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Influence of pediatric vaccines on amygdala growth and opioid ligand binding in rhesus macaque infants: A pilot study

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This longitudinal, case-control pilot study examined amygdala growth in rhesus macaque infants receiving the complete US childhood vaccine schedule (1994-1999). Longitudinal structural and functional neuroimaging was undertaken to examine central effects of the vaccine regimen on the developing brain. Vaccine-exposed and saline-injected control infants underwent MRI and PET imaging at approximately 4 and 6 months of age, representing two specific timeframes within the vaccination schedule. Volumetric analyses showed that exposed animals did not undergo the maturational changes over time in amygdala volume that was observed in unexposed animals. After controlling for left amygdala volume, the binding of the opioid antagonist [^{11}C]diprenorphine (DPN) in exposed animals remained relatively constant over time, compared with unexposed animals, in which a significant decrease in [^{11}C]DPN binding occurred. These results suggest that maturational changes in amygdala volume and the binding capacity of [^{11}C]DPN in the amygdala was significantly altered in infant macaques receiving the vaccine schedule. The macaque infant is a relevant animal model in which to investigate specific environmental exposures and structural/functional neuroimaging during neurodevelopment.

Key Words: rhesus macaques, *Macaca mulatta*, non-human primates, animal model, neuroimaging, PET, MRI, amygdala, opioids, ethyl mercury, thimerosal, neurotoxicity

INTRODUCTION

The amygdala, a complexly interconnected limbic system structure located in the temporal lobe of the brain, is thought to play a central role in the expression of emotions (reviewed by Aggleton 1992). In rhesus macaques the amygdala has been associated with the development of social and emotional behavior (reviewed by Brothers 1990). When neonatal macaques received lesions to the amygdala they showed increasing socio-emotional disturbances including abnormal social interaction, absence of facial and body expression, and stereotypic behaviors (Bachevalier 1994). Amaral and colleagues reported that infant monkeys with bilateral amygdala lesions were still capable of interpreting and generating social behaviors (Prather et al. 2001) but failed to develop an appropriate fear response (Antoniadis et al. 2009), implicating an important role for the amygdala in regulating such responses (reviewed by Amaral and Corbett 2003, Amaral et al. 2008, Machado et al. 2009, Roozendaal et al. 2009). While the human amygdala has been well studied longitudinally in both normal and disease states, there is a paucity of information regarding amygdala growth during non-human primate development.

Evidence from animal model systems indicates that endogenous opioids play an important role in neural and behavioral ontogeny (Zagon et al. 1982). The primate amygdala has been shown to have a high avidity for opioids. For example, high levels of [^{3}H]diprenorphine (DPN)-binding in the amygdala of healthy adult male cynomolgus monkeys (*Macaca fascicularis*) were

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