

Understanding Alterations in Brain Connectivity in Attention-Deficit/Hyperactivity Disorder Using Imaging Connectomics

Martha E. Shenton, Marek Kubicki, and Nikos Makris

Evaluation of neural systems and brain connections is an important new area of research to understand both normal brain connectivity and alterations in brain connectivity in neuropsychiatric disorders. The study of brain connectivity is also a major focus of current neuroscience. In humans, very little is known about neural networks in the living brain, although the Human Connectome Project (<http://www.neuroscienceblueprint.nih.gov/connectome/>) has as one of its main goals to understand better brain connections using the highest quality imaging data available today. The focus on brain networks (or connectomes), as opposed to single connections between brain regions, is a significant step forward because neural networks can be studied using new sophisticated models that open up avenues of research that make possible comprehensive analysis of structural and functional brain connectivity in normal individuals and in individuals with neuropsychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD) (1,2). A connectomic approach to studying brain networks is also important because this approach includes a deeper appreciation of the fact that even the smallest, seemingly simplest task performed by humans engages multiple regions of the brain in organized networks. Sporns (3) described several developmental and possible evolutionary factors that shape such network topology.

Hong *et al.* (2) combine a connectomics approach with cognitive tasks to understand network impairments in ADHD. This approach is particularly important in ADHD, which is a multisystem developmental disorder that is heterogeneous in presentation and likely also in alterations in brain circuitry and in genetics. It is among the most common psychiatric disorders diagnosed in children, affecting 5%–11% of school-aged children (4), and many symptoms persist into adulthood. There is also evidence to suggest that there are both persistent and remitting types of ADHD (5), which adds to the heterogeneity of this disorder. However, there is still very little known about the neurobiology of ADHD. Some studies suggest the importance of prefrontal and striatal regions in the brain and their interregional connections (6), which has led to what is referred to as “the frontostriatal model of ADHD,” although other brain regions are known to be impaired. Also, there is more recent evidence, presented here and by Makris *et al.* (7) and by Cao *et al.* (1), that the cerebellum may also be part of a distributed neural network that is affected in ADHD.

From the Departments of Psychiatry (MES, MK) and Radiology (MES, MK, NM), Brigham and Women's Hospital; Harvard Medical School (MES, MK, NM), Boston; Department of Veterans Affairs Boston Healthcare System (MES), Brockton Division, Brockton; and Departments of Psychiatry and Neurology (NM), Massachusetts General Hospital, Boston, Massachusetts
Address correspondence to Martha E. Shenton, Ph.D., Psychiatry Neuroimaging Laboratory, 1249 Boylston Street, Boston, MA, 02215; E-mail: Shenton@bwh.harvard.edu.

Received Aug 20, 2014; accepted Aug 21, 2014.

0006-3223/\$36.00

<http://dx.doi.org/10.1016/j.biopsych.2014.08.018>

Nonetheless, it is only quite recently—with powerful techniques such as diffusion tensor imaging and still more recently with the new ability to investigate interregional brain connectivity using both diffusion tractography, a means of extracting information about specific fiber bundles in the brain, and imaging connectomics techniques, a way to map neural connections in the brain at synaptic and macrostructural and functional levels—that we are now able to characterize more precisely disrupted interconnected networks in the brain. The current study is important because its focus is to identify and to characterize connectomic disturbances in ADHD using whole-brain tractography. The term connectomic refers to the study of connectomes, or mapping of neural connections in the brain. This mapping can be performed at the synaptic level, or it can be performed at the macrostructural and functional level as reported in this article, where white matter fiber topological connections are investigated simultaneously to understand better the connectivity among neural networks that are impaired or, at a minimum, differ between children and adolescents with a diagnosis of ADHD and age-matched healthy control subjects.

Hong *et al.* use diffusion tensor imaging and whole-brain tractography, the latter an unbiased, data-driven approach, as opposed to a hypothesis-driven, single-tract a priori approach, along with an imaging connectomics approach to investigate altered white matter connectivity in 71 children and adolescents with a diagnosis of ADHD and 26 control subjects. A further aim of the study is to investigate the functional correlates of disturbed connectivity in ADHD by correlating the connectivity measures with performance measures of attention derived from a continuous performance task.

Results show a single network comprising 25 links that involve 23 brain regions, which clearly differentiate the ADHD group from healthy control subjects. This abnormal network involves prefrontal and striatal alterations, where ventral frontal areas include orbitofrontal cortex, pars triangularis, and gyrus rectus. The basal ganglia are also involved and include putamen and globus pallidus, but not caudate nucleus. When the investigators controlled for age and gender, the only brain regions to drop out of this network were links between left amygdala and left pallidum and links between right postcentral gyrus and right pallidum. This network was characterized by prefrontal and striatal connections, but they were part of a larger network of connections, in contrast to what the investigators describe as “direct pair-wise links between the two, as previously implied.” This larger network included cerebellar connections.

The disturbed pattern of connectivity involved frontal, striatal, and cerebellar brain regions, suggesting that abnormalities in brain circuitry in ADHD go beyond the frontostriatal model and include cerebellar brain regions, which the investigators suggest may be important both to top-down regulation by inferior prefrontal cortex to other cortical and subcortical structures and to regulation of “bottom-up multimodal sensory convergence and

BIOL PSYCHIATRY 2014;76:601–602

Published by Elsevier Inc on behalf of Society of Biological Psychiatry

attention allocation mediated by the parietal cortex." Additionally, this network was functionally correlated with indices of attention derived from the continuous performance task. Findings from this study provide novel and important insights into the next generation of imaging techniques by applying the power of the techniques available today to inform specific disease states such as ADHD. Using tractography methods and combining them with connectomics methods led to findings that go beyond regional or local alterations and instead provide insight into interconnections among brain regions that suggest a brain network involving frontostriatal and cerebellum alterations in the brain in children and adolescents with ADHD compared with control subjects, which likely play a key role in the neurobiology of ADHD.

Hong *et al.* note some limitations of the study, including the fact that patients and control subjects were not matched for gender or IQ; there were many more boys in the ADHD sample, and IQ was higher in control subjects. Issues with differences in medication and crossing fibers were also reviewed. Additionally, future studies would benefit from attending to the heterogeneity of ADHD using the kind of rigorous methods that were employed here, particularly given that there were some differences between the different subtypes (impulsivity and hyperactivity compared with the combined subtype). These latter findings underscore the heterogeneity of this disorder and highlight further the importance of using information such as subtypes and persistent versus remitting forms of ADHD as separate entities in future studies to reduce the variance when applying connectivity analyses because these subtypes may demonstrate different patterns of disruption in brain networks. The investigators also note that functional magnetic resonance imaging might add to our understanding of the neurobiology of ADHD, in conjunction with the methods employed in this study.

The study by Hong *et al.* shows the potential of applying connectomics for the identification of brain circuitries that may be associated with particular genotypes and clinical-phenotypic manifestations. Addressing the question of clinical heterogeneity and its association with brain circuitries is very important, and a comprehensive approach using connectomics seems most appropriate. The emergence of the cerebellum as a structure involved in large-scale cognitive and emotional aspects of behavior as well as known motor behaviors is well represented in this study, and its relevance to ADHD should be emphasized given the hyperactive and inattentive phenotypic manifestations in this disorder. Additionally, given the comprehensive and multimodal nature of connectomics, we are able to perform analyses of different networks involving cognitive functioning such as attention, executive functioning, language, and working memory or affective behaviors such as emotional regulation and reward that are associated with anatomic and neurochemical systems affected in ADHD. Other important questions for future studies are related to

the timing of maturation in the different neural circuitries in ADHD (8). For example, what are these neural circuitries, do they vary among subtypes of ADHD, and which remain altered throughout adolescence and into adulthood? Another important question is how might connectomes differ in response to different medications and between individuals who are treatment-naïve versus individuals treated with medication for ADHD.

In conclusion, the connectomics approach, combined with multimodal imaging that includes diffusion measures as well as functional magnetic resonance imaging, will likely be of great importance in addressing these issues in terms of maturation, course of altered neural circuitries, and different patterns of altered neural circuitries in different subtypes of ADHD. These initial applications reflect an important new inroad to identifying brain circuitries and linking structural and functional variation in given brain circuitries to genetics, which will likely be delineated further by attending to more homogeneous groupings of ADHD.

This work was supported by a U.S. Department of Veterans Affairs Merit grant (MES) and Grant Nos. W81XWH-08-2-0159 (MES), R01AG042512 (MK, NM), R21EB016449 (NM), R21NS079905 (NM), R01 MH102377 (MK), and R01 MH074794 (MK).

The authors report no biomedical financial interests or potential conflicts of interest.

1. Cao Q, Shu N, An L, Wang P, Sun L, Xia MR, *et al.* (2013): Probabilistic diffusion tractography and graph theory analysis reveal abnormal white matter structural connectivity networks in drug-naïve boys with attention deficit/hyperactivity disorder. *J Neurosci* 33:10676–10687.
2. Hong S-B, Zalesky A, Fornito A, Park S, Yang Y-H, Park M-H, *et al.* (2014): Connectomic disturbances in attention-deficit/hyperactivity disorder: A whole-brain tractography analysis. *Biol Psychiatry* 76:656–663.
3. Sporns O (2010): *Networks of the Brain*. Cambridge, MA: The MIT Press.
4. Visser SN, Danielson ML, Bitsko RH, Holbrook JR, Kogan MD, Ghandour RM, *et al.* (2014): Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003–2011. *J Am Acad Child Adolesc Psychiatry* 53:34–46.
5. Mattfeld AT, Gabrieli JD, Biederman J, Spencer T, Brown A, Kotte A, *et al.* (2014): Brain differences between persistent and remitted attention deficit hyperactivity disorder. *Brain* 137:2423–2428.
6. Casey BJ, Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Schubert AB, *et al.* (1997): Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 36:374–383.
7. Makris N, Biederman J, Monuteaux MC, Seidman LJ (2009): Towards conceptualizing a neural systems-based anatomy of attention-deficit/hyperactivity disorder. *Dev Neurosci* 31:36–49.
8. Shaw P, Gilliam M, Liverpool M, Weddle C, Malek M, Sharp W, *et al.* (2011): Cortical development in typically developing children with symptoms of hyperactivity and impulsivity: Support for a dimensional view of attention deficit hyperactivity disorder. *Am J Psychiatry* 168: 143–151.