Neuroanatomical Diversity of Corpus Callosum and Brain Volume in Autism: Meta-analysis, Analysis of the Autism Brain Imaging Data Exchange Project, and Simulation.

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Commentary

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Brain Connectivity in Autism: The Significance of Null Findings

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Autism spectrum disorder (ASD) has become a case study for illustrating the difficulty in tracing a psychiatric disorder to its underlying causes—psychological, genetic, or neurological. Aside from theories derived from the very criteria used to diagnose ASD, one would be hard-pressed to find a psychological theory that is not hotly disputed. Genetic investigations revealed that very large sample sizes are required to tease out the very small effects of very many genes, or large effects of genes present in only very few cases. Meanwhile, investigators doing work at the neurological level have held out hope that their theories might, finally, serve to provide a compact and reliable explanation of ASD that could best mediate between the genes and the phenotype. A new study by Lefebvre *et al.* (1) in this issue of *Biological Psychiatry* is beginning to cast some doubt that a simple anatomical story will emerge.

Arguably the leading neurological theory of ASD is about brain connectivity (2). The popularity of this theory is unsurprising, as ASD is a neurodevelopmental disorder affecting most of the brain and because the emergent properties of brain function are based on neural connectivity. Yet the connectivity hypothesis has been vague ever since its inception, and slowly morphing from a theory about underconnectivity in ASD, to one about distal underconnectivity paired with local overconnectivity, to one about atypical connectivity in either direction (or both).

The new work by Lefebvre *et al.* (1) suggests that at least one specific indication of atypical connectivity may be a false positive altogether. Their study looked at the largest white matter tract in the human brain, the corpus callosum, whose 200 million axons enable rapid communication between the two cerebral hemispheres (i.e., interhemispheric communication). The corpus callosum arose only once in phylogeny, with the evolution of placental mammals: Marsupials such as opossums and kangaroos have no corpus callosum. The most parsimonious explanation for evolution of the corpus callosum is that it arose to facilitate long-distance integration within large brains. As cognitive and clinical branches of neuroscience have shifted away from a focus on individual brain areas studied in isolation and toward greater appreciation of how these brain areas operate within and across brain networks, there has been a proliferation of studies targeting the corpus callosum in the search for neural bases of psychiatric disorders.

Abnormalities of the corpus callosum are found in a wide range of developmental disorders caused by genetic and environmental factors. For example, enlargement of the corpus callosum has been reported in neurofibromatosis 1 and in 22q11.2 deletion syndrome; callosal reduction has been reported in Williams syndrome, low-birth weight, fetal alcohol syndrome, attention deficit/hyperactivity disorder - and ASD. Furthermore, recent work confirmed that congenital abnormalities of the corpus callosum can produce ASD symptoms largely indistinguishable from idiopathic ASD (3). So there is little question that developing in the absence of a corpus callosum can result in an atypical mind and behavior. People with ASD do not generally lack a corpus callosum altogether. But how strong is the evidence that it is even abnormal at all?

In their investigation of size of the corpus callosum in idiopathic ASD, Lefebvre *et al.* capitalized on a data-sharing initiative, the Autism Brain Imaging Data Exchange (ABIDE) consortium (4), to overcome the power limitations from small sample sizes evident in prior studies. Using a subset of this large sample ($N = 694$) gave the study sufficient power to identify even a weak effect, yet they found no evidence of diminished callosal size in ASD. This finding is largely corroborated by another large recent study showing only a weak effect in a specific portion of the corpus callosum (5). If there is reduced connectivity in ASD, it is not manifest in reduced size of the corpus callosum.

In providing compelling negative findings, Lefebvre *et al.* (1) help us to focus our search on the possibilities for positive findings. First, it may be that the corpus callosum in particular and gross white matter volume in general are simply too coarse a measure and that the structural signature of atypical connectivity in ASD resides in the microstructure of axons. This question could be addressed by focusing on the histologic study of postmortem brains or on different kinds of imaging methods, such as diffusion imaging (Figure 1). However, it is possible that measures based on structural connectivity may be too insensitive, and we should be looking more closely at the phenotype: functional connectivity. Indeed, studies of functional connectivity in ASD are now more common than studies of structural connectivity, but no clear picture has yet emerged here either. Recent work suggested that functional connectivity is atypical in ASD, but in ways that are both idiosyncratic and heterogeneous across individuals (6), a pattern that also recently emerged in neural activation studies using complex stimuli (7) and that may represent a general principle of the condition. This heterogeneity would make it more difficult to find group differences on a single structural measure and highlights the need for more nuanced analysis of individual variations to find the most salient connections between brain and behavior. Finally, the negative findings in the present study apply only to individuals 7.5–40 years old, leaving open the possibility that structural abnormalities of the corpus callosum may be present and detectable earlier in development (8,9) but become less apparent later in life.

The study by Lefebvre *et al.* (1) also is valuable in raising numerous specific methodologic considerations. First, studies of

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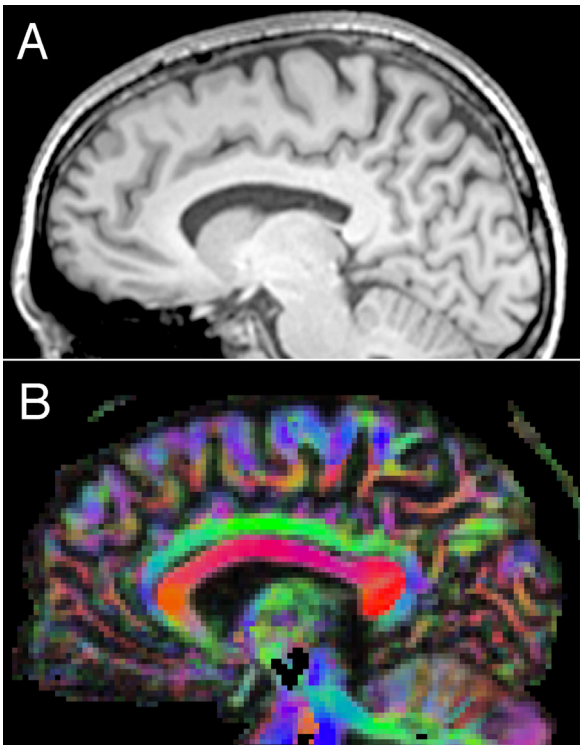

Figure 1. Examples of two types of magnetic resonance imaging–based structural images of the corpus callosum. **(A)** T1-weighted magnetic resonance imaging can be used to quantify cross-sectional area, volume, and morphology of the corpus callosum. **(B)** Diffusion magnetic resonance imaging can provide more detailed information about microstructural properties (e.g., white matter fiber orientation [indicated by different colors] and organization). (Images courtesy of Mike Tyszka, California Institute of Technology.)

callosal size must consider variations in brain volume in the most effective manner. Although there is a robust relationship between the size of the corpus callosum and brain size across and within mammalian species (including humans), the correlation is nonlinear—as a result, larger brains have proportionally smaller corpora callosa. Based on simulations, the authors conclude that owing to this nonlinearity, brain volume is more accurately controlled through covariation rather than normalization.

The second consideration relates to presumptions about potential confounds. Carefully matching ASD and control groups on IQ is typical to ensure that observed group differences cannot simply be explained by differences in IQ. However, Lefebvre *et al.* (1) found a weaker correlation between verbal IQ and brain volume in the ASD group, and therefore matching groups on IQ may introduce unintended artifactual differences in callosal size. In short, controlling for potentially confounding covariates sometimes can create spurious group differences.

There is perhaps an even more important message from the study by Lefebvre *et al.* (1). Despite their failure to find abnormal callosal size in such a large sample with ASD, the authors also conducted a meta-analysis of prior studies, of which more than half reported significant reductions in callosal size. All of those prior studies were vastly underpowered in sample size, and from the pattern of publications it is also apparent that there was a strong bias to publish studies with findings that happened to achieve the "magical" $p < .05$ threshold. The problems inherent in this kind of reporting are by now well known but unfortunately not yet eliminated. A p value is among the least reliable metrics we can report, so much so that some journals recommend dispensing with it altogether (10). If a question is important and the research is done carefully, it should be irrelevant whether the finding is deemed "statistically significant" or not. So-called negative findings can be as informative as positive findings and help to narrow our search for causal explanations of psychiatric illness. The study by Lefebvre *et al.* (1) provides a patent demonstration of the value of this approach.

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