Atypical Prefrontal Connectivity in Attention-Deficit/Hyperactivity Disorder: Pathway to Disease or Pathological End Point?

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Functional neuroimaging studies have identified multiple nodes of dysfunction in frontostriatal and mesocorticolimbic networks in attention-deficit/hyperactivity disorder (ADHD). Yet relatively few studies have examined how structural and functional connectivity between nodes in these networks might relate to the behavioral symptoms of ADHD. Moreover, it is unknown whether abnormalities in connectivity are a primary cause of symptoms or arise secondary to common etiologic mechanisms. We review the most recent diffusion tensor imaging and functional magnetic resonance imaging studies of connectivity in ADHD to characterize associations between frontostriatal connectivity abnormalities and the behavioral symptoms of inattention and impulsivity in ADHD. Furthermore, we examine how structural and functional connectivity measures relate to environmental and genetic pathways to ADHD. Diffusion tensor imaging studies indicate that ADHD is associated with significant irregularities in white matter microstructure, especially in frontostriatal and select corticocortical tracts. Resting state functional magnetic resonance imaging studies implicate altered connectivity within a default mode network of structures active during introspective, task-free processes and disrupted interactions between this network and frontostriatal attentional systems. Deficits in functional connectivity within frontostriatal and mesocorticolimbic networks might give rise, in part, to ADHD symptoms. Conversely, structural connectivity deficits and ADHD symptoms might arise incidentally from a common etiologic mechanism, involving altered modulation of synaptic potentiation and pruning by dopamine and other factors during development. Collectively, these studies suggest that the core symptoms of ADHD might derive from dysregulated modulation of cortical plasticity in the developing brain, resulting in altered patterns of corticocortical connectivity that might persist into adulthood.

Key Words: Attention-deficit/hyperactivity disorder (ADHD), diffusion tensor imaging (DTI), functional connectivity, prefrontal cortex (PFC), resting state functional magnetic resonance imaging (fMRI), white matter

Attention-deficit/hyperactivity disorder (ADHD) is a common, heterogeneous condition characterized clinically by symptoms of inattention and hyperactivity/impulsivity. Symptoms arise in childhood and frequently persist indefinitely. The neurobiology of ADHD is complex. The DSM-IV recognizes three distinct subtypes comprising symptoms in domains of inattention, hyperactivity/impulsivity, or both (1). Subsequent work has shown that these subtypes might be highly unstable over time (2), and clinical evaluation of affected children along a quantitative continuum in each of the two symptom domains might be useful for predicting functional impairment and school performance (3). Concomitant efforts to identify more precise phenotypes that encapsulate this heterogeneity have facilitated increasingly sophisticated, network-based models of pathophysiology. Deficits in cognitive control—the capacity to suppress inappropriate thoughts and actions and initiate more appropriate ones—are understood to relate closely to the core symptoms of the inattention domain and to dysfunction in a frontostriatal network (4,5). A distinct set of "hot" cognitive control deficits—characterized by altered processing of reward and salience—are thought to play a more central role in symptoms of hyperactivity/impulsivity domain and have been linked to a mesocorticolimbic network (6,7).

These models build on earlier, seminal work identifying nodes of dysfunction in ADHD, with functional magnetic resonance imaging (fMRI) studies consistently reporting reduced ventrolateral prefrontal, anterior cingulate, and striatal activity during tasks requiring cognitive control (8–10). Dysfunction within one or more of these nodes might give rise to dysfunction in the network as a whole. Importantly, dysfunction in the connections between nodes in a network might be equally and independently disruptive. To assess this possibility, investigators have recently begun to study how MRI-based measures of connectivity are altered in ADHD, with two relatively new techniques. Diffusion tensor imaging (DTI) assesses the integrity of white matter fiber tracts by quantifying their effects on water diffusion. Resting state fMRI is a complementary tool that assesses the strength of functional connections within a network by quantifying correlated activity between brain regions at rest.

A recent review addressed neuroimaging studies of connectivity in ADHD (11). Here, we provide an updated review of this rapidly growing field and evaluate potential causes and consequences of altered connectivity in ADHD. We conclude by considering two nonorthogonal hypotheses. Dysfunctional connectivity in frontostriatal and mesocorticolimbic networks might give rise, in part, to ADHD symptoms. Conversely, altered connectivity and ADHD symptoms might arise incidentally from a common etiologic mechanism, a possibility that has received less attention. Collectively, these studies suggest that the core symptoms of ADHD might derive in part from dysregulated modulation of cortical plasticity in the developing brain, by dopamine and other factors, resulting in altered patterns of corticocortical connectivity that might persist into adulthood.

Structural Connectivity Deficits in ADHD: DTI

Diffusion tensor imaging is a neuroimaging tool that has been used to quantify the microstructural integrity of white matter tracts. This technique exploits the fact that myelinated axons restrict water diffusion. Because water is repelled by the fatty myelin sheaths that coat axonal membranes, it tends to diffuse more readily in parallel to a white matter tract than perpendicular to it, in proportion to the degree of myelination and the orientation, regularity, and density

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Table 1. Summary of DTI Studies of ADHD

Study	ADHD/Ctrl, *n*	Ages	Analysis	Measures	SLF	ACR	Other Affected Tracts	Comments
Ashtari (15)	18/15	7–11	Whole brain	FA	Yes	Yes	Cerebellar peduncles	
Casey (19)	20/10	15–19	Tract-based PFC ROI	FA		Yes		
Makris (27)	12/17	37–46	2 ROIs	FA	Yes		Cingulum bundle	Adults
Hamilton (26)	17/16	~10–14	9 tract-based ROIs	FA	Yes		Corticospinal tract	
Silk (25)	15/15	8–18	Whole brain TBSS	FA, MD	No	No	Increased FA in occipitoparietal cortex, temporal cortex	
Pavuluri (22)	13/15	~10–16	8 tract-based ROIs	FA, ADC	Yes	Yes	Cingulum bundle, corpus callosum, corticospinal tract	+BPAD group
Konrad (11)	37/34	18–49	Whole brain	FA, MD	Yes	Yes	Cingulum bundle	Adults
Davenport (20)	14/26	12–18	Whole brain	FA	No	Yes	Increased FA in prefrontal white matter	+SZ group
Qiu (24)	15/15	10–15	Whole brain	FA	No	Yes	Internal capsule, corpus callosum	
Skranes (28)[a]	34/47	12–17	Whole brain	FA	Yes		Posterior and external capsules, middle and inferior long fasciculi	Comorbid VLBW[a]
Rusch (23)	20/20	18–45	Small PFC ROI	FA, MD		Yes		Comorbid BPD, adults[a]
Silk (46)	15/15	8–18	Basal ganglia ROIs	FA, MD			Basal ganglia	
Bechtel (31)	14/12	9–14	Cerebellar white matter	FA			Cerebellar white matter	+Epilepsy/ADHD group
Cao (47)	28/27	11–16	Corpus callosum ROI	FA			Corpus callosum	

Various studies have examined changes in fractional anisotropy (FA), mean diffusivity (MD), and apparent diffusion coefficient (ADC) on the basis of whole brain voxel-wise comparisons, manually selected regions of interest (ROIs), or ROIs specified by automated tractography algorithms and tract-based spatial statistical techniques (TBSS). The most consistently replicated findings include reduced white matter integrity in the superior longitudinal fasciculus (SLF) and the anterior corona radiata (ACR), which carry frontostriatal projections. Studies that did ("yes") or did not ("no") identify changes in these areas are listed in the corresponding columns, whereas others did not examine these tracts. Other studies have compared structural connectivity in attention-deficit/hyperactivity disorder (ADHD) with other psychiatric conditions, including bipolar affective disorder (BPAD) and schizophrenia (SZ).

BPD, borderline personality disorder; Ctrl, control subjects; DTI, diffusion tensor imaging; PFC, prefrontal cortex; VLBW, very low birth weight.

[a]Structural connectivity changes in SLF and ACR white matter cannot be assessed in these studies, either because they did not assess connectivity in either tract or because they examined subjects with comorbid conditions (e.g., history of very low birth weight or borderline personality disorder). Other structural connectivity changes that have been implicated in ADHD are also noted, and represent decreased FA (or equivalent) in ADHD except where noted.

of the axons in a tract. This tendency—anisotropic diffusion—can be quantified by MRI by sensitizing the scan to the magnitude and directionality of water movement (12,13). By quantifying anisotropy, DTI can approximate the microstructural integrity of maturing white matter: increased myelination and axonal regularity correlate with increased anisotropy, as confirmed by histological studies in animal models (14).

Several groups have used DTI techniques to probe white matter integrity in ADHD patients (Table 1). In a whole brain analysis of 18 children with ADHD—13 medicated, 5 drug-naive—Ashtari *et al.* (15) found that structural connectivity, as measured by fractional anisotropy (FA), was significantly reduced relative to control subjects in right frontostriatal projections and in the right superior longitudinal fasciculus (SLF), among several other areas of cerebral and cerebellar white matter. Both are critical for prefrontal cortical function, connecting the PFC to the basal ganglia (16) and to the other three cortical lobes (17), respectively. It is also worth noting that these tracts are located adjacent to areas of cortical thinning that have been identified in ADHD subjects in medial and superior prefrontal cortex (PFC) (18): because the DTI data suggest that myelination is reduced in these areas, it might be more likely that reductions in cortical thickness are due to cortical processes like altered dendritic pruning rather than increased white matter volume.

Among the eight DTI studies that have examined white matter integrity in ADHD in frontostriatal projections (or anterior corona radiata), seven have identified structural connectivity deficits in patients versus control subjects (15,19–24), either by whole brain or region-of-interest analysis, whereas one did not (25). Likewise, among the nine DTI studies that have examined white matter integrity in the SLF, six have identified structural connectivity deficits in ADHD patients (15,21,22,26–28), but three others did not replicate this finding (20,24,25). Abnormalities in other white matter tracts involving the cerebellum, corpus callosum, basal ganglia, anterior cingulate, and corticospinal tract have also been identified but less consistently reported (Table 1 and the discussion that follows identify some important interpretive caveats, including varying methodologies and differences in the ages and comorbid diagnoses of the patients studied).

At least in some cases, it seems that these structural connectivity deficits might persist into adulthood: two studies have reported reduced FA in the SLF in adults with ADHD (21,27), with frontostriatal projections persistently affected in the second one (21). It is also worth noting that subjects in the second study were medication-naive, discounting the possibility that these changes are solely a consequence of treatment rather than a marker of disease. Trends suggestive of an association between connectivity deficits and measures of inattention and impulsivity were also observed, although these might be difficult to assess with smaller sample sizes.

More recently, investigators have begun to evaluate the functional significance of connectivity changes by combining DTI with fMRI and by applying fiber tractography algorithms to reconstruct white matter tracts and assess the role of connectivity within anatomically specified projections (29,30). Analysis of connectivity within specific fiber tracts is advantageous in that it provides for intuitive constraints on data interpretation and facilitates an understanding of the functional significance of differences in white matter integrity. A recent study combined fMRI and DTI tractography to