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Review

REVIEW

The structural connectome in ADHD

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) has been conceptualized as a brain dysconnectivity disorder. In the past decade, noninvasive diffusion magnetic resonance imaging (dMRI) studies have demonstrated that individuals with ADHD have alterations in the white matter structural connectome, and that these alterations are associated with core symptoms and cognitive deficits in patients. This review aims to summarize recent dMRI-based structural connectome studies in ADHD from voxel-, tractography-, and network-based perspectives. Voxel- and tractography-based studies have demonstrated disrupted microstructural properties predominantly located in the frontostriatal tracts, the corpus callosum, the corticospinal tracts, and the cingulum bundle in patients with ADHD. Network-based studies have suggested abnormal global and local efficiency as well as nodal properties in the prefrontal and parietal regions in the ADHD structural connectomes. The altered structural connectomes in those with ADHD provide significant signatures for prediction of symptoms and diagnostic classification. These studies suggest that abnormalities in the structural connectome may be one of the neural underpinnings of ADHD psychopathology and show potential for establishing imaging biomarkers in clinical evaluation. However, given that there are inconsistent findings across studies due to sample heterogeneity and analysis method variations, these ADHD-related white matter alterations are still far from informing clinical practice. Future studies with larger and more homogeneous samples are needed to validate the consistency of current results; advanced dMRI techniques can help to generate much more precise estimation of white matter pathways and assure specific fiber configurations; and finally, dimensional analysis frameworks can deepen our understanding of the neurobiology underlying ADHD.

Key words: attention-deficit/hyperactivity disorder; white matter; diffusion MRI; connectomics

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders, with a worldwide prevalence of 3.4% [95% confidence interval (CI): 2.6–4.5] in children and adolescents (Polanczyk *et al.*, 2015) and 2.5% (95% CI: 2.1–3.1) in adults (Simon *et al.*, 2009), and is characterized by inattention, impulsivity, and/or hyperactivity. The onset of ADHD usually occurs in children, and it persists until adulthood in 70% of these individuals. Previous neuroimaging studies have characterized regional brain structural (Hoogman *et al.*, 2017; Hoogman *et al.*, 2019; Shen *et al.*, 2020) and functional (Zang *et al.*, 2007; An *et al.*, 2013; Li *et al.*, 2021) alterations, which has helped to elucidate the pathophysiology of ADHD. Modern hypotheses regard ADHD as a disorder of brain dysconnectivity. For more than a decade, functional brain imaging studies have investigated alterations in the functional connectome of individuals with ADHD (Konrad and Eickhoff, 2010; Castellanos and Proal, 2012). Substantial evidence has revealed (Posner *et al.*, 2014; Castellanos and Aoki, 2016; Gao *et al.*, 2019; Sutcubasi *et al.*, 2020) dysfunctional interactions among the default, frontoparietal, affective, and attention networks in ADHD, which suggests a multinetwork model as a neurobiological substrate of ADHD.

When studying the brain connectome or network, white matter functions as a physical connection that transfers information through the brain network. Axons conduct nerve impulses between cortical regions, and the pattern of cortical connectivity linked by white matter may contribute to cortical specializations (Wandell, 2016). Thus, the properties of white matter are likely to provide insights into the organization of brain networks and the functions they perform. On the other hand, white matter undergoes profound changes throughout childhood and adolescence, playing a fundamental role in the development of normal cognition and behavior (Simmonds *et al.*, 2014; Tamnes *et al.*, 2018). To understand how the brain network operates, we need to understand not only the properties of the cortical regions, but also the structural connectivity between them. Diffusion magnetic resonance imaging (dMRI) is an effective tool for investigating the microstructural and network properties of white matter *in vivo*. Diffusion microstructural parameters can reflect several axonal conditions, such as myelination, axonal size, and axonal packing, all of which coincide with cognitive abilities and behavior (Qiu *et al.*, 2015). In addition, network measures derived from the structural connectivity matrix can reflect the topological organization of the brain and indicate information segregation and integration. Hence, our understanding of structural connectome dysfunction in ADHD will be incomplete until we understand the pattern of microstructural and macroscopic network properties of white matter, which can be explored by dMRI.

In this review, we aim to summarize recent structural connectome studies based on dMRI techniques in patients with ADHD. First, we provide a brief introduction to dMRI and the structural connectome. Then, we review dMRI-based structural connectome findings on ADHD based on voxel-, tractography-, and network-level studies. Next, we discuss the application of structural connectome studies in ADHD for diagnostic classification and symptom prediction. Finally, we will discuss the limitations and future directions of dMRI-based connectome studies in ADHD.

dMRI and structural connectome

Basic concepts of dMRI

Water in the white matter diffuses in a very particular orientation: the intracellular water tends to diffuse along the axis of the axons in a coherent fiber bundle, which is called restricted diffusion, whereas the extracellular water tends to reflect hindered diffusion due to lattice structures formed by the axons (Rowe *et al.*, 2016).) (Fig. 1). Therefore, the diffusion characteristics of water in white matter can provide information on the axonal orientation and microscopic architecture in brain tissue. This is of critical importance as dMRI probes the underlying axonal organization noninvasively *in vivo* based on water diffusion patterns.

There are two types of diffusion pattern: isotropic diffusion, which occurs in an environment where water diffusion is free and the same in all directions; and anisotropic diffusion, which means that diffusion along the axon is much stronger than diffusion perpendicular to the axon. The latter situation mostly occurs in white matter because the water in white matter encounters coherently oriented axons or myelin (Beaulieu, 2002). Three eigenvalues and three eigenvectors can be used to describe the degree and orientation of diffusion. Several quantitative parameters, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), can then be derived from eigenvalues to reflect the microstructure of white matter. The most commonly used parameter is FA, which describes the degree of anisotropy in each voxel and is related to the presence and coherence of oriented bundles. FA values range from 0 to 1, with 0 meaning completely isotropic diffusion and 1 indicating diffusion constrained in a single direction. FA was originally considered a summary measure of white matter microstructural "integrity." However, some researchers later argued that FA changes should not be simply interpreted as changes in microstructural integrity because FA can be naturally low when there is a large axon diameter, low packing density, or fiber crossing (Jones *et al.*, 2013). Although FA is sensitive to myelination, axonal coherence, and axonal diameter and density, it is less specific to the exact type of change. MD characterizes the average degree of water diffusion and is low within white matter but high in the cerebrospinal fluid where the movement of water molecules is free, which usually decreases during development (Lebel *et al.*, 2008). RD reflects diffusion perpendicular to the principal direction of diffusion and often increases in demyelinated white matter

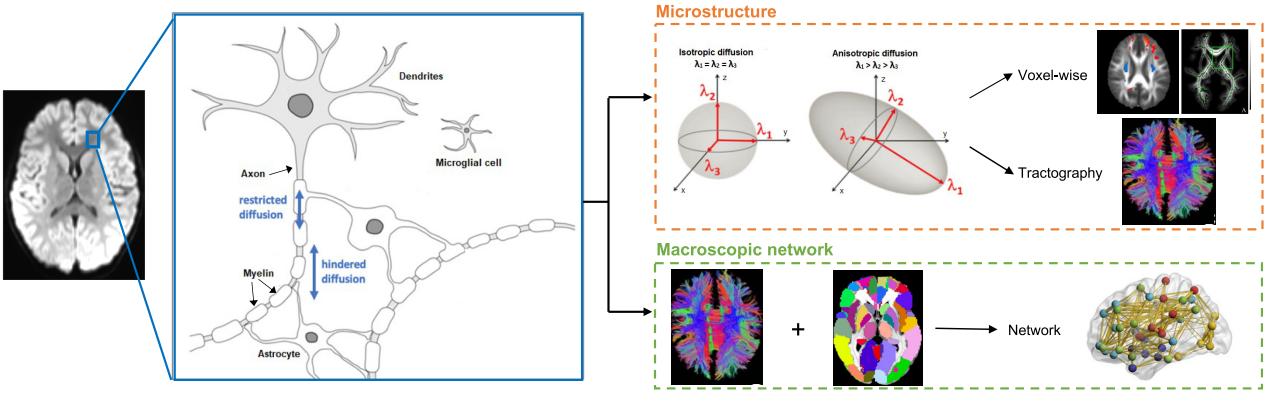

Figure 1: dMRI assesses water diffusion in white matter to probe the structural connectome from both the regional microstructure and macroscopic network organization perspectives. Part of figures were taken and adapted from (Rowe *et al.*, 2016).

(Song *et al.*, 2002). AD is the diffusivity along the principal axis of diffusion and decreases when there is axonal injury (or partial volume effect) (Winklewski *et al.*, 2018). These four parameters can be calculated in each voxel using the following equations, where λ1 denotes the diffusion degree along principal direction, and λ2 and λ3 represent the diffusion degrees perpendicular to principal direction (Fig. 1).

$$\mathrm{FA} = \sqrt{\frac{1}{2}}\frac{\sqrt{(\lambda 1-\lambda 2)^2+(\lambda 2-\lambda 3)^2+(\lambda 3-\lambda 1)^2}}{\sqrt{\lambda 1^2+\lambda 2^2+\lambda 3^2}}$$

$$\mathrm{MD} = \frac{\lambda 1+\lambda 2+\lambda 3}{3}$$

$$\mathrm{RD} = \frac{\lambda 2+\lambda 3}{2}$$

$$\mathrm{AD} = \lambda_1$$

Structural connectome analyses using dMRI

For the investigation of the structural connectome with dMRI, three main analysis methods can be employed: voxel-, tractography-, and network-based methods (Fig. 1). In voxel-based analyses (VBA), brains are usually normalized to the template space, and then whole-brain voxel-by-voxel exploratory analyses are performed. Notably, this type of analysis assumes that the normalization is perfect and often suffers from poor statistical power due to a high level of noise from a large number of voxels. An approach to ameliorate this problem is tract-based spatial statistics (TBSS), which includes a skeletonization step to alleviate misalignment and results in greater statistical power based on voxel reduction. Since TBSS addresses major concerns in traditional VBA methods, it is currently the popular technique for voxelwise diffusion tensor imaging (DTI) analysis. Some recommendations for the appropriate use of TBSS can be found in Bach *et al.* (2014). In conclusion, whole-brain VBA and TBSS reflect the white matter microstructure properties of the regional structural connectome from a voxel perspective without the need for previous hypotheses regarding specific white matter pathways, which is a suitable approach for exploratory investigation.

Another method is to reconstruct the white matter fiber pathways with fiber tractography and quantitatively investigate diffusion parameters in specific tracts. The methodology of tractography is beyond the scope of this review, and technical details can be found in Jeurissen *et al.* (2019) and Shi and Toga (Shi and Toga, 2017). After accurate reconstruction of the tract, diffusion parameters along each tract trajectory (pointwise values) can be extracted to create a ''tract profile'' to describe variations in diffusion parameters at different locations along the tracts (Yeatman *et al.*, 2012). This tract profile approach preserves more information than the mean value of diffusion parameters and helps identify specific locations of changes along a tract. Compared with the voxel-based method (VBA and TBSS), tractography can evaluate more specific and complete fiber tracts to delineate alterations in the edges of the structural connectome.

The third option is to apply graph theory modeling methods. While conventional diffusion parameters provide information about microstructural properties, imaging structural connectomes via dMRI can delineate structural connectivity patterns among regions from a macroscopic network perspective and reveal global and local information communication to shed light on the organization of the brain. The brain can be mapped as a complex network consisting of a set of nodes (cortical voxels or regions from segmentation) and a set of edges between the nodes (streamlines from tractography). Once network nodes and edges are defined, several key graph theory metrics, including path length, clustering coefficient, and global and nodal efficiency, can be calculated to describe the topological organization of brain networks. Specifically, for a given network, path length quantities the capability of parallel or distributed information transmission within the network; clustering coefficient reflects the extent of local density of interconnectivity within the network; if a network has a small shortest path-length and a high clustering coefficient, so the network tends to have a small-world configuration that allows efficient information segregation and

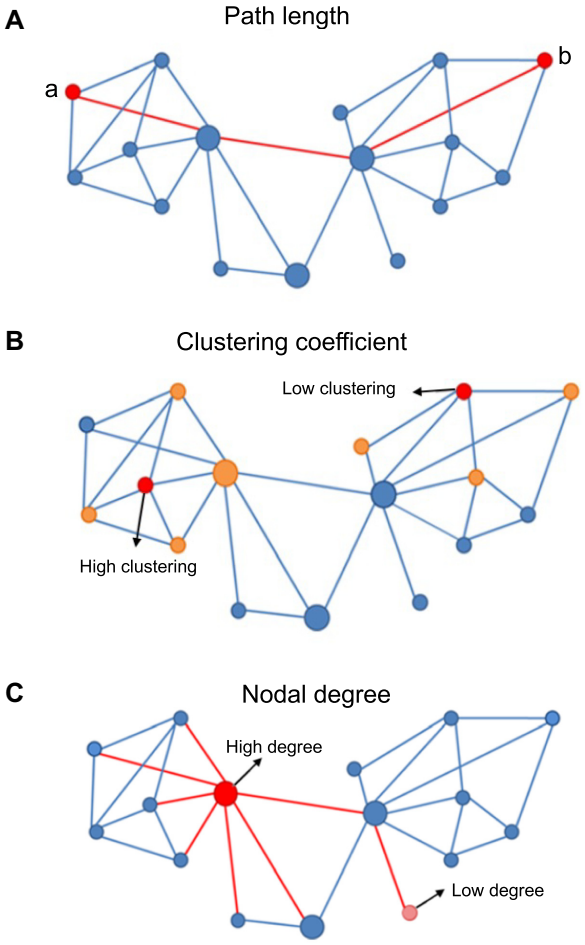

Figure 2: Illustrations of basic network metrics. (A) The shortest path between two nodes (a and b) are indicated by the red line. (B) The node labeled with high clustering (red) has four neighbors (yellow) that are linked to each other. However, the node labeled with low clustering (red) has a clustering coefficient value of zero because there are no existing edges among its three neighbors (yellow). (C) The nodal degree is calculated as the number of edges linking with it. The high degree node (red) has a degree of seven, whereas the low degree node (pink) has a degree of zero. Figures were taken and adapted from Cao *et al.*, (2014).

integration at a low wiring cost. Some basic metrics are illustrated in Fig. 2. Based on these metrics, the structural connectomes of the human brain have been found to have small-world organization, modular architecture, and hubs, which represent patterns of network segregation and integration (Liao *et al.*, 2017). For a more detailed introduction to the brain connectome and graph theory and the delineation of brain network development, see the reviews by Bullmore and Sporns (2009), He and Evans (2010), Cao *et al.* (2016), and Cao *et al.* (2017).

Disrupted structural connectome patterns in ADHD

In this section, we summarize the findings of dMRI studies that applied voxel-based methods, tractography-based methods, and network-based methods in ADHD and further discuss how they impact our understanding of ADHD pathophysiology.

Voxel-based studies

The number of DTI studies in ADHD has progressively increased, and three meta-analyses have summarized the results. Initially, van Ewijk *et al.* (van Ewijk *et al.*, 2012) reviewed seven region-of-interest (ROI) studies and pooled nine VBA studies (two TBSS studies were included) using activation likelihood estimation (ALE) meta-analysis, comprising 173 ADHD patients and 169 healthy participants (ages ranging from 7 to 49 years old). The summary of ROI studies and VBA meta-analyses yielded different results. The seven ROI studies reported reduced FA across a wide range of white matter regions, including the anterior corona radiata, corticospinal tract (CST), cingulum, corpus callosum (CC), inferior and superior longitudinal fasciculus, internal capsule, caudate nucleus, and cerebellum, whereas the VBA meta-analyses revealed increased or decreased FA in the following five regions: right anterior corona radiata, left cerebellum, bilateral internal capsule, and right forceps minor. Some of the abnormal regions, such as the anterior corona radiata, internal capsule, and cerebellum, overlapped between the two types of analysis. However, divergent findings were still evident, especially in terms of the direction of FA alterations. This might be a result of differences in processing methodology and more regions with fiber crossings in VBA studies. Overall, their findings provided evidence that altered white matter microstructure is mainly located in the fronto-striatal-cerebellar neurocircuitry in ADHD populations, including children, adolescents, and adults.

Later, Chen *et al.* (Chen *et al.*, 2016) meta-analyzed ten TBSS studies including 470 adult and nonadult ADHD patients and 477 healthy controls using seed-based *d* mapping since the combination meta-analysis of VBA and TBSS studies could be problematic due to methodological differences. They found reduced FA in the splenium of the CC, left tapetum of the CC, and right sagittal stratum in patients with ADHD. Additional meta-regression analyses found that decreased FA in the splenium of the CC was negatively correlated with the age of patients with ADHD, suggesting a potential age effect on the progression of white matter abnormalities. Their results emphasized the involvement of the CC in ADHD and indicated that in addition to the fronto-striatal-cerebellar circuit, the disrupted interhemispheric communication, and the occipital and temporal fiber pathways also play a role in the pathophysiology of ADHD.

Recently, Aoki *et al.* (Aoki *et al.*, 2018) performed updated and separate meta-analyses of 14 VBA and 13 TBSS studies and evaluated the influence of head motion in TBSS studies given that head motion in DTI, which is particularly evident in the ADHD population, yields spurious findings. Of note, the two meta-analyses obtained quite different results: the VBA meta-analysis found increased FA in the left cingulate, anterior CC,

and left inferior fronto-occipital fasciculus in individuals with ADHD, while there were decreased FA values in the anterior cingulate and bilateral orbitofrontal white matter; however, TBSS meta-analysis showed decreased FA only in the isthmus of the CC, posterior midbody of the CC, right inferior fronto-occipital fasciculus, left inferior longitudinal fasciculus, and right superior longitudinal fasciculus. Given the concerns regarding head motion in ADHD, they also qualitatively evaluated the effect of head motion in TBSS studies. As a result, approximately half of the studies examined the group differences in head motion. The studies showing no difference in head motion reported no significant difference in FA. This meta-analysis, on the one hand, provided evidence of involvement of the CC in pathophysiology of ADHD suggesting atypical interhemispheric connection in ADHD. On the other hand, it demonstrated that the DTI results may be influenced by group differences in head motion. Therefore, future DTI studies should control and correct head motion to avoid the influence of group differences in head motion.

It has been several years since these meta-analyses were published, and therefore, we performed an updated search of whole-brain VBA and TBSS studies in ADHD in the PubMed/MEDLINE database ranging from April 1, 2016, which is the latest search date of Aoki *et al.*, to September 6, 2021, and found 11 published TBSS studies. Notably, only three of these studies found significant between-group differences: two studies (Wu *et al.*, 2017; Ohta *et al.*, 2020) showed decreased FA and increased RD mostly overlapping in the genu and posterior of the CC after relatively rigorous head motion was controlled for (participants with heavy motion were excluded; no group differences in head motion were detected; and head motion was used as a covariate); one study reported higher FA in anterior thalamic radiations, bilateral inferior longitudinal fasciculus, and left CST for patients in the predominantly inattentive ADHD presentation and higher FA in the bilateral cingulum bundle in those in the combined ADHD presentation compared with healthy controls (Svatkova *et al.*, 2016). The other eight studies, which also accounted for head motion, reported negative results regarding group differences between ADHD patients and healthy controls in DTI parameters, such as FA and MD, while some of the studies showed significant correlations between FA/MD and symptoms/cognitive performance using a dimensional approach (Ercan *et al.*, 2016; Aoki *et al.*, 2017; Bos *et al.*, 2017; Bouziane *et al.*, 2018; Albaugh *et al.*, 2019; Bessette and Stevens, 2019; Albajara Saenz *et al.*, 2020; Saad *et al.*, 2021).

Taken together, all previous studies concluded that alterations in the white matter microstructure in the fronto-striatal-cerebellar circuitry and interhemispheric CC are evident findings in ADHD from the voxel-level perspective (Fig. 3). Specifically, microstructural alterations in the CC are the most robust and consistent findings when controlling for head motion.

Tractography-based studies

Even though whole-brain voxelwise studies have advantages, they do not focus on or identify a specific fiber tract of interest. The dMRI-based tractography technique enables three-dimensional reconstruction of fiber tracts, allowing integration of diffusion properties along the entire length of specific and well-defined white matter pathways. Therefore, tractography potentially provides greater power to detect certain effects that might be neglected using voxelwise approaches.

(i) Frontostriatal tracts

Deficits in frontostriatal circuits have been associated with impairments in cognitive functions and the ability to flexibly adapt behavior to changing circumstances. There are two major dopaminergic pathways connecting the striatum to the prefrontal cortex and other regions: one pathway connects the striatum to the medial and dorsolateral prefrontal cortices, and the other pathway connects the striatum to the orbitofrontal cortex and amygdala (Schweren *et al.*, 2016). Previous VBA and TBSS DTI studies have repeatedly reported abnormal white matter microstructures in various regions within the frontostriatal tracts. In addition, disrupted neuroanatomy and decreased functional activity in the prefrontal cortex and striatum have been consistently reported in individuals with ADHD (Konrad *et al.*, 2006; Sheridan *et al.*, 2007; Shaw *et al.*, 2011; Hoogman *et al.*, 2017). As research trends are moving away from investigating regional and discrete alterations toward considering connectivity of brain networks, it is of interest to investigate the frontostriatal tracts in ADHD.

There were eight tractography studies investigating frontostriatal tracts as an ROI, and most reported reduced FA in these frontostriatal tracts in individuals with ADHD, although the dMRI technique (diffusion spectrum imaging, high angular resolution diffusion imaging, DTI), scan parameters (field strength, diffusion gradient direction, *b* value), tractography algorithm (deterministic and probabilistic), and diffusion model (tensor, constrained spherical deconvolution) differed greatly among these studies. Two studies that investigated the frontostriatal tracts as a whole ROI found decreased FA that was associated with worse attention problems, school functioning, and nonverbal intelligence (de Zeeuw *et al.*, 2012; Tung *et al.*, 2021). Two studies (Chiang *et al.*, 2016; Schweren *et al.*, 2016) investigated white matter pathways between different subregions of the prefrontal cortex, such as the orbitofrontal, dorsolateral prefrontal, ventrolateral prefrontal and medial prefrontal-striatal regions, and the striatum. Both studies found reduced FA in the orbitofrontal-striatal pathway, while Chiang *et al.* also reported reduced generalized FA in the left striatum-ventrolateral

prefrontal cortex and striatum-dorsolateral prefrontal cortex tracts, which were associated with deficits in several types of executive function. Regarding the tracts connecting subregions of the striatum, two studies (Shang *et al.*, 2013; Wu *et al.*, 2014) using diffusion spectrum imaging tractography reported lower generalized FA values in the dorsolateral prefrontal cortex–caudate, medial prefrontal–caudate, orbitofrontal–caudate, and ventrolateral prefrontal cortex–caudate tracts, which were correlated with symptom severity and executive function performance. Cha *et al.* (Cha *et al.*, 2015) showed reduced probabilistic tract measures between the ventral prefrontal cortex and nucleus accumbens, which were associated with increased aggression in children with ADHD. However, Silk *et al.* (Silk *et al.*, 2016), using high angular resolution diffusion imaging, found no significant between-group differences in any of the tracts between the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, orbitofrontal cortex and caudate, and the putamen but pronounced lateralization to the left for FA in the ventrolateral prefrontal cortex–putamen tracts in children with ADHD, which was associated with greater symptom severity.

(ii) Corpus callosum

The CC is the main and largest commissural white matter bundle and is responsible for brain lateralization and interhemispheric communication. The involvement of the CC in ADHD has been supported by three previous meta-analyses, but these ADHD tractography studies of the CC reported divergent results. A recent diffusion spectrum imaging (Tung *et al.*, 2021) tractography study conducted at the whole-brain level including 279 probands with ADHD (aged from 7 to 60), 121 unaffected siblings, and 626 controls showed reduced generalized FA in the splenium of the CC in those with ADHD. Using a normative approach, children with ADHD showed no deviation in the CC, while adults with ADHD showed reduced deviation in the CC-prefrontal cortex tracts and increased generalized FA variability in the CC-sensorimotor and CC-parietal cortex tracts. In addition, the link between cognition, including executive function, attention and verbal IQ, and the CC was indicated by canonical correlation analysis. Another whole-brain diffusion spectrum imaging tractography study (Chiang *et al.*, 2020) with a sibling design including medication-naïve children with ADHD found higher AD values in the CC only in children with ADHD. These AD values were associated with ADHD symptoms, sustained attention and working memory. To focus on different segments of the CC, Langevin *et al.* (Langevin *et al.*, 2014) segmented CC tracts into anterior and superior frontal, superior, and posterior parietal, temporal, and occipital sections, and found FA reductions in the frontal regions of the CC in children with ADHD. Correlation analysis across groups showed that FA values in the CC, anterior and superior frontal CC, and superior and posterior parietal CC were positively correlated with scores for auditory attention and executive function. Lin *et al.* (Lin *et al.*, 2020) examined callosum forceps major and callosum forceps minor in girls with ADHD and found decreased FA and increased RD values on the right side of the occipital CC tract within the callosum forceps major, which were correlated with hyperactivity-impulsivity and control ability.

(iii) Cingulum bundle

The cingulum bundle connects to the cingulate cortex, which is associated with emotional control and cognitive processes (Catani, 2012). The cingulum cortex has been associated with response inhibition and emotional dysregulation (Hung *et al.*, 2020). The tractography results of the cingulum in ADHD seem to be inconsistent. Versace *et al.* (Versace *et al.*, 2021) examined focal abnormalities in 18 major white matter tracts in 126 adults with childhood ADHD (mean age = 34.3 years) and 58 healthy adults (mean age = 33.9 years) and observed lower FA in the middle portion of the bilateral cingulum angular bundle. Subgroup analysis showed that participants with both persisting and remitted ADHD symptoms showed lower FA than non-ADHD adults, suggesting a potential negative effect of childhood ADHD on cingulum angular bundle. Stephens *et al.* (2021) explored the fiber tracts related to the limbic system in children with ADHD and ASD. They also observed significantly lower FA in the bilateral cingulum. In contrast, Damatac *et al.* (2020) systematically investigated 18 major fiber tracts using automated global probabilistic tractography from 654 participants aged 7 to 20 years. They found no significant effects on FA in any tract. Of note, they reported that lower FA in the right cingulum angular bundle was associated with higher hyperactivity-impulsivity symptom severity, emphasizing the particular role that the right cingulum angular bundle played in hyperactivity and impulsivity. An ROI tractography study focusing on the subgenual cingulum (Cooper *et al.*, 2015) also reported negative between-group differences but a significant correlation between FA and RD in the left subgenual cingulum and ADHD symptom severity.

(iv) Corticospinal tracts

Children with ADHD often present with deficits in fine motor control. The CST is critical for voluntary motor control. The first study by Bu *et al.* (2020) applied tensor-based deterministic tractography and an along-tract quantitative approach focusing exclusively on the CST and found that those with ADHD showed opposite FA directions in the cerebral peduncle and posterior limb portions of the right CST. They further observed associations between diffusion parameters and attention performance and response inhibition. There were two limitations in this study. First, it adopted a tensor to estimate the fiber tract orientation within a given voxel, which

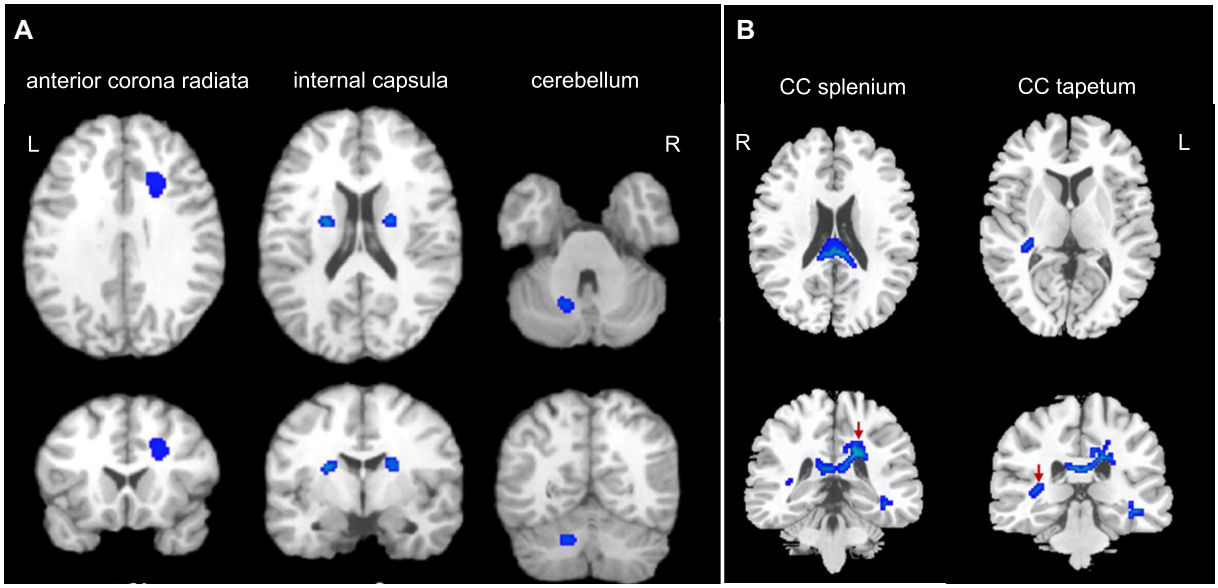

Figure 3: White matter microstructure abnormalities in fronto-striatal-cerebellar circuit (A) and CC (B) in ADHD. (A) The results of VBA meta-analysis in ADHD (van Ewijk *et al.*, 2012) showing altered (increased or decreased) FA in fronto-striatal-cerebellar circuit. (B) The results of TBSS meta-analysis in ADHD (Chen *et al.*, 2016) suggesting decreased FA in CC. Red arrows in (B) indicated the CC splenium and CC tapetum from coronal view. Figures were taken and adapted from van Ewijk *et al.* (2012) and Chen *et al.* (2016).

is unable to overcome the fiber crossing issue. Second, given the role that the CST plays in motor function, it did not examine the link between motor function in children with ADHD and white matter microstructure of the CST. Later, Hyde *et al.* (Hyde *et al.*, 2021) examined the relationship between atypical CST microstructure and low motor abilities in those with ADHD by an advanced fixel-based analysis based on a constrained spherical deconvolution model to overcome the aforementioned limitations. They observed significantly lower fiber density, fiber cross-section, and fiber density-cross section in the right CST. Although children with ADHD performed significantly worse in the fine motor task, no correlations were detected between motor performance and microstructure of the CST. Recently, Fuelscher *et al.* (Fuelscher *et al.*, 2021) also performed a fixel-based analysis based on whole-brain tractography of 14 major tracts, including the CST. Similar group differences were observed for the bilateral CSTs, but there were still no significant associations between ADHD symptom severity and microstructure of the CST.

In conclusion, tractography studies using various diffusion modalities and models, on the one hand, support the involvement of frontostriatal circuits and the CC, as suggested by VBA and TBSS studies (Fig. 4A and B). On the other hand, microstructural alterations in the cingulum and CST were also detected given their association with motor function, response inhibition, and emotional regulation (Fig. 4C and D). The tractography results revealed more specific fiber tracts related to ADHD psychopathology and implied disrupted structural connectivity in ADHD.

Network-based studies

Previously, Cao *et al.* (Cao *et al.*, 2014) reviewed functional and structural brain connectomes in ADHD, and only two diffusion magnetic resonance studies had been included. Regarding the white matter network, they concluded that children with ADHD had a closer-to-regular small-world network structure, which manifested as lower global efficiency and higher local efficiency, and the abnormal structural connectivity mainly involved the prefrontal, orbitofrontal-striatal, and cerebellum circuits (Cao *et al.*, 2013) (Fig. 5). After conducting an updated search, we provided a complementary summary on white matter network topology and characterized the alterations of structural connectivity in ADHD. For children with ADHD, the findings were in line with previous studies. For example, Beare *et al.* (Beare *et al.*, 2017) examined the white matter networks in 21 boys with ADHD and 21 healthy boys using a range of commonly used methodologies, including deterministic and probabilistic tractography, tensor, and constrained spherical deconvolution models, and different edge weighting methods. They observed lower global efficiency and higher local efficiency in those with ADHD and stronger structural connectivity in frontostriatal connections with occipital, temporal, and parietal regions, of which FA was positively associated with ADHD symptom severity. They further suggested that probabilistic tractography with the constrained spherical deconvolution model and the Hagmann weighting method produced the highest stability. Another study of rich-club organization (Ray *et al.*, 2014) reported lower generalized FA within the rich-club networks in children with ADHD that included superior frontal, posterior cingulate, inferior temporal, and superior parietal regions. However, one study reported

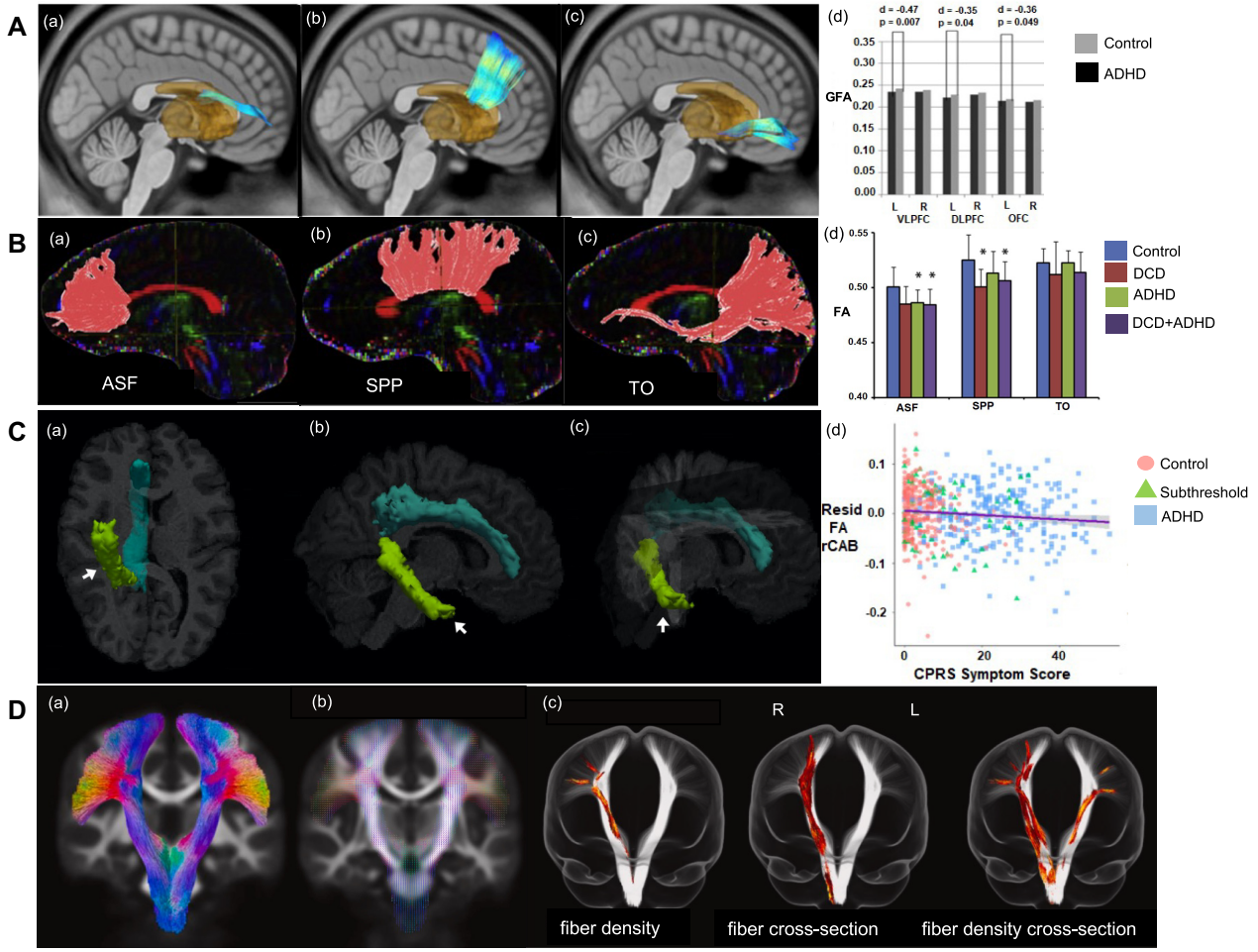

Figure 4: Illustration of four commonly reported fiber tracts in ADHD. (A) Reconstruction of the (a) striatum-ventrolateral prefrontal tract; (b) striatum-dorsolateral prefrontal tract; (c) striatum-orbitofrontal tract; and (d) Comparisons of the mean generalized FA for these three tracts between ADHD (black) and controls (grey). Children with ADHD had lower mean GFA values in all three left frontostriatal tracts. Figures were taken and adapted from Chiang *et al.* (2016). (B) CC was segmented into (a) anterior/superior frontal (ASF) tract, (b) superior/posterior parietal (SPP) tract, and (c)temporal/occipital (TO) tract. (d) Comparisons of the mean FA for these three tracts among ADHD (green), developmental coordination disorder (DCD) (red), ADHD + DCD (purple), and controls (blue). Children with ADHD had reduced FA only in the ASF tract as indicated by asterisk in (d). Figures were taken and adapted from Langevin *et al.* (2014). (C) Reconstruction of right cingulum angular bundle (rCAB) which is in green and indicated by white arrows from (a) inferior, (b) right, and (c) ventral anterior views. The cingulum cingulate gyrus bundle is in blue. (d) Mean FA of right cingulum angular bundle was negatively correlated with ADHD symptom score across ADHD (blue square), subthreshold ADHD (green triangle), and controls (red dot). Figures were taken and adapted from Damatac *et al.* (2020). (D) (a) Corticospinal tracts (CST) reconstructed and analyzed by fixel-based analysis. (b) Fixels belonging to the corticospinal tract. (c) Specific segments of CST that showed a significant decrease in fiber density (FD), fiber cross-section (FC), and fiber density cross-section (FDC) in the children with ADHD. Figures were taken and adapted from Hyde *et al.* (2021).

no group differences in global topological properties and decreased nodal degree in the right amygdala and right parahippocampal gyrus in children with ADHD (Qian *et al.*, 2021).

Regarding adults with ADHD, lower global efficiency and reduced hemispheric asymmetry were the most significant findings (Li *et al.*, 2019; Li *et al.*, 2021; Wang *et al.*, 2021). At the global level, the left hemisphere exhibited better small-world properties, while the right hemisphere had better global efficiency. At the nodal level, the superior frontal gyrus, rolandic operculum, and putamen showed prominent leftward asymmetries in nodal efficiency. Meanwhile, Sidlauskaite *et al.* (2015) found no differences between adults with ADHD and healthy controls in terms of global network metrics. However, they found that lower local efficiency values in the left superior temporal and supramarginal gyri were associated with higher ADHD symptom scores, and greater local clustering in the right putamen and lower local clustering in the left supramarginal gyrus were correlated with more serious ADHD symptom severity.

In summary, network topology in children with ADHD consistently presented as lower global efficiency, higher local efficiency, and disrupted structural connectivity inside the rich-club networks, whereas adults with ADHD showed lower global efficiency, disrupted nodal properties, and reduced hemispheric asymmetry. In addition, these network abnormalities were

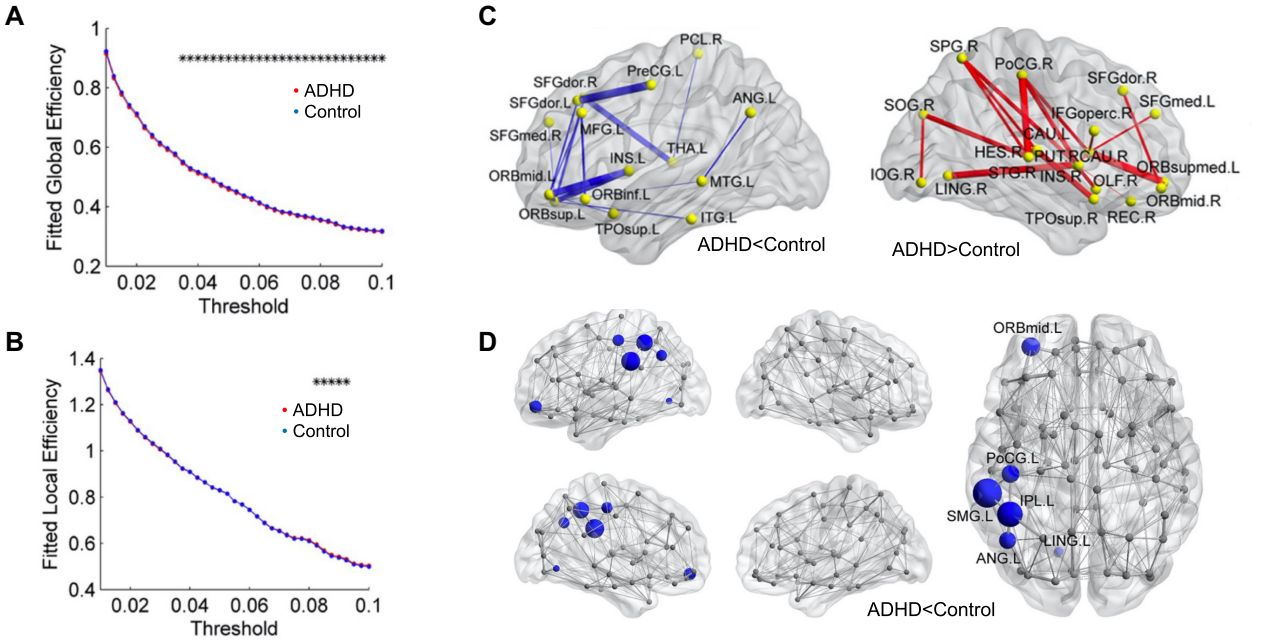

Figure 5: Using graph theory-based network analysis, children with ADHD had (A) lower global efficiency and (B) higher local efficiency with different probability thresholds. Data points marked with an asterisk indicate a significant group difference ($P < 0.05$) under the threshold. (C) Decreased structural connectivity decreased in prefrontal regions while increased in orbitofrontal-striatal regions. (D) Reduced nodal efficiency in the left parietal, left frontal, and left occipital cortices. Figures were taken and adapted from Cao *et al.* (2013).

associated with ADHD symptom severity. Longitudinal studies are further needed to depict the trajectory of network changes in ADHD from childhood to adulthood. Taken together, these results, as well as a previous review (Cao *et al.*, 2014), indicate the existence of white matter network dysfunction in ADHD.

Predicting the diagnosis and prognosis of ADHD using connectome-based approaches

Motivated by the challenge of the assessment of psychiatric disorders based on subjective experience, machine-learning approaches are increasingly being used to seek objective neuroimaging biomarkers for ADHD diagnosis and prognosis. In this section, we review recent studies using dMRI for ADHD classification and symptom prediction to evaluate the potential predictive value of white matter features.

Diagnostic classification

One early study applied stepwise binary logistic regression on several DTI measures (FA, MD, RD, AD, mode of anisotropy) and demographic and clinical measures to investigate their effect on ADHD diagnosis (Yoncheva *et al.*, 2016). The results showed that the global mode of anisotropy combined with Conners' Rating Scale achieved the highest classification accuracy in both children (94.12%) and adult ADHD samples (92.11%), and it improved classification accuracy compared with either the model containing Conners' Rating Scales alone (children ADHD = 92.42%, adult ADHD = 88.89%) or the model including only the mode of anisotropy (AUC for children ADHD = 0.70; AUC for adult ADHD = 0.88). This study highlighted the potential diagnostic value of white matter microstructure in ADHD. More recent work selected features from multimodal MRI data. For example, Sun *et al.* (2018) extracted both gray matter morphometry and white matter microstructure and used random forest classifiers to discriminate children with ADHD from control participants. The classification accuracy reached 73.7%, with FA in the left cerebral peduncle as the most significant discriminating feature among the white matter features. By using a multimodal machine learning approach based on structural, functional, and dMRI features, Zhou *et al.* (2021) reported 64.3% classification accuracy for the diagnosis of children with ADHD, which was higher than the classification performance of any single modality alone. The most predictive white matter regions included the isthmus cingulate, post central, amygdala, pars orbitalis, and thalamus proper. Yoo *et al.* (2020) integrated structural MRI, functional MRI, and DTI features with genetic and clinical information to distinguish children with ADHD from controls. The best feature among DTI measures was all tensors, which reached only 65.9% accuracy. When combining all tensors with gray matter morphometry and volume, the accuracy increased to 84.4%. Among all the unimodal and multimodal features, cortical thickness and volume achieved the highest accuracy of 85.1%.

For adults with ADHD, using structural MRI and DTI data, Chaim-Avancini *et al.* (2017) applied support vector

machine with a nonlinear kernel and reported a diagnostic accuracy of 66.0% with an increased accuracy of 74.0% in a male-only analysis, which suggested that more homogenous participants with ADHD may lead to better diagnostic performance. FA and traces of white matter with high classification weights were located mainly in the frontal region, CC, cingulum, and brain stem. Later, Luo *et al.* (2020) combined several basic machine learning models into one, which was then trained by several neuroimaging features, including cortical thickness, surface area, gray matter volume, volume, and FA of white matter, functional connectivity, and functional network topological properties. This model yielded a classification accuracy of 76.6% with nodal efficiency of the right inferior frontal gyrus, functional connectivity between the right middle frontal gyrus and right inferior parietal lobule, and right amygdala volume as the top three important features.

Prognosis prediction

Impulsivity and aggression are widely observed in children with ADHD. One study (Elliott *et al.*, 2021) used LASSO regression to predict impulsivity from the six white matter tracts between the substantia nigra (SN)/ventral tegmental area (VTA) and three striatal regions (limbic, executive, and motor regions) since SN/VTA-striatal circuits implicated in the dopamine system provide a neurobiological basis for impulsivity. The study found that SN/VTA-striatum tract strength measures significantly predicted impulsivity validated by leave-one-subject-out cross-validation. Another study (Cha *et al.*, 2015) demonstrated that fronto-accumbal white matter connectivity was predictive of aggression in children with ADHD examined by two independent multivariate pattern analyses: partial least square regression and support vector regression.

Griffiths *et al.* (2021) used a support vector machine to explore both the prognostic and diagnostic value of graph measures obtained from tractography. The results showed that reduced local efficiency in subcortical regions was able to distinguish ADHD patients from controls with 76% accuracy. On the other hand, higher global efficiency and local efficiency in the right supramarginal gyrus at baseline could predict symptom relief after 6 weeks of methylphenidate treatment.

After reviewing recent results regarding ADHD neuroimaging biomarkers based on dMRI, we found that most of the diagnostic accuracies were below 80%, and, of note, diffusion features combined with structural and clinical features, compared with diffusion measures alone, yielded higher accuracy. These results indicate that white matter microstructure reflected by diffusion measures may not be the best or most sensitive neuroimaging biomarker for ADHD diagnosis. Pulini *et al.* (2019) concluded that there were two major pitfalls in classification and prediction neuroimaging studies in individuals with ADHD based on a review of structural and functional MRI results: (i) circular analysis, which means lack of internal and external validation; and (ii) small sample sizes. These are the same issues in regard to the diffusion magnetic resonance studies that we reviewed. Only one study (Yoo *et al.*, 2020) performed a validation analysis in another small independent sample (18 ADHD and 18 controls), and the number of participants in most training datasets was no larger than 100. Thus, methodological robustness and good generalizability should be adequately addressed in future classification and prediction studies.

Limitations and future directions

Even though dMRI studies have provided much information about structural connectome differences in ADHD, there are some shortcomings in current studies that hinder our understanding of the neural mechanisms related to ADHD. We propose some important issues for future directions of study.

First, it is hard to ignore that many researchers have reported negative between-group differences in TBSS (Aoki *et al.*, 2017; Bos *et al.*, 2017; Albaugh *et al.*, 2019; Bessette and Stevens, 2019; Saad *et al.*, 2021), tractography (Lawrence *et al.*, 2013; de Luis-Garcia *et al.*, 2015; Damatac *et al.*, 2020), and network studies (Sidlauskaite *et al.*, 2015; Griffiths *et al.*, 2021; Qian *et al.*, 2021; Saad *et al.*, 2021). We assume that the lack of significant differences could be related to heterogeneity of both participants and ADHD per se, and the methodology used by most studies. Although most studies have recruited age- and sex-matched participants, the presence of comorbidities and a medication history among participants will definitely increase inter-subject variability and could be confounding variables. Therefore, future studies should include homogenous participants in terms of age range, sex (male or female only), and treatment history (drug-naïve, psychostimulant, or behavioral therapy).

Second, ADHD has been regarded as a complex and heterogeneous disorder. Patients differ from each other in core symptoms, cognitive dysfunction, environmental factors, genetic risks, and brain function and structure. For these reasons, the current case-control strategy may not be appropriate, as it cannot reflect the underlying reality of the disorder. A dimensional approach should be more consistently used to better parse ADHD heterogeneity (Thapar and Cooper, 2016; Posner *et al.*, 2020). On the other hand, identifying biological subtypes based on brain structure and function and building valid behavioral prediction models using data-driven methods should be encouraged. Recently, some researchers have identified the subtype of ADHD and predicted symptoms and cognitive control function based on the functional connectivity mode of the brain network (Costa Dias *et al.*, 2015). However, few studies have explored the possibility of building subtypes and predicting symptoms based on white matter. Therefore, it is necessary to integrate the symptoms, cognitive function, and structural connectome in future research to explore biosubtypes of ADHD to deepen our understanding of the pathogenesis

and to promote precision medicine approaches in ADHD treatment.

Third, a prominent neurodevelopmental hypothesis proposes that ADHD involves a delay in brain maturation. Structural and functional studies have demonstrated a delay to reach peak thickness in prefrontal regions (Shaw *et al.*, 2007) and in functional connectivity within and between the default mode network and task-positive networks (Sripada *et al.*, 2014). However, the age trajectory regarding white matter in individuals with ADHD remains unclear. Large datasets with longitudinal study designs will be helpful to delineate the development of the microstructural and connectome patterns in white matter in individuals with ADHD. For these reasons, the availability of large imaging datasets is of paramount importance. The ADHD-200 Consortium (Consortium, 2012) has been established and released resting-state functional MRI, structural MRI, and basic phenotypic information from >900 individuals, including patients with ADHD and typical developing controls aged 7 to 27 years old. A multimodal dataset including dMRI in the ADHD-200 would need to be created in the near future to enhance our understanding of the neurobiological basis for ADHD based on the structural connectome. Notably, the cortical morphometric features (e.g. cortical thickness) derived from structural MRI have been used to study structural covariance of the brain (He *et al.*, 2007), which has been considered as one part of structural connectomes. Although a previous study has suggested that inter-regional structural covariance can partly reflect white matter pathways (Gong *et al.*, 2012), this review mainly focuses on direct white matter connectivity among regions. Future studies of the structural connectomes in ADHD needs to integrate structural covariance and white matter pathways, which allows a full picture to examine network disruption in this disorder from a multi-scale and multi-modal perspective (Li *et al.*, 2021; Yang *et al.*, 2021).

Fourth, the coupling relationship between structural and functional networks in ADHD still needs to be determined. Investigating the relationships between multimodal networks will help to understand how functional information transfers through the structural connectome and how the structural backbone shapes the functional network. Studies in a normally developing population revealed greater structural–functional coupling with increasing age, which positively correlated with better executive function during development (Hagmann *et al.*, 2010; Baum *et al.*, 2020). The questions of whether an atypical pattern of coupling relationship between structural and functional connectivity exists in individuals with ADHD and what the associations between structure–function coupling and ADHD psychopathology are, remain to be answered.

Fifth, studies that examined medication effects on white matter are scarce. Only one randomized double-blind placebo-controlled trial explored the influence of methylphenidate on white matter using DTI (Bouziane *et al.*, 2019). The authors observed increased FA in several association fiber tracts and the CC after 16 weeks of treatment in boys with ADHD and no FA changes in adult men with ADHD and participants receiving placebo, which implied an age-dependent effect of methylphenidate on white matter. More studies with larger sample sizes are needed to further investigate white matter correlates based on different medications.

Sixth, some methodological issues of dMRI analysis should be noted. Head motion in MRI has been regarded as a nontrivial interference factor, especially in patients with ADHD. As suggested by Aoki *et al.* (Aoki *et al.*, 2018), given that head motion during scans would lead to false positive findings in DTI, efforts should be made to minimize the influence of head motion. We suggest rigorous quality control throughout data collection and processing, including education or mock scanning for children, implementing rests during several scanning sessions, evaluating motion qualitatively (visual check) and quantitatively (rotation, translation, and intervolume displacement), and motion correction using statistical analysis. The following are promising software packages for consideration for the implementation of motion correction: FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) (Jenkinson *et al.*, 2012), MRtrix3 (https://www.mrtrix.org/) (Tournier *et al.*, 2019), ExploreDTI (http://exploredti.com/) (Leemans *et al.*, 2009), and QSIPrep (https://qsiprep.readthedocs.io/en/latest/index.html) (Cieslak *et al.*, 2021).

Finally, since conventional DTI has some intrinsic limitations in terms of modeling crossing fibers and partial volume effects, more advanced diffusion techniques and models are emerging and could be considered. Fiber reconstruction based on diffusion spectrum imaging, high angular resolution diffusion imaging, and spherical deconvolution algorithms can provide more accurate methods to delineate real complex fiber configurations because they can estimate multiple fiber orientations in a single voxel. In contrast to these mathematical models, biophysical tissue models, such as neurite orientation dispersion and density imaging, can separate tissue classes within a voxel into intracellular, extracellular, and free-water compartments (Zhang *et al.*, 2012; Nazeri *et al.*, 2020). The measures related to neurite orientation dispersion and density imaging may have greater potential for capturing cellular and synaptic microstructures in both gray and white matter than DTI measures. In the future, the application of more advanced dMRI methods would provide more detailed insight into the neuropathology underlying ADHD. In addition, with more evidence for the presence and significance of fMRI signal in white matter (Ji *et al.*, 2017; Li *et al.*, 2019; Wang *et al.*, 2021), it is worth investigating functional properties of white matter in the future study of connectome besides the microstructural property. In fact, our recent study (Bu *et al.*, 2020) has revealed two distinct white matter functional network patterns in children with ADHD, which are the hyperactivity-related hyperactivated network and inattention-related hypoactivated network. More research is needed to probe the functional

organization of white matter in ADHD, which can lead to a new perspective to understand ADHD psychopathology.

Conclusions

Our review of ADHD dMRI studies using voxel-, tractography-, and network-based methods demonstrated disrupted microstructure mainly in the frontostriatal tracts, CC, CST, and cingulum bundle. From a network perspective, the white matter network in children with ADHD presented a topology more similar to a regular configuration, whereas adults with ADHD had lower efficiency at the global level and reduced hemispheric asymmetry. In addition, these disruptions were associated with symptom and cognitive impairment. However, the classification accuracy for ADHD diagnosis based on the structural connectome has been too low to be regarded as an independent promising biomarker, while the prediction of symptoms and treatment response using microstructure and network topology was relatively well achieved. Future studies with larger and more homogeneous samples, using advanced dMRI techniques, and dimensional analysis frameworks are needed to validate the current conclusions and to provide further evidence regarding the neurobiology underlying ADHD.

Author contributions

X.B. and Y. H. conceptualized and designed the review. X.B. drafted the manuscript. All authors revised the manuscript and approved the final version.

Conflicts of interest statement

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

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