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Increased brain size in autism—what it will take to solve a mystery

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The past decade has witnessed an explosion of research into the neurodevelopmental origins of Autism Spectrum Disorders (ASD). Magnetic resonance imaging (MRI) studies support the hypothesis that an increased brain size (BS) is the underlying cause of macrocephaly, which develops in approximately 20% of patients within the first two years of life (see (1) for a review). As compared to both typically-developing controls or non-autistic individuals with mental retardation, individuals with ASD have a 5-10% enlargement in total brain volume at 18 months-4 years of age. The increased BS was attributed to an increase in both the gray and white matter volumes. Differences in BS and head circumference appear most robust in early childhood. Whether the brain enlargement persists in ASD after age 5 is not clear, although several studies have reported a 6-12% increase in gray matter volume in adolescents and adults with ASD (see (1) for a review). While there are many unanswered questions regarding how the neuroanatomical perturbations seen in ASD lead to the cognitive and behavioral manifestations of these diseases, it is becoming increasingly clear that the altered trajectory of brain development in ASD is probably the most reliable biomarker in this disorder.

In this issue of *Biological Psychiatry*, several articles confirm the increased BS in ASD and add intriguing details towards the underlying causes of autism. Freitag et al show that while ASD individuals have increased total brain volume (TBV), subcortical white matter volume (WMV) and gray matter volume (GMV), they also show decreased volume of the corpus callosum (CC). Furthermore, CC size was positively correlated with TBV, WMV and GMV in controls but not in autism. This study fits with earlier neuroimaging study (2,3), which found a relative increase in the upper (radiate) cortical WM but not in the inner cortical WM, and decreased long-range tracts like the CC (Table). Freitag et al also suggest that positive correlations of brain volumetric indices with ASD diagnosis were primarily observed in ASD children with low IQ scores. Controlling for IQ poses a challenging conundrum for the interpretation of neuroimaging studies of ASD, for while lower IQ is part of the autistic phenotype, IQ is correlated with increased BS in the typically developing population. The authors confirm the finding that BS and IQ are positively correlated in normal children, *whereas BS and IQ do not show any correlation in ASD children*. This finding provides initial clues that the increase in BS in autism is not an adaptive phenomenon.

Hardan et al. provide the first longitudinal data suggesting that ASD individuals exhibiting a greater GM volume also exhibit accelerated GM pruning in the periadolescent period. Coupled with the Freitag data, these findings suggest that both BS increase and excessive pruning may be part of the same maladaptive phenomenon, as greater decrease in volume (interpreted as pruning) was associated with more severe symptoms. Despite the low power, these findings

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confirm earlier suspicions based on cross sectional data (4) that the trajectory of brain development is fundamentally different in ASD. However, the biological underpinnings of the maladaptive growth and pruning phenomena are not understood. In normal development, genesis and pruning of connections (axons, dendrites, spines and synapses) occur concurrently, and either or both these phenomena may be altered in ASD. Thus, more research will be needed to understand the pathogenesis and implications of the BS dynamics in ASD.

Molecular & pathogenetic links

1. Dysregulated increase in neuron number, i.e., altered cell proliferation, survival or migration

Since there is both increased GMV and WMV in ASD, it is likely that a preexisting altered neuron number is coupled to altered pruning in this disorder. The increased density of cortical minicolumns in ASD as assessed by neuropathological studies (5) also suggests an altered cortical neuron number arising in embryonic development. This could result in macroscopic changes in brain size at the time when axons grow and undergo myelination. It is interesting to note that the two areas of the brain that are most profoundly altered in ASD, the medial prefrontal and the temporal cortex (2), are enriched in Fibroblast Growth factors (FGF) during development. FGF bind to receptor tyrosine kinases (RTK), FGFRs, that are prominent regulators of neural cell growth and survival during development through the MAP kinase and Akt pathways (see Figure) (6). Rodent studies have shown that the medial prefrontal and temporal cortex are more severely disrupted when FGF receptors are inactivated (7). No FGFs have been as yet directly implicated in ASD; however, another RTK ligand, i.e., BDNF, and the RTK MET have been implicated (reviewed by (8)) (Table). Furthermore, mutations in several RTK downstream signaling molecules have been associated with ASD: for example, mutations in PTEN have been observed in patients with macrocephaly and ASD, and patients harboring mutations in the tuberous sclerosis complex (TSC) have autism-like symptoms (reviewed by (8)). PTEN and TSC act downstream from several RTKs including cMET and FGF receptors, and through their regulation of the mTOR pathway they affect protein synthesis, cell survival, cell size and neurite outgrowth during development (Figure).

Very recently, a large gene association study (9) has shown association between common variants on the 5p14.1 chromosome and ASD. This region contains putative regulatory elements for two cadherin genes, CDH10 and CDH9. This is the first demonstration of common genetic variants associated with ASD. Cadherins are multifunctional cell adhesion molecules that interact among themselves to regulate cell adhesion. Cadherins also associate with FGF receptors to influence MAPK, intracellular calcium transients and other FGF downstream pathways (10,11). Through these interactions, cadherins are known to regulate many developmental events during CNS morphogenesis, including cell proliferation, migration, neurite outgrowth and regional specification (Figure).

2. Dysregulated connectivity

Mutations in neuroligins, neurexins, contactins, and SHANK, which are molecules expressed within spines and synapses, have been associated with rare cases (1% or less) of ASD (8,12). In addition, FGF, MET and BDNF are thought to increase the outgrowth and branching of axons and dendrites via MAPK, calcium and Akt signaling (10). Furthermore, cell adhesion molecules including cadherins are known to regulate axon fasciculation and guidance, either by ways of their own catenin-mediated signaling and by stimulating RTK pathways (Figure 1). Hence, cumulative evidence from both rare and common mutations in ASD strongly suggests that alterations in the formation and pruning of axons, dendrites and synapses may contribute to the dysregulated growth of gray matter in ASD.

3. Neuronal systems affected in ASD

A future challenge is to understand how the gene variants implicated in the pathogenesis of ASD generate imbalances in the harmonious growth of the CNS, leading to the structural and neuroimaging alterations found in the disorder. We propose that in some cases of ASD, a dysregulation in the signaling of growth factor pathways at a particular time in development could produce a relative excess of “local circuit” neurons, mostly in upper cortical layers, and a relative paucity of long range pyramidal neurons located in lower cortical layers. This could explain the increase in size of cortical GM and WM coupled to decreased CC volume described by Freitag et al in this issue. This theory fits with numerous cognitive and neuroimaging studies suggesting a lack of integrative capacity and “underconnectivity” in ASD (3). In this respect, the study of Langen et al, showing an altered growth trajectory of the caudate nucleus, is particularly fitting, as the basal ganglia are thought to participate in functional integration of cognitive abilities, with the caudate receiving associative connections from the prefrontal cortex.

To understand whether the dysregulated growth and increased BS are causally related to ASD, we will need parallel genetic studies and brain imaging studies of sufficient power to identify susceptibility genes underlying the BS increase. Both rare and common genetic variants will need to be investigated (12). It will be crucial to develop animal models for human genetic variants in which the human mutations are introduced in the mouse germline to understand the implication of these variants for brain development. However, the absence of abnormalities in the mouse brain does not necessarily exclude a pathogenic role for a relevant mutation or gene variant in people. To date, our ability to study the phenotypic consequences of human gene variation has been limited by our inability to investigate human brain development at the cellular and molecular level. Future experimental systems based on reprogramming human cells to pluripotent cells may allow us to correlate variation at the genetic and epigenetic levels with variation gene expression and in biological phenotype, allowing us to study the genetic underpinnings of dynamic events such as cell proliferation and differentiation.

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Figure.

Pathways implicated in ASD. In purple are molecules which have been associated with ASD (see text). The Cadherins extracellular domain binds with FGF receptors to activate three main intracellular pathways, the MAP kinase (MAPK), PI3K-Akt and PLC γ pathways. At least two of these, the MAPK and PI3K-Akt are also activated by the cMET receptors. These pathways regulate cell proliferation, cell survival and neurite outgrowth, depending upon the stage of development.

Neurodevelopmental Model	Neuroanatomical Evidence	Genetic Evidence
Increased Neurogenesis (due to altered generation or death of neurons)	-Increased total brain volume -Increased cortical thickness -Increased gray matter and white matter -High incidence of macrocephaly -Altered trajectory of brain growth -Increased density of cortical minicolumns -Increased short range radiate fibers in subcortical WM	PTEN, MET, TSC1, TSC2, BDNF CDH9 and CDH10
Increased Gliogenesis	-Increased total brain volume -Increased cortical thickness -Increased gray matter and white matter	PTEN, MET, TSC1, TSC2
Altered Myelination	-Reduced callosal volume -Increased white matter	
Inappropriate Synaptic Pruning or Remodeling	-Increased total brain volume -Increased cortical thickness -Increased gray matter -High incidence of macrocephaly -Altered trajectory of brain volume -Altered synaptic spine maturation in Fragile X syndrome and Rett Syndrome	CNTNAP2, SHANK, MECP2, FMR1, NRG1, NRXN, CDH9 and CDH10, Met
Altered Cortical Connectivity	-Increased short range radiate fibers in subcortical WM -Reduced callosal volume	MET, Cell adhesion molecules- CDH9 and CDH10, CNTNAP2
Altered Balance of Cortical Excitatory and Inhibitory Neurons or their Downstream Signaling	- Increased density of cortical minicolumns -Increased cortical volume -High comorbidity with Epilepsy	MET, BDNF, 15q CNV

Note several genes associated with Autism could be contributing to more than one model of dysfunction, while several anatomical findings are consistent with more than one model. Also, neurodevelopmental models are not mutually exclusive: for example, altered neurogenesis or pruning may be the underlying cause for an altered balance of cortical excitatory and inhibitory neurons