

Large Brains in Autism: The Challenge of Pervasive Abnormality

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The most replicated finding in autism neuroanatomy—a tendency to unusually large brains—has seemed paradoxical in relation to the specificity of the abnormalities in three behavioral domains that define autism. We now know a range of things about this phenomenon, including that brains in autism have a growth spurt shortly after birth and then slow in growth a few short years afterward, that only younger but not older brains are larger in autism than in controls, that white matter contributes disproportionately to this volume increase and in a nonuniform pattern suggesting postnatal pathology, that functional connectivity among regions of autistic brains is diminished, and that neuroinflammation (including microgliosis and astrogliosis) appears to be present in autistic brain tissue from childhood through adulthood. Alongside these pervasive brain tissue and functional abnormalities, there have arisen theories of pervasive or widespread neural information processing or signal coordination abnormalities (such as weak central coherence, impaired complex processing, and underconnectivity), which are argued to underlie the specific observable behavioral features of autism. This convergence of findings and models suggests that a systems- and chronic disease-based reformulation of function and pathophysiology in autism needs to be considered, and it opens the possibility for new treatment targets. *NEUROSCIENTIST* 11(5):417–440; 2005. DOI: 10.1177/0091270005278866

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Autism is a developmental disorder defined behaviorally by a triad of abnormalities involving language, social interaction, and a marked lack of flexibility that may include repetitive or ritualistic behaviors (American Psychiatric Association, 1994); full criteria must be met by the age of three. The behavioral features of autism appear to be continuously distributed, and autism is part of a spectrum that also includes more mildly affected individuals (Dawson and others 2002).

Given that the atypical behaviors defining autism appear specifically characterizable, there has naturally been the expectation that we will find anatomical correlates for each feature of the behavioral phenotype. Indeed, there are findings in the limbic system and cerebellum (parts of the brain subserving functions that include some impaired in autism) that have been common (Cody and others 2002), yet they are troublingly not consistently encountered. Instead, the most replicated finding in autism, and one that has been found in multiple reliably characterized cohorts and artifact-free samples, has been that the brains are on average unusually large. This finding has had a paradoxical impact. On one

hand, the consistency of an anatomical measure was an encouraging sign of convergence upon unraveling the neurobiology of this disorder. On the other hand, large brains did not make sense in terms of neural systems models of autism or brain-behavior correlations. How would such a generalized phenomenon relate to a disorder characterized by three specific classes of atypical behaviors? This conundrum has been sitting in the center of the autism field almost like a zen koan, awaiting a mental frame shift that would allow its obscure significance to become clear.

In the past few years, a series of discoveries about the autistic brain are appearing to converge toward a model that integrates biological, processing, and behavioral levels in autism. These discoveries potentially shed light on large brains regarding both underlying mechanisms and functional consequences. Moreover, these findings point toward a disease model that departs from earlier formulations of autism in having several new levels of potential treatment implications. The recent findings prominently include identification of pervasive volume scaling alterations, widespread reductions in connectivity and perfusion, and neuroinflammation and microgliosis that had previously been unappreciated. Identification of these features of the autistic brain for the most part was driven by investigation of tissue and processing in autism and not by seeking specific correlates for specific behaviors, at the level of either brain or gene. Nevertheless, these features hold implications for

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