue: an experimental study on rats. Eur Rev Med Pharmacol Sci. 18(7):992-1000, 2014. (AS, CE, CH)

INTRODUCTION: The concern about mobile phone effects is increasing as the number of users increasing too. Different studies have different results, so this topic is still open to discussion. Aim of this report was to investigate the effects of the mobile phones on the Bcl-2 gene and p53 proteins in rat brains. **MATERIALS AND METHODS:** In the study group of 10 rats; mobile phones that spread EMW at a frequency between 1900-2100 MHz and Specific Absorption Rate range between 0.005 W/kg and 0.288 W/kg (Dialing mode), 0.004 W/kg and 0.029 W/kg (Calling mode) were attached to rat ears for simulating usage in daily life for 7 times a day during 5 minutes (3 seconds dialing mode, 4 minutes and 47 seconds of calling mode) for a four

week period. Sham group (n=10) rats were only immobilized without EMW exposure. Another group of rats (n=10) were counted as control without any application. immunohistopathological examination was performed for p53 and Bcl-2 expression. **RESULTS:** Immunohistopathological examinations revealed that the samples in the study group had more p53 and Bcl-2 positive stained cells and they were stained denser. In both evaluations, these differences between the study and control group were found statistically significant ($p < 0.003$); In Bcl-2 evaluation statistically significant difference was found between study and sham group to ($p < 0.005$); however, the p53 evaluation between the study and the sham group did not show any statistically significant difference ($p > 0.005$). **CONCLUSIONS:** Our results showed that the electro-magnetic waves emitted by the mobile phones may have effect on apoptosis. Besides, obtained data revealed that more realistic application of mobile phones during experiments is more important as expected.

(E) Yogesh S, Abha S, Priyanka S. Mobile usage and sleep patterns among medical students. Indian J Physiol Pharmacol. 58(1):100-103, 2014. (HU, CE, BE, SL)

Exposure of humans to radio frequency electromagnetic field (EMF) both during receiving and transmitting the signals has amplified public and scientific debate about possible adverse effects on human health. The study was designed with the objective of assessing the extent of mobile phone use amongst medical students and finding correlation if any between the hours of usage of mobile to sleep pattern and quality. hundred medical students grouped as cases (n = 57) (> 2 hours/day of mobile usage) and control (n = 43) (≤ 2 hours/day of mobile usage) were examined for their sleep quality & pattern by Pittsburg sleep Quality Index (PSQI). Differences between groups were examined with the Mann Whitney "U" test for proportions (Quantitative values) and with Student's t test for continuous variables. The association of variables was analyzed by Spearman Rank's correlation. Probability was set at < 0.05 as significant. Sleep disturbance, latency and day dysfunction was more in cases especially females. A significant association of hours of usage and sleep indices were observed in both genders (males $r = 0.25$; $p = 0.04$, females $r = 0.31$; $p = 0.009$). Evening usage of mobile phone in cases showed a statistically significant negative association (-0.606 ; $p = 0.042$) with Sleep quality (higher PSQI means sleep deprivation). Students using mobile for > 2 hours/day may cause sleep deprivation and day sleepiness affecting cognitive and learning abilities of medical students.

***(E) Yuan K, Qin W, Wang G, Zeng F, Zhao L, Yang X, Liu P, Liu J, Sun J, von Deneen KM, Gong Q, Liu Y, Tian J. Microstructure abnormalities in adolescents with internet addiction disorder. PLoS One. 6(6):e20708, 2011. (HU, ME) (*Effects observed probably not caused by exposure to RFR.)**

BACKGROUND: Recent studies suggest that internet addiction disorder (IAD) is associated with structural abnormalities in brain gray matter. However, few studies have investigated the effects of internet addiction on the microstructural integrity of major neuronal fiber pathways, and almost no studies have assessed the microstructural changes with the duration of internet addiction. **METHODOLOGY/PRINCIPAL FINDINGS:** We investigated the morphology of the brain in adolescents with IAD (N = 18) using an optimized voxel-based morphometry

(VBM) technique, and studied the white matter fractional anisotropy (FA) changes using the diffusion tensor imaging (DTI) method, linking these brain structural measures to the duration of IAD. We provided evidences demonstrating the multiple structural changes of the brain in IAD subjects. VBM results indicated the decreased gray matter volume in the bilateral dorsolateral prefrontal cortex (DLPFC), the supplementary motor area (SMA), the orbitofrontal cortex (OFC), the cerebellum and the left rostral ACC (rACC). DTI analysis revealed the enhanced FA value of the left posterior limb of the internal capsule (PLIC) and reduced FA value in the white matter within the right parahippocampal gyrus (PHG). Gray matter volumes of the DLPFC, rACC, SMA, and white matter FA changes of the PLIC were significantly correlated with the duration of internet addiction in the adolescents with IAD. **CONCLUSIONS:** Our results suggested that long-term internet addiction would result in brain structural alterations, which probably contributed to chronic dysfunction in subjects with IAD. The current study may shed further light on the potential brain effects of IAD.

(E) Zareen N, Khan MY, Ali Minhas L. Derangement of chick embryo retinal differentiation caused by radiofrequency electromagnetic fields. Congenit Anom (Kyoto). 49(1):15-19, 2009. (AS, CE, ME, DE)

The possible adverse effects of radiofrequency electromagnetic fields (EMF) emitted from mobile phones present a major public concern. Biological electrical activities of the human body are vulnerable to interference from oscillatory aspects of EMF, which affect fundamental cellular activities, in particular, the highly active development process of embryos. Some studies highlight the possible health hazards of EMF, while others contest the hypothesis of biological impact of EMF. The present study was designed to observe the histomorphological effects of EMF emitted by a mobile phone on the retinae of developing chicken embryos. Fertilized chicken eggs were exposed to a ringing mobile set on silent tone placed in the incubator at different ages of development. After exposure for the scheduled duration the retinae of the embryos were dissected out and processed for histological examination. The control and experimental embryos were statistically compared for retinal thickness and epithelial pigmentation grades. Contrasting effects of EMF on the retinal histomorphology were noticed, depending on the duration of exposure. The embryos exposed for 10 post-incubation days exhibited decreased retinal growth and mild pigmentation of the epithelium. Growth retardation reallocated to growth enhancement on increasing EMF exposure for 15 post-incubation days, with a shift of pigmentation grade from mild to intense. We conclude that EMF emitted by a mobile phone cause derangement of chicken embryo retinal differentiation.

(E) Zhang SZ, Yao GD, Lu DQ, Chiang H, Xu ZP. [Effect of 1.8 GHz radiofrequency electromagnetic fields on gene expression of rat neurons]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 26(8):449-452, 2008. [Article in Chinese] (CS, CH, WS)

OBJECTIVE: To investigate the changes of gene expression in rat neuron induced by 1.8 GHz radiofrequency electromagnetic fields (RF EMF) to screen for RF EMF-responsive genes and the effect of different exposure times and modes on the gene expression in neuron. **METHODS:** Total RNA was extracted immediately and purified from the primary culture of neurons after

intermittent exposed or sham-exposed to a frequency of 1.8 GHz RF EMF for 24 hours at an average special absorption rate (SAR) of 2 W/kg. Affymetrix Rat Neurobiology U34 array was applied to investigate the changes of gene expression in rat neuron. Differentially expressed genes (Egr-1, Mbp and Plp) were further confirmed by semi-quantitative reverse transcription polymerase chain reaction (RT PCR). The expression levels of Egr-1, Mbp and Plp were observed at different exposure times (6, 24 h) and modes (intermittent and continuous exposure). RESULTS: Among 1200 candidate genes, 24 up-regulated and 10 down-regulated genes were found by using Affymetrix microarray suite software 5.0 which are associated with multiple cellular functions (cytoskeleton, signal transduction pathway, metabolism, etc.) after functional classification. Under 24 h and 6 h intermittent exposure, Egr-1 and Plp in experiment groups showed statistic significance ($P < 0.05$) compared with the control groups, while expression of Mbp did not change significantly ($P > 0.05$). After 24 h continuous exposure, Egr-1 and Mbp in experiment groups showed statistic significance ($P < 0.05$) compared with the control group, while expression of Plp did not change significantly ($P > 0.05$). Under the same exposure mode 6 h, expression of all the 3 genes did not change significantly. Different times (6, 24 h) and modes (intermittent and continuous exposure) of exposure exerted remarkable different influences on the expression of Egr-1, Mbp, Plp genes ($P < 0.01$). CONCLUSION: The changes of many genes transcription were involved in the effect of 1.8 GHz RF EMF on rat neurons; Down-regulation of Egr-1 and up-regulation of Mbp, Plp indicated the negative effects of RF EMF on neurons; The effect of RF intermittent exposure on gene expression was more obvious than that of continuous exposure; The effect of 24 h RF exposure (both intermittent and continuous) on gene expression was more obvious than that of 6 h (both intermittent and continuous).

(E) Zhang Y, She F, Li L, Chen C, Xu S, Luo X, Li M, He M, Yu Z. p25/CDK5 is partially involved in neuronal injury induced by radiofrequency electromagnetic field exposure. Int J Radiat Biol. 2013 Jul 29. [Epub ahead of print] (CS, CC)

Purpose: Several studies suggest that radiofrequency electromagnetic field (RF-EMF) exposure can induce neuronal injury. The aim of the present work was to investigate whether the cyclin-dependent kinase 5 (CDK5) pathway is involved in neuronal injury induced by RF-EMF exposure. Materials and methods: Newborn Sprague-Dawley rats' primary cultured cortical neurons were exposed to pulsed 2.45 GHz RF-EMF for 10 min. The cellular viability was assessed using the 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. The apoptosis was assessed by Hoechst 33342 and terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick-end labeling co-staining. The protein expressions of CDK5, p35, p25, and phosphorylated tau at Ser⁴⁰⁴ were examined by Western blot analysis. The CDK5 activity was detected using a histone-H1 kinase assay. Results: The cellular viability of neurons was significantly decreased ($p < 0.01$, Partial Eta Squared [η_p^2]: 0.554), and the percentage of apoptotic nuclei ($p < 0.01$, $\eta_p^2 = 0.689$), activity of CDK5 ($p < 0.05$, $\eta_p^2 = 0.589$), ratio of p25 and p35 ($p < 0.05$, $\eta_p^2 = 0.670$), levels of tau phosphorylation at Ser⁴⁰⁴ ($p < 0.01$, $\eta_p^2 = 0.896$) were significantly increased after RF-EMF exposure. No significant change was detected in CDK5 expression after RF-EMF exposure. Pretreatment with Roscovitine (a CDK5 inhibitor) significantly blocked the RF-EMF-induced decrease of cellular viability ($p < 0.05$, $\eta_p^2 = 0.398$) and tau hyperphosphorylation at Ser⁴⁰⁴ ($p <$

0.01, $\eta_p^2 = 0.917$), but did not significantly block the RF-EMF-induced apoptosis ($p > 0.05$, $\eta_p^2 = 0.130$). Conclusions: These results suggest that abnormal activity of p25/CDK5 is partially involved in primary cultured cortical neuron injury induced by RF-EMF exposure.

(E) Zhang Y, Li Z, Gao Y, Zhang C. Effects of fetal microwave radiation exposure on offspring behavior in mice. J Radiat Res. 2014 Oct 30. pii: rru097. [Epub ahead of print] (AS, CE, BE, DE)

The recent rapid development of electronic communication techniques is resulting in a marked increase in exposure of humans to electromagnetic fields (EMFs). This has raised public concerns about the health hazards of long-term environmental EMF exposure for fetuses and children. Some studies have suggested EMF exposure in children could induce nervous system disorders. However, gender-dependent effects of microwave radiation exposure on cognitive dysfunction have not previously been reported. Here we investigated whether in utero exposure to 9.417-GHz microwave throughout gestation (Days 3.5-18) affected behavior, using the open field test (OFT), elevated-plus maze (EPM), tail suspension test (TST), forced swimming test (FST) and Morris water maze (MWM). We found that mice showed less movement in the center of an open field (using the OFT) and in an open arm (using the EPM) after in utero exposure to 9.417-GHz radiation, which suggested that the mice had increased anxiety-related behavior. Mice demonstrated reduced immobility in TST and FST after in utero exposure to 9.417-GHz radiation, which suggested that the mice had decreased depression-related behavior. From the MWM test, we observed that male offspring demonstrated decreased learning and memory, while females were not affected in learning and memory, which suggested that microwaves had gender-dependent effects. In summary, we have provided the first experimental evidence of microwaves inducing gender-dependent effects.

(E) Zhao R, Zhang S, Xu Z, Ju L, Lu D, Yao G. Studying gene expression profile of rat neuron exposed to 1800MHz radiofrequency electromagnetic fields with cDNA microarray. Toxicology. 235(3):167-175, 2007. (CS, CH)

A widespread use of mobile phone (MP) evokes a growing concern for their possible adverse effects on human, especially the brain. Gene expression is a unique way of characterizing how cells and organism adapt to changes in the external environment, so the aim of this investigation was to determine whether 1800 MHz radiofrequency electromagnetic fields (RF EMF) can influence the gene expression of neuron. Affymetrix Rat Neurobiology U34 array was applied to investigate the changes of gene expression in rat neuron after exposed to the pulsed RF EMF at a frequency of 1800 MHz modulated by 217 Hz which is commonly used in MP. Among 1200 candidate genes, 24 up-regulated genes and 10 down-regulated genes were identified after 24-h intermittent exposure at an average special absorption rate (SAR) of 2 W/kg, which are associated with multiple cellular functions (cytoskeleton, signal transduction pathway, metabolism, etc.) after functional classification. The results were further confirmed by quantitative real-time polymerase chain reaction (RT PCR). The present results indicated that the gene expression of rat neuron could be altered by exposure to RF EMF under our experimental conditions.

(E) Zhao TY, Zou SP, Knapp PE. Exposure to cell phone radiation up-regulates apoptosis genes in primary cultures of neurons and astrocytes. Neurosci Lett. 412(1):34-38, 2007. (CS, CH)

The health effects of cell phone radiation exposure are a growing public concern. This study investigated whether expression of genes related to cell death pathways are dysregulated in primary cultured neurons and astrocytes by exposure to a working Global System for Mobile Communication (GSM) cell phone rated at a frequency of 1900MHz. Primary cultures were exposed to cell phone emissions for 2h. We used array analysis and real-time RT-PCR to show up-regulation of caspase-2, caspase-6 and Asc (apoptosis associated speck-like protein containing a card) gene expression in neurons and astrocytes. Up-regulation occurred in both "on" and "stand-by" modes in neurons, but only in "on" mode in astrocytes. Additionally, astrocytes showed up-regulation of the Bax gene. The effects are specific since up-regulation was not seen for other genes associated with apoptosis, such as caspase-9 in either neurons or astrocytes, or Bax in neurons. The results show that even relatively short-term exposure to cell phone radiofrequency emissions can up-regulate elements of apoptotic pathways in cells derived from the brain, and that neurons appear to be more sensitive to this effect than astrocytes.

(E) Zheng F, Gao P, He M, Li M, Wang C, Zeng Q, Zhou Z, Yu Z, Zhang L. Association between mobile phone use and inattention in 7102 Chinese adolescents: a population-based cross-sectional study. BMC Public Health. 2014 Oct 1;14(1):1022. [Epub ahead of print] (HU, CE, BE)

BACKGROUND: The dramatic growth of mobile phone (MP) use among young people has increased interest in its possible health hazards in this age group. The aim of this cross-sectional study was to investigate the association between MP use and inattention in adolescents. METHODS: A total of 7720 middle school students were involved in this cross-sectional study. Inattention was assessed as defined for the Attention Deficit component of Attention deficit/Hyperactivity disorder (ADHD) by the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev. [DSM-IV-TR]). The demographic characteristics and information on MP use were included in the questionnaire. Chi-square tests and logistic regression models were used to analyze the data. RESULTS: In total, 7102 (91.99%) valid questionnaires were obtained. After adjusted for confounders, inattention in adolescents was significantly associated with MP ownership, the time spent on entertainment on MP per day, the position of the MP during the day and the mode of the MP at night. The strongest association between inattention and the time spent on the MP was among students who spent more than 60 minutes per day playing on their MP. CONCLUSIONS: Our study shows some associations between MP use and inattention in Chinese adolescents. Decreasing MP usage to less than 60 minutes per day may help adolescents to stay focused and centered.

(E) Zuo H, Lin T, Wang D, Peng R, Wang S, Gao Y, Xu X, Zhao L, Wang S, Su Z. RKIP regulates neural cell apoptosis induced by exposure to microwave radiation partly through the MEK/ERK/CREB pathway. Mol Neurobiol. 2014 Aug 10. [Epub ahead of print] (CS, CC)

In the present study, we investigated whether Raf-1 kinase inhibitory protein (RKIP) is important for neural cell apoptosis induced by microwave exposure and explored the role of MEK/ERK/CREB pathway regulated by RKIP in the apoptosis. Differentiated PC12 cells were exposed to continuous microwave radiation at 2.856 GHz for 5 min with average power density of 30 mW/cm². RKIP sense and anti-sense recombinant plasmids were constructed and transfected into PC12 cells, respectively. Terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick end labeling (TUNEL) staining and caspase-3 activity assay were used to detect cell apoptosis. The results showed that RKIP was downregulated after microwave exposure while the MEK/ERK/CREB signaling pathway was activated excessively. Moreover, the ratio of Bcl-2/Bax decreased, activity of caspase-3 increased, and thus apoptotic DNA fragmentation increased. RKIP overexpression significantly inhibited the phosphorylation of MEK, ERK, and CREB, while RKIP downregulation had the reverse effect. Furthermore, U0126 was found to antagonize the changes caused by RKIP downregulation after exposure to radiation. In conclusion, RKIP plays an important role in the neural cell apoptosis induced by microwave radiation, and the regulation of cell apoptosis by RKIP is partly through the MEK/ERK/CREB pathway. This suggests that RKIP may act as a key regulator of neuronal damage caused by microwave radiation. Extremely Low-Frequency Electromagnetic Fields Cause G1 Phase Arrest through the Activation of the ATM-Chk2-p21 Pathway

Literature on neurological effects of extremely-low frequency electromagnetic fields (2007-2017)

Keys: **(E)** - effect observed; **(NE)** -no significant effect observed.

AS- animal study; **CS**- cell/in vitro study; **CE**- chronic/repeated exposure; **AE**- acute exposure; **HU**- human study; **MC**- morphological changes; **CC**- chemical changes; **FC**- functional changes; **EE**- electrophysiological changes; **BE**- behavioral effect ; **OX**- oxidative changes; **DE**- development; **MA**- possible medical application; **ND**- neurodegenerative disease; **EF**- electric field.

(E) Ahmed Z, Wieraszko A. The mechanism of magnetic field-induced increase of excitability in hippocampal neurons. *Brain Res.* 1221:30-40, 2008. **(CS, AE, EE)**

The influence of a pulsed magnetic field (PMF) on hippocampal evoked potentials has been investigated in vitro. The exposure to PMF (0.16 Hz, 15 mT) applied for 30 min amplified the population spike and the slope of EPSP recorded from stratum pyramidale and stratum radiatum respectively. This amplification was additive to previously induced LTP and occurred in an NMDA-independent way. The increase in the activity of electrical synapses accompanied PMF-induced amplification of evoked potentials. Since PMF exposure modified paired-pulse facilitation and paired-pulse inhibition, it was concluded that it modifies excitatory and inhibitory processes in the hippocampus. Control experiments revealed that observed effects were exclusively related to PMF exposure. The results support and extend our previous research indicating a significant influence of magnetic fields on hippocampal physiology.

(E) Akdag MZ, Dasdag S, Ulukaya E, Uzunlar AK, Kurt MA, Taşkin A. Effects of extremely low-frequency magnetic field on caspase activities and oxidative stress values in rat brain. *Biol Trace Elem Res.* 138(1-3):238-249, 2010. **(OX, AS, CC, CE)**

This study was aimed to investigate the effect of extremely low-frequency magnetic field (ELF-MF) on apoptosis and oxidative stress values in the brain of rat. Rats were exposed to 100 and 500 μ T ELF-MF, which are the safety standards of public and occupational exposure for 2 h/day for 10 months. Brain tissues were immunohistochemically stained for the active (cleaved) caspase-3 in order to measure the apoptotic index by a semi-quantitative scoring system. In addition, the levels of catalase (CAT), malondialdehyde (MDA), myeloperoxidase (MPO), total antioxidative capacity (TAC), total oxidant status (TOS), and oxidative stress index (OSI) were measured in rat brain. Final score of apoptosis and MPO activity were not significantly different between the groups. CAT activity decreased in both exposure groups ($p < 0.05$), while TAC was found to be lower in ELF 500 group than those in ELF-100 and sham groups ($p < 0.05$). MDA, TOS, and OSI values were found to be higher in ELF-500 group than those in ELF-100 and sham groups ($p < 0.05$). In conclusion, apoptosis was not changed by long-term ELF-MF exposure, while both 100 and 500 μ T ELF-MF exposure induced toxic effect in the rat brain by increasing oxidative stress and diminishing antioxidant defense system.

(E) Akdag MZ, Dasdag S, Cakir DU, Yokus B, Kizil G, Kizil M. Do 100- and 500- μ T ELF magnetic fields alter beta-amyloid protein, protein carbonyl and malondialdehyde in rat brains? Electromagn Biol Med. 32(3):363-372, 2013. (AS, CE, CC, OX)

Several studies still state that presently accepted safety standards for extremely low-frequency magnetic fields (ELF-MFs) do not provide adequate protection, and therefore the standards are still open to question. To help resolve this question, the aim of this study was to illuminate the interaction between biomolecules and ELF-MFs by investigating the effect of ELF-MFs on beta-amyloid protein (BAP), protein carbonyl (PC) and malondialdehyde (MDA) in rat brain. For this study, 30 adult male Sprague-Dawley rats were used, which were divided into two experimental groups and a sham exposed group. Rats in two experimental groups were exposed to 100- and 500- μ T ELF-MFs (50 Hz) for 2 h/day for 10 months, which are the generally accepted safety standards for public and occupational exposures. The same procedures were applied to the rats in the sham group, but with the generator turned off. The results of this study showed that neither ELF-MFs used in this study altered BAP level significantly ($p > 0.05$). However, PC and MDA levels were increased by the exposure to 100- and 500- μ T ELF-MFs ($p < 0.0001$). In conclusion, both PC and MDA levels were altered by long-term exposure to either 100 or 500 μ T ELF-MF. However, many further and more comprehensive studies will be required to elucidate the interaction mechanisms between ELF-MFs exposure and living organisms.

(E) Akpinar D, Ozturk N, Ozen S, Agar A, Yargicoglu P. The effect of different strengths of extremely low-frequency electric fields on antioxidant status, lipid peroxidation, and visual evoked potentials. Electromagn Biol Med. 31(4):436-448, 2012. (AS, CE, OX, EE)

The aim of the study was to investigate the effects of extremely low-frequency electric field (ELF EF) on visual evoked potential (VEP), thiobarbituric acid reactive substances (TBARS), total antioxidant status (TAS), total oxidant status (TOS), and oxidant stress index (OSI). Thirty female Wistar rats, aged 3 months, were divided into three equal groups: Control (C), the group exposed to EF at 12 kV/m strength (E12), and the group exposed to EF at 18 kV/m strength (E18). Electric field was applied to the E12 and E18 groups for 14 days (1 h/day). Brain and retina TBARS, TOS, and OSI were significantly increased in the E12 and E18 groups with respect to the control group. Also, TBARS levels were significantly increased in the E18 group compared with the E12 group. Electric fields significantly decreased TAS levels in both brain and retina in E12 and E18 groups with respect to the control group. All VEP components were significantly prolonged in rats exposed to electric fields compared to control group. In addition, all latencies of VEP components were increased in the E18 group with respect to the E12 group. It is conceivable to suggest that EF-induced lipid peroxidation may play an important role in changes of VEP parameters.

(NE) Aldinucci C, Carretta A, Maiorca SM, Leoncini S, Signorini C, Ciccoli L, Pessina GP. Effects of 50 Hz electromagnetic fields on rat cortical synaptosomes. Toxicol Ind Health. 25(4-5):249-252, 2009. (CS, CC, AE)

Nerve cells are very responsive to weak pulsed electromagnetic fields (EMFs). Such non-ionizing radiation, with frequencies of 0-300 Hz and 0.1-100 mT, can affect several cellular activities, with unusual dose-response characteristics. The present study examined the effect of a 2-h exposure of synaptosomes on a system generating a peak magnetic field of 2 mT. We evaluated the changes of the synaptosomal mitochondrial respiration rate and ATP production, membrane potential, intrasynaptosomal Ca^{2+} concentration, and the release of free iron and F2-isoprostanes. O_2 consumption and ATP production remained unchanged in exposed synaptosomes. The intrasynaptosomal Ca^{2+} concentration decreased slowly and no depolarization of the synaptosomal membrane was detected. Finally, the release of free iron and F2-isoprostanes by synaptosomal suspensions also remained unchanged after EMF exposure. These results indicate that the physiological behavior of cortical synaptosomes was unaffected by weak pulsed EMFs.

(E) Alsaeed I, Al-Somali F, Sakhnini L, Aljarallah OS, Hamdan RM, Bubishate SA, Sarfaraz ZK, Kamal A. Autism-relevant social abnormalities in mice exposed perinatally to extremely low frequency electromagnetic fields. Int J Dev Neurosci. 2014 Jun 23. pii: S0736-5748(14)00092-6. doi: 10.1016/j.ijdevneu.2014.06.010. [Epub ahead of print]. (AS, CE, BE, DE)

The incidence of autism spectrum disorders (ASD) has been rising, but the causes of ASD remain largely unidentified. Collective data have implicated the increased human exposure to electromagnetic fields (EMF) in the increasing incidence of ASD. There are established biological effects of extremely low-frequency (ELF) EMF, but the relation to ASD is not investigated enough. In this study we examined the effects of perinatal exposure to ELF EMF on some ASD-relevant behavioral parameters in mice. The EMF was delivered via a Helmholtz coil pair. Male BALB/C mice were used and divided into exposed and control groups ($n=8$ and $n=9$, respectively). Tests were used to assess sociability, preference for social novelty, locomotion, anxiety, exploratory behavior, motor coordination, and olfaction. The examined mice were all males and exposed to EMF during the last week of gestation and for 7 days after delivery. The exposed mice demonstrated a lack of normal sociability and preference for social novelty while maintaining normal anxiety-like behavior, locomotion, motor coordination, and olfaction. Exposed mice also demonstrated decreased exploratory activity. We concluded that these results are supportive of the hypothesis of a causal link between exposure to ELF-EMF and ASD; however, replications of the study with further tests are recommended.

(E) Amirifalah Z, Firoozabadi SM, Shafiei SA. Local Exposure of Brain Central Areas to a Pulsed ELF Magnetic Field for a Purposeful Change in EEG. Clin EEG Neurosci. 44(1):44-52, 2013. (HU, EE)

This study examines the simultaneous exposure of 2 brain areas in the location of central electrodes (C3 and C4) to a weak and pulsed extremely low-frequency magnetic field (ELF-MF) on the electroencephalogram (EEG). The intent is to change the EEG for a therapeutic application, such as neurofeedback, by inducing the "resonance effect." A total of 10 healthy women received 9 minutes of ELF-MF (intensity 200 μT) and sham in a counterbalanced design. ELF-MF exposure frequencies were 10, 14, and 18 Hz. The paired t test revealed that local

pulsed ELF-MF significantly decreases beta (15-25 Hz), sensorimotor rhythm (13-15 Hz), and theta (4-8 Hz) powers at a frequency of 10 Hz in C3 and C4 regions (12.0%-26.6%) after exposure, in comparison with that achieved during the exposure ($P < .05$). Variations during the exposure were transient and different from those after. The resonance effect was observed nowhere around the regions. The study suggests that this technique may be applied in the treatment of anxiety; however, further investigation is needed.

(NE) Azanza MJ, del Moral A, Calvo AC, Pérez-Bruzón RN, Junquera C. Synchronization dynamics induced on pairs of neurons under applied weak alternating magnetic fields. Comp Biochem Physiol A Mol Integr Physiol. 166(4):603-618, 2013.(CS, AE, EE, MC)

Pairs of *Helix aspersa* neurons show an alternating magnetic field dependent frequency synchronization (AMFS) when exposed to a weak (amplitude B_0 between 0.2 and 150 Gauss (G)) alternating magnetic field (AMF) of extremely low frequency (ELF, $f_M = 50$ Hz). We have compared the AMFS patterns of discharge with: i) the synaptic activity promoted by glutamate and acetylcholine; ii) the activity induced by caffeine; iii) the bioelectric activity induced on neurons interconnected by electric synapses. AMFS activity reveals several specific features: i) a tight coincidence in time of the pattern and frequency, f , of discharge; ii) it is induced in the time interval of field application; iii) it is dependent on the intensity of the sinusoidal applied magnetic field; iv) elicited biphasic responses (excitation followed by inhibition) run in parallel for the pair of neurons; and v) some neuron pairs either spontaneously or AMF synchronized can be desynchronized under applied higher AMF. Our electron microscopy studies reveal gap-like junctions confirming our immunocytochemistry results about expression of connexin 26 (Cx26) in 4.7% of *Helix* neurons. AMF and carbenoxolone did not induce any significant effect on spontaneous synchronization through electric synapses.

(E) Bai WF, Xu WC, Feng Y, Huang H, Li XP, Deng CY, Zhang MS. Fifty-Hertz electromagnetic fields facilitate the induction of rat bone mesenchymal stromal cells to differentiate into functional neurons. Cytotherapy. 15(8):961-970, 2013. (CS, CE, MC, MA, ND)

BACKGROUND AIMS: Research results have shown that bone mesenchymal stromal cells (BMSC) can differentiate into neural cells. Electromagnetic fields (EMF) play a role in regulating cell proliferation and differentiation, but the mechanisms behind this are unknown. In the present study, we explored the efficacy of EMF on the induction of rat BMSC differentiation into neurons in vitro. **METHODS:** First, rat BMSC were induced in a nerve cell culture environment and divided into three groups: an EMF induction treatment group (frequency of 50 Hz, magnetic induction of 5 mT, 60 min per day for 12 days), an induction-only group and a control group. Second, we observed cell phenotypes in a confocal microscope, tested gene expression through the use of reverse transcriptase-polymerase chain reaction, and detected postsynaptic currents by means of a cell patch-clamp. We analyzed the cell cycles and the portion of cells expressing neural cell markers with the use of flow cytometry. **RESULTS:** The results indicated that EMF can facilitate BMSC differentiation into neural cells, which expressed neuronal-specific markers and genes; they formed synaptic junctions and pulsed excitatory postsynaptic currents.

At the same time, the G0-G1 phase ratio recorded by means of flow cytometry gradually decreased under the EMF treatment, whereas there was an increase of S-phase ratio, and the portion of cells expressing neuronal-specific markers increased. CONCLUSIONS: Given that a noninvasive treatment of 50-Hz EMF could significantly facilitate BMSC to differentiate into functional neurons, EMF appears to be a promising clinical option for stem cell transplantation therapies to combat central nervous system diseases.

(E) Balassa T, Szemerszky R, Bárdos G. Effect of short-term 50 Hz electromagnetic field exposure on the behavior of rats. Acta Physiol Hung. 96(4):437-448, 2009. (AS, BE, AE)

Extremely low-frequency electromagnetic field generated by transformer stations located within buildings has been suspected to initiate non-specific health problems. This possibility was examined in model experiments in rats. Following short-term exposure (50 Hz, 500 microT, 20 min), situational and social anxiety as well as locomotor activity pattern were examined by several different tests (elevated plus-maze, novel object exploration, social interaction and territoriality). Based on our results having obtained so far, it seems that these field parameters (that equals the official reference limit for workers) may cause some kind of discomfort, may influence behavior, increase passivity and situational anxiety, but has no verified effect on the social and territorial behavior.

(E) Balassa T, Varró P, Elek S, Drozdovszky O, Szemerszky R, Világi I, Bárdos G. Changes in synaptic efficacy in rat brain slices following extremely low-frequency magnetic field exposure at embryonic and early postnatal age. Int J Dev Neurosci. 31(8):724-730, 2013. (AS, CE, EE, DE)

An earlier study demonstrated changes in synaptic efficacy and seizure susceptibility in adult rat brain slices following extremely low-frequency magnetic field (ELF-MF) exposure. The developing embryonic and early postnatal brain may be even more sensitive to MF exposure. The aim of the present study was to determine the effects of a long-term ELF-MF (0.5 and 3 mT, 50 Hz) exposure on synaptic functions in the developing brain. Rats were treated with chronic exposure to MF during two critical periods of brain development, i.e. in utero during the second gestation week or as newborns for 7 days starting 3 days after birth, respectively. Excitability and plasticity of neocortical and hippocampal areas were tested on brain slices by analyzing extracellular evoked field potentials. We demonstrated that the basic excitability of hippocampal slices (measured as amplitude of population spikes) was increased by both types of treatment (fetal 0.5 mT, newborn 3 mT). Neocortical slices seemed to be responsive mostly to the newborn treatment, the amplitude of excitatory postsynaptic potentials was increased. Fetal ELF-MF exposure significantly inhibited the paired-pulse depression (PPD) and there was a significant decrease in the efficacy of LTP (long-term potentiation induction) in neocortex, but not in hippocampus. On the other hand, neonatal treatment had no significant effect on plasticity phenomena. Results demonstrated that ELF-MF has significant effects on basic neuronal functions and synaptic plasticity in brain slice preparations originating from rats exposed either in fetal or in newborn period.

(E) Ben Yakir-Blumkin M, Loboda Y, Schächter L, Finberg JP. Neuroprotective effect of weak static magnetic fields in primary neuronal cultures. Neuroscience. 2014 Aug 26. pii: S0306-4522(14)00706-4. doi: 10.1016/j.neuroscience.2014.08.029. [Epub ahead of print] (CS, CE, CC, MA)

Low intensity static magnetic fields (SMFs) interact with various biological tissues including the CNS, thereby affecting key biological processes such as gene expression, cell proliferation and differentiation, as well as apoptosis. Previous studies describing the effect of SMFs on apoptotic cell death in several non-neuronal cell lines, emphasize the importance of such a potential modulation in the case of neurodegenerative disorders, where apoptosis constitutes a major route via which neurons degenerate and die. In this study, we examine the effect of SMFs on neuronal survival in primary cortical and hippocampal neurons that constitute a suitable experimental system for modeling the neurodegenerative state in vitro. We show that weak SMF exposure interferes with the apoptotic programming in rat primary cortical and hippocampal neurons, thereby providing protection against etoposide-induced apoptosis in a dose- and time-dependent manner. Primary cortical neurons exposed to SMF (50 G) for 7 days exhibited a $57.1 \pm 6.3\%$ decrease in the percentage of cells undergoing apoptosis induced by etoposide ($12 \mu\text{M}$), accompanied by a marked decrease in the expression of the pro-apoptotic markers: cleaved poly ADP ribose polymerase-1, cleaved caspase-3, active caspase-9 and the phospho- histone H2A variant (Ser 139) by $41.0 \pm 5.0\%$, $81.2 \pm 5.0\%$, $72.9 \pm 6.4\%$, $42.75 \pm 2.9\%$, respectively, and by a $57.2 \pm 1.0\%$ decrease in the extent of mitochondrial membrane potential collapse. Using the L-type voltage-gated Ca^{2+} channel inhibitor nifedipine, which is selective to Ca^{2+} influx through $\text{Ca}_v1.2$, we found that the anti-apoptotic effect of SMFs was mediated by Ca^{2+} influx through these channels. Our findings demonstrating altered Ca^{2+} -influx in response to thapsigargin stimulation in SMF-exposed cortical neurons, along with enhanced inhibition of KCl-induced Ca^{2+} -influx through $\text{Ca}_v1.2$ channels and enhanced expression of $\text{Ca}_v1.2$ and $\text{Ca}_v1.3$ channels, allude to the involvement of voltage and store operated Ca^{2+} channels in various aspects of the protective effect exerted by SMFs. These findings show the potential susceptibility of the CNS to weak SMF exposure and have implications for the design of novel strategies for the treatment and/or prevention of neurodegenerative diseases.

(E) Calabrò E, Condello S, Magazù S, Ientile, R. Static and 50 Hz electromagnetic fields effects on human neuronal-like cells vibration bands in the mid-infrared region. J Electromagnetic Analysis and Applications 3(2) 69-78, 2011. (CS, AE, CC)

Human neuronal-like cells were exposed to static and 50 Hz electromagnetic fields at the intensities of 2 mT and 1 mT, respectively. The effects of exposure were investigated in the mid-infrared region by means of Fourier self deconvolution spectroscopic analysis. After exposure of 3 hours to static and 50 Hz electromagnetic fields, the vibration bands of CH₂ methylene group increased significantly after both exposures, suggesting a relative increase of lipid related to conformational changes in the cell membrane due to electromagnetic fields. In addition, PO₂-stretching phosphate bands decreased after both exposures, suggesting that alteration in DNA/RNA can be occurred. In particular, exposure of 3 hours to 50 Hz electromagnetic fields produced significant increases in β -sheet contents in amide I, and around the 1740 cm^{-1} band

assigned to non-hydrogen-bonded ester carbonyl stretching mode, that can be related to unfolding processes of proteins structure and cells death. Further exposure up to 18 hours to static magnetic field produced an increase in β -sheet contents as to α -helix components of amide I region, as well.

(E) Calabrò E, Condello S, Currò M, Ferlazzo N, Vecchio M, Caccamo D, Magazù S, Ientile R. 50 Hz Electromagnetic Field Produced Changes in FTIR Spectroscopy Associated with Mitochondrial Transmembrane Potential Reduction in Neuronal-Like SH-SY5Y Cells. Oxid Med Cell Longev. 2013;2013:414393. doi: 10.1155/2013/414393. Epub 2013 Jul 16. (CS, AE, EE)

SH-SY5Y neuroblastoma cells were used as an experimental model to study the effects of 50 Hz electromagnetic field, in the range from 50 μ T to 1.4 mT. Fourier transform infrared spectroscopy analysis evidenced a reduction in intensity of the amide A band and a slight increase of vibration bands at 2921 cm^{-1} and 2853 cm^{-1} corresponding to methylene groups. A further increase of the magnetic field intensity of exposure up to 0.8 mT and 1.4 mT produced a clear increase in intensity of CH₂ vibration bands. Moreover, it has been observed some alterations in the amide I region, such as a shifted peak of the amide I band to a smaller wavenumber, probably due to protein conformational changes. These results suggested that exposure to extremely low electromagnetic fields influenced lipid components of cellular membrane and the N-H in-plane bending and C-N stretching vibrations of peptide linkages, modifying the secondary structures of α -helix and β -sheet contents and producing unfolding process in cell membrane proteins. The observed changes after exposure to 50 Hz electromagnetic field higher than 0.8 mT were associated with a significant reduction of cell viability and reduced mitochondrial transmembrane potential.

(NE) Canseven AG, Keskil ZA, Keskil S, Seyhan N. Pentylenetetrazol-induced seizures are not altered by pre- or post-drug exposure to a 50 Hz magnetic field. Radiat Biol. 83(4):231-235, 2007. (AS, AE, BE)

PURPOSE: To investigate whether pre- and post-drug magnetic field (MF) exposure of 50 Hz, 0.2 mT has any significant effect on pentylenetetrazol (PTZ)-induced seizures in mice. MATERIAL AND METHODS: MF was generated by a pair of Helmholtz coils. Seizures were induced by PTZ injection intraperitoneally (i.p.) at a dose of 60 mg/kg. A total of 48 locally bred adult female mice 25-35 g in weight were used. Latency to seizure, total seizure duration, and mortality were recorded for each mouse. RESULTS: Neither pre- nor post-drug exposure to a 50 Hz, 0.2 mT MF was found to have any effect on PTZ-induced epileptic seizures or mortality rates in mice. CONCLUSION: The present study failed to provide any support for a therapeutic potential of a 50 Hz, 0.2 mT MF for epilepsy.

(E) Capone F, Dileone M, Profice P, Pilato F, Musumeci G, Minicuci G, Ranieri F, Cadossi R, Setti S, Tonali PA, Di Lazzaro V. Does exposure to extremely low frequency magnetic fields produce functional changes in human brain? J Neural Transm. 116(3):257-265, 2009. (HU, FC)

Behavioral and neurophysiological changes have been reported after exposure to extremely low frequency magnetic fields (ELF-MF) both in animals and in humans. The physiological bases of these effects are still poorly understood. In vitro studies analyzed the effect of ELF-MF applied in pulsed mode (PEMFs) on neuronal cultures showing an increase in excitatory neurotransmission. Using transcranial brain stimulation, we studied noninvasively the effect of PEMFs on several measures of cortical excitability in 22 healthy volunteers, in 14 of the subjects we also evaluated the effects of sham field exposure. After 45 min of PEMF exposure, intracortical facilitation produced by paired pulse brain stimulation was significantly enhanced with an increase of about 20%, while other parameters of cortical excitability remained unchanged. Sham field exposure produced no effects. The increase in paired-pulse facilitation, a physiological parameter related to cortical glutamatergic activity, suggests that PEMFs exposure may produce an enhancement in cortical excitatory neurotransmission. This study suggests that PEMFs may produce functional changes in human brain.

(E) Carrubba S, Frilot C 2nd, Chesson AL Jr, Marino AA. Mobile-phone pulse triggers evoked potentials. *Neurosci Lett.* 469(1):164-168, 2010. (HU, EE)

If mobile-phone electromagnetic fields (EMFs) are hazardous, as suggested in the literature, processes or mechanisms must exist that allow the body to detect the fields. We hypothesized that the low-frequency pulses produced by mobile phones (217 Hz) were detected by sensory transduction, as evidenced by the ability of the pulses to trigger evoked potentials (EPs). Electroencephalograms (EEGs) were recorded from six standard locations in 20 volunteers and analyzed to detect brain potentials triggered by a pulse of the type produced by mobile phones. Evoked potentials having the expected latency were found in 90% of the volunteers, as assessed using a nonlinear method of EEG analysis. Evoked potentials were not detected when the EEG was analyzed using time averaging. The possibility of systematic error was excluded by sham-exposure analyses. The results implied that mobile-phones trigger EP at the rate of 217 Hz during ordinary phone use. Chronic production of the changes in brain activity might be pertinent to the reports of health hazards among mobile-phone users.

(E) Carrubba S, Frilot C, Chesson AL, Marino AA. Nonlinear EEG activation evoked by low-strength low-frequency magnetic fields. *Neurosci Lett.* 417(2):212-216, 2007. (HU, AE, EE)

Recent electrophysiological evidence suggested the existence of a human magnetic sense, but the kind of dynamical law that governed the stimulus-response relationship was not established. We tested the hypothesis that brain potentials evoked by the onset of a weak, low-frequency magnetic field were nonlinearly related to the stimulus. A field of 1G, 60 Hz was applied for 2s, with a 5s inter-stimulus period, and brain potentials were recorded from occipital electrodes in eight subjects, each of whom were measured twice, with at least 1 week between measurements. The recorded signals were subjected to nonlinear (recurrence analysis) and linear (time averaging) analyses. Using recurrence analysis, magnetosensory evoked potentials (MEPs) were detected in each subject in both the initial and replicate studies, with one exception. All MEPs exhibited the expected latency but differed in dynamical characteristics, indicating that they were nonlinearly related to the stimulus. MEPs were not

detected using time averaging, thereby further confirming their nonlinearity. Evolutionarily conditioned structures that help mediate linear field-transduction in lower life forms may be expressed and functionally utilized in humans, but in a role where they facilitate vulnerability to man-made environmental fields.

(E) Celik MS, Guven K, Akpolat V, Akdag MZ, Naziroglu M, Gul-Guven R, Celik MY, Erdogan S. Extremely low-frequency magnetic field induces manganese accumulation in brain, kidney and liver of rats. Toxicol Ind Health. 2013 Feb 28. [Epub ahead of print] (AS, CE, CC)

The aim of the present study was to determine the effects of extremely low-frequency magnetic field (ELF-MF) on accumulation of manganese (Mn) in the kidney, liver and brain of rats. A total of 40 rats were randomly divided into eight groups. Four control groups received 0, 3.75, 15 and 60 mg Mn per kg body weight orally every 2 days for 45 days, respectively. The remaining four groups received same concentrations of Mn and were also exposed to ELF-MF (1.5 mT; 50 Hz) for 4 h for 5 days a week during 45 days. Following the last exposure, kidney, liver and brain were taken from all rats and they were analyzed for Mn accumulation levels using an inductively coupled plasma-optical emission spectrometer. In result of the current study, we observed that Mn levels in brain, kidney and liver were higher in Mn groups than in control groups. Mn levels in brain, kidney and liver were also higher in Mn plus ELF-MF groups than in Mn groups. In conclusion, result of the current study showed that the ELF-MF induced manganese accumulation in kidney, liver and brain of rats.

(E) Che Y, Sun H, Cui Y, Zhou D, Ma Y. Effects of exposure to 50 Hz magnetic field of 1 mT on the performance of detour learning task by chicks. Brain Res Bull. 74(1-3):178-182, 2007. (AS, CE, BE)

In the present study, we examined the effects of exposure to an extremely low-frequency magnetic field of 1 mT intensity on learning and memory in Lohmann brown domestic chicks using detour learning task. These results show that 20 h/day exposure to a low-frequency magnetic field induces a significant impairment in detour learning but 50 min/day exposure has no effect.

(E) Cho H, Seo YK, Yoon HH, Kim SC, Kim SM, Song KY, Park JK. Neural stimulation on human bone marrow-derived mesenchymal stem cells by extremely low frequency electromagnetic fields (ELF-EMFs). Biotechnol Prog. 2012 Jul 31. doi: 10.1002/btpr.1607. [Epub ahead of print] (CS, CE, MC, DE, MA)

Adult stem cells are considered to be multipotent. Especially, human bone marrow-derived mesenchymal stem cells (hBM-MSCs) have the potential to differentiate into nerve type cells. Electromagnetic fields (EMFs) are widely distributed in the environment, and recently there have been many reports on the biological effects of EMFs. hBM-MSCs are weak and sensitive pluripotent stem cells, therefore extremely low frequency- electromagnetic fields (ELF-EMFs) could be affect the changes of biological functions within the cells. In our experiments, ELF-EMFs inhibited the growth of hBM-MSCs in 12 days exposure. Their gene level was changed and

expression of the neural stem cell marker like nestin was decreased but the neural cell markers like MAP2, NEUROD1, NF-L and Tau were induced. In immunofluorescence study, we confirmed the expression of each protein of neural cells. And also both oligodendrocyte and astrocyte related proteins like O4 and GFAP were expressed by ELF-EMFs. **We suggest that EMFs can induce neural differentiation in BM-MSCs without any chemicals or differentiation factors.**

(E) Cho SI, Nam YS, Chu LY, Lee JH, Bang JS, Kim HR, Kim HC, Lee YJ, Kim HD, Sul JD, Kim D, Chung YH, Jeong JH. Extremely low-frequency magnetic fields modulate nitric oxide signaling in rat brain. Bioelectromagnetics. 33(7):568-574, 2012. (AS, CE, CC, OX)

Our previous study has shown that an extremely low-frequency magnetic field (ELF-MF) induces nitric oxide (NO) synthesis by Ca(2+) -dependent NO synthase (NOS) in rat brain. The present study was designed to confirm that ELF-MF affects neuronal NOS (nNOS) in several brain regions and to investigate the correlation between NO and nNOS activation. The exposure of rats to a 2 mT, 60 Hz ELF-MF for 5 days resulted in increases of NO levels in parallel with cGMP elevations in the cerebral cortex, striatum, and hippocampus. Cresyl violet staining and electron microscopic evaluation revealed that there were no significant differences in the morphology and number of neurons in the cerebral cortex, striatum, and hippocampus. Differently, the numbers of nNOS-immunoreactive (IR) neurons were significantly increased in those cerebral areas in ELF-MF-exposed rats. These data suggest that the increase in NO could be due to the increased expression and activation of nNOS in cells. Based on NO signaling in physiological and pathological states, ELF-MF created by electric power systems may induce various physiological changes in modern life.

(E) Choi YK, Lee DH, Seo YK, Jung H, Park JK, Cho H. Stimulation of neural differentiation in human bone marrow mesenchymal stem cells by extremely low-frequency electromagnetic fields incorporated with MNPs. Appl Biochem Biotechnol. 2014 Aug 7. [Epub ahead of print] (CS, AE, MC, MA)

Human bone marrow-derived mesenchymal stem cells (hBM-MSCs) have been investigated as a new cell-therapeutic solution due to their capacity that could differentiate into neural-like cells. Extremely low-frequency electromagnetic fields (ELF-EMFs) therapy has emerged as a novel technique, using mechanical stimulus to differentiate hBM-MSCs and significantly enhance neuronal differentiation to affect cellular and molecular reactions. Magnetic iron oxide (Fe₃O₄) nanoparticles (MNPs) have recently achieved widespread use for biomedical applications and polyethylene glycol (PEG)-labeled nanoparticles are used to increase their circulation time, aqueous solubility, biocompatibility, and nonspecific cellular uptake as well as to decrease immunogenicity. Many studies have used MNP-labeled cells for differentiation, but there have been no reports of MNP-labeled neural differentiation combined with EMFs. In this study, synthesized PEG-phospholipid encapsulated magnetite (Fe₃O₄) nanoparticles are used on hBM-MSCs to improve their intracellular uptake. The PEGylated nanoparticles were exposed to the cells under 50 Hz of EMFs to improve neural differentiation. First, we measured cell viability and intracellular iron content in hBM-MSCs after treatment with MNPs. Analysis was conducted by RT-PCR, and immunohistological analysis using neural cell type-specific genes and antibodies

after exposure to 50 Hz electromagnetic fields. These results suggest that electromagnetic fields enhance neural differentiation in hBM-MSCs incorporated with MNPs and would be an effective method for differentiating neural cells.

(E) Chu LY, Lee JH, Nam YS, Lee YJ, Park WH, Lee BC, Kim D, Chung YH, Jeong JH. Extremely low frequency magnetic field induces oxidative stress in mouse cerebellum. Gen Physiol Biophys. 30(4):415-421, 2011. (AS, CE, OX)

We have investigated whether extremely low frequency magnetic field (ELF-MF) induces lipid peroxidation and reactive oxygen species in mouse cerebellum. After exposure to 60 Hz ELF-MF at 2.3 mT intensity for 3 hours, there was a significant increase in malondialdehyde level and hydroxyl radical. ELF-MF significantly induced concomitant increase in superoxide dismutase without alteration in glutathione peroxidase activity. While glutathione contents were not altered, ascorbic acid levels were significantly decreased by ELF-MF exposure. These results indicate that ELF-MF may induce oxidative stress in mouse cerebellum. However, the mechanism remains further to be characterized.

(E) Ciejk E, Kleniewska P, Skibska B, Goraca A. Effects of extremely low frequency magnetic field on oxidative balance in brain of rats. J Physiol Pharmacol. 62(6):657-661, 2011. (AS, CE, OX)

Extremely low frequency magnetic field (ELF-MF) may result in oxidative DNA damage and lipid peroxidation with an ultimate effect on a number of systemic disturbances and cell death. The aim of the study is to assess the effect of ELF-MF parameters most frequently used in magnetotherapy on reactive oxygen species generation (ROS) in brain tissue of experimental animals depending on the time of exposure to this field. The research material included adult male Sprague-Dawley rats, aged 3-4 months. The animals were divided into 3 groups: I - control (shame) group; II - exposed to the following parameters of the magnetic field: 7 mT, 40 Hz, 30 min/day, 10 days; III - exposed to the ELF-MF parameters of 7 mT, 40 Hz, 60 min/day, 10 days. The selected parameters of oxidative stress: thiobarbituric acid reactive substances (TBARS), hydrogen peroxide (H_2O_2), total free sulphhydryl groups (-SH groups) and protein in brain homogenates were measured after the exposure of rats to the magnetic field. ELF-MF parameters of 7 mT, 40 Hz, 30 min/day for 10 days caused a significant increase in lipid peroxidation and insignificant increase in H_2O_2 and free -SH groups. The same ELF-MF parameters but applied for 60 min/day caused a significant increase in free -SH groups and protein concentration in the brain homogenates indicating the adaptive mechanism. The study has shown that ELF-MF applied for 30 min/day for 10 days can affect free radical generation in the brain. Prolongation of the exposure to ELF-MF (60/min/day) caused adaptation to this field. The effect of ELF-MF irradiation on oxidative stress parameters depends on the time of animal exposure to magnetic field.

(E) Cook CM, Saucier DM, Thomas AW, Prato FS. Changes in human EEG alpha activity following exposure to two different pulsed magnetic field sequences. Bioelectromagnetics. 30(1):9-20, 2009. (AE, HU, EE)

The present study investigates the effects of a weak (± 200 microT(pk)), pulsed, extremely low frequency magnetic field (ELF MF) upon the human electroencephalogram (EEG). We have previously determined that exposure to pulsed ELF MFs can affect the EEG, notably the alpha frequency (8-13 Hz) over the occipital-parietal region of the scalp. In the present study, subjects ($n = 32$) were exposed to two different pulsed MF sequences (1 and 2, used previously) that differed in presentation rate, in order to examine the effects upon the alpha frequency of the human EEG. Results suggest that compared to sham exposure, alpha activity was lowered over the occipital-parietal regions of the brain during exposure to Sequence 1, while alpha activity over the same regions was higher after Sequence 2 exposure. These effects occurred after approximately 5 min of pulsed MF exposure. The results also suggest that a previous exposure to the pulsed MF sequence determined subjects' responses in the present experiment. This study supports our previous observation of EEG changes after 5 min pulsed ELF MF exposure. The results of this study are also consistent with existing EEG experiments of ELF MF and mobile phone effects upon the brain.

(E) Corbacio M, Brown S, Dubois S, Goulet D, Prato FS, Thomas AW, Legros A. Human cognitive performance in a 3 mT power-line frequency magnetic field. Bioelectromagnetics. 32(8):620-633, 2011. (HU, AE, BE)

Extremely low frequency (ELF, <300 Hz) magnetic fields (MF) have been reported to modulate cognitive performance in humans. However, little research exists with MF exposures comparable to the highest levels experienced in occupations like power line workers and industrial welders. This research aims to evaluate the impact of a 60 Hz, 3 mT MF on human cognitive performance. Ninety-nine participants completed the double-blind protocol, performing a selection of psychometric tests under two consecutive MF exposure conditions dictated by assignment to one of three groups (sham/sham, MF exposure/sham, or sham/MF exposure). Data were analyzed using a 3×2 mixed model analysis of variance. Performance between repetitions improved in 11 of 15 psychometric parameters (practice effect). A significant interaction effect on the digit span forward test ($F = 5.21$, $P < 0.05$) revealed an absence of practice effects for both exposure groups but not the control group. **This memory test indicates MF-induced abolition of the improvement associated with practice.** Overall, this study does not establish any clear MF effect on human cognition. It is speculated that an ELF MF may interfere with the neuropsychological processes responsible for this short-term learning effect supported by brain synaptic plasticity.

(E) Coşkun S, Balabanlı B, Canseven A, Seyhan N. Effects of continuous and intermittent magnetic fields on oxidative parameters in vivo. Neurochem Res. 34(2):238-243, 2009. (AS, CE, CC, OX)

Continuous and intermittent 50 Hz, 1.5 mT magnetic field with the exposure period of 4 h/day for 4 days was used to investigate its possible effect on adult guinea pigs. Tissues and plasma specimens were assessed by biochemical parameters. Malondialdehyde (MDA), glutathione (GSH), nitric oxide (NO) levels and myeloperoxidase activity (MPO) were examined in plasma, liver and brain tissues. All parameters were determined by spectrophotometer. While

intermittent magnetic field was effective on plasma lipid peroxidation, continuous magnetic field was found to be effective on plasma MPO activity and NO levels. Augmentation of lipid peroxidation was also observed in liver tissue both intermittent and continuous magnetic field exposures. These results indicate that both the intermittent and continuous magnetic field exposures affect various tissues in a distinct manner because of having different tissue antioxidant status and responses.

(E) Cuccurazzu B, Leone L, Podda MV, Piacentini R, Riccardi E, Ripoli C, Azzena GB, Grassi C. Exposure to extremely low-frequency (50 Hz) electromagnetic fields enhances adult hippocampal neurogenesis in C57BL/6 mice. Exp Neurol. 226(1):173-182, 2010. (AS, CE, MC, MA)

Throughout life, new neurons are continuously generated in the hippocampus, which is therefore a major site of structural plasticity in the adult brain. We recently demonstrated that extremely low-frequency electromagnetic fields (ELFEFs) promote the neuronal differentiation of neural stem cells in vitro by up-regulating Ca(v)1-channel activity. The aim of the present study was to determine whether 50-Hz/1 mT ELFEF stimulation also affects adult hippocampal neurogenesis in vivo, and if so, to identify the molecular mechanisms underlying this action and its functional impact on synaptic plasticity. ELFEF exposure (1 to 7 h/day for 7 days) significantly enhanced neurogenesis in the dentate gyrus (DG) of adult mice, as documented by increased numbers of cells double-labeled for 5-bromo-deoxyuridine (BrdU) and double cortin. Quantitative RT-PCR analysis of hippocampal extracts revealed significant ELFEF exposure-induced increases in the transcription of pro-neuronal genes (Mash1, NeuroD2, Hes1) and genes encoding Ca(v)1.2 channel $\alpha(1C)$ subunits. Increased expression of NeuroD1, NeuroD2 and Ca(v)1 channels was also documented by Western blot analysis. Immunofluorescence experiments showed that, 30 days after ELFEF stimulation, roughly half of the newly generated immature neurons had survived and become mature dentate granule cells (as shown by their immunoreactivity for both BrdU and NeuN) and were integrated into the granule cell layer of the DG. Electrophysiological experiments demonstrated that the new mature neurons influenced hippocampal synaptic plasticity, as reflected by increased long-term potentiation. Our findings show that ELFEF exposure can be an effective tool for increasing in vivo neurogenesis, and they could lead to the development of novel therapeutic approaches in regenerative medicine.

(E) Cui Y, Ge Z, Rizak JD, Zhai C, Zhou Z, Gong S, Che Y. Deficits in water maze performance and oxidative stress in the hippocampus and striatum induced by extremely low frequency magnetic field exposure. PLoS One. 7(5):e32196, 2012. (AS, CE, BE, OX)

The exposures to extremely low frequency magnetic field (ELF-MF) in our environment have dramatically increased. Epidemiological studies suggest that there is a possible association between ELF-MF exposure and increased risks of cardiovascular disease, cancers and neurodegenerative disorders. Animal studies show that ELF-MF exposure may interfere with the activity of brain cells, generate behavioral and cognitive disturbances, and produce deficits in attention, perception and spatial learning. Although, many research efforts have been

focused on the interaction between ELF-MF exposure and the central nervous system, the mechanism of interaction is still unknown. In this study, we examined the effects of ELF-MF exposure on learning in mice using two water maze tasks and on some parameters indicative of oxidative stress in the hippocampus and striatum. We found that ELF-MF exposure (1 mT, 50 Hz) induced serious oxidative stress in the hippocampus and striatum and impaired hippocampal-dependent spatial learning and striatum-dependent habit learning. This study provides evidence for the association between the impairment of learning and the oxidative stress in hippocampus and striatum induced by ELF-MF exposure.

(E) Cvetkovic D, Cosic I. Alterations of human electroencephalographic activity caused by multiple extremely low frequency magnetic field exposures. Med Biol Eng Comput. 47(10):1063-1073, 2009. (HU, AE, EE, MA)

In the past, many studies have claimed that extremely low frequency (ELF) magnetic field (MF) exposures could alter the human electroencephalographic (EEG) activity. This study aims at extending our ELF pilot study to investigate whether MF exposures at ELF in series from 50, 16.66, 13, 10, 8.33 to 4 Hz could alter relative power within the corresponding EEG bands. 33 human subjects were tested under a double-blind and counter-balanced conditions. The multiple repeated three-way analysis of variance (ANOVA) mixed design (within and between-subject) analysis was employed followed by post-hoc t-tests and Bonferroni alpha-correction. The results from this study have shown that narrow alpha1 (7.5-9.5 Hz) and alpha2 (9-11 Hz) bands, associated with 8.33 and 10 Hz MF exposures, were significantly ($p < 0.0005$) lower than control over the temporal and parietal regions within the 10-16 min of first MF exposure session and the MF exposures were significantly higher than control of the second session MF exposure (60-65 min from the commencement of testing). Also, it was found that the beta1 (12-14 Hz) band exhibited a significant increase from before to after 13-Hz first MF exposure session at frontal region. The final outcome of our result has shown that it is possible to alter the human EEG activity of alpha and beta bands when exposed to MF at frequencies corresponding to those same bands, depending on the order and period of MF conditions. This type of EEG synchronisation of driving alpha and beta EEG by alpha and beta sinusoidal MF stimulation, demonstrated in this study, could possibly be applied as therapeutic treatment(s) of particular neurophysiological abnormalities such as sleep and psychiatric disorders.

(E) Das S, Kumar S, Jain S, Avelev VD, Mathur R. Exposure to ELF- magnetic field promotes restoration of sensori-motor functions in adult rats with hemisection of thoracic spinal cord. Electromagn Biol Med. 31(3):180-194, 2012. (AS, CE, ME, BE, MA)

Clinically effective modalities of treatment for spinal cord injury (SCI) still remain unsatisfactory and are largely invasive in nature. There are reports of accelerated regeneration in injured peripheral nerves by extremely low-frequency pulsed electromagnetic field (ELF-EMF) in the rat. In the present study, the effect of (50 Hz), low-intensity (17.96 μ T) magnetic field (MF) exposure of rats after-hemisection of T13 spinal cord (hSCI) was investigated on sensori-motor and locomotor functions. Rats were divided into hSCI (sham-exposed) and hSCI+MF (MF: 2 h/d X 6 weeks) groups. Besides their general conditions, locomotor function by Basso, Beattie, and

Brenahan (BBB) score; motor responses to noxious stimuli by threshold of tail flick (TTF), simple vocalization (TSV), tail flick latency (TFL), and neuronal excitability by H-reflex were noted. It is found that, in the hSCI+MF group, a statistically significant improvement over the hSCI control group was noted in BBB score from post-SCI wk2 and TFL and TTF by post-hSCI wk1 and wk3, respectively. Correspondingly, TSV gradually restored by post-hSCI wk5. The threshold of H-reflex was reduced on ipsilateral side vs. contralateral side in hSCI and hSCI+MF group. A complete bladder control was dramatically restored on post-hSCI day4 (vs. day7 of hSCI group) and the survival rate was 100% in the hSCI+MF group (vs. 90% of hSCI group). The results of our study suggest that extremely low-frequency (50 Hz), low-intensity (17.96 μ T) MF exposure for 2 h/d x 6wks promotes recovery of sensori-motor behavior including locomotion and bladder control both in terms of temporal pattern and magnitude in hemisection injury of (T13) spinal cord rats.

(E) Davanipour Z, Tseng C-C, Lee PJ, Markides KS, Sobel E. Severe Cognitive Dysfunction and Occupational Extremely Low Frequency Magnetic Field Exposure among Elderly Mexican Americans. Brit J Med Med Res 4 (8): 1641-1662, 2014. (HU, BE)

Aims: This report is the first study of the possible relationship between extremely low frequency (50-60 Hz, ELF) magnetic field (MF) exposure and severe cognitive dysfunction. Earlier studies investigated the relationships between MF occupational exposure and Alzheimer's disease (AD) or dementia. These studies had mixed results, depending upon whether the diagnosis of AD or dementia was performed by experts and upon the methodology used to classify MF exposure. **Study Design:** Population-based case-control. **Place and Duration of Study:** Neurology and Preventive Medicine, Keck School of Medicine, University of Southern California, 2 years. **Methodology:** The study population consisted of 3050 Mexican Americans, aged 65+, enrolled in Phase 1 of the Hispanic Established Population for the Epidemiologic Study of the Elderly (H-EPESE) study. Mini-Mental State Exam (MMSE) results, primary occupational history, and other data were collected. Severe cognitive dysfunction was defined as an MMSE score below 10. The MF exposure methodology developed and used in earlier studies was used. **Results:** Univariate odds ratios (OR) were 3.4 ($P < .03$; 95% CI: 1.3-8.9) for high and 1.7 ($P = .27$; 95% CI: 0.7-4.1) for medium or high (M/H) MF occupations. In multivariate main effects models, the results were similar. When interaction terms were allowed in the models, the interactions between M/H or high occupational MF exposure and smoking history or age group were statistically significant, depending upon whether two (65-74, 75+) or three (65-74, 75-84, 85+) age groups were considered, respectively. When the analyses were limited to subjects aged 75+, the interactions between M/H or high MF occupations and a positive smoking history were statistically significant. **Conclusion:** The results of this study indicate that working in an occupation with high or M/H MF exposure may increase the risk of severe cognitive dysfunction. Smoking and older age may increase the deleterious effect of MF exposure.

(NE) de Groot MW, Kock MD, Westerink RH. Assessment of the neurotoxic potential of exposure to 50Hz extremely low frequency electromagnetic fields (ELF-EMF) in naïve and chemically-stressed PC12 cells. *Neurotoxicology*. 2014 Aug 8. pii: S0161-813X(14)00138-7. doi: 10.1016/j.neuro.2014.07.009. [Epub ahead of print] **(CS, AE, CC, OX)**

Increasing exposure to extremely low frequency electromagnetic fields (ELF-EMF), generated by power lines and electric appliances, raises concern about potential adverse health effects of ELF-EMF. The central nervous system is expected to be particularly vulnerable to ELF-EMF as its function strongly depends on electrical excitability. We therefore investigated effects of acute (30min) and sub-chronic (48h) exposure to 50Hz ELF-EMF on naïve and chemically-stressed pheochromocytoma (PC12) cells. The latter have higher levels of iron and/or reactive oxygen species (ROS) and display increased vulnerability to environmental insults. Effects of ELF-EMF on Ca^{2+} -homeostasis, ROS production and membrane integrity were assessed using Fura-2 single cell fluorescence microscopy, H_2 -DCFDA and CFDA assays, respectively. Our data demonstrate that acute exposure of naïve PC12 cells to 50 Hz ELF-EMF up to 1000 μT fails to affect basal or depolarization-evoked $[\text{Ca}^{2+}]$. Moreover, sub-chronic ELF-EMF exposure up to 1000 μT has no consistent effects on Ca^{2+} -homeostasis in naïve PC12 cells and does not affect ROS production and membrane integrity. Notably, in chemically-stressed PC12 cells both acute and sub-chronic ELF-EMF exposure also failed to exert consistent effects on Ca^{2+} -homeostasis, ROS production and membrane integrity. Our combined findings thus indicate that exposure to 50Hz ELF-EMF up to 1000 μT , i.e. 10,000 times above background exposure, does not induce neurotoxic effects in vitro, neither in naïve nor in chemically-stressed PC12 cells. Though our data require confirmation, e.g. in developing neuronal cells in vitro or (developing) animals, it appears that the neurotoxic risk of ELF-EMF exposure is limited.

(E) Del Giudice E, Facchinetti F, Nofrate V, Boccaccio P, Minelli T, Dam M, Leon A, Moschini G. Fifty Hertz electromagnetic field exposure stimulates secretion of beta-amyloid peptide in cultured human neuroglioma. *Neurosci Lett*. 418(1):9-12, 2007. **(CS, CE, ND)**

Recent epidemiological studies raise the possibility that individuals with occupational exposure to low frequency (50-60 Hz) electromagnetic fields (LF-EMF), are at increased risk of Alzheimer's disease (AD). However, the mechanisms through which LF-EMF may affect AD pathology are unknown. We here tested the hypothesis that the exposure to LF-EMF may affect amyloidogenic processes. We examined the effect of exposure to 3.1 mT 50 Hz LF-EMF on Abeta secretion in H4 neuroglioma cells stably overexpressing human mutant amyloid precursor protein. We found that overnight exposure to LF-EMF induces a significant increase of amyloid-beta peptide (Abeta) secretion, including the isoform Abeta 1-42, without affecting cell survival. These findings show for the first time that exposure to LF-EMF stimulates Abeta secretion in vitro, thus alluding to a potential link between LF-EMF exposure and APP processing in the brain.

(E) Deng Y, Zhang Y, Jia S, Liu J, Liu Y, Xu W, Liu L. Effects of aluminum and extremely low frequency electromagnetic radiation on oxidative stress and memory in brain of mice. *Biol Trace Elem Res*. 156(1-3):243-252, 2013. **(AS, CE, BE, OX)**

This study was aimed to investigate the effect of aluminum and extremely low-frequency magnetic fields (ELF-MF) on oxidative stress and memory of SPF Kunming mice. Sixty male SPF Kunming mice were divided randomly into four groups: control group, ELF-MF group (2 mT, 4 h/day), load aluminum group (200 mg aluminum/kg, 0.1 ml/10 g), and ELF-MF + aluminum group (2 mT, 4 h/day, 200 mg aluminum/kg). After 8 weeks of treatment, the mice of three experiment groups (ELF-MF group, load aluminum group, and ELF-MF + aluminum group) exhibited firstly the learning memory impairment, appearing that the escaping latency to the platform was prolonged and percentage in the platform quadrant was reduced in the Morris water maze (MWM) task. Secondly are the pathologic abnormalities including neuronal cell loss and overexpression of phosphorylated tau protein in the hippocampus and cerebral cortex. On the other hand, the markers of oxidative stress were determined in mice brain and serum. The results showed a statistically significant decrease in superoxide dismutase activity and increase in the levels of malondialdehyde in the ELF-MF group ($P < 0.05$ or $P < 0.01$), load aluminum group ($P < 0.01$), and ELF-MF + aluminum group ($P < 0.01$). However, the treatment with ELF-MF + aluminum induced no more damage than ELF-MF and aluminum did, respectively. In conclusion, both aluminum and ELF-MF could impact on learning memory and pro-oxidative function in Kunming mice. However, there was no evidence of any association between ELF-MF exposure with aluminum loading.

(E) Di Loreto S, Falone S, Caracciolo V, Sebastiani P, D'Alessandro A, Mirabilio A, Zimmitti V, Amicarelli F. Fifty hertz extremely low-frequency magnetic field exposure elicits redox and trophic response in rat-cortical neurons. J Cell Physiol. 219(2):334-343, 2009. (CS, AE, CC, OX)

Large research activity has raised around the mechanisms of interaction between extremely low-frequency magnetic fields (ELF-MFs) and biological systems. ELF-MFs may interfere with chemical reactions involving reactive oxygen species (ROS), thus facilitating oxidative damages in living cells. Cortical neurons are particularly susceptible to oxidative stressors and are also highly dependent on the specific factors and proteins governing neuronal development, activity and survival. The aim of the present work was to investigate the effects of exposures to two different 50 Hz sinusoidal ELF-MFs intensities (0.1 and 1 mT) in maturing rat cortical neurons' major anti-oxidative enzymatic and non-enzymatic cellular protection systems, membrane peroxidative damage, as well as growth factor, and cytokine expression pattern. Briefly, our results showed that ELF-MFs affected positively the cell viability and concomitantly reduced the levels of apoptotic death in rat neuronal primary cultures, with no significant effects on the main anti-oxidative defences. Interestingly, linear regression analysis suggested a positive correlation between reduced glutathione (GSH) and ROS levels in 1 mT MF-exposed cells. On this basis, our hypothesis is that GSH could play an important role in the antioxidant defence towards the ELF-MF-induced redox challenge. Moreover, the GSH-based cellular response was achieved together with a brain-derived neurotrophic factor over-expression as well as with the interleukin 1 β -dependent regulation of pro-survival signaling pathways after ELF-MF exposure.

(E) Dimitrijević D, Savić T, Anđelković M, Prolić Z, Janać B. Extremely low frequency magnetic field (50 Hz, 0.5 mT) modifies fitness components and locomotor activity of *Drosophila subobscura*. Int J Radiat Biol. 2014 Mar19. [Epub ahead of print] (AS, AE, DE, BE)

Purpose: Extremely low frequency (ELF) magnetic fields are essential ecological factor which may induce changes in many organisms. The aim of this study was to examine the effects in *Drosophila subobscura* exposed for 48 h to ELF magnetic field (50 Hz, 0.5 mT) at different developmental stages. Materials and methods: Egg-first instar larvae developmental stage of *D. subobscura* isofemale lines was exposed to ELF magnetic field, and fitness components (developmental time, developmental dynamics, viability and sex ratio) and locomotor activity of 3-days old males and females were monitored. Also, just eclosed *D. subobscura* isofemale adults were exposed to ELF magnetic field and their locomotor activity was monitored just after. Results: ELF magnetic field shortens developmental time, increases viability and does not affect sex ratio of *D. subobscura*. No matter which developmental stage is exposed, ELF magnetic field significantly decreases locomotor activity of adult flies, but after exposure of just eclosed adults observed change lasts longer. Conclusions: Applied ELF magnetic field modifies fitness components and locomotor activity of *D. subobscura*. Observed effects can be attributed to the influence of magnetic field on different stages of development where the hormonal and nervous systems play important role in the control of examined parameters.

(E) Duan Y, Wang Z, Zhang H, He Y, Lu R, Zhang R, Sun G, Sun X. The preventive effect of lotus seedpod procyanidins on cognitive impairment and oxidative damage induced by extremely low frequency electromagnetic field exposure. Food Funct. 4(8):1252-1262, 2013. (AS, CE, BE, OX)

The present study investigated the effects of lotus seedpod procyanidins (LSPCs) administered by oral gavage on the cognitive deficits and oxidative damage of mice at extremely low frequency electromagnetic field (ELF-EMF) exposure (50 Hz, 8 mT, 28 days). The results showed that 90 mg kg⁻¹ LSPCs treatment significantly increased body weight compared with the ELF-EMF group at ELF-EMF exposure and effectively maintained liver index, thymus index, kidney index and spleen index close to normal. A water maze test indicated that learning and memory abilities of the ELF-EMF group deteriorated significantly with ELF-EMF exposure when compared with the control group, but the ELF-EMF + LSPCs90 group had remarkably improved learning and memory abilities compared with the ELF-EMF group. Malondialdehyde (MDA), reactive oxygen species (ROS), nitric oxide (NO) and nitric oxide synthase (NOS) mostly exhibited significant increases, while the activities of glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) decreased significantly under ELF-EMF exposure in the ELF-EMF group. LSPCs (especially 60, 90 mg kg⁻¹) administration decreased MDA, ROS, NO content and lowered NOS activity in LSPCs treatment groups. Furthermore, LSPCs (60, 90 mg kg⁻¹) treatment significantly augmented GPx, CAT, SOD activity in the hippocampus and serum. Pathological observation showed that number of pyramidal cells of the CA1 and CA3 regions of the hippocampus of the LSPCs treatment groups was significantly greater than the ELF-EMF group. All the data suggested that the LSPCs can effectively prevent learning and memory

damage and oxidative damage caused by the ELF-EMF, most likely through the ability of LSPCs to scavenge oxygen free radicals and to stimulate antioxidant enzyme activity.

(E) Duan Y, Wang Z, Zhang H, He Y, Fan R, Cheng Y, Sun G, Sun X. Extremely low frequency electromagnetic field exposure causes cognitive impairment associated with alteration of the glutamate level, MAPK pathway activation and decreased CREB phosphorylation in mice hippocampus: reversal by procyanidins extracted from the lotus seedpod. Food Funct. 2014 Jul 28. [Epub ahead of print] (AS, CE, CC)

Lotus seedpod procyanidins (LSPCs) could effectively prevent learning and memory damage and oxidative damage caused by extremely low frequency electromagnetic field (ELF-EMF) exposure. However, LSPCs protect neurons from ELF-EMF-induced damage by mechanisms currently not clear. An excessive release of glutamate is considered to be one of the molecular mechanisms of neuronal damage in several neurological diseases. In this study we determined whether the ELF-EMF (50 Hz, 8 mT, 28 days) exposure induced alterations of glutamate release in mice hippocampus and explored the possible mechanism, and if LSPC treatment normalized its alterations. The results showed that ELF-EMF exposure induced the increased contents of glutamate, GABA, excessively activated NMDA receptors, increasing the number of NMDA receptor 2B (NR2B) and intracellular Ca^{2+} concentration $[\text{Ca}^{2+}]_i$ in hippocampus. In addition, ELF-EMF exposure decreased the ERK1/2 and CREB phosphorylation, which suggested that the Ca^{2+} influx induced by the ELF-EMF exposure stimulated activity of the ERK, in turn, influences the expression of downstream proteins in this signaling pathway. Besides, ELF-EMF exposure also increased JNK1/2 phosphorylation through the activated ASK1, which plays a pivotal role in hippocampal neuronal cell death. However, oral administration of LSPCs (especially 60 and 90 mg kg^{-1}) markedly improved expressions of p-CREB, p-ERK1/2 and p-JNK1/2, accompanied by decreased levels of glutamate, GABA, $[\text{Ca}^{2+}]_i$ and NR2B. Thus, the results from the present study suggest that p-ERK1/2, p-JNK1/2, $[\text{Ca}^{2+}]_i$ and p-CREB expression normalized, possibly via a NMDA receptor-channel through the changes of GABA, glutamate and NR2B, which might be responsible for the neuroprotective or memory enhancing effects of LSPCs.

(E) El Gohary MI, Salama AA, El Saeid AA, El Sayed TM, Kotb HS. Influence of Magnetic Field on Brain Activity During Administration of Caffeine. Cell Biochem Biophys. 67(3):929-933, 2013. (AS, CE, EE)

The aim of the present work is to evaluate the effect of caffeine, the world's most popular psychoactive drug, on the electric activity of the rat's brain that exposed to extremely low-frequency magnetic field (ELF-MF), during 15 days. The obtained results showed that administration of caffeine in a group of rats by dose of 10 mg/kg (equivalent to human daily consumption) caused a reduction in the mean power amplitude of electroencephalogram (EEG) trace for almost all frequency bands especially α (8-12 Hz). It was observed that the influence of caffeine was more evident in motor cortex than in visual cortex. While the exposure of another group to ELF-MF of intensity 0.2 mT during the same period caused an enhancement in the mean power amplitude of most EEG frequency bands; this was more observed in the right hemisphere of the brain than that of the left hemisphere. The administration of caffeine while

rats were exposed to ELF-MF, led, after 5 days of exposure, to a great increase in the mean power amplitude of α band at all places of recording electrodes. It may be concluded that caffeine administration was more effective in reducing the hazardous of ELF-MF in motor cortex than in visual cortex.

(E) Esmekaya MA, Acar SI, Kiran F, Canseven AG, Osmanagaoglu O, Seyhan N. Effects of ELF magnetic field in combination with Iron(III) chloride (FeCl₃) on cellular growth and surface morphology of Escherichia coli (E. coli). Appl Biochem Biotechnol. 169(8):2341-2349, 2013. (CS, AE, MC)

This study investigated the effects of extremely low frequency (ELF) magnetic field with/without iron(III) chloride (FeCl₃) on bacterial growth and morphology. The ELF exposures were carried out using a pair of Helmholtz coil-based ELF exposure system which was designed to generate 50 Hz sinusoidal magnetic field. The field was approximately uniform throughout the axis of the coil pair. The samples which were treated or non-treated with different concentrations FeCl₃ were exposed to 50 Hz, 2 millitesla (mT) magnetic field for 24 h. ELF effect on viability was assessed in terms of viable colony counts (in colony-forming unit per milliliter) with the standard plate count technique. Scanning electron microscopy was used to investigate the magnetic field effect on surface morphology of Escherichia coli. No significant results were seen in terms of cell viability between ELF and sham-exposed bacterial strains. Similarly, FeCl₃ treatment did not change cell viability of E. coli samples. However, we observed some morphological changes on E. coli cell surfaces. Pore formations and membrane destruction were seen on the surface of 24 h ELF field-exposed cells. We concluded that ELF magnetic field exposure at 2 mT does not affect cell viability; however, it may affect bacterial surface morphology.

(E) Falone S, Mirabilio A, Carbone MC, Zimmitti V, Di Loreto S, Mariggiò MA, Mancinelli R, Di Ilio C, Amicarelli F. Chronic exposure to 50Hz magnetic fields causes a significant weakening of antioxidant defence systems in aged rat brain. Int J Biochem Cell Biol. 40(12):2762-2770, 2008. (AS, CE, CC, OX)

Several studies suggest that extremely low-frequency magnetic fields (ELF-MFs) may enhance the free radical endogenous production. It is also well known that one of the unavoidable consequences of ageing is an overall oxidative stress-based decline in several physiological functions and in the general resistance to stressors. On the basis of these assumptions, the aim of this study was to establish whether the ageing process can increase susceptibility towards widely present ELF-MF-mediated pro-oxidative challenges. To this end, female Sprague-Dawley rats were continuously exposed to a sinusoidal 50 Hz, 0.1 mT magnetic field for 10 days. Treatment-induced changes in the major antioxidant protection systems and in the neurotrophic support were investigated, as a function of the age of the subjects. All analyses were performed in brain cortices, due to the high susceptibility of neuronal cells to oxidative injury. Our results indicated that ELF-MF exposure significantly affects anti-oxidative capability, both in young and aged animals, although in opposite ways. Indeed, exposed young individuals enhanced their neurotrophic signalling and anti-oxidative enzymatic defence against a possible

ELF-MF-mediated increase in oxygen radical species. In contrast, aged subjects were not capable of increasing their defences in response to ELF-MF treatment but, on the contrary, they underwent a significant decrease in the major antioxidant enzymatic activities. In conclusion, our data seem to suggest that the exposure to ELF-MFs may act as a risk factor for the occurrence of oxidative stress-based nervous system pathologies associated with ageing.

(E) Fournier NM, Mach QH, Whissell PD, Persinger MA. Neurodevelopmental anomalies of the hippocampus in rats exposed to weak intensity complex magnetic fields throughout gestation. Int J Dev Neurosci. 2012 Jul 31. [Epub ahead of print] (AS, CE, DE, BE, MC)

There has been increasing interest on the possible harmful effects of prenatal exposure to magnetic fields. To investigate the effect of weak intensity magnetic fields on the prenatal brain, pregnant Wistar rats were continuously exposed to one of four intensities (reference: 5-20nT; low 30-50nT; medium 90-580nT; high 590-1200nT) of a complex magnetic field sequence designed to interfere with brain development. As adults, rats exposed to the low-intensity (30-50nT) complex magnetic field displayed impairments in contextual fear learning and showed anomalies in the cytological and morphological development of the hippocampus. In particular, low-intensity exposures resulted in a reduction in overall hippocampal size and promoted subtle dysgenesis of the CA1 and CA3 regions. In contrast, exposure to weaker or stronger intensities of the same complex magnetic field pattern did not interfere with hippocampal development or fear behavior. These findings suggest that prenatal exposure to complex magnetic fields of a narrow intensity window during development can result in subtle but permanent alterations in hippocampal microstructure and function that can have lasting effects on behavior.

(E) Frilot C 2nd, Carrubba S, Marino AA. Transient and steady-state magnetic fields induce increased fluorodeoxyglucose uptake in the rat hindbrain. Synapse. 65(7):617-623, 2011. (HU, AE, CC)

We inquired into the biophysical basis of the ability of weak electromagnetic fields (EMFs) to trigger onset and offset evoked potentials, and to produce steady-state changes in the electroencephalogram (EEG). Rats were exposed to a 2.5-G, 60-Hz magnetic field and the neuroanatomical region of glucose activation associated with the effect of the field on the EEG was identified by positron emission tomography (PET) using fluorodeoxyglucose (FDG). Paired emission scans from the same animal with and without field treatment were differenced and averaged, and t values of the brain voxels computed using the pooled standard deviation were compared with a calculated critical t value to identify the field-activated voxels. Increased glucose utilization occurred in hindbrain voxels when the field was applied orthogonally to the sagittal plane, but not when the angle between the field and the sagittal plane varied randomly. Distinct FDG activation effects were observed in response to transient (both onset and offset) and steady-state magnetic stimuli. Observations of increased glucose utilization induced by magnetic stimuli and its dependence on the direction of the field suggested that signal transduction was mediated by a force detector and that the process and/or early post-transduction processing occurred in the hindbrain.

(E) Frilot C 2nd, Carrubba S, Marino AA. Sensory transduction of weak electromagnetic fields: role of glutamate neurotransmission mediated by NMDA receptors. Neuroscience. 258:184-191, 2014. (AS, AE, EE)

Subliminal electromagnetic fields (EMFs) triggered nonlinear evoked potentials in awake but not anesthetized animals, and increased glucose metabolism in the hindbrain. Field detection occurred somewhere in the head and possibly was an unrecognized function of sensory neurons in facial skin, which synapse in the trigeminal nucleus and project to the thalamus via glutamate-dependent pathways. If so, anesthetic agents that antagonize glutamate neurotransmission would be expected to degrade EMF-evoked potentials (EEPs) to a greater extent than agents having different pharmacological effects. We tested the hypothesis using ketamine which blocks N-methyl-d-aspartate (NMDA) receptors (NMDARs), and xylazine which is an α_2 -adrenoreceptor agonist. Electroencephalograms (EEGs) of rats were examined using recurrence analysis to observe EEPs in the presence and absence of ketamine and/or xylazine anesthesia. Auditory evoked potentials (AEPs) served as positive controls. The frequency of observation of evoked potentials in a given condition (wake or anesthesia) was compared with that due to chance using the Fisher's exact test. EEPs were observed in awake rats but not while they were under anesthesia produced using a cocktail of xylazine and ketamine. In another experiment each rat was measured while awake and while under anesthesia produced using either xylazine or ketamine. EEPs and AEPs were detected during wake and under xylazine ($P < 0.05$ in each of the four measurements). In contrast, neither EEPs nor AEPs were observed when anesthesia was produced partly or wholly using ketamine. The duration and latency of the EEPs was unaltered by xylazine anesthesia. The afferent signal triggered by the transduction of weak EMFs was likely mediated by NMDAR-mediated glutamate neurotransmission.

(E) Fu Y, Wang C, Wang J, Lei Y, Ma Y. Long-term exposure to extremely low-frequency magnetic fields impairs spatial recognition memory in mice. Clin Exp Pharmacol Physiol. 35(7):797-800, 2008. (AS, CE, BE)

In the present study, we investigated the short- and long-term effects of extremely low-frequency (ELF) magnetic fields on spatial recognition memory in mice by using a two-trial recognition Y-maze that is based on the innate tendency of rodents to explore novel environments. 2. Mice were exposed to 25 or 50 Hz electromagnetic fields for either 7 (short term) or 25 days (long term) and then tested in the Y-maze. 3. The results indicated that neither short- nor long-term exposure to magnetic fields affected the locomotor activity of mice in the Y-maze. However, long-term exposure to 50 Hz fields reduced recognition of the novel arm. 4. Our findings suggest that ELF magnetic fields impair spatial recognition memory in the Y-maze depending on the field strength and/or duration of exposure.

(NE) Gavoçi E, Zironi I, Remondini D, Virelli A, Castellani G, Del Re B, Giorgi G, Aicardi G, Bersani F. ELF magnetic fields tuned to ion parametric resonance conditions do not affect TEA-sensitive voltage-dependent outward K(+) currents in a human neural cell line. Bioelectromagnetics. 34(8):579-88, 2013. (CS, AE, CC)

Despite the experimental evidence of significant biological effects of extremely low frequency (ELF) magnetic fields (MFs), the underlying mechanisms are still unclear. Among the few mechanisms proposed, of particular interest is the so called "ion parametric resonance (IPR)" hypothesis, frequently referred to as theoretical support for medical applications. We studied the effect of different combinations of static (DC) and alternating (AC) ELF MFs tuned on resonance conditions for potassium (K(+)) on TEA-sensitive voltage-dependent outward K(+) currents in the human neuroblastoma BE(2)C cell line. Currents through the cell membrane were measured by whole-cell patch clamp before, during, and after exposure to MF. No significant changes in K(+) current density were found. This study does not confirm the IPR hypothesis at the level of TEA-sensitive voltage-dependent outward K(+) currents in our experimental conditions. However, this is not a direct disprove of the hypothesis, which should be investigated on other ion channels and at single channel levels also.

Giorgi G, Lecciso M, Capri M, Lukas Yani S, Virelli A, Bersani F, Del Re B. An evaluation of genotoxicity in human neuronal-type cells subjected to oxidative stress under an extremely low frequency pulsed magnetic field. *Mutat Res Genet Toxicol Environ Mutagen.* 775-776:31-37, 2014.

The possible genotoxicity of extremely low frequency magnetic field (ELF-MF) exposure is still a controversial topic. The most of the reported data suggests that it alone does not affect DNA integrity, but several recent reports have suggested that sinusoidal ELF-MF may increase the effect of known genotoxic agents. Only a few studies deal with non sinusoidal ELF-MF, including pulsed magnetic field (PMF), which are produced by several devices. The aim of this study is to investigate whether PMF exposure can interfere with DNA damage and repair in the presence of a genotoxic oxidative agent in neuronal type cells. To this purpose gamma-H2AX foci formation, which is a sensitive marker of DNA double strand breaks (DSB), was investigated at different points of time (1, 24, 48, 72h) after the H2O2 treatment (300µM for 1h) under PMF exposure (1mT, 50Hz) in human neuroblastoma BE(2)C cells. Moreover, cytotoxicity evaluation, by MTT assay and cell cycle analysis, was performed at various points of time after the treatment. Taken together, results suggest that PMF exposure does not interfere with genotoxicity and cytotoxicity induced by oxidative stress.

(NE) Glover PM, Eldeghaidy S, Mistry TR, Gowland PA. Measurement of visual evoked potential during and after periods of pulsed magnetic field exposure. *J Magn Reson Imaging.* 26(5):1353-1356, 2007. (HU, EE)

PURPOSE: To study the effect of switched magnetic fields used in MR scanners on the visual evoked potential (VEP) in human subjects. **MATERIALS AND METHODS:** We have used an MRI gradient coil, remote from an MRI magnet to produce a time-varying magnetic field (0.5 kHz, peak field approximately 8.7 T/second) in the human brain without the confounding effects of static field exposure or accompanying acoustic noise. The VEP response to a 2-Hz reversal, 8 x 8 checkerboard, occupying 20 degrees of the visual field was recorded from occipital locations O1 and O2. VEP recordings were made every five minutes before, during, and after a 10-minute magnetic field exposure period for seven subjects. **RESULTS:** In contradiction to studies previously reported in the literature for fields of 50 Hz and 60 mT, no significant effects on the

peak amplitude or latency of the VEP P100 O1 and O2 responses were found. **CONCLUSION:** Switched magnetic fields of a level and frequency comparable to those used in MRI do not have a significant effect on primary retinal or visual processing.

(E) Gulturk S, Demirkazik A, Kosar I, Cetin A, Dökmets HS, Demir T. Effect of exposure to 50 Hz magnetic field with or without insulin on blood-brain barrier permeability in streptozotocin-induced diabetic rats. Bioelectromagnetics. 31(4):262-269, 2010. (AS, CE, ME)

We investigated the effect of long-term exposure to modulation magnetic field (MF), insulin, and their combination on blood-brain barrier (BBB) permeability in a diabetic rat model. Fifty-three rats were randomly assigned to one of six groups: sham, exposed to no MF; MF, exposed to MF; diabetes mellitus (DM), DM induced with streptozotocin (STZ); DM plus MF (DMMF); DM plus insulin therapy (DMI); and DM plus insulin therapy plus MF (DMIMF). All the rats underwent Evans blue (EB) measurement to evaluate the BBB 30 days after the beginning of experiments. The rats in MF, DMMF, and DMIMF groups were exposed to MF ($B = 5$ mT) for 165 min every day for 30 days. Mean arterial blood pressure (MABP), body mass, and serum glucose level of the study rats were recorded. The extravasation of brain EB of the MF, DM, DMMF, DMI, and DMIMF groups was higher than that of the sham group and the extravasation of right hemisphere of the DMIMF group was highest ($P < 0.05$). The post-procedure body mass of the sham and MF groups were significantly higher than those of the DM and DMMF groups ($P < 0.05$). In the DM, DMMF, DMI, and DMIMF groups, the baseline glucose was significantly lower than the post-procedure glucose ($P < 0.05$). DM and MF increase BBB permeability; in combination, they cause more increase in BBB permeability, and insulin decreases their effect on BBB. Improved glucose metabolism may prevent body mass loss and the hypoglycemic effect of MF. DM increases MABP but MF causes no additional effect.

(E) Gupta SK, Mesharam MK, Krishnamurthy S. Electromagnetic radiation 2450 MHz exposure causes cognition deficit with mitochondrial dysfunction and activation of intrinsic pathway of apoptosis in rats. J Biosci. 43(2):263-276, 2018. (AS, CE, BE, MA, CC)

Electromagnetic radiation (EMR) can induce or modulate several neurobehavioral disorders. Duration and frequency of exposure of EMR is critical to develop cognitive disorders. Even though EMR-2450 is widely used, its effects on cognition in relation to mitochondrial function and apoptosis would provide better understanding of its pathophysiological effects. Therefore, a comparative study of different frequencies of EMR exposure would give valuable information on effects of discrete frequencies of EMR on cognition. Male rats were exposed to EMR (900, 1800 and 2450 MHz) every day for 1 h for 28 consecutive days. The cognitive behavior in terms of novel arm entries in Y-maze paradigm was evaluated every week after 1 h to last EMR exposure. Animals exposed to EMR-2450 MHz exhibited significant cognitive deficits. EMR-2450 MHz caused loss of mitochondrial function and integrity, an increase in amyloid beta expression. There was release of cytochrome-c and activation of apoptotic factors such as caspase-9 and -3 in the hippocampus. Further, there was decrease in levels of acetylcholine, and increase in activity of acetyl cholinesterase, indicating impairment of cholinergic system.

Therefore, exposure of EMR-2450 in rats caused cognitive deficit with related pathophysiological changes in mitochondrial and cholinergic function, and amyloidogenesis.

(E) Gutiérrez-Mercado YK, Cañedo-Dorantes L, Gómez-Pinedo U, Serrano-Luna G, Bañuelos-Pineda J, Feria-Velasco A. Increased vascular permeability in the circumventricular organs of adult rat brain due to stimulation by extremely low frequency magnetic fields. Bioelectromagnetics. 34(2):145-155, 2013. (AS, CE, MC)

It has been demonstrated that the exposure of biological systems to magnetic fields (MFs) can produce several beneficial effects: tissue recovery in chronic wounds, re-establishment of blood circulation after tissue ischemia or in necrotic tissues, improvement after epileptic episodes, angiogenesis, etc. In the current study, the effects of extremely low frequency (ELF) MF on the capillaries of some circumventricular organs (CVOs) are demonstrated; a vasodilator effect is reported as well as an increase in their permeability to non-liposoluble substances. For this study, 96 Wistar male rats (250 g body mass) were used and divided into three groups of 32 rats each: a control group (no treatment); a sham ELF-MF group; and an experimental group subjected to ELF-MF (120 Hz harmonic waves and 0.66 mT, root mean square) by the use of Helmholtz coils. All animals were administered colloidal carbon (CC) intravenously to study, through optical and transmission electron microscopy, the capillary permeability in CVOs and the blood-brain barrier (BBB) in brain areas. An increase in capillary permeability to CC was detected in the ELF-MF-exposed group as well as a significant increase in vascular area (capillary vasodilation); none of these effects were observed in individuals of the control and sham ELF-MF groups. It is important to investigate the mechanisms involved in the phenomena reported here in order to explain the effects of ELF-MF on brain vasculature.

(E) Harakawa S, Nedachi T, Hori T, Takahashi K, Tochio K, Inoue N. Effect of electric field in conditioned aversion response. J Vet Med Sci. 70(6):611-613, 2008. (AS, AE, BE, EF)

The aim of the present study was to estimate whether rat sense exogenous electric field (EF) including one used in our previous studies. Employing a conditioned place aversion response paradigm based on an aversive behavior against light environment, alteration in both voluntary behavior of Wistar rat to a 50 Hz sinusoidal EF was examined. Following conditioning without EF, the times spent in white place in rats was significantly shortened ($P < 0.05$). While, such changes were not shown in rats conditioned with EF. Thus, it was considered that the aversion response to light environment was interfered by exposure to EF. An interference in recognition of brightness via EF induced effect to visual system or in learning system via direct effect to central nerve system was considerable as a factor for EF-induced effect. In addition, it was remained that rat possibly sense exposure to EF as preferable. In order to confirm which factor functioned, further studies are needed.

(E) He LH, Shi HM, Liu TT, Xu YC, Ye KP, Wang S. Effects of extremely low frequency magnetic field on anxiety level and spatial memory of adult rats. Chin Med J (Engl). 124(20):3362-3366, 2011. (AS, CE, BE)

BACKGROUND: As the widespread use of electric devices in modern life, human are exposed to extremely low frequency magnetic fields (ELF MF) much more frequently than ever. Over the past decades, a substantial number of epidemiological and experimental studies have demonstrated that ELF MF (50 Hz) exposure is associated with increased risk of various health effects. The present study examined the effects of chronic exposure to ELF MF on anxiety level and spatial memory of adult rats. **METHODS:** The 50-Hz ELF MF was used during the whole experimental procedures and the value of magnetic field (MF) was set to 2 mT. Adult rats were divided randomly to control, MF 1 hour and MF 4 hours group. Anxiety-related behaviors were examined in the open field test and the elevated plus maze; changes in spatial learning and memory were determined in Morris water maze after 4 weeks of daily exposure. **RESULTS:** Rats in MF 4 hours group had increased anxiety-like behaviors with unaltered locomotor activity. In the Morris water maze test, rats had reduced latency to find the hidden platform and improved long-term memory of former location of platform without changes in short-term memory and locomotor activity. **CONCLUSION:** Chronic ELF MF exposure has anxiogenic effect on rats, and the promoting effects on spatial learning and long-term retention of spatial memory.

(E) He YL, Liu DD, Fang YJ, Zhan XQ, Yao JJ, Mei YA. Exposure to extremely low-frequency electromagnetic fields modulates Na⁺ currents in rat cerebellar granule cells through increase of AA/PGE₂ and EP receptor-mediated cAMP/PKA pathway. PLoS One. 2013;8(1):e54376. doi: 10.1371/journal.pone.0054376. (CS, AE, CC, EE)

Although the modulation of Ca(2+) channel activity by extremely low-frequency electromagnetic fields (ELF-EMF) has been studied previously, few reports have addressed the effects of such fields on the activity of voltage-activated Na(+) channels (Na(v)). Here, we investigated the effects of ELF-EMF on Na(v) activity in rat cerebellar granule cells (GCs). Our results reveal that exposing cerebellar GCs to ELF-EMF for 10-60 min significantly increased Na(v) currents (I(Na)) by 30-125% in a time- and intensity-dependent manner. The Na(v) channel steady-state activation curve, but not the steady-state inactivation curve, was significantly shifted (by 5.2 mV) towards hyperpolarization by ELF-EMF stimulation. This phenomenon is similar to the effect of intracellular application of arachidonic acid (AA) and prostaglandin E(2) (PGE(2)) on I(Na) in cerebellar GCs. Increases in intracellular AA, PGE(2) and phosphorylated PKA levels in cerebellar GCs were observed following ELF-EMF exposure. Western blottings indicated that the Na(V) 1.2 protein on the cerebellar GCs membrane was increased, the total expression levels of Na(V) 1.2 protein were not affected after exposure to ELF-EMF. Cyclooxygenase inhibitors and PGE(2) receptor (EP) antagonists were able to eliminate this ELF-EMF-induced increase in phosphorylated PKA and I(Na). In addition, ELF-EMF exposure significantly enhanced the activity of PLA(2) in cerebellar GCs but did not affect COX-1 or COX-2 activity. Together, these data demonstrate for the first time that neuronal I(Na) is significantly increased by ELF-EMF exposure via a cPLA2 AA PGE(2) EP receptors PKA signaling pathway.

(E) Hernádi L, László JF. Pharmacological analysis of response latency in the hot plate test following whole-body static magnetic field-exposure in the snail *Helix pomatia*. Int J Radiat Biol. 2014 Mar 6. [Epub ahead of print] (AS, AE, BE)

Purpose: The effect of single, 30 min long, whole-body static magnetic field (SMF)-exposure on the response latency of the snail *Helix pomatia* has been the focus of this study. Materials and methods: The response was investigated using the hot plate test. Results: The effect caused by exposure to homogeneous SMF (147 ± 3 mT) was compared to sham-exposure and resulted in significant differences (up to 47.1%, $p < 0.001$). The response latency depended on the day-night cycle; response latency was higher by 51.2% ($p < 0.001$) during the night. This trend also held for SMF-exposure (28.6%, $p < 0.001$). Serotonin alone increased response latency (55.7%, $p < 0.001$), whereas serotonin antagonist tryptamine decreased it (-97.8%, $p < 0.001$). Using naloxone, response latency decreased (-52.5%, $p < 0.001$); however both SMF-exposure and serotonin in combination with naloxone rose it back to above the control level (116.9%, $p < 0.001$ or 150.2%, $p < 0.001$, respectively). Conclusions: This study provides evidence that SMF-exposure mediates peripheral thermal nociceptive threshold by affecting the serotonergic as well as the opioidergic system.

(E) Hung CS, Anderson C, Horne JA, McEvoy P. Mobile phone 'talk-mode' signal delays EEG-determined sleep onset. Neurosci Lett. 421(1):82-86, 2007. (HU, AE, EE, BE)

Mobile phones signals are pulse-modulated microwaves, and EEG studies suggest that the extremely low-frequency (ELF) pulse modulation has sleep effects. However, 'talk', 'listen' and 'standby' modes differ in the ELF (2, 8, and 217Hz) spectral components and specific absorption rates, but no sleep study has differentiated these modes. We used a GSM900 mobile phone controlled by a base-station simulator and a test SIM card to simulate these three specific modes, transmitted at 12.5% (23dBm) of maximum power. At weekly intervals, 10 healthy young adults, sleep restricted to 6h, were randomly and single-blind exposed to one of: talk, listen, standby and sham (nil signal) modes, for 30 min, at 13:30 h, whilst lying in a sound-proof, lit bedroom, with a thermally insulated silent phone beside the right ear. Bipolar EEGs were recorded continuously, and subjective ratings of sleepiness obtained every 3 min (before, during and after exposure). After exposure the phone and base-station were switched off, the bedroom darkened, and a 90 min sleep opportunity followed. We report on sleep onset using: (i) visually scored latency to onset of stage 2 sleep, (ii) EEG power spectral analysis. There was no condition effect for subjective sleepiness. Post-exposure, sleep latency after talk mode was markedly and significantly delayed beyond listen and sham modes. This condition effect over time was also quite evident in 1-4Hz EEG frontal power, which is a frequency range particularly sensitive to sleep onset. It is possible that 2, 8, 217Hz modulation may differentially affect sleep onset.

(E) Ishay JS, Plotkin M, Volynchik S, Shaked M, Schuss Z, Bergman DJ. Exposure to an additional alternating magnetic field affects comb building by worker hornets. Physiol Chem Phys Med NMR. 39(1):83-88, 2007. (AS, CE, BE)

Oriental hornet workers, kept in an Artificial Breeding Box (ABB) without a queen, construct within a few days brood combs of hexagonal cells with apertures facing down. These combs possess stems that fasten the former to the roof of the ABB. In an ABB with adult workers (more than 24 h after eclosion), exposed to an AC (50 Hz) magnetic field of a magnitude of $B = 50\text{--}70$ mGauss, the combs and cells are built differently from those of a control ABB, subjected only to the natural terrestrial magnetic field. The effects of the additional magnetic field consist of (a) 35-55% smaller number of cells and fewer eggs in each comb, (b) disrupted symmetry of building, with many deformed and imperfectly hexagonal cells, and (c) more delicate and slender comb stems.

(E) Jadidi M, Firoozabadi SM, Rashidy-Pour A, Sajadi AA, Sadeghi H, Taherian AA. Acute exposure to a 50 Hz magnetic field impairs consolidation of spatial memory in rats. Neurobiol Learn Mem. 88(4):387-392, 2007. (AS, CE, BE)

This study was planned to evaluate the effect of an exposure to magnetic fields on consolidation and retrieval of hippocampus dependent spatial memory using a water maze. In Experiments 1 and 2, rats were trained in a hidden version (spatial) of water maze task with two blocks of four trials. The retention of spatial memory was evaluated 48 h later. Exposure to a 50 Hz 8 mT, but not 2 mT magnetic fields for 20 min immediately after training impaired retention performance. The same time exposure shortly before retention testing had no effect. In Experiment 3, rats were trained in a cued version of water maze with two blocks of four trials. Exposure to magnetic field at 8 mT for 20 min immediately after training did not impair retention performance. These findings indicate that acute exposure to a 50 Hz magnetic field at 8 mT for short time can impair consolidation of spatial memory.

(E) Janać B, Tovilović G, Tomić M, Prolić Z, Radenović L. Effect of continuous exposure to alternating magnetic field (50 Hz, 0.5 mT) on serotonin and dopamine receptors activity in rat brain. Gen Physiol Biophys. 28 Spec No:41-46, 2009. (AS, CE, FC)

External magnetic fields (MFs) have the ability to modify motor activity of animals, complex type of behaviour connected with dopaminergic and serotonergic neurotransmissions in the brain. Thus, the purpose of this study was to examine MF-induced changes in the activity of serotonin 5-HT(2A) receptors in the prefrontal cortex, as well as dopamine D(1) and D(2) receptors in the striatum of adult Wistar rats, considering their involvement in motor behavior regulation. Experimental animals were continuously exposed to extremely low frequency MF (ELF-MF, 50 Hz, 0.5 mT) for 1, 3, and 7 days. Subsequently, binding properties ($K(d)$ and $B(max)$) of receptors were determined by in vitro radioligand receptor binding assays. It was shown that the affinity of serotonin 5-HT(2A) receptors decreased and their density increased in the prefrontal cortex of rats after ELF-MF exposure. Regarding affinity, this effect was duration-dependent and most prominent after 7-day of ELF-MF exposure. In contrast to serotonin 5-HT(2A) receptors in the prefrontal cortex, ELF-MF had no significant effect on the affinity and density of dopamine D(1) and D(2) receptors in the striatum. We can conclude that continuous exposure to ELF-MF up to 7 days affects cortical serotonergic neurotransmission, whereby intensity of these changes depends on ELF-MF exposure duration.

(E) Janać B, Selaković V, Rauš S, Radenović L, Zrnić M, Prolić Z. Temporal patterns of extremely low frequency magnetic field-induced motor behavior changes in Mongolian gerbils of different age. Int J Radiat Biol. 88(4):359-366, 2012. (AS, CE, BE)

PURPOSE: The aim of this study was to investigate the influence of extremely low frequency magnetic field (ELF-MF) on different behavior parameters (locomotion, stereotypy, and immobility) in 3- and 10-month-old male Mongolian gerbils. MATERIALS AND METHODS: The animals were continuously exposed to ELF-MF (50 Hz; 0.1, 0.25 and 0.5 mT) for seven days. Their behavior was monitored for 60 min in the open field after the 1st, 2nd, 4th, and 7th day of exposure (immediate effect), and three days after ELF-MF exposure had been ceased (delayed effect). RESULTS: In 3-month-old gerbils, exposure to ELF-MF (0.1, 0.25 and 0.5 mT) increased motor behavior (locomotion and stereotypy), and consequently decreased immobility. Additionally, ELF-MF had delayed effect (except 0.25 mT) on stereotypy and immobility. In 10-month-old gerbils, ELF-MF of 0.1, 0.25 and 0.5 mT induced decrease, slight increase, and pronounced stimulation of motor behavior, respectively. Regardless of magnetic induction value, increased motor behavior was observed three days after ELF-MF exposure has been ceased (delayed effect). CONCLUSIONS: It can be proposed that the specific temporal patterns of ELF-MF-induced motor behavior changes in 3- and 10-month-old gerbils are a consequence of age-dependent morpho-functional differences in the brain structures responsible for a control of motor behavior.

(E) Kantar Gok D, Akpinar D, Yargicoglu P, Ozen S, Aslan M, Demir N, Derin N, Agar A. Effects of extremely low-frequency electric fields at different intensities and exposure durations on mismatch negativity. Neuroscience. 272C:154-166, 2014. (EE, AS, CE, EE, OX)

The effects of extremely low-frequency electric fields (ELF-EFs, 3-300Hz) on lipid peroxidation levels and antioxidant enzyme activities have been shown in many tissues and plasma after exposure to 50-Hz alternating current (AC) electric fields. However, similar studies investigating brain lipid peroxidation status are limited. Moreover and as far as we know, no study has been conducted to examine mismatch negativity (MMN) response in rats following exposure to a 50-Hz AC electric field. Therefore, the purpose of the study was to investigate different intensities and exposure durations of ELF-EFs on MMN component of event-related potentials (ERPs) as well as apoptosis and oxidative brain damage in rats. Ninety male rats, aged 3months were used in our study. A total of six groups, composed of 15 animals each, was formed as follows: sham-exposed rats for 2weeks (C2), sham-exposed rats for 4weeks (C4), rats exposed to 12-kV/m and 18-kV/m electric fields for 2weeks (E12-2 and E18-2), rats exposed to 12- and 18-kV/m electric fields for 4weeks (E12-4 and E18-4). At the end of the experimental period, MMN responses were recorded in urethane-anesthetized rats by electrodes positioned stereotaxically to the surface of the dura. After MMN recordings, animals were killed by exsanguination and their brain tissues were removed for 4-hydroxy-2-nonenal (4-HNE), protein carbonyl and TUNEL analysis. In the current study, different change patterns in ERP parameters were observed dependent on the intensity and exposure duration of ELF-EFs. There were differences in the amplitudes of ERP between the responses to the standard and the deviant tones in all groups. When peak-to-peak amplitude of the difference curves was evaluated, MMN amplitude was

significantly decreased in the E18-4 group compared with the C4 group. Additionally, the amount of 4-HNE was increased in all experimental groups compared with the control group. Consequently, it could be concluded that electric field decreased MMN amplitudes possibly induced by lipid peroxidation.

(E) Kim HJ, Jung J, Park JH, Kim JH, Ko KN, Kim CW. Extremely low-frequency electromagnetic fields induce neural differentiation in bone marrow derived mesenchymal stem cells. Exp Biol Med (Maywood). 238(8):923-931, 2013. (CS, AE, MC, MA)

Extremely low-frequency electromagnetic fields (ELF-EMF) affect numerous biological functions such as gene expression, cell fate determination and even cell differentiation. To investigate the correlation between ELF-EMF exposure and differentiation, bone marrow derived mesenchymal stem cells (BM-MSCs) were subjected to a 50-Hz electromagnetic field during in vitro expansion. The influence of ELF-EMF on BM-MSCs was analysed by a range of different analytical methods to understand its role in the enhancement of neural differentiation. ELF-EMF exposure significantly decreased the rate of proliferation, which in turn caused an increase in neuronal differentiation. The ELF-EMF-treated cells showed increased levels of neuronal differentiation marker (MAP2), while early neuronal marker (Nestin) was down-regulated. In addition, eight differentially expressed proteins were detected in two-dimensional electrophoresis maps, and were identified using ESI-Q-TOF LC/MS/MS. Among them, ferritin light chain, thioredoxin-dependent peroxide reductase, and tubulin β -6 chain were up-regulated in the ELF-EMF-stimulated group. Ferritin and thioredoxin-dependent peroxide reductase are involved in a wide variety of functions, including $\text{Ca}(2+)$ regulation, which is a critical component of neurodegeneration. We also observed that the intracellular $\text{Ca}(2+)$ content was significantly elevated after ELF-EMF exposure, which strengthens the modulatory role of ferritin and thioredoxin-dependent peroxide reductase, during differentiation. Notably, western blot analysis indicated significantly increased expression of the ferritin light chain in the ELF-EMF-stimulated group (0.60 vs. 1.08; $P < 0.01$). These proteins may help understand the effect of ELF-EMF stimulation on BM-MSCs during neural differentiation and its potential use as a clinically therapeutic option for treating neurodegenerative diseases.

(E) Kitaoka K, Kitamura M, Aoi S, Shimizu N, Yoshizaki K. Chronic exposure to an extremely low-frequency magnetic field induces depression-like behavior and corticosterone secretion without enhancement of the hypothalamic-pituitary-adrenal axis in mice. Bioelectromagnetics. 34(1):43-51, 2013. (AS, CE, BE, CC)

An extremely low-frequency magnetic field (ELF-MF) is generated by power lines and household electrical devices. Many studies have suggested an association between chronic ELF-MF exposure and anxiety and/or depression. The mechanism of these effects is assumed to be a stress response induced by ELF-MF exposure. However, this mechanism remains controversial. In the present study, we investigated whether chronic ELF-MF exposure (intensity, 3 mT; total exposure, 200 h) affected emotional behavior and corticosterone synthesis in mice. ELF-MF-treated mice showed a significant increase in total immobility time in a forced swim test and

showed latency to enter the light box in a light-dark transition test, compared with sham-treated (control) mice. Corticosterone secretion was significantly high in the ELF-MF-exposed mice; however, no changes were observed in the amount of the adrenocorticotrophic hormone and the expression of genes related to stress response. Quantification of the mRNA levels of adrenal corticosteroid synthesis enzymes revealed a significant reduction in Cyp17a1 mRNA in the ELF-MF-exposed mice. Our findings suggest the possibility that high intensity and chronic exposure to ELF-MF induces an increase in corticosterone secretion, along with depression- and/or anxiety-like behavior, without enhancement of the hypothalamic-pituitary-adrenal axis.

(E) Komaki A, Khalili A, Salehi I, Shahidi S, Sarihi A. Effects of exposure to an extremely low frequency electromagnetic field on hippocampal long-term potentiation in rat. Brain Res. 2014 Apr 10. pii: S0006-8993(14)00419-3. doi: 10.1016/j.brainres.2014.03.041. [Epub ahead of print] (AS, CE, EE)

Modern lifestyle exposes nearly all humans to electromagnetic fields, particularly extremely low frequency electromagnetic field (ELF-EMF). Prolonged exposure to ELF-EMF induces persistent changes in neuronal activity. However, the modulation of synaptic efficiency by ELF-EMF in vivo is still unclear. In the present study, we investigated whether ELF-EMF can change induction of long-term potentiation (LTP) and paired-pulse ratio (PPR) in rat hippocampal area. Twenty-nine adult male Wistar rats were divided into 3 groups (ELF-EMF exposed, sham and control groups). ELF-EMF group was exposed to the magnetic field for 90 consecutive days (2 hours/day). ELF-EMF was produced by a circular coil (50Hz, 100 micro Tesla). The sham-exposed controls were placed in an identical chamber with no electromagnetic field. After this period, rats were deeply anesthetized with urethane (2.0mg/kg) and then a bipolar stimulating and recording electrode was implanted into the perforant pathway (PP) and dentate gyrus (DG), respectively. LTP in hippocampal area was induced by high-frequency stimulation (HFS). Prolonged exposure to ELF-EMF increased LTP induction. There was a significant difference in the slope of EPSP and amplitude of PS between the ELF-EMF and other groups. In conclusion, our data suggest that exposure to ELF-EMF produces a marked change in the synaptic plasticity generated in synapses of the PP-DG. No significant difference in PPR of ELF-EMF group before and after HFS suggests a postsynaptic expression site of LTP.

(E) Korpınar MA, Kalkan MT, Tuncel H. The 50 Hz (10 mT) sinusoidal magnetic field: effects on stress-related behavior of rats. Bratisl Lek Listy. 113(9):521-524, 2012. (AS, CE, BE)

Purpose: The purpose of this study was to investigate the behavioral changes induced by 50 Hz, 10 mT flux density Sinusoidal Magnetic Field (MF). Material and methods: Seventy-six young adult male Wistar albino rats were used in the study. They were separated into two groups: control group (C) n=38; MF group n=38. C animals were left under the same conditions with the MF group for 21 days but with prevented or avoided exposure to MF. Anxiety and stress-related behavioral changes were investigated by elevated plus-maze and hole-board systems. Just before being tested in the maze, each animal was tested by means of the hole-board method in order to separate the directed exploration behavior and locomotion activity changes from anxiety-related behavior. Results: In the hole-board system parameters there were no

statistically significant differences between the two groups. There was a statistically significant difference between MF and C groups when the ratio of time spent on open arms to the total time spent on all arms was evaluated (0.12 ± 0.08 and 0.34 ± 0.18 respectively and $p < 0.01$).

Conclusion: Our results suggest that after 21 days, a continuous exposure to extremely low frequency of magnetic field (50 Hz, 10 mT) has no significant effect on activity and exploration activity but significantly induces stress and anxiety-related behavior in rats (Tab. 2, Fig. 9, Ref. 19).

(E) Kumar S, Jain S, Behari J, Avelev VD, Mathur R. Effect of magnetic field on food and water intake and body weight of spinal cord injured rats. Indian J Exp Biol. 48(10):982-986, 2010. (AS, CE, MA)

Chronic (2 h/d x 8 weeks) exposure to magnetic field (MF; 50 Hz, 17.9 microT) in complete spinal cord (T13) transected rats restored food intake (FI), water intake (WI) and body weight (BW) which were decreased in the spinal cord injured rats. The results suggest a significant beneficial effect of chronic exposure to magnetic field of paraplegic rats.

(E) Kumar S, Jain S, Velpandian T, Petrovich Gerasimenko Y, D Avelev V, Behari J, Behari M, Mathur R. Exposure to extremely low-frequency magnetic field restores spinal cord injury-induced tonic pain and its related neurotransmitter concentration in the brain. Electromagn Biol Med. 32(4):471-483, 2013. (AS, CE, BE, CC, MA)

Spinal cord injury (SCI) is unequivocally reported to produce hyperalgesia to phasic stimuli, while both hyper- and hypoalgesia to tonic stimuli. The former is spinally mediated and the latter centrally. Besides, its management is unsatisfactory. We report the effect of magnetic field (MF; 17.96 μ T, 50 Hz) on tonic pain behavior and related neurotransmitters in the brain of complete thoracic (T13) SCI rats at week 8. Adult male Wistar rats were divided into Sham, SCI and SCI+MF groups. Formalin-pain behavior was compared utilizing 5 min block pain rating (PR), 60 min session-PR, time spent in various categories of increasing pain (T0-T3) and flinch incidences. Serotonin (5-HT), dopamine (DA), norepinephrine (NE), gamma-aminobutyric acid (GABA), glutamate and glycine were estimated in brain tissue by liquid chromatography-mass spectrometry. Session-PR, block-PR and number of flinches were significantly lower, while time spent in categories 0-1 was higher in the SCI versus Sham group. These parameters were comparable in the SCI+MF versus Sham group. 5-HT concentration in cortex, remaining forebrain areas and brain stem (BS), was lower while GABA and NE were higher in BS of SCI, which were comparable with Sham in the SCI+MF group. The concentration of DA, glutamate and glycine was comparable amongst the groups. The data indicate significant hypoalgesia in formalin pain while increased in GABA, NE and decreased in 5-HT post-SCI, which were restored in the SCI+MF group. We suggest beneficial effect of chronic (2 h/day x 8 weeks) exposure to MF (50 Hz, 17.96 μ T) on tonic pain that is mediated by 5-HT, GABA and NE in complete SCI rats.

(E) Lahijani MS, Bigdeli MR, Kalantary S. Effects of sinusoidal electromagnetic fields on histopathology and structures of brains of preincubated white Leghorn chicken embryos. Electromagn Biol Med. 30(3):146-157, 2011. (AS, AE, MC, DE)

There are several reports indicating linkages between exposures to 50-60 Hz electromagnetic fields and abnormalities in the early stages of chicken embryonic development. Based on our previous published research carried out at the Department of Animal Sciences, Faculty of Biological Sciences, Shahid Beheshti University, effects of sinusoidal electromagnetic fields on histopathology and structures of brains of preincubated white leghorn hen eggs were investigated. Three hundred healthy fresh fertilized eggs (55-65 gr) were divided into three groups of experimental (n = 50), control (n = 75), and sham (n = 75). Experimental eggs (inside the coil) were exposed to 3 different intensities of 1.33, 2.66, and 7.32 mT and sham groups were located inside the same coil with no exposure, for 24 h before incubation. Control, sham, and experimental groups were all incubated in an incubator ($38 \pm 0.5(^{\circ})\text{C}$, 60% humidity) for 14 days. 14-day old chicken embryos were removed by C-sections, and the brains of all embryos of all groups were fixed in formalin(10%), stained with H&E and TUNEL assay, for studying the histopathology and process of apoptosis. The brains of other embryos were prepared for Scanning Electron Microscope. Results showed electromagnetic fields have toxic effects on brain cells by increasing the number of apoptotic cells and degeneration of brains' tissues of exposed chicken embryos. These findings suggest that the electromagnetic fields induce brain damages at different levels.

(E) Legros A, Corbacio M, Beuter A, Modolo J, Goulet D, Prato FS, Thomas AW. Neurophysiological and behavioral effects of a 60 Hz, 1,800 μT magnetic field in humans. Eur J Appl Physiol. 112(5):1751-1762, 2012. (HU, AE, BE)

The effects of time-varying magnetic fields (MF) on humans have been actively investigated for the past three decades. One important unanswered question is the potential for MF exposure to have acute effects on human biology. Different strategies have been used to tackle this question using various physiological, neurophysiological and behavioral indicators. For example, researchers investigating electroencephalography (EEG) have reported that extremely low frequency (ELF, <300 Hz) MF can increase resting occipital alpha rhythm (8-12 Hz). Interestingly, other studies have demonstrated that human motricity can be modulated by ELF MF: a reduction of anteroposterior standing balance or a decrease of physiological tremor intensity have been reported as consequences of exposure. However, the main limitation in this domain lies in the lack of results replication, possibly originating from the large variety of experimental approaches employed. Therefore, the present study aimed to investigate the effects of a 60 Hz, 1,800 μT MF exposure on neurophysiological (EEG) and neuromotor (standing balance, voluntary motor function, and physiological tremor) aspects in humans using a single experimental procedure. Though results from this study suggest a reduction of human standing balance with MF exposure, as well as an increase of physiological tremor amplitude within the frequency range associated with central nervous system contribution, no exposure effect appeared on other investigated parameters (e.g., EEG or voluntary motor control). These results suggest that 1 h of 60 Hz, 1,800 μT MF exposure may modulate human involuntary motor control without being detected in the cortical electrical activity.

(E) Leone L, Fusco S, Mastrodonato A, Piacentini R, Barbati SA, Zaffina S, Pani G, Podda MV, Grassi C. Epigenetic Modulation of Adult Hippocampal Neurogenesis by Extremely Low-

Frequency Electromagnetic Fields. Mol Neurobiol. 2014 Feb 16. [Epub ahead of print] (AS, CS, CE, AE, BE, CC, MA)

Throughout life, adult neurogenesis generates new neurons in the dentate gyrus of hippocampus that have a critical role in memory formation. Strategies able to stimulate this endogenous process have raised considerable interest because of their potential use to treat neurological disorders entailing cognitive impairment. We previously reported that mice exposed to extremely low-frequency electromagnetic fields (ELFEFs) showed increased hippocampal neurogenesis. Here, we demonstrate that the ELFEF-dependent enhancement of hippocampal neurogenesis improves spatial learning and memory. To gain insights on the molecular mechanisms underlying ELFEFs' effects, we extended our studies to an in vitro model of neural stem cells (NSCs) isolated from the hippocampi of newborn mice. We found that ELFEFs enhanced proliferation and neuronal differentiation of hippocampal NSCs by regulation of epigenetic mechanisms leading to pro-neuronal gene expression. Upon ELFEF stimulation of NSCs, we observed a significant enhancement of expression of the pro-proliferative gene hairy enhancer of split 1 and the neuronal determination genes NeuroD1 and Neurogenin1. These events were preceded by increased acetylation of H3K9 and binding of the phosphorylated transcription factor cAMP response element-binding protein (CREB) on the regulatory sequence of these genes. Such ELFEF-dependent epigenetic modifications were prevented by the Ca_v1-channel blocker nifedipine, and were associated with increased occupancy of CREB-binding protein (CBP) to the same loci within the analyzed promoters. Our results unravel the molecular mechanisms underlying the ELFEFs' ability to improve endogenous neurogenesis, pointing to histone acetylation-related chromatin remodeling as a critical determinant. These findings could pave the way to the development of novel therapeutic approaches in regenerative medicine.

(E) Li C, Xie M, Luo F, He C, Wang J, Tan G, Hu Z. The extremely low-frequency magnetic field exposure differently affects the AMPAR and NMDAR subunit expressions in the hippocampus, entorhinal cortex and prefrontal cortex without effects on the rat spatial learning and memory. Environ Res. 2014 Jul 18;134C:74-80. doi: 10.1016/j.envres.2014.06.025. [Epub ahead of print] (AS; CE; CC)

In the present study, we investigated the effects of chronic exposure (14 and 28 days) to a 50Hz, 0.5mT extremely low-frequency magnetic field (ELF-MF) on the NMDAR and AMPAR subunit expressions and rat spatial learning and memory. Using the Western blotting method, we found ELF-MF exposure specifically decreased the expressions of GluA2 in the EC post 28 day exposure and GluA3 of AMPAR subunits in the PFC after 14 day exposure, while it did not affect the AMPAR subunit expression in the hippocampus at both time points. As for NMDAR subunits, 14 day ELF-MF exposure significantly increased the levels of GluN2A and GluN2B in the hippocampus. Moreover, the levels of GluN1 and GluN2A were enhanced in the EC and PFC after two weeks of ELF-MF exposure. Interestingly, 28 day ELF-MF exposure induced a different expression pattern for NMDAR subunits. The increased GluN2A expression observed at 14 day post ELF-MF exposure was recovered after prolonged exposure in the hippocampus and PFC. In the EC, the increased expression of GluN1 achieved to control level and, specifically, a decrease

in GluN2A level was observed. Surprisingly, neither 14 nor 28 day ELF-MF did affect the rat spatial reference memory as assessed by water maze. These results indicate that the dynamic and brain-region specific changes in ionotropic glutamate receptor expression induced by ELF-MF are insufficient to influence the rat spatial learning ability.

(NE) Li L, Xiong DF, Liu JW, Li ZX, Zeng GC, Li HL. No effects of power line frequency extremely low frequency electromagnetic field exposure on selected neurobehavior tests of workers inspecting transformers and distribution line stations versus controls. Australas Phys Eng Sci Med. 2013 Dec 31. [Epub ahead of print] (HU, BE, CE)

We aimed to evaluate the interference of 50 Hz extremely low frequency electromagnetic field (ELF-EMF) occupational exposure on the neurobehavior tests of workers performing tour-inspection close to transformers and distribution power lines. Occupational short-term "spot" measurements were carried out. 310 inspection workers and 300 logistics staff were selected as exposure and control. The neurobehavior tests were performed through computer-based neurobehavior evaluation system, including mental arithmetic, curve coincide, simple visual reaction time, visual retention, auditory digit span and pursuit aiming. In 500 kV areas electric field intensity at 71.98 % of total measured 590 spots were above 5 kV/m (national occupational standard), while in 220 kV areas electric field intensity at 15.69 % of total 701 spots were above 5 kV/m. Magnetic field flux density at all the spots was below 1,000 μ T (ICNIRP occupational standard). The neurobehavior score changes showed no statistical significance. Results of neurobehavior tests among different age, seniority groups showed no significant changes. Neurobehavior changes caused by daily repeated ELF-EMF exposure were not observed in the current study.

(E) Li Y, Yan X, Liu J, Li L, Hu X, Sun H, Tian J. Pulsed electromagnetic field enhances brain-derived neurotrophic factor expression through L-type voltage-gated calcium channel- and Erk-dependent signaling pathways in neonatal rat dorsal root ganglion neurons. Neurochem Int. 75:96-104, 2014. (CS, AE, CC)

Although pulsed electromagnetic field (PEMF) exposure has been reported to promote neuronal differentiation, the mechanism is still unclear. Here, we aimed to examine the effects of PEMF exposure on brain-derived neurotrophic factor (Bdnf) mRNA expression and the correlation between the intracellular free calcium concentration ($[Ca(2+)]_i$) and Bdnf mRNA expression in cultured dorsal root ganglion neurons (DRGNs). Exposure to 50Hz and 1mT PEMF for 2h increased the level of $[Ca(2+)]_i$ and Bdnf mRNA expression, which was found to be mediated by increased $[Ca(2+)]_i$ from $Ca(2+)$ influx through L-type voltage-gated calcium channels (VGCCs). However, calcium mobilization was not involved in the increased $[Ca(2+)]_i$ and BDNF expression, indicating that calcium influx was one of the key factors responding to PEMF exposure. Moreover, PD098059, an extracellular signal-regulated kinase (Erk) inhibitor, strongly inhibited PEMF-dependant Erk1/2 activation and BDNF expression, indicating that Erk activation is required for PEMF-induced upregulation of BDNF expression. These findings indicated that PEMF exposure increased BDNF expression in DRGNs by activating $Ca(2+)$ - and Erk-dependent signaling pathways.

(NE) Li Y, Zhang C, Song T. Disturbance of the magnetic field did not affect spatial memory. Physiol Res. 2014 Feb 24. [Epub ahead of print] (AS, CE, BE)

Extremely low-frequency magnetic field (ELF-MF) has been suggested to influence the cognitive capability and has to be dynamically evaluated in a longitudinal study. Previous training can affect performance, but the influence under magnetic field is unclear. This study aims to evaluate the effects of previous training and ELF-MF exposure on learning and memory using the Morris water maze (MWM). Sprague-Dawley rats were subjected to MWM training, ELF-MF exposure (50 Hz, 100 microT), or ELF-MF exposure combined with MWM training for 90 days. Normal rats were used as controls. The MWM was used to test. The data show that the rats exposed to training and ELF-MF with training performed better on spatial acquisition when re-tested. However, during the probe trial the rats showed no change between the training phase and the test phase. Compared with the control group, the ELF-MF group showed no significant differences. These results confirm that previous training can improve the learning and memory capabilities regarding spatial acquisition in the MWM and this effect can last for at least 90 days. However, this improvement in learning and memory capabilities was not observed during the probe trial. Furthermore, ELF-MF exposure did not interfere with the improvement in learning and memory capabilities.

(E) Liu DD, Ren Z, Yang G, Zhao QR, Mei YA. Melatonin protects rat cerebellar granule cells against electromagnetic field-induced increases in Na⁺ currents through intracellular Ca²⁺ release. J Cell Mol Med. 2014 Feb 18. doi: 10.1111/jcmm.12250. [Epub ahead of print] (CS, AE, CC, OX)

Although melatonin (MT) has been reported to protect cells against oxidative damage induced by electromagnetic radiation, few reports have addressed whether there are other protective mechanisms. Here, we investigated the effects of MT on extremely low-frequency electromagnetic field (ELF-EMF)-induced Na_v activity in rat cerebellar granule cells (GCs). Exposing cerebellar GCs to ELF-EMF for 60 min. significantly increased the Na_v current (I_{Na}) densities by 62.5%. MT (5 μM) inhibited the ELF-EMF-induced I_{Na} increase. This inhibitory effect of MT is mimicked by an MT₂ receptor agonist and was eliminated by an MT₂ receptor antagonist. The Na_v channel steady-state activation curve was significantly shifted towards hyperpolarization by ELF-EMF stimulation but remained unchanged by MT in cerebellar GC that were either exposed or not exposed to ELF-EMF. ELF-EMF exposure significantly increased the intracellular levels of phosphorylated PKA in cerebellar GCs, and both MT and IIC-7 did not reduce the ELF-EMF-induced increase in phosphorylated PKA. The inhibitory effects of MT on ELF-EMF-induced Na_v activity was greatly reduced by the calmodulin inhibitor KN93. Calcium imaging showed that MT did not increase the basal intracellular Ca²⁺ level, but it significantly elevated the intracellular Ca²⁺ level evoked by the high K⁺ stimulation in cerebellar GC that were either exposed or not exposed to ELF-EMF. In the presence of ruthenium red, a ryanodine-sensitive receptor blocker, the MT-induced increase in intracellular calcium levels was reduced. Our data show for the first time that MT protects against neuronal I_{Na} that result from ELF-EMF exposure through Ca²⁺ influx-induced Ca²⁺ release.

(E) Liu H, Chen G, Pan Y, Chen Z, Jin W, Sun C, Chen C, Dong X, Chen K, Xu Z, Zhang S, Yu Y. (2014) Occupational Electromagnetic Field Exposures Associated with Sleep Quality: A Cross-Sectional Study. PLoS ONE 9(10): e110825. doi:10.1371/journal.pone.0110825. (HU, CE, BE)

BACKGROUND: Exposure to electromagnetic field (EMF) emitted by mobile phone and other machineries concerns half the world's population and raises the problem of their impact on human health. The present study aims to explore the effects of electromagnetic field exposures on sleep quality and sleep duration among workers from electric power plant. METHODS: A cross-sectional study was conducted in an electric power plant of Zhejiang Province, China. A total of 854 participants were included in the final analysis. The detailed information of participants was obtained by trained investigators using a structured questionnaire, which including socio-demographic characteristics, lifestyle variables, sleep variables and electromagnetic exposures. Physical examination and venous blood collection were also carried out for every study subject. RESULTS: After grouping daily occupational electromagnetic exposure into three categories, subjects with long daily exposure time had a significantly higher risk of poor sleep quality in comparison to those with short daily exposure time. The adjusted odds ratios were 1.68 (95%CI: 1.18, 2.39) and 1.57 (95%CI: 1.10, 2.24) across tertiles. Additionally, among the subjects with long-term occupational exposure, the longer daily occupational time apparently increased the risk of poor sleep quality (OR (95%CI): 2.12 (1.23~3.66) in the second tertile; 1.83 (1.07~3.15) in the third tertile). There was no significant association of long-term occupational exposure duration, monthly electric fee or years of mobile-phone use with sleep quality or sleep duration. CONCLUSIONS: The findings showed that daily occupational EMF exposure was positively associated with poor sleep quality. It implies EMF exposure may damage human sleep quality rather than sleep duration.

(E) Liu T, Wang S, He L, Ye K. Anxiogenic effect of chronic exposure to extremely low frequency magnetic field in adult rats. Neurosci Lett. 434(1):12-17, 2008a. (AS, CE, BE)

Previous study has suggested some relations between extremely low frequency magnetic field (ELF MF) and the emotional state of human beings and animals. The aim of the present study was to investigate whether the anxiety level could be affected by repeated ELF MF exposure of different daily durations. Adult SD rats were submitted to no exposure, MF exposure 1h/day or 4h/day for 25 days. Anxiety-related behaviors were examined in the open field test (OFT), the elevated plus maze (EPM), and light/dark box on the 21th, 23th and 25th exposure day, respectively. Results demonstrated that MF exposure 4h/day increased the anxiety-like behaviors in rats in the open field test and the elevated plus maze test, without altering their locomotor activity, but had no effect in the light/dark box test. Moreover, MF exposure 1h/day had no effect in any test. These findings indicate that chronic ELF MF exposure has anxiogenic effect in rats, which is dependent on the daily exposure duration and it is more sensitive to void space than to strong light.

(E) Liu T, Wang S, He L, Ye K. Chronic exposure to low-intensity magnetic field improves acquisition and maintenance of memory. Neuroreport. 19(5):549-552, 2008b. (AS, CE, BE)

Although past research has suggested that acute exposure to extremely low-frequency magnetic field (ELF MF) impairs learning and memory function, data on chronic exposure remain scarce. In this study, we examined the changes in spatial learning and memory by the Morris water maze test after 4 weeks of daily exposure of rats to a 50-Hz magnetic field of 2 mT for either 1 or 4 h. We found that chronic exposure to ELF MF reduced the latency to find the hidden platform and improved long-term memory of former location of platform without affecting the short-term memory and motor activity. These findings for the first time indicate that chronic exposure to ELF MF exerts a positive effect on the acquisition and maintenance of spatial memory.

(E) Maestú C, Blanco M, Nevado A, Romero J, Rodríguez-Rubio P, Galindo J, Bautista Lorite J, de las Morenas F, Fernández-Argüelles P. Reduction of pain thresholds in fibromyalgia after very low-intensity magnetic stimulation: a double-blinded, randomized placebo-controlled clinical trial. Pain Res Manag. 18(6):e101-106, 2013. (HU, BE, MA)

BACKGROUND: Exposure to electromagnetic fields has been reported to have analgesic and antinociceptive effects in several organisms. **Objective:** To test the effect of very low-intensity transcranial magnetic stimulation on symptoms associated with fibromyalgia syndrome. **METHODS:** A double-blinded, placebo-controlled clinical trial was performed in the Sagrado Corazón Hospital, Seville, Spain. Female fibromyalgia patients (22 to 50 years of age) were randomly assigned to either a stimulation group or a sham group. The stimulation group (n=28) was stimulated using 8 Hz pulsed magnetic fields of very low intensity, while the sham group (n=26) underwent the same protocol without stimulation. Pressure pain thresholds before and after stimulation were determined using an algometer during the eight consecutive weekly sessions of the trial. In addition, blood serotonin levels were measured and patients completed questionnaires to monitor symptom evolution. **RESULTS:** A repeated-measures ANOVA indicated statistically significant improvement in the stimulation group compared with the control group with respect to somatosensory pain thresholds, ability to perform daily activities, perceived chronic pain and sleep quality. While improvement in pain thresholds was apparent after the first stimulation session, improvement in the other three measures occurred after the sixth week. No significant between-group differences were observed in scores of depression, fatigue, severity of headaches or serotonin levels. No adverse side effects were reported in any of the patients. **CONCLUSIONS:** Very low-intensity magnetic stimulation may represent a safe and effective treatment for chronic pain and other symptoms associated with fibromyalgia.

Mahdavi SM, Sahraei H, Yaghmaei P, Tavakoli H. Effects of Electromagnetic Radiation Exposure on Stress-Related Behaviors and Stress Hormones in Male Wistar Rats. Biomol Ther (Seoul). 22(6):570-576, 2014.

Studies have demonstrated that electromagnetic waves, as the one of the most important physical factors, may alter cognitive and non-cognitive behaviors, depending on the frequency and

energy. Moreover, non-ionizing radiation of low energy waves e.g. very low frequency waves could alter this phenomenon via alterations in neurotransmitters and neurohormones. In this study, short, medium, and long-term exposure to the extremely low frequency electromagnetic field (ELF-EMF) (1 and 5 Hz radiation) on behavioral, hormonal, and metabolic changes in male Wistar rats (250 g) were studied. In addition, changes in plasma concentrations for two main stress hormones, noradrenaline and adrenocorticotrophic hormone (ACTH) were evaluated. ELF-EMF exposure did not alter body weight, and food and water intake. Plasma glucose level was increased and decreased in the groups which exposed to the 5 and 1Hz wave, respectively. Plasma ACTH concentration increased in both using frequencies, whereas nor-adrenaline concentration showed overall reduction. At last, numbers of rearing, sniffing, locomotor activity was increased in group receiving 5 Hz wave over the time. In conclusions, these data showed that the effects of 1 and 5 Hz on the hormonal, metabolic and stress-like behaviors may be different. Moreover, the influence of waves on stress system is depending on time of exposure.

(E) Manikonda PK, Rajendra P, Devendranath D, Gunasekaran B, Channakeshava, Aradhya RS, Sashidhar RB, Subramanyam C. Influence of extremely low frequency magnetic fields on Ca²⁺ signaling and NMDA receptor functions in rat hippocampus. Neurosci Lett. 413(2):145-149, 2007. (AS, CE, CC)

Extremely low frequency (ELF<300Hz) electromagnetic fields affect several neuronal activities including memory. Because ELF magnetic fields cause altered Ca²⁺ homeostasis in neural tissues, we examined their influence on Ca²⁺ signaling enzymes in hippocampus and related them with NMDA receptor functions. Hippocampal regions were obtained from brains of 21-day-old rats that were exposed for 90 days to 50Hz magnetic fields at 50 and 100 microT intensities. In comparison to controls, ELF exposure caused increased intracellular Ca²⁺ levels concomitant with increased activities of Ca²⁺-dependent protein kinase C (PKC), cAMP-dependent protein kinase and calcineurin as well as decreased activity of Ca²⁺-calmodulin-dependent protein kinase in hippocampal regions. Simultaneous ligand-binding studies revealed decreased binding to N-methyl-D-aspartic acid (NMDA) receptors. The combined results suggest that perturbed neuronal functions caused by ELF exposure may involve altered Ca²⁺ signaling events contributing to aberrant NMDA receptor activities.

(E) Manikonda PK, Rajendra P, Devendranath D, Gunasekaran B, Channakeshava, Aradhya SR, Sashidhar RB, Subramanyam C. Extremely low frequency magnetic fields induce oxidative stress in rat brain. Gen Physiol Biophys. 2013 Dec 13. [Epub ahead of print] (AS, CE, OX, CC)

The present investigation was conducted to understand the influence of long-term exposure of rats to extremely low frequency magnetic fields (ELF-MF), focusing on oxidative stress (OS) on different regions of rat's brain. Male Wistar rats (21-day-old) were exposed to ELF-MF (50 Hz; 50 and 100 µT) for 90 days continuously; hippocampal, cerebellar and cortical regions from rats were analyzed for (i) reactive oxygen species (ROS), (ii) metabolites indicative of OS and (iii) antioxidant enzymes. In comparison to control group rats, the rats that were continuously exposed to ELF-MF caused OS and altered glutathione (GSH/GSSG) levels in dose-dependent manner in all the regions of the brain. Accumulation of ROS, lipid peroxidation end products and activity of superoxide dismutase in different regions was in the descending order of

cerebellum < hippocampus < cortex. Decrement in GSH/GSSG levels and increment in glutathione peroxidase activity were in the descending order of hippocampus < cerebellum < cortex. The continuous exposure to ELF-MF caused OS in all the examined regions of brain more significantly at 100 μ T than at 50 μ T. Varied influences observed in different regions of the brain, as documented in this study, may contribute to altered metabolic patterns in its related regions of the central nervous system, leading to aberrant neuronal functions.

(E) Manjhi J, Kumar S, Behari J, Mathur R. Effect of extremely low frequency magnetic field in prevention of spinal cord injury-induced osteoporosis. J Rehabil Res Dev. 50(1):17-30, 2013. (AS, CE, MA)

The present study was designed to investigate the effect of extremely low frequency (ELF) magnetic field (MF) on spinal cord injury (SCI)-induced osteoporosis in rats. Adult male Wistar rats (n = 24) were equally divided into sham, SCI, and SCI+MF groups. Complete transection of spinal cord (thoracic 11 vertebra) was surgically performed under anesthesia, whereas in the sham group only laminectomy was done. Post-SCI day 1, rats were either exposed (2 h/d \times 8 wk) to ELF-MF (17.96 micro-Tesla, 50 Hz; SCI+MF group) or sham exposed (SCI group). Basso, Beattie, and Bresnahan (BBB) score was recorded weekly. All the rats were sacrificed 8 wk post-SCI; tibia and femur bones were isolated for the analysis of bone mineral content (BMC; total calcium [Ca], phosphorus [P], carbon [C]), bone mineral density (BMD), and biochemical status (osteocalcin, collagen I, alkaline phosphatase). The BBB score decreased post-SCI, which partially recovered after ELF-MF. In SCI rats, there was a statistically significant decrease in BMC, Ca, P, C, BMD, and biochemical level in both the bones as compared with the sham group, which was attenuated in SCI+MF rats except the C content. Electron microscopic study revealed the enhancement of microstructural composition and compactness in cortical and trabecular parts of treated bones. The results suggest that the chronic (2 h/d \times 8 wk) ELF-MF exposure (17.96 micro-Tesla, 50 Hz) to SCI rats is effective in attenuating SCI-induced osteoporosis.

(E) Marchesi N, Osera C, Fassina L, Amadio M, Angeletti F, Morini M, Magenes G, Venturini L, Biggiogera M, Ricevuti G, Govoni S, Caorsi S, Pascale A, Comincini S. Autophagy is modulated in human neuroblastoma cells through direct exposition to low frequency electromagnetic fields. J Cell Physiol. 229(11):1776-1786, 2014. (CS, AE, CC, ND, MA)

In neurogenerative diseases, comprising Alzheimer's (AD), functional alteration in autophagy is considered one of the pathological hallmarks and a promising therapeutic target.

Epidemiological investigations on the possible causes undergoing these diseases have suggested that electromagnetic fields (EMF) exposition can contribute to their etiology. On the other hand, EMF have therapeutic implications in reactivating neuronal functionality. To partly clarify this dualism, the effect of low-frequency EMF (LF-EMF) on the modulation of autophagy was investigated in human neuroblastoma SH-SY5Y cells, which were also subsequently exposed to A β peptides, key players in AD. The results primarily point that LF-EMF induce a significant reduction of microRNA 30a (miR-30a) expression with a concomitant increase of Beclin1 transcript (BECN1) and its corresponding protein. Furthermore, LF-EMF counteract the

induced miR-30a up-regulation in the same cells transfected with miR-30a mimic precursor molecules and, on the other side, rescue Beclin1 expression after BECN1 siRNA treatment. The expression of autophagy-related markers (ATG7 and LC3B-II) as well as the dynamics of autophagosome formation were also visualized after LF-EMF exposition. Finally, different protocols of repeated LF-EMF treatments were assayed to contrast the effects of A β peptides in vitro administration. Overall, this research demonstrates, for the first time, that specific LF-EMF treatments can modulate in vitro the expression of a microRNA sequence, which in turn affects autophagy via Beclin1 expression. Taking into account the pivotal role of autophagy in the clearance of protein aggregates within the cells, our results indicate a potential cytoprotective effect exerted by LF-EMF in neurodegenerative diseases such as AD.

(E) Martínez-Sámano J, Torres-Durán PV, Juárez-Oropeza MA, Verdugo-Díaz L. Effect of acute extremely low frequency electromagnetic field exposure on the antioxidant status and lipid levels in rat brain. Arch Med Res. 43(3):183-189, 2012. (AS, AE, CC, OX)

BACKGROUND AND AIMS: It is generally accepted that electromagnetic fields (EMF) can exert biological effects; however, the mechanisms by which EMF elicits responses are still unknown. The present study was designed to assess the immediate effects of acute EMF exposure, movement restriction, and the combination of both on the antioxidant systems and lipid content in the whole brain of rat. METHODS: Thirty two male Wistar rats were arranged in four groups: control, EMF exposed, movement restrained (MR), and EMF + MR for 2 h. Rats were then sacrificed and their brains analyzed for superoxide dismutase and catalase activities, reduced glutathione, nitric oxide, total cholesterol, and triacylglycerol levels, as well as plasma corticosterone concentrations. RESULTS: Acute exposure to EMF induces reduction in catalase and superoxide dismutase activities, whereas the combination of EMF + MR also decreases both reduced glutathione and nitric oxide levels. Our results show that the acute exposure to EMF does not induce elevation of stress-hormone corticosterone but impairs the antioxidant status in rat brain. CONCLUSIONS: Plasma corticosterone concentration and antioxidant data indicate that the acute exposure to EMF appears to be a mild stressor that leads to some adaptive responses due to the activation of systems controlling the brain oxidative balance.

(NE) Masuda H, de Gannes FP, Haro E, Billaudel B, Ruffié G, Lagroye I, Veyret B. Lack of effect of 50-Hz magnetic field exposure on the binding affinity of serotonin for the 5-HT 1B receptor subtype. Brain Res. 1368:44-51, 2011. (CS, AE, CC)

There is some concern that exposure to extremely low-frequency magnetic fields (MF) causes adverse health effects via signal transduction pathways. Two previous studies reported that exposure to 50-Hz MF decreased the binding affinity of the 1B receptor subtype of serotonin (5-HT) in rat brain membranes. The aim of this study was to investigate whether the exposure to MF affects binding to the 5-HT(1B) receptor and a physiological function associated with 5-HT(1B) receptor activation. Rat brain crude membrane fractions, including 5-HT(1B) receptor and C6-glia cells transfected with human 5-HT(1B) receptor gene, were exposed to 50-Hz MF at 1 mT using Merritt coils under temperature-regulated conditions. In the rat crude membrane, there was no significant difference in the affinity constant of [(3)H]-5-HT between exposed

(K(d): 0.92 ± 0.38 nM) and sham-exposed (K(d): 1.00 ± 0.32 nM). The lack of affinity change after exposure was also confirmed using a chemical agonist of the 5-HT receptor, [(3)H]-5-carboxytryptamine (K(d): 0.59 ± 0.06 nM for exposed and 0.71 ± 0.08 nM for sham). Similar negative results in terms of affinity constant were obtained on the human 5-HT(1B) receptor in C6-glia cells. In addition, forskolin-stimulated cAMP production was inhibited by 5-HT administration in a dose-dependent manner in C6-glia cells, but exposure did not modify the inhibitory response. This study thus failed to confirm the previous results and findings suggest that exposure to MF below the current occupational limit does not affect the physiological function involved in 5-HT(1B) receptor subtypes.

(E) Monazzam MR, Hosseini M, Matin LF, Aghaei HA, Khosroabadi H, Hesami A. Sleep quality and general health status of employees exposed to extremely low frequency magnetic fields in a petrochemical complex. Journal of Environmental Health Science and Engineering 2014, 12:78. (CE, HU, BE)

Background. Advances in science and technology of electrical equipment, despite increasing human welfare in everyday life, have increased the number of people exposed to Electro-Magnetic Fields (EMFs). Because of possible adverse effects on the health of exposed individuals, the EMFs have been the center of attention. This study was performed to determine possible correlation between Extremely Low Frequency Electro-Magnetic Fields (ELF EMFs) and sleep quality and public health of those working in substation units of a petrochemical complex in southern Iran. Materials and method. To begin with, magnetic flux density was measured at different parts of a Control Building and two substations in accordance with IEEE std 644 1994. Subsequently, the questionnaires Pittsburgh Sleep Quality Index (PSQI) and General Health Quality (GHQ) were used to investigate relationship between ELF exposure level and sleep quality and public health, respectively. Both questionnaires were placed at disposal of a total number of 40 workers at the complex. The filled out questionnaires were analyzed by T-test, Duncan and the Chi-square tests. Results. The obtained results revealed that 28% of those in case group suffered from poor health status and 61% were diagnosed with a sleep disorder. However, all members in control group were in good health condition and only 4.5% of them had undesirable sleep quality. Conclusion. In spite of a significant difference between the case and control groups in terms of sleep quality and general health, no significant relationship was found between the exposure level and sleep quality and general health. It is worth noting that the measured EMF values were lower than the standard limits recommended by American Conference of Industrial Hygienists (ACGIH). However, given the uncertainties about the pathogenic effects caused by exposure to ELF EMFs, further epidemiological studies and periodic testing of personnel working in high voltage substations are of utmost importance.

(E) Murugan NJ, Persinger MA. Comparisons of Responses by Planarian to Micromolar to Attomolar Dosages of Morphine or Naloxone and/or Weak Pulsed Magnetic Fields: Revealing Receptor Subtype Affinities and Nonspecific Effects. Int J Radiat Biol. 2014 Apr 10. [Epub ahead of print] (AS, AE, BE)

Purpose: The behavioral responses of planaria to the exposures of a range of concentrations of morphine (μM to attoM) or the μ -opiate antagonist naloxone or to either of these compounds and a burst-firing magnetic field ($5 \mu\text{T}$) were studied. Material and Methods: The locomotor velocity (LMV) of planaria was measured after individual worms were exposed to increasing concentrations from attomolar to micromolar of morphine or naloxone, physiologically patterned magnetic fields or a combination of the two. Results: Compared to spring water controls, the two-hour exposure to the patterned magnetic field before measurement reduced activity by about 50% which was comparable to the non-specific effects of morphine and naloxone across all dosages except 1 attomolar that did not differ from spring water. The specific dosage of 100 nM produced additional marked reduction in activity for planaria exposed to either morphine or naloxone while only 1 pM of morphine produced this effect. Conclusion: The results support the presence of at least two receptor subtypes that mediate the diminished activity effects elicited by morphine specifically and suggests that exposure to the specifically patterned magnetic field produces a behavioral suppression whose magnitude is similar to the "dose independent" effects from this opiate.

(E) Partsvania B, Sulaberidze T, Modebadze Z, Shoshiashvili L. Extremely low-frequency magnetic fields effects on the snail single neurons. Electromagn Biol Med. 27(4):409-417, 2008. (CS, EE)

The aim of present work is to explore the influence of extremely low-frequency electromagnetic fields (8.34 and 217 Hz) utilized in cell phones on habituation of the mollusk single neuron to intracellular stimuli. The isolated nervous system of the mollusk *Helix Pomatia* was used in the experiments. Helmholtz coils were used to expose brain ganglia to the low-frequency electromagnetic fields. Peak values of the extremely low-frequency fields were between 1 and 6 mT. Neuron electrophysiology was investigated using a standard microelectrode technique. Exposure of the neuron to the low-frequency electromagnetic fields caused dehabituation to intracellular stimulus. The effect was proportional to the magnetic induction peak value. The observed dehabituation occurs by degradation of the signal to noise ratio and by alteration of the neuron's normal function.

(E) Perentos N, Croft RJ, McKenzie RJ, Cvetkovic D, Cosic I. The effect of GSM-like ELF radiation on the alpha band of the human resting EEG. Conf Proc IEEE Eng Med Biol Soc. 2008:5680-5683, 2008. (HU, EE)

Mobile phone handsets such as those operating in the GSM network emit extremely low frequency electromagnetic fields ranging from DC to at least 40 kHz. As a subpart of an extended protocol, the influence of these fields on the human resting EEG has been investigated in a fully counter balanced, double blind, cross-over design study that recruited 72 healthy volunteers. A decrease in the alpha frequency band was observed during the 20 minutes of ELF exposure in the exposed hemisphere only. This result suggests that ELF fields as emitted from GSM handsets during the DTX mode may have an effect on the resting alpha band of the human EEG.

(E) Piacentini R, Ripoli C, Mezzogori D, Azzena GB, Grassi C. Extremely low-frequency electromagnetic fields promote in vitro neurogenesis via upregulation of Ca(v)1-channel activity. J Cell Physiol. 215(1):129-139, 2008. (CS, AE, MC, MA)

We previously reported that exposure to extremely low-frequency electromagnetic fields (ELFEFs) increases the expression and function of voltage-gated Ca²⁺ channels and that Ca²⁺ influx through Ca(v)1 channels plays a key role in promoting the neuronal differentiation of neural stem/progenitor cells (NSCs). The present study was conducted to determine whether ELFEFs influence the neuronal differentiation of NSCs isolated from the brain cortices of newborn mice by modulating Ca(v)1-channel function. In cultures of differentiating NSCs exposed to ELFEFs (1 mT, 50 Hz), the percentage of cells displaying immunoreactivity for neuronal markers (beta-III-tubulin, MAP2) and for Ca(v)1.2 and Ca(v)1.3 channels was markedly increased. NSC-differentiated neurons in ELFEF-exposed cultures also exhibited significant increases in spontaneous firing, in the percentage of cells exhibiting Ca²⁺ transients in response to KCl stimulation, in the amplitude of these transients and of Ca²⁺ currents generated by the activation of Ca(v)1 channels. When the Ca(v)1-channel blocker nifedipine (5 microM) was added to the culture medium, the neuronal yield of NSC differentiation dropped significantly, and ELFEF exposure no longer produced significant increases in beta-III-tubulin- and MAP2-immunoreactivity rates. In contrast, the effects of ELFEFs were preserved when NSCs were cultured in the presence of either glutamate receptor antagonists or Ca(v)2.1- and Ca(v)2.2-channel blockers. ELFEF stimulation during the first 24 h of differentiation caused Ca(v)1-dependent increases in the number of cells displaying CREB phosphorylation. Our data suggest that ELFEF exposure promotes neuronal differentiation of NSCs by upregulating Ca(v)1-channel expression and function.

(E) Podda MV, Leone L, Barbati SA, Mastrodonato A, Li Puma DD, Piacentini R, Grassi C. Extremely low-frequency electromagnetic fields enhance the survival of newborn neurons in the mouse hippocampus. Eur J Neurosci. 2013 Dec 30. doi: 10.1111/ejn.12465. [Epub ahead of print] (AS, CS, CE, AE, BE, CC, MA)

In recent years, much effort has been devoted to identifying stimuli capable of enhancing adult neurogenesis, a process that generates new neurons throughout life, and that appears to be dysfunctional in the senescent brain and in several neuropsychiatric and neurodegenerative diseases. We previously reported that in vivo exposure to extremely low-frequency electromagnetic fields (ELFEFs) promotes the proliferation and neuronal differentiation of hippocampal neural stem cells (NSCs) that functionally integrate in the dentate gyrus. Here, we extended our studies to specifically assess the influence of ELFEFs on hippocampal newborn cell survival, which is a very critical issue in adult neurogenesis regulation. Mice were injected with 5-bromo-2'-deoxyuridine (BrdU) to label newborn cells, and were exposed to ELFEFs 9 days later, when the most dramatic decrease in the number of newly generated neurons occurs. The results showed that ELFEF exposure (3.5 h/day for 6 days) enhanced newborn neuron survival as documented by double staining for BrdU and doublecortin, to identify immature neurons, or NeuN labeling of mature neurons. The effects of ELFEFs were associated with enhanced spatial learning and memory. In an in vitro model of hippocampal NSCs, ELFEFs exerted their pro-

survival action by rescuing differentiating neurons from apoptotic cell death. Western immunoblot assay revealed reduced expression of the pro-apoptotic protein Bax, and increased levels of the anti-apoptotic protein Bcl-2, in the hippocampi of ELFEF-exposed mice as well as in ELFEF-exposed NSC cultures, as compared with their sham-exposed counterparts. Our results may have clinical implications for the treatment of impaired neurogenesis associated with brain aging and neurodegenerative diseases.

(E) Rauš S, Selaković V, Manojlović-Stojanoski M, Radenović L, Prolić Z, Janać B. Response of Hippocampal Neurons and Glial Cells to Alternating Magnetic Field in Gerbils Submitted to Global Cerebral Ischemia. Neurotox Res. 23(1):79-91, 2013. (AS, CE, MC, MA)

The purpose of this study was to determine whether exposure to an extremely low-frequency magnetic field (ELF-MF, 50 Hz) affects the outcome of postischemic damage in the hippocampus of Mongolian gerbils. After 10-min bilateral carotid occlusion, the gerbils were continuously exposed to ELF-MF (average magnetic induction at the center of the cage was 0.5 mT) for 7 days. The impact of ELF-MF was estimated immediately (the 7th day after reperfusion) and 7 days after cessation of exposure (the 14th day after reperfusion) compared with ischemic gerbils without ELF-MF exposure. Applying stereological methods, histological evaluation of changes in the hippocampus was done for determining its volume, volume densities of degenerating neurons and astrocytes, as well as the number of microglial cells per unit area. ELF-MF per se did not induce any morphological changes, while 10-min global cerebral ischemia led to neuronal death, especially in CA1 region of the hippocampus, as expected. Ischemic gerbils exposed to ELF-MF had significantly a lower degree of cell loss in the examined structure and greater responses of astrocytes and microglial cells than postischemic gerbils without exposure on the seventh day after reperfusion (immediate effect of ELF-MF). Similar response was observed on the 14th day after reperfusion (delayed effect of ELF-MF); however, differences in measured parameters were low and insignificant. Applied ELF-MF has possible neuroprotective function in the hippocampus, as the most sensitive brain structure in the model of global cerebral ischemia, through reduction of neuronal death and activation of astrocytes and microglial cells.

(E) Rauš S, Selaković V, Radenović L, Prolić Z, Janać B. Extremely low frequency magnetic field induced changes in motor behaviour of gerbils submitted to global cerebral ischemia. Behav Brain Res. 228(2):241-246, 2012. (AS, CE, BE, MA)

The purpose of this study was to evaluate behavioural effects of an extremely low frequency magnetic field (ELF-MF) in 3-month-old Mongolian gerbils submitted to global cerebral ischemia. After 10-min occlusion of both common carotid arteries, the gerbils were placed in the vicinity of an electromagnet and continuously exposed to ELF-MF (50Hz, 0.5mT) for 7 days. Their behaviour (locomotion, stereotypy, rotations, and immobility) was monitored on days 1, 2, 4, 7, and 14 after reperfusion for 60 min in the open field. It was shown that the 10-min global cerebral ischemia per se induced a significant motor activity increase (locomotion, stereotypy and rotations), and consequently immobility decrease until day 4 after reperfusion, compared to control gerbils. Exposure to ELF-MF inhibited development of ischemia-induced

motor hyperactivity during the whole period of registration, but significantly in the first 2 days after reperfusion, when the postischemic hyperactivity was most evident. Motor activity of these gerbils was still significantly increased compared to control ones, but only on day 1 after reperfusion. Our results revealed that the applied ELF-MF (50Hz, 0.5mT) decreased motor hyperactivity induced by the 10-min global cerebral ischemia, via modulation of the processes that underlie this behavioural response.

(E) Rauš Balind S, Selaković V, Radenović L, Prolić Z, Janać B. Extremely Low Frequency Magnetic Field (50 Hz, 0.5 mT) Reduces Oxidative Stress in the Brain of Gerbils Submitted to Global Cerebral Ischemia. PLoS One. 2014 Feb 19;9(2):e88921. doi: 10.1371/journal.pone.0088921. eCollection 2014. (AS, CE, OX, CC, MA)

Magnetic field as ecological factor has influence on all living beings. The aim of this study was to determine if extremely low frequency magnetic field (ELF-MF, 50 Hz, 0.5 mT) affects oxidative stress in the brain of gerbils submitted to 10-min global cerebral ischemia. After occlusion of both carotid arteries, 3-month-old gerbils were continuously exposed to ELF-MF for 7 days. Nitric oxide and superoxide anion production, superoxide dismutase activity and index of lipid peroxidation were examined in the forebrain cortex, striatum and hippocampus on the 7(th) (immediate effect of ELF-MF) and 14(th) day after reperfusion (delayed effect of ELF-MF). Ischemia per se increased oxidative stress in the brain on the 7(th) and 14(th) day after reperfusion. ELF-MF also increased oxidative stress, but to a greater extent than ischemia, only immediately after cessation of exposure. Ischemic gerbils exposed to ELF-MF had increased oxidative stress parameters on the 7(th) day after reperfusion, but to a lesser extent than ischemic or ELF-MF-exposed animals. On the 14(th) day after reperfusion, oxidative stress parameters in the brain of these gerbils were mostly at the control levels. Applied ELF-MF decreases oxidative stress induced by global cerebral ischemia and thereby reduces possible negative consequences which free radical species could have in the brain. The results presented here indicate a beneficial effect of ELF-MF (50 Hz, 0.5 mT) in the model of global cerebral ischemia.

(E) Ravera S, Bianco B, Cugnoli C, Panfoli I, Calzia D, Morelli A, Pepe IM. Sinusoidal ELF magnetic fields affect acetylcholinesterase activity in cerebellum synaptosomal membranes. Bioelectromagnetics. 31(4):270-276, 2010. (CS, AE, CE)

The effects of extremely low frequency magnetic fields (ELF-MF) on acetylcholinesterase (AChE) activity of synaptosomal membranes were investigated. Sinusoidal fields with 50 Hz frequency and different amplitudes caused AChE activity to decrease about 27% with a threshold of about 0.74 mT. The decrease in enzymatic activity was independent of the time of permanence in the field and was completely reversible. Identical results were obtained with exposure to static MF of the same amplitudes. Moreover, the inhibitory effects on enzymatic activity are spread over frequency windows with different maximal values at 60, 200, 350, and 475 Hz. When synaptosomal membranes were solubilized with Triton, ELF-MF did not affect AChE activity, suggesting the crucial role of the membrane, as well as the lipid linkage of the enzyme, in determining the conditions for inactivation. The results are discussed in order to give an

interpretation at molecular level of the macroscopic effects produced by ELF-MF on biological systems, in particular the alterations of embryo development in many organisms due to acetylcholine accumulation.

**** (E) Rageh MM, El-Gebaly RH, El-Bialy NS. Assessment of genotoxic and cytotoxic hazards in brain and bone marrow cells of newborn rats exposed to extremely low-frequency magnetic field. J Biomed Biotechnol. 2012;2012:716023. (AS, CE, OX, DE)**

The present study aimed to evaluate the association between whole body exposure to extremely low frequency magnetic field (ELF-MF) and genotoxic, cytotoxic hazards in brain and bone marrow cells of newborn rats. Newborn rats (10 days after delivery) were exposed continuously to 50 Hz, 0.5 mT for 30 days. The control group was treated as the exposed one with the sole difference that the rats were not exposed to magnetic field. Comet assay was used to quantify the level of DNA damage in isolated brain cells. Also bone marrow cells were flushed out to assess micronucleus induction and mitotic index. Spectrophotometric methods were used to measure the level of malondialdehyde (MDA) and the activity of glutathione (GSH) and superoxide dismutase (SOD). The results showed a significant increase in the mean tail moment indicating DNA damage in exposed group ($P < 0.01$, 0.001, 0.0001). Moreover ELF-MF exposure induced a significant ($P < 0.01$, 0.001) four folds increase in the induction of micronucleus and about three folds increase in mitotic index ($P < 0.0001$). Additionally newborn rats exposed to ELF-MF showed significant higher levels of MDA and SOD ($P < 0.05$). Meanwhile ELF-MF failed to alter the activity of GSH. In conclusion, the present study suggests an association between DNA damage and ELF-MF exposure in newborn rats.

(E) Reale M, Kamal MA, Patruno A, Costantini E, D'Angelo C, Pesce M, Greig NH. Neuronal Cellular Responses to Extremely Low Frequency Electromagnetic Field Exposure: Implications Regarding Oxidative Stress and Neurodegeneration. PLoS One. 2014 Aug 15; 9(8):e104973. doi: 10.1371/journal.pone.0104973. eCollection 2014. (CS, AE, OX, ND)

Neurodegenerative diseases comprise both hereditary and sporadic conditions characterized by an identifying progressive nervous system dysfunction and distinctive neuropathophysiology. The majority are of non-familial etiology and hence environmental factors and lifestyle play key roles in their pathogenesis. The extensive use of and ever increasing worldwide demand for electricity has stimulated societal and scientific interest on the environmental exposure to low frequency electromagnetic fields (EMFs) on human health. Epidemiological studies suggest a positive association between 50/60-Hz power transmission fields and leukemia or lymphoma development. Consequent to the association between EMFs and induction of oxidative stress, concerns relating to development of neurodegenerative diseases, such as Alzheimer disease (AD), have been voiced as the brain consumes the greatest fraction of oxygen and is particularly vulnerable to oxidative stress. Exposure to extremely low frequency (ELF)-EMFs are reported to alter animal behavior and modulate biological variables, including gene expression, regulation of cell survival, promotion of cellular differentiation, and changes in cerebral blood flow in aged AD transgenic mice. Alterations in inflammatory responses have also been reported, but how these actions impact human health remains unknown. We hence evaluated the effects of an

electromagnetic wave (magnetic field intensity 1mT; frequency, 50-Hz) on a well-characterized immortalized neuronal cell model, human SH-SY5Y cells. ELF-EMF exposure elevated the expression of NOS and O2-, which were countered by compensatory changes in antioxidant catylase (CAT) activity and enzymatic kinetic parameters related to CYP-450 and CAT activity. Actions of ELF-EMFs on cytokine gene expression were additionally evaluated and found rapidly modified. Confronted with co-exposure to H2O2-induced oxidative stress, ELF-EMF proved not as well counteracted and resulted in a decline in CAT activity and a rise in O2- levels. Together these studies support the further evaluation of ELF-EMF exposure in cellular and in vivo preclinical models to define mechanisms potentially impacted in humans.

(E) Reyes-Guerrero G, Guzmán C, García DE, Camacho-Arroyo I, Vázquez-García M. Extremely low-frequency electromagnetic fields differentially regulate estrogen receptor-alpha and -beta expression in the rat olfactory bulb. Neurosci Lett. 471(2):109-13, 2010. (AS, AE, CC)

Recently, the effects of extremely low-frequency electromagnetic fields (ELF EMF) on biological systems have been extensively investigated. In this report, the influence of ELF EMF on olfactory bulb (OB) estrogen receptor-alpha (ER alpha) mRNA and -beta (ER beta) mRNA expression was studied by RT-PCR in adult female and male rats. Results reveal for the first time that ELF EMF exerted a biphasic effect on female OB ER beta mRNA gene expression, which increased during diestrous and decreased during estrous. We did not observe any influence of ELF EMF on female OB ER alpha mRNA expression. Our data demonstrate a fluctuating pattern of ER-alpha and -beta mRNA expression in the female OB throughout the phases of the estrous cycle in non-ELF EMF-exposed animals. Thus the highest ER alpha expression was observed in diestrous and the lowest in proestrous. The pattern of ER beta mRNA was less variable, the lowest expression was observed in diestrous. ER-alpha mRNA and -beta mRNA expression level in the male OB did not exhibit any variation either in ELF EMF-exposed or non-ELF EMF-exposed animals. In summary, ELF EMF modulate ER beta gene expression in the OB of female adult rats but not in males.

(E) Ross ML, Koren SA, Persinger MA. Physiologically patterned weak magnetic fields applied over left frontal lobe increase acceptance of false statements as true. Electromagn Biol Med. 27(4):365-371, 2008. (HU, AE, BE)

Fifty men and women were exposed to only one of four experimentally generated magnetic fields over the left prefrontal region (above the eyebrow) or to a sham field immediately after the words "true" or "false" were presented following statements of definitions of words for a "foreign language". Three of the patterns (25 Hz, 50 Hz, or burst-firing) with intensities between 1 and 10 microT were presented for 1 s during the refutation process (immediately after the offset of "true" or "false") for specific statements from a total of 28 statements. The fourth pattern was a variable approximately 7-10 Hz (10 nT) field generated from the circuitry that was present continuously during the entire experiment. When the statements were presented again, the groups who had received the burst-firing ("limbic") or 25 Hz pulsed magnetic fields during the refutation process accepted about twice the number of false statements as true compared to those exposed to the 50 Hz field or sham-field conditions. The treatments did not

significantly affect the numbers of true statements accepted as false. These results suggest that the appropriately pulsed magnetic field during the refutation process of what one has been told or has heard can increase the probability a person will accept a false statement as true.

(E) Sakhnini L, Al Ali H, Al Qassab N, Al Arab E, Kamal A. Subacute exposure to 50-Hz electromagnetic fields affect prenatal and neonatal mice's motor coordination. J. Appl. Phys. 111(7):07B314, 2012. (AS, CE, BE, DE)

In this study, we investigate the possible effect of ELF-EMFs on motor performance in mice (prenatal and neonatal exposed mice). The mice performance is evaluated after 5 days of subacute exposure. Immature mice have been chosen for this study because the immature rodent brain still has the capacity to undergo proliferation, differentiation, and reorganization. Results from the rotarod experiments demonstrated a pronounced deficit in the learning abilities of the prenatal exposed groups, but no pronounced effect was observed for the neonatal exposed group.

(E) Salunke BP, Umathe SN, Chavan JG. Involvement of NMDA receptor in low-frequency magnetic field-induced anxiety in mice. Electromagn Biol Med. 2013 Oct 16. [Epub ahead of print] (AS, CE, CC, BE)

It had been reported that exposure to extremely low-frequency magnetic field (ELFMF) induces anxiety in human and rodents. Anxiety mediates via the activation of N-methyl-D-aspartate (NMDA) receptor, whereas activation of γ -aminobutyric acid (GABA) receptor attenuates the same. Hence, the present study was carried out to understand the contribution of NMDA and/or GABA receptors modulation in ELFMF-induced anxiety for which Swiss albino mice were exposed to ELFMF (50 Hz, 10 G) by subjecting them to Helmholtz coils. The exposure was for 8 h/day for 7, 30, 60, 90 and 120 days. Anxiety level was assessed in elevated plus maze, open field test and social interaction test, on 7th, 30th, 60th, 90th and 120th exposure day, respectively. Moreover, the role of GABA and glutamate in ELFMF-induced anxiety was assessed by treating mice with muscimol [0.25 mg/kg intraperitoneally (i.p.)], bicuculline (1.0 mg/kg i.p.), NMDA (15 mg/kg i.p.) and MK-801 (0.03 mg/kg i.p.), as a GABA_A and NMDA receptor agonist and antagonist, respectively. Glutamate receptor agonist exacerbated while inhibitor attenuated the ELFMF-induced anxiety. In addition, levels of GABA and glutamate were determined in regions of the brain viz, cortex, striatum, hippocampus and hypothalamus. Experiments demonstrated significant elevation of GABA and glutamate levels in the hippocampus and hypothalamus. However, GABA receptor modulators did not produce significant effect on ELFMF-induced anxiety and elevated levels of GABA at tested dose. Together, these findings suggest that ELFMF significantly induced anxiety behavior, and indicated the involvement of NMDA receptor in its effect.

(E) Salunke BP, Umathe SN, Chavan JG. Experimental evidence for involvement of nitric oxide in low frequency magnetic field induced obsessive compulsive disorder-like behavior.

Pharmacol Biochem Behav. 2014 Apr 26. pii: S0091-3057(14)00115-4. doi: 10.1016/j.pbb.2014.04.007. [Epub ahead of print] (AS, CE, BE, OX)

It is well documented that extremely low frequency magnetic field (ELF MF) produced effects on the function of nervous system in humans and laboratory animals. Dopaminergic and serotonergic pathways have been implicated in obsessive compulsive disorder (OCD). Recently involvement of nitric oxide (NO) in OCD-like behavior is suggested. Hence, the present study was carried out to understand the involvement of dopamine, serotonin and NO in ELF MF induced OCD-like behavior. Swiss albino mice were exposed to ELF MF (50Hz, 10G) for 8h/day for 7, 30, 60, 90 and 120days by subjecting them to Helmholtz coils. OCD-like behavior was assessed in terms of marble burying behavior (MBB) test. Results revealed that ELF MF induced time dependant MBB, on 7th, 30th, 60th, 90th, and 120th exposure day. Further, levels of dopamine, serotonin and NO after 120days of ELF MF exposure were determined in regions of the brain. The neurohumoral studies revealed that exposure to ELF MF increased NO levels in cortex, hippocampus and hypothalamus, and levels of dopamine and serotonin remain unaffected. As OCD-like behavior after ELF MF exposure was associated with higher levels of NO with no significant change in serotonin and dopamine, the effect of such exposure was studied in groups concurrently treated with NO modulators, NO precursor, L-ARG (400mg/kg) or NOS inhibitor, L-NAME (15.0mg/kg) or 7-NI (10.0mg/kg). These treatments revealed that NO precursor exacerbated and NOS inhibitors attenuated ELF MF induced OCD-like behavior with corresponding changes in the levels of NO.

(E) Schmid MR, Murbach M, Lustenberger C, Maire M, Kuster N, Achermann P, Loughran SP. Sleep EEG alterations: effects of pulsed magnetic fields versus pulse-modulated radio frequency electromagnetic fields. J Sleep Res. 2012 Jun 22. doi: 10.1111/j.1365-2869.2012.01025.x. [Epub ahead of print] (HU, AE, EE)

Studies have repeatedly shown that electroencephalographic power during sleep is enhanced in the spindle frequency range following radio frequency electromagnetic field exposures pulse-modulated with fundamental frequency components of 2, 8, 14 or 217 Hz and combinations of these. However, signals used in previous studies also had significant harmonic components above 20 Hz. The current study aimed: (i) to determine if modulation components above 20 Hz, in combination with radio frequency, are necessary to alter the electroencephalogram; and (ii) to test the demodulation hypothesis, if the same effects occur after magnetic field exposure with the same pulse sequence used in the pulse-modulated radio frequency exposure. In a randomized double-blind crossover design, 25 young healthy men were exposed at weekly intervals to three different conditions for 30 min before sleep. Cognitive tasks were also performed during exposure. The conditions were a 2-Hz pulse-modulated radio frequency field, a 2-Hz pulsed magnetic field, and sham. Radio frequency exposure increased electroencephalogram power in the spindle frequency range. Furthermore, delta and theta activity (non-rapid eye movement sleep), and alpha and delta activity (rapid eye movement sleep) were affected following both exposure conditions. No effect on sleep architecture and no clear impact of exposure on cognition was observed. These results demonstrate that both pulse-modulated radio frequency and pulsed magnetic fields affect brain physiology, and the

presence of significant frequency components above 20 Hz are not fundamental for these effects to occur. Because responses were not identical for all exposures, the study does not support the hypothesis that effects of radio frequency exposure are based on demodulation of the signal only.

(E) Selaković V, Rauš Balind S, Radenović L, Prolić Z, Janać B. Age-Dependent Effects of ELF-MF on Oxidative Stress in the Brain of Mongolian Gerbils. Cell Biochem Biophys. 66(3):513-521, 2013. (AS, CE, OX)

The aim of study was to investigate the effects of extremely low frequency magnetic field (ELF-MF; 50 Hz; 0.1, 0.25 and 0.5 mT) on oxidative stress in the brain of 3- (adult) and 10-month-old (middle-aged) gerbils. Nitric oxide (NO) level, superoxide (O(2) (-)) production, superoxide dismutase (SOD) activity, and index of lipid peroxidation (ILP) were measured in the forebrain cortex, striatum, hippocampus, and cerebellum immediately and 3 days after cessation of 7-day exposure. In all gerbils, ELF-MF significantly increased oxidative stress in all tested brain regions. This effect was correlated with the value of magnetic induction and was higher in middle-aged gerbils. Three days after cessation of exposure, the values of examined parameters were closer to control levels. In adult gerbils, the effect of ELF-MF of 0.1 mT on NO level, O(2) (-) production and SOD activity was almost fully disappeared, and ILP was at the control level regardless of the value of magnetic induction. In middle-aged gerbils, the effect of ELF-MF was still present but to a lesser degree than those observed immediately after cessation of exposure. These findings pointed out the ability of ELF-MF to induce age- and magnetic induction-dependent modification of oxidative stress in the brain.

(E) Shafiei SA, Firoozabadi SM, Rasoulzadeh Tabatabaie K, Ghabaee M. Study of the frequency parameters of EEG influenced by zone-dependent local ELF-MF exposure on the human head. Electromagn Biol Med. 31(2):112-12, 2012. (HU, AE, EE)

It has been reported that human subjects exposed to electromagnetic fields exhibit changes in human EEG signals at the frequency of stimulation. The aim of the present study was to expose different parts of the brain to extremely low-frequency magnetic fields locally and investigate EEG power spectrum alters at the frequency of stimulation. EEG relative power spectrum were evaluated at 3, 5, 10, 17, and 45 Hz frequencies at T4, T3, F3, Cz, and F4 points, respectively, when these points were exposed to magnetic fields with similar frequencies and 100 μ T intensity. The paired t-test results showed that power value of EEG did not alter significantly at the frequency of stimulation ($P < 0.05$). Further, significant changes in different EEG bands caused by locally exposing to ELF-MF in different points of brain were observed. The changes in the EEG bands were not limited necessarily to the exposure point.

(E) Shafiei SA, Firoozabadi SM, Tabatabaie KR, Ghabaee M. Investigation of EEG changes during exposure to extremely low-frequency magnetic field to conduct brain signals. Neurol Sci. 2014 May 27. [Epub ahead of print] (HU, AE, EE)

There are evidences that confirm the effect of magnetic fields (MFs) on brain signals and some psychological disorders such as headache, migraine and depression. The aim of the present study was to investigate changes in EEG power spectrum due to localized exposure in different parts of the brain by extremely low-frequency magnetic fields (ELF-MFs) to extract some protocols for treatment of some psychological disorders. In addition, regular effects were investigated by increasing intensity of ELF-MF. Therefore, EEG relative power spectrum was evaluated at T4, T3, F3, F4, and Cz points, when all the points were exposed to MFs with 45, 17, 10, 5, and 3 Hz frequencies, separately. Intensity of MF was 0, 100, 240, or 360 μ T in four sessions. Significant changes were observed in different EEG bands caused by locally exposing to ELF-MF in different points of brain ($P < 0.05$). Some exposure to MFs decreased alpha band of frontal and central areas in closed-eyes state. Based on the findings in this study, some protocols can be designed using a combination of various MFs exposures to conduct the brain signals that is necessary to evaluate clinically.

(E) Shin EJ, Jeong JH, Kim HJ, Jang CG, Yamada K, Nabeshima T, Kim HC. Exposure to extremely low frequency magnetic fields enhances locomotor activity via activation of dopamine D1-like receptors in mice. J Pharmacol Sci. 105(4):367-371, 2007. (AS, AE, CE, BE, CC)

We demonstrated that exposure to extremely low frequency magnetic fields (ELF-MF) enhanced dopamine levels in the rat striatum. To extend our understanding, we examined the role of dopaminergic receptors in ELF-MF-induced behavioral changes. Exposure to ELF-MF (2.4 mT, 1 h/day, for one or seven days) enhanced locomotor activity in a time-dependent manner. This hyperlocomotor activity paralleled an increase in c-Fos-like immunoreactivity (c-Fos-IR). Pretreatment with SCH23390, a dopaminergic D(1)-like receptor antagonist, but not with sulpiride, a dopaminergic D(2)-like receptor antagonist, inhibited ELF-MF-induced increased locomotor activity and c-Fos-IR. Thus, our results suggest that ELF-MF-induced behavioral responses are, at least in part, mediated by activation of dopamine D(1)-like receptors.

(E) Shin EJ, Nguyen XK, Nguyen TT, Pham DT, Kim HC. Exposure to extremely low frequency magnetic fields induces fos-related antigen-immunoreactivity via activation of dopaminergic D1 receptor. Exp Neurobiol. 20(3):130-6, 2011. (CE, BE, CC)

We previously demonstrated that repeated exposure to extremely low frequency magnetic fields (ELF-MF) increases locomotor activity via stimulation of dopaminergic D1 receptor (J. Pharmacol. Sci., 2007;105:367-371). Since it has been demonstrated that activator protein-1 (AP-1) transcription factors, especially 35-kDa fos-related antigen (FRA), play a key role in the neuronal and behavioral adaptation in response to various stimuli, we examined whether repeated ELF-MF exposure induces FRA-immunoreactivity (FRA-IR) in the striatum and nucleus accumbens (striatal complex) of the mice. Repeated exposure to ELF-MF (0.3 or 2.4 mT, 1

h/day, for consecutive fourteen days) significantly induced hyperlocomotor activity and FRA-IR in the striatal complex in a field intensity-dependent manner. ELF-MF-induced FRA-IR lasted for at least 1 year, while locomotor activity returned near control level 3 months after the final exposure to ELF-MF. Pretreatment with SCH23390, a dopaminergic D1 receptor antagonist, but not with sulpiride, a dopaminergic D2 receptor antagonist, significantly attenuated hyperlocomotor activity and FRA-IR induced by ELF-MF. Our results suggest that repeated exposure to ELF-MF leads to prolonged locomotor stimulation and long-term expression of FRA in the striatal complex of the mice via stimulation of dopaminergic D1 receptor.

(NE) Sorahan T, Mohammed N. Neurodegenerative disease and magnetic field exposure in UK electricity supply workers. Occup Med (Lond). 2014 Aug 7. pii: kqu105. [Epub ahead of print]. (CE, HU, ND)

BACKGROUND: Previous research has suggested a possible link between neurodegenerative disease and exposure to extremely low-frequency electric and magnetic fields. AIMS: To investigate whether risks of Alzheimer's, motor neurone or Parkinson's disease are related to occupational exposure to magnetic fields. METHODS: The mortality experienced by a cohort of 73051 employees of the former Central Electricity Generating Board of England and Wales was investigated for the period 1973-2010. All employees were hired in the period 1952-82, were employed for at least 6 months and had some employment after 1 January 1973. Detailed calculations had been performed by others to enable an assessment to be made of exposures to magnetic fields. Poisson regression was used to calculate relative risks (rate ratios) of developing any of the three diseases under investigation for categories of lifetime, distant (lagged) and recent (lugged) exposure. RESULTS: No statistically significant trends were shown for risks of any of these diseases to increase with estimates of lifetime, recent or distant exposure to magnetic fields. CONCLUSIONS: There is no convincing evidence that UK electricity generation and transmission workers have suffered elevated risks from neurodegenerative diseases as a consequence of exposure to magnetic fields.

(E) Stevens P. Affective response to 5 microT ELF magnetic field-induced physiological changes. Bioelectromagnetics. 28(2):109-114, 2007. (HU, AE, BE)

Research into effects of weak magnetic fields (MFs) at biologically relevant frequencies has produced ambiguous results. Although they do affect human physiology and behaviour, the direction of effects is inconsistent, with a range of complex and unrelated behaviours being susceptible. A possible explanation is that these effects, rather than being directly caused, are instead related to changes in affective state. A previous study showed that MFs altered the affective content of concurrent perceptions, but it was unclear whether the emotional response was direct or indirect. Here it is shown that exposure to a 0-5 microT MF (DC-offset sinusoidal wave form) within EEG alpha-band frequencies (8-12 Hz), results in a reported

change in emotional state. This relates to a decrease global field power but lacks the frontal alpha-asymmetry that would physiologically indicate a directly induced emotional state, suggesting that participant experiences are due to an interpretation of the effects of MF exposure.

(E) Strasák L, Bártoová E, Krejci J, Fojt L, Vetterl V. Effects of ELF-EMF on brain proteins in mice. Electromagn Biol Med. 28(1):96-104, 2009. (AS, AE, CC)

Effect of electromagnetic low frequency fields was studied on mice. We analyzed level of protein in brain of mouse. The levels of c-Jun and c-Fos in brains were measured using Western-blot techniques. Female and male laboratory mice were exposed for 4 days to magnetic field ($B_m = 2 \text{ mT}$, $f = 50 \text{ Hz}$). The exposure took place in cylindrical coil at laboratory temperature. After the experiment they were sacrificed and the level of protein c-Jun and c-Fos in different parts of brain were estimated. The expression of c-Fos was not affected by magnetic field on the other hand the expression of c-Jun decreased after magnetic field exposure. The results did not depend on sex of mice.

(E) Sun H, Che Y, Liu X, Zhou D, Miao Y, Ma Y. Effects of prenatal exposure to a 50-Hz magnetic field on one-trial passive avoidance learning in 1-day-old chicks. Bioelectromagnetics. 31(2):150-155, 2010. (AS, CE, BE, DE)

We investigated memory impairment in newly hatched chicks following in ovo exposure to a 50-Hz magnetic field (MF) of 2 mT (60 min/day) on embryonic days 12-18. Isolated and paired chicks were used to test the effect of stress during training, and memory retention was tested at 10, 30, and 120 min, following exposure to a bitter-tasting bead (100% methylantranilate). Results showed that memory was intact at 10 min in both isolated and paired chicks with or without MF exposure. However, while isolated chicks had good memory retention levels at 30 and 120 min, those exposed to MF did not. The results suggest a potential disruption of memory formation following in ovo exposure to MF, with this effect only evident in the more stressed, isolated chicks.

(E) Szemerszky R, Zelena D, Barna I, Bárdos G. Stress-related endocrinological and psychopathological effects of short- and long-term 50Hz electromagnetic field exposure in rats. Brain Res Bull. 81(1):92-99, 2010. (AS, CE, BE, CC)

It is believed that different electromagnetic fields do have beneficial and harmful biological effects. The aim of the present work was to study the long-term consequences of 50 Hz electromagnetic field (ELF-EMF) exposure with special focus on the development of chronic stress and stress-induced psychopathology. Adult male Sprague-Dawley rats were exposed to ELF-EMF (50 Hz, 0.5 mT) for 5 days, 8h daily (short) or for 4-6 weeks, 24h daily (long). Anxiety was studied in elevated plus maze test, whereas depression-like behavior of the long-treated group was examined in the forced swim test. Some days after behavioral examination, the animals were decapitated among resting conditions and organ weights, blood hormone levels as well as proopiomelanocortin mRNA level from the anterior lobe of the pituitary gland were

measured. Both treatments were ineffective on somatic parameters, namely none of the changes characteristic to chronic stress (body weight reduction, thymus involution and adrenal gland hypertrophy) were present. An enhanced blood glucose level was found after prolonged ELF-EMF exposure ($p=0.013$). The hormonal stress reaction was similar in control and short-term exposed rats, but significant proopiomelanocortin elevation ($p<0.000$) and depressive-like behavior (enhanced floating time; $p=0.006$) were found following long-term ELF-EMF exposure. Taken together, long and continuous exposure to relatively high intensity electromagnetic field may count as a mild stress situation and could be a factor in the development of depressive state or metabolic disturbances. Although we should stress that the average intensity of the human exposure is normally much smaller than in the present experiment.

(E) Tasset I, Medina FJ, Jimena I, Agüera E, Gascón F, Feijóo M, Sánchez-López F, Luque E, Peña J, Drucker-Colín R, Túnez I. Neuroprotective effects of extremely low-frequency electromagnetic fields on a Huntington's disease rat model: effects on neurotrophic factors and neuronal density. Neuroscience. 209:54-63, 2012a. (AS, CE, MC, CC, BE, OX, MA, ND)

There is evidence to suggest that the neuroprotective effect of exposure of extremely low-frequency electromagnetic fields (ELF-EMF) may be due, at least in part, to the effect of these fields on neurotrophic factors levels and cell survival, leading to an improvement in behavior. This study was undertaken to investigate the neuroprotective effects of ELFEF in a rat model of 3-nitropropionic acid (3NP)-induced Huntington's disease. Behavior patterns were evaluated, and changes in neurotrophic factor, cell damage, and oxidative stress biomarker levels were monitored in Wistar rats. Rats were given 3NP over four consecutive days (20 mg/kg body weight), whereas ELFEF (60 Hz and 0.7 mT) was applied over 21 days, starting after the last injection of 3NP. Rats treated with 3NP exhibited significantly different behavior in the open field test (OFT) and the forced swim test (FST), and displayed significant differences in neurotrophic factor levels and oxidative stress biomarkers levels, together with a neuronal damage and diminished neuronal density, with respect neuronal controls. ELFEF improved neurological scores, enhanced neurotrophic factor levels, and reduced both oxidative damage and neuronal loss in 3NP-treated rats. ELFEF alleviates 3NP-induced brain injury and prevents loss of neurons in rat striatum, thus showing considerable potential as a therapeutic tool.

(E) Tasset I, Pérez-Herrera A, Medina FJ, Arias-Carrión O, Drucker-Colín R, Túnez I. Extremely low-frequency electromagnetic fields activate the antioxidant pathway Nrf2 in a Huntington's disease-like rat model. Brain Stimul. 2012b Apr 15. [Epub ahead of print] (AS, CE, CC, MA, ND)

Transcranial magnetic stimulation (TMS) is a non-invasive technique used recently to treat different neuropsychiatric and neurodegenerative disorders. Despite its proven value, the mechanisms through which TMS exerts its beneficial action on neuronal function remain unclear. Recent studies have shown that its beneficial effects may be at least partly due to a neuroprotective effect on oxidative and cell damage. This study shows that TMS can modulate the Nrf2 transcriptor factor in a Huntington's disease-like rat model induced by 3-nitropropionic acid (3-NP). Western blot analysis demonstrated that 3-NP caused a reduction in Nrf2 in both

cytoplasm and nucleus, while TMS applied to 3-NP-treated rats triggered an increase in cytoplasm and nucleus Nrf2 levels. It was therefore concluded that TMS modulates Nrf2 expression and translocation and that these mechanisms may partly explain the neuroprotective effect of TMS, as well as its antioxidant and cell protection capacity.

(E) Todorović D, Kalauzi A, Prolić Z, Jović M, Mutavdžić D. A method for detecting the effect of magnetic field on activity changes of neuronal populations of *Morimus funereus* (Coleoptera, Cerambycidae). Bioelectromagnetics. 28(3):238-241, 2007. (AC, AS, EE)

Modification of a new method for detecting changes in the activities of neuronal population and the nearest neuron is described. Preliminary measurements of the influence of a static magnetic field (2 mT) on neuronal population activity on eight individuals of an endangered insect species *Morimus funereus* are included. Five minutes exposure produced both excitatory (5/8) and inhibitory (3/8) effect on the activity of neuronal population of *M. funereus* antennal lobe. However, when the reversibility of induced effects was quantitatively analyzed, our results showed that they were prevailing irreversible: (7/8) for the population, (6/8) for the nearest neuron.

(E) Todorović D, Marković T, Prolić Z, Mihajlović S, Rauš S, Nikolić L, Janać B. The influence of static magnetic field (50 mT) on development and motor behaviour of *Tenebrio* (Insecta, Coleoptera). Int J Radiat Biol. 2012 Aug 1. [Epub ahead of print] (AS, CE, DE, BE)

PURPOSE: There is considerable concern about potential effects associated with exposure to magnetic fields on organisms. Therefore, duration of pupa-adult development and motorbehaviour of adults were analyzed in *Tenebrio obscurus* and *Tenebrio molitor* after exposure to static magnetic field (50 mT). MATERIAL AND METHODS: The experimental groups were: control (kept 5 m from the magnets), groups which pupae and adults were placed closer to the North pole, or closer to the South pole of magnetic dipole. The pupae were exposed to the magnetic field until the moment of adult eclosion. The pupa-adult development dynamics were recorded daily. Subsequently, behaviour (distance travelled, average speed and immobility) of adults exposed to the magnetic field was monitored in a circular open field arena. RESULTS: Static magnetic field did not affect pupa-adult developmental dynamic of examined *Tenebrio* species. Exposure to magnetic field did not significantly change motor behaviour of *T. obscurus* adults. The changes in the motor behaviour of *T. molitor* induced by static magnetic field were opposite in two experimental groups developed closer to the North pole or closer to the South pole of magnetic dipole. CONCLUSION: Static magnetic field (50 mT) did not affect on pupa-adult development dynamic of two examined *Tenebrio* species, but modulated their motor behaviour.

(NE) Türközer Z, Güler G, Seyhan N. Effects of exposure to 50 Hz electric field at different strengths on oxidative stress and antioxidant enzyme activities in the brain tissue of guinea pigs. Int J Radiat Biol. 84(7):581-590, 2008. (AS, CE, OX)

PURPOSE: The aim of this study was to evaluate the possible effects of varied exposure to 50 Hz extremely low frequency (ELF) electric field (EF) on the lipid peroxidation levels and

antioxidant enzyme activities in the brain homogenates of guinea pigs. Subjects were exposed to 2 kV/m, 2.5 kV/m, 3 kV/m, 3.5 kV/m, 4 kV/m, 4.5 kV/m and 5 kV/m electric fields for three days, 8 h a day in both vertical and horizontal directions. **MATERIALS AND METHODS:** Malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities were measured in order to identify possible alterations in lipid peroxidation levels and antioxidant status due to electric field exposure. Xanthine oxidase (XO), myeloperoxidase (MPO) and adenosine deaminase (ADA) activities were also evaluated in the same samples. **RESULTS:** Although the study showed several positive but non-significant findings ($p > 0.05$), we did not find significant differences among all of the exposed groups and sham groups in lipid peroxidation levels and enzyme activities ($p > 0.05$) at all strengths and in both directions. Furthermore, the result was the same when the comparison was made between the groups in vertical directions and horizontal directions ($p > 0.05$). **CONCLUSION:** The present study observed effects of 50 Hz EF exposure on lipid peroxidation levels and antioxidant defense mechanisms but these were not statistically significant at the 95% confidence level. Further research on the effects ELF-EF exposure on lipid peroxidation levels and antioxidant defence mechanisms are warranted.

(NE) van der Mark M, Vermeulen R, Nijssen PC, Mulleners WM, Sas AM, van Laar T, Kromhout H, Huss A. Extremely low-frequency magnetic field exposure, electrical shocks and risk of Parkinson's disease. *Int Arch Occup Environ Health*. 2014 Jun 18. [Epub ahead of print] **(HU, ND)**

PURPOSE: Previous studies did not provide strong evidence for an increased Parkinson's disease (PD) risk after exposure to extremely low-frequency magnetic fields (ELF-MF), but were limited in their scope to address other exposures related to the use of electricity such as electrical shocks. We evaluated the associations of PD with exposure to ELF-MF, electrical shocks and having worked in "electrical occupations." **METHODS:** We conducted a hospital-based case-control study, including 444 PD patients and 876 age- and sex-matched controls. Occupational histories were collected in telephone interviews and were linked to job-exposure matrices on ELF-MF exposure and on electrical shocks. In addition, questions on use of household appliances involving ELF-MF exposure, experienced electrical shocks and potential confounders were asked. **RESULTS:** No association of PD risk with any of the evaluated exposures related to electricity was observed. We did, however, observe quite consistently reduced risk estimates across the majority of the exposure categories explored. Given the results of the previous studies and the absence of any postulated mechanism, this is unlikely to represent a true protective effect of ELF-MF or electrical shocks on the occurrence of PD. **CONCLUSIONS:** The results of this study suggest that no association exists between PD and exposure to ELF-MF, electrical shocks or having worked in "electrical occupations."

(E) van Nierop LE, Slottje P, van Zandvoort MJE, de Vocht F, Kromhout H. Effects of magnetic stray fields from a 7 Tesla MRI scanner on neurocognition: a double-blind randomised crossover study. *Occup Environ Med* doi:10.1136/oemed-2011-100468 **(HU, BE)**

Objective: This study characterises neurocognitive domains that are affected by movement-induced time-varying magnetic fields (TVMF) within a static magnetic stray field (SMF) of a 7 Tesla (T) MRI scanner. Methods: Using a double-blind randomised crossover design, 31 healthy volunteers were tested in a sham (0 T), low (0.5 T) and high (1.0 T) SMF exposure condition. Standardised head movements were made before every neurocognitive task to induce TVMF. Results: Of the six tested neurocognitive domains, we demonstrated that attention and concentration were negatively affected when exposed to TVMF within an SMF (varying from 5.0% to 21.1% per Tesla exposure, $p < 0.05$), particular in situations where high working memory performance was required. In addition, visuospatial orientation was affected after exposure (46.7% per Tesla exposure, $p = 0.05$). Conclusion: Neurocognitive functioning is modulated when exposed to movement-induced TVMF within an SMF of a 7 T MRI scanner. Domains that were affected include attention/concentration and visuospatial orientation. Further studies are needed to better understand the mechanisms and possible practical safety and health implications of these acute neurocognitive effects.

(E) van Nierop LE, Slottje P, van Zandvoort M, Kromhout H. Simultaneous exposure to MRI-related static and low-frequency movement-induced time-varying magnetic fields affects neurocognitive performance: A double-blind randomized crossover study. Magn Reson Med. 2014 Sep 15. doi: 10.1002/mrm.25443. [Epub ahead of print] (AE, HU, BE)

PURPOSE: This experimental study aims to separate neurocognitive effects resulting from exposure to static magnetic stray fields (SMF) alone and the combination of SMF and low-frequency movement-induced time-varying magnetic fields (TVMF) using a 7 Tesla (T) MRI scanner in stand-by mode. METHODS: In a double-blind randomized crossover experiment, 36 healthy volunteers underwent four sessions, two exposed conditions, and two corresponding sham conditions. The exposure conditions were in front of the scanner bore and consisted of 1.0 T SMF with or without 2.4 T/s TVMF, induced by standardized head movements before each of the five neurocognitive tasks. These specific tasks were selected because previous experiments showed negative effects of SMF + TVMF exposure on test performance. RESULTS: Exposure to SMF in combination with TVMF decreased verbal memory performance significantly and changed visual acuity. Similarly, attention and concentration were negatively affected with borderline significance. Exposure to SMF only did not have significant effects on the performance on any of the tasks. CONCLUSION: Neurocognitive effects were only observed when simultaneously exposed to SMF and TVMF from a 7 T MRI scanner. Therefore, exposure to TVMF seems essential in eliciting the neurocognitive effects in our present study and, presumably, previous experiments.

(E) Varró P, Szemerszky R, Bárdos G, Világi I. Changes in synaptic efficacy and seizure susceptibility in rat brain slices following extremely low-frequency electromagnetic field exposure. Bioelectromagnetics. 30(8):631-640, 2009. (AS, CS, FC)

The effects of electromagnetic fields (EMFs) on living organisms are recently a focus of scientific interest, as they may influence everyday life in several ways. Although the neural effects of EMFs have been subject to a considerable number of investigations, the results are difficult to compare since dissimilar exposure protocols have been applied on different preparations or animals. In the present series of experiments, whole rats or excised rat brain slices were exposed to a reference level-intensity (250-500 microT, 50 Hz) EMF in order to examine the effects on the synaptic efficacy in the central nervous system. Electrophysiological investigation was carried out ex vivo, on neocortical and hippocampal slices; basic synaptic functions, short- and long-term plasticity and seizure susceptibility were tested. The most pronounced effect was a decrease in basic synaptic activity in slices treated directly ex vivo observed as a diminution in amplitude of evoked potentials. On the other hand, following whole-body exposure an enhanced short- and long-term synaptic facilitation in hippocampal slices and increased seizure susceptibility in neocortical slices was also observed. However, these effects seem to be transient. We can conclude that ELF-EMF exposure exerts significant effects on synaptic activity, but the overall changes may strongly depend on the synaptic structure and neuronal network of the affected region together with the specific spatial parameters and constancy of EMF.

(E) Volkow ND, Tomasi D, Wang GJ, Fowler JS, Telang F, Wang R, Alexoff D, Logan J, Wong C, Pradhan K, Caparelli EC, Ma Y, Jayne M. Effects of low-field magnetic stimulation on brain glucose metabolism. Neuroimage. 51(2):623-628, 2010. (HU, AE, FC)

Echo planar imaging (EPI), the gold standard technique for functional MRI (fMRI), is based on fast magnetic field gradient switching. These time-varying magnetic fields induce electric (E) fields in the brain that could influence neuronal activity; but this has not been tested. Here we assessed the effects of EPI on brain glucose metabolism (marker of brain function) using PET and 18F 2-fluoro-2-deoxy-D-glucose ((18)FDG). Fifteen healthy subjects were in a 4 T magnet during the (18)FDG uptake period twice: with (ON) and without (OFF) EPI gradients pulses along the z-axis (G(z): 23 mT/m; 250 μ s rise-time; 920 Hz). The E-field from these EPI pulses is non-homogeneous, increasing linearly from the gradient's isocenter (radial and z directions), which allowed us to assess the correlation between local strength of the E-field and the regional metabolic differences between ON and OFF sessions. Metabolic images were normalized to metabolic activity in the plane positioned at the gradient's isocenter where E=0 for both ON and OFF conditions. Statistical parametric analyses used to identify regions that differed between ON versus OFF ($p < 0.05$, corrected) showed that the relative metabolism was lower in areas at the poles of the brain (inferior occipital and frontal and superior parietal cortices) for ON than for OFF, which was also documented with individual region of interest analysis. Moreover the magnitude of the metabolic decrements was significantly correlated with the estimated strength of E ($r = 0.68$, $p < 0.0001$); the stronger the E-field the larger the decreases. However, we did not detect differences between ON versus OFF conditions on mood ratings nor on absolute whole brain metabolism. This data provides preliminary evidence that EPI sequences may affect neuronal activity and merits further investigation.

(E) Wang X, Liu Y, Lei Y, Zhou D, Fu Y, Che Y, Xu R, Yu H, Hu X, Ma Y. Extremely low-frequency electromagnetic field exposure during chronic morphine treatment strengthens downregulation of dopamine D2 receptors in rat dorsal hippocampus after morphine withdrawal. *Neurosci Lett.* 433(3):178-82, 2008. (AS, CE, CC)

The aim of this study was to investigate the effect of extremely low-frequency electromagnetic field (ELF-EMF) exposure during morphine treatment on dopamine D2 receptor (D2R) density in the rat dorsal hippocampus following withdrawal. Rats were exposed to ELF-EMF (20 Hz, 14 mT) or sham exposed for 1h per day before injection of morphine (10mg/kg, i.p.) once daily for 12 days. The saline control group was sham exposed for the same period. Immunohistochemistry was used to detect the density of D2Rs on the 1st, 3rd and 5th morphine withdrawal days. The results showed that the density of D2Rs in sham-exposed morphine-treated rats on the 1st and 3rd days of morphine withdrawal was significantly lower than that of the saline control group. The ELF-EMF-exposed morphine group also exhibited a significantly lower density of D2Rs on the 1st and 3rd withdrawal days relative to the sham-exposed morphine group. However, the D2R density in both groups tended to recover as morphine withdrawal days increased. The results suggest that dorsal hippocampal D2Rs are sensitive to morphine withdrawal and that this is potentiated by ELF-EMF pre-exposure during morphine treatment.

(E) Wang X, Zhao K, Wang D, Adams W, Fu Y, Sun H, Liu X, Yu H, Ma Y. Effects of exposure to a 50 Hz sinusoidal magnetic field during the early adolescent period on spatial memory in mice. *Bioelectromagnetics.* 34(4):275-284, 2013. (AS, CE, BE)

Adolescence is a critical developmental stage during which substantial remodeling occurs in brain areas involved in emotional and learning processes. Although a robust literature on the biological effects of extremely low frequency magnetic fields (ELF-MFs) has been documented, data on the effects of ELF-MF exposure during this period on cognitive functions remain scarce. In this study, early adolescent male mice were exposed from postnatal day (P) 23-35 to a 50 Hz MF at 2 mT for 60 min/day. On P36-45, the potential effects of the MF exposure on spatial memory performance were examined using the Y-maze and Morris water maze tasks. The results showed that the MF exposure did not affect Y-maze performance but improved spatial learning acquisition and memory retention in the water maze task under the present experimental conditions.

(E) Wang Z, Che PL, Du J, Ha B, Yarema KJ. Static magnetic field exposure reproduces cellular effects of the Parkinson's disease drug candidate ZM241385. *PLoS One.* 5(11):e13883, 2010. (AE, CS, CC)

BACKGROUND: This study was inspired by coalescing evidence that magnetic therapy may be a viable treatment option for certain diseases. This premise is based on the ability of moderate strength fields (i.e., 0.1 to 1 Tesla) to alter the biophysical properties of lipid bilayers and in turn modulate cellular signaling pathways. In particular, previous results from our laboratory (Wang et al., *BMC Genomics*, 10, 356 (2009)) established that moderate strength static magnetic field (SMF) exposure altered cellular endpoints associated with neuronal function and

differentiation. Building on this background, the current paper investigated SMF by focusing on the adenosine A(2A) receptor (A(2A)R) in the PC12 rat adrenal pheochromocytoma cell line that displays metabolic features of Parkinson's disease (PD). **METHODOLOGY AND PRINCIPAL FINDINGS:** SMF reproduced several responses elicited by ZM241385, a selective A(2A)R antagonist, in PC12 cells including altered calcium flux, increased ATP levels, reduced cAMP levels, reduced nitric oxide production, reduced p44/42 MAPK phosphorylation, inhibited proliferation, and reduced iron uptake. SMF also counteracted several PD-relevant endpoints exacerbated by A(2A)R agonist CGS21680 in a manner similar to ZM241385; these include reduction of increased expression of A(2A)R, reversal of altered calcium efflux, dampening of increased adenosine production, reduction of enhanced proliferation and associated p44/42 MAPK phosphorylation, and inhibition of neurite outgrowth. **CONCLUSIONS AND SIGNIFICANCE:** When measured against multiple endpoints, SMF elicited qualitatively similar responses as ZM241385, a PD drug candidate. Provided that the in vitro results presented in this paper apply in vivo, SMF holds promise as an intriguing non-invasive approach to treat PD and potentially other neurological disorders.

(E) Xiong J, He C, Li C, Tan G, Li J, Yu Z, Hu Z, Chen F. Changes of dendritic spine density and morphology in the superficial layers of the medial entorhinal cortex induced by extremely low-frequency magnetic field exposure. PLoS One. 2013 Dec 20; 8(12):e83561. doi: 10.1371/journal.pone.0083561. eCollection 2013. (AS, CE, MC)

In the present study, we investigated the effects of chronic exposure (14 and 28 days) to a 0.5 mT 50 Hz extremely low-frequency magnetic field (ELM) on the dendritic spine density and shape in the superficial layers of the medial entorhinal cortex (MEC). We performed Golgi staining to reveal the dendritic spines of the principal neurons in rats. The results showed that ELM exposure induced a decrease in the spine density in the dendrites of stellate neurons and the basal dendrites of pyramidal neurons at both 14 days and 28 days, which was largely due to the loss of the thin and branched spines. The alteration in the density of mushroom and stubby spines post ELM exposure was cell-type specific. For the stellate neurons, ELM exposure slightly increased the density of stubby spines at 28 days, while it did not affect the density of mushroom spines at the same time. In the basal dendrites of pyramidal neurons, we observed a significant decrease in the mushroom spine density only at the later time point post ELM exposure, while the stubby spine density was reduced at 14 days and partially restored at 28 days post ELM exposure. ELM exposure-induced reduction in the spine density in the apical dendrites of pyramidal neurons was only observed at 28 days, reflecting the distinct vulnerability of spines in the apical and basal dendrites. Considering the changes in spine number and shape are involved in synaptic plasticity and the MEC is a part of neural network that is closely related to learning and memory, these findings may be helpful for explaining the ELM exposure-induced impairment in cognitive functions.

(E) Yi G, Wang J, Wei X, Deng B, Tsang KM, Chan WL, Han C. Effects of extremely low-frequency magnetic fields on the response of a conductance-based neuron model. Int J Neural Syst. 2014 Feb; 24(1):1450007. doi: 10.1142/S0129065714500075. Epub 2013 Dec 11. (CS, AE, EE)

To provide insights into the modulation of neuronal activity by extremely low-frequency (ELF) magnetic field (MF), we present a conductance-based neuron model and introduce ELF sinusoidal MF as an additive voltage input. By analyzing spike times and spiking frequency, it is observed that neuron with distinct spiking patterns exhibits different response properties in the presence of MF exposure. For tonic spiking neuron, the perturbations of MF exposure on spike times is maximized at the harmonics of neuronal intrinsic spiking frequency, while it is maximized at the harmonics of bursting frequency for burst spiking neuron. As MF intensity increases, the perturbations also increase. Compared with tonic spiking, bursting dynamics are less sensitive to the perturbations of ELF MF exposure. Further, ELF MF exposure is more prone to perturb neuronal spike times relative to spiking frequency. Our finding suggests that the resonance may be one of the neural mechanisms underlying the modulatory effects of the low-intensity ELF MFs on neuronal activities. The results highlight the impacts of ELF MFs exposure on neuronal activity from the single cell level, and demonstrate various factors including ELF MF properties and neuronal spiking characteristics could determine the outcome of exposure. These insights into the mechanism of MF exposure may be relevant for the design of multi-intensity magnetic stimulus protocols, and may even contribute to the interpretation of MF effects on the central nervous systems.

(NE) Zhang C, Li Y, Wang C, Lv R, Song T. Extremely low-frequency magnetic exposure appears to have no effect on pathogenesis of Alzheimer's disease in aluminum-overloaded rat. PLoS One. 2013 Aug 12;8(8):e71087. doi: 10.1371/journal.pone.0071087. eCollection 2013. (AS, CE, BE, MC, ND)

OBJECTIVE: Extremely low-frequency magnetic field (ELF-MF) has been reported to be of potential pathogenetic relevance to Alzheimer's disease (AD) for years. However, evidence confirming this function remains inconclusive. Chronic Al treatment has been identified as a contributing factor to cognitive function impairment in AD. This study aims to examine whether or not ELF-MF and Al have synergistic effects toward AD pathogenesis by investigating the effects of ELF-MF with or without chronic Al treatment on SD rats. **METHODS:** Sprague-Dawley (SD) rats were subjected one of the following treatments: sham (control group), oral Al (Al group), ELF-MF (100 μ T at 50 Hz) with oral Al (MF+Al group), or ELF-MF (100 μ T at 50 Hz) without oral Al (MF group). **RESULTS:** After 12 wk of treatment, oral Al treatment groups (Al and MF+Al groups) showed learning and memory impairment as well as morphological hallmarks, including neuronal cell loss and high density of amyloid- β (A β) in the hippocampus and cerebral cortex. ELF-MF without Al treatment showed no significant effect on AD pathogenesis. ELF-MF+Al treatment induced no more damage than Al treatment did. **CONCLUSIONS:** Our results showed no evidence of any association between ELF-MF exposure (100 μ T at 50 Hz) and AD, and ELF-MF exposure does not influence the pathogenesis of AD induced by Al overload.

(NE) Zhang Y, Liu X, Zhang J, Li N. Short term effects of extremely low frequency electromagnetic fields exposure on Alzheimer's disease in rats. Int J Radiat Biol. 2014 Aug 13:1-35. [Epub ahead of print] (AS, CE, BE, ND)

Purpose: With the development and widespread use of electromagnetic field (EMF) technology, recent studies are focusing on the effects of EMF on human health. Recently, extremely low frequency electromagnetic fields (ELF-EMF) have been studied with great interest due to their possible effects on Alzheimer's disease (AD). The objective of the present study was to investigate the interaction between ELF-EMF exposure and memory impairment in rats. Materials and methods: Twenty healthy male Sprague Dawley (SD) rats were randomly divided into two groups (n=10). Animals were exposed to 100 μ T/50Hz ELF-EMF or subjected to sham exposure when 12 weeks old. After 12 weeks, Morris water maze (MWM) was used to test the changes in cognitive and memory ability. Amyloid-beta (A β) content in cortex, hippocampus and plasma were measured by ELISA assays. The morphology of neuron was detected by HE staining. Results: After exposure, the body weight of rats showed no difference compared with control group. The application of ELF-EMF did not induce any cognitive and memory impairment compared with sham exposure group. The determination of A β showed no significant change between two groups. And there was no histological change in ELF-EMF exposure group. Conclusion: The present study indicated that short term exposure of 100 μ T/50Hz ELF-EMF had no effects on cognition and memory of rats, and did not alter the expression of A β and the neuron morphology. However, more comprehensive studies are still required to elucidate the possible effects and underlying mechanisms of ELF-EMF exposure on living organisms.

Bodera P, Makarova K, Zawada K, Antkowiak B, Paluch M, Sobiczewska E, Sirav B, Siwicki AK, Stankiewicz W. The effect of 1800MHz radio-frequency radiation on NMDA receptor subunit NR1 expression and peroxidation in the rat brain in healthy and inflammatory states. Biomed Pharmacother. 92:802-809, 2017.

BACKGROUND: The aim of this study was to evaluate the effect of repeated exposure (5 times for 15min) of 1800MHz radio-frequency radiation (RFR) on N-methyl-d-aspartate receptor subunit NR1 (NMDA-NR1) expression in the brains of rats in a persistent inflammatory state. We also measured the effect of RFR combined with tramadol (TRAM) to determine the potential antioxidant capacity of this agent. METHODS: The effects of the Global System for Mobile Communication (GSM) modulated 1800MHz RFR exposure on the expression and activity of glutamate receptor channels with antioxidative activity in brain tissue was measured using oxygen radical absorbance capacity (ORAC) and electron spin resonance (ESR) detection of the hydroxyl radical generated by the Fenton reaction. NMDA-NR1 was measured in the cerebral tissue of rats with inflammation (complete Freund's adjuvant) and those injected with tramadol after RFR exposure (RFR, RFR/TRAM) and in non-exposed (baseline, TRAM) rats. RESULTS: No differences between the baseline group and the exposed group (RFR) were

observed. NMDA-NR1 expression decreased after CFA injection and RFR exposure, and an elevated expression of NMDA-NR1 was observed in healthy control rats of both groups: TRAM/RFR and RFR. CONCLUSIONS: ORAC assessment revealed a robust effect of RFR, however the other experiments revealed equivocal effects. Further studies examining the combination of ORAC with NMDA are warranted to elucidate more clearly the effect of RFR on the brain.