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A question of balance: a proposal for new mouse models of autism

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Abstract

Autism spectrum disorder (ASD) represents a major mental health problem with estimates of prevalence ranging from 1/500 to 1/2000. While generally recognized as developmental in origin, little to nothing is certain about its etiology. Currently, diagnosis is made on the basis of a variety of early developmental delays and/or regressions in behavior. There are no universally agreed upon changes in brain structure or cell composition. No biomarkers of any type are available to aid or confirm the clinical diagnosis. In addition, while estimates of the heritability of the condition range from 60 to 90%, as of this writing no disease gene has been unequivocally identified. The prevalence of autism is three- to four-fold higher in males than in females, but the reason for this sexual dimorphism is unknown. In light of all of these ambiguities, a proposal to discuss potential animal models may seem the heart of madness. However, parsing autism into its individual genetic, behavioral, and neurobiological components has already facilitated a 'conversation' between the human disease and the neuropathology and biochemistry underlying the disorder. Building on these results, it should be possible to not just replicate one aspect of autism but to connect the developmental abnormalities underlying the ultimate behavioral phenotype. A reciprocal conversation such as this, wherein the human disease informs on how to make a better animal model and the animal model teaches of the biology causal to autism, would be highly beneficial.

Keywords: Autism; PDDs; ASD

1. The human biology of autistic disorder

In humans, the range of pervasive developmental disorders (PDDs) covers a broad spectrum; from the restricted interests and repetitive behaviors of Asperger syndrome to the complete lack of social interaction found in patients with classical autism. This spectrum of severity, although classified as independent disorders, may in fact represent variation over a continuum rather than a series of diseases. While there are clinical distinctions among the PDDs, the accurate diagnosis of an individual child still represents a clinical challenge.

1.1. Neuropathology of autistic disorder

In many human neurological disorders, there are structural changes in the brain that are apparent on pathological exam. In some instances, such as Alzheimer's disease, information on the details of the neuropathology drives the final diagnosis and serves as the 'gold standard' by which behavioral and clinical interpretations are validated. The situation for autism is the exact opposite. The behavioral and neurological symptoms serve as the sole basis of the diagnosis as there are no disease-related structural defects for which a consensus exists. Having said this, however, pathological studies have revealed an association between autistic symptoms and the appearance of certain pathological changes in brain structure or cellularity in a number of different brain regions. The value of these findings is mitigated somewhat by the fact that in the entire pathological literature only a few dozen different

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Table 1
Neuropathological changes associated with autistic disorder

Measurement	Finding	References
Total brain weight	Increased	Bauman and Kemper (1985), Kemper and Bauman (1998), Bailey et al. (1998)
Cerebellum		
Purkinje cells	Decreased numbers	Ritvo et al. (1986), Kemper and Bauman (1993), Bailey et al. (1998)
Deep cerebellar nuclei	Cell size decrease	Kemper and Bauman (1993)
	No change	Bailey et al. (1998)
Inferior olive	Focal cell loss	Bauman and Kemper (1985)
Limbic system		
Amygdala (medial nuclei)	Cell size decrease	Kemper and Bauman (1993)
	No change	Bailey et al. (1998)
Hippocampal formation	Cell size decrease	Kemper and Bauman (1993)
	Reduced dendrites	
	Cell density increase	Bailey et al. (1998)
Mammillary nuclei	Cell size decrease	Kemper and Bauman (1993)
Brain stem		
Facial nucleus, superior olive	Cell loss	Rodier et al. (1996)
Inferior olive	Cell density increase	Kemper and Bauman (1993)
Cortex	Enlarged	Bailey et al. (1998)
Minicolumns	Smaller, more numerous	Casanova et al. (2002)

cases have come to autopsy. This is changing rapidly, but given the heterogeneity that is likely inherent in the disorder, larger studies are clearly needed. Of the studies to date, there have been consistent findings in the olivo-cerebellar system, the limbic system, the brainstem, and the cortex. These are summarized in Table 1.

In addition to histopathological changes, differences in brain volume (measured by modern methods of imaging) have also been noted. These anomalies are summarized in Table 2; each has been documented in one or more studies. As autism is likely to be a common outcome initiated by a number of different insults to different brain areas at different developmental times (genetic analysis suggests on the order of a dozen different genes could be involved), even those changes that are found in only a minority of the cases of autism might nonetheless hold one or more keys to the biology of the disorder. For an animal model of autism to be truly useful, however, it will be necessary for it to replicate at least a subset of the reported pathologies.

1.2. The genetics of autism

While the precise anatomical defects are yet unspecified, twin and family genetic studies have shown a robust genetic component for the disorder. The concordance rate for monozygotic twins varies from 60 to 95%, while that of dizygotic twins ranges from 0 to 24% (Ritvo et al., 1985; Steffenburg et al., 1989; Bailey et al., 1995). The prevalence rate of non-twin siblings of children with autism varies from 1 to 6% (Hallmayer et al., 2002). Differences in diagnostic criteria and inclusion of ''spectrum'' phenotypes lends to the variability in estimates

Table 2
Volumetric findings in autism

Measurement	Finding	References
Total brain volume	Increased	Piven et al. (1995), Davidovitch et al. (1996), Piven et al. (1996), Lainhart et al. (1997), Courchesne et al. (2001), Bailey et al. (1998), Aylward et al. (2002), Sparks et al. (2002), Herbert et al. (2003)
White matter	Increased	Courchesne et al. (2001), Herbert et al. (2003)
Limbic system volume	Decreased	Aylward et al. (1999), Herbert et al. (2003)
Amygdala	Decreased	Aylward et al. (1999), Herbert et al. (2003), Pierce et al. (2001)
	Increased	Howard et al. (2000)
	Variable	Abell et al. (1999), Sparks et al. (2002)
Hippocampus	Decreased	Aylward et al. (1999), Herbert et al. (2003), Saitoh et al. (2001)
	No change	Piven et al. (1998), Saitoh et al. (1995)
Other limbic cortex	Decreased	Abell et al. (1999)
Cerebellar cortex	Focal decrease	Courchesne et al. (1988)
(Lobules VI and VII)	Focal increase	Saitoh and Courchesne (1998)
	No decrease	Holttum et al. (1992)