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Imaging Functional and Structural Brain Connectomics in Attention-Deficit/Hyperactivity Disorder

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Abstract Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopment disorders in childhood. Clinically, the core symptoms of this disorder include inattention, hyperactivity, and impulsivity. Previous studies have documented that these behavior deficits in ADHD children are associated with not only regional brain abnormalities but also changes in functional and structural connectivity among regions. In the past several years, our understanding of how ADHD affects the brain's connectivity has been greatly advanced by mapping topological alterations of large-scale brain networks (i.e., connectomes) using non-invasive neurophysiological and neuroimaging techniques (e.g., electroencephalograph, functional MRI, and diffusion MRI) in combination with graph theoretical approaches. In this review, we summarize the recent progresses of functional and structural brain connectomics in ADHD, focusing on graphic analysis of large-scale brain systems. Convergent evidence suggests that children with ADHD had abnormal small-world properties in both functional and structural brain networks characterized by higher local clustering and lower global integrity, suggesting a disorder-related shift of network topology toward regular configurations. Moreover, ADHD children showed the redistribution of regional nodes and connectivity involving the default-mode, attention, and sensorimotor systems. Importantly, these ADHD-associated alterations significantly correlated with behavior disturbances (e.g., inattention and hyperactivity/impulsivity symptoms) and exhibited differential patterns between clinical subtypes. Together, these connectome-based studies highlight brain network dysfunction in ADHD, thus opening up a new window into our understanding of the pathophysiological mechanisms of this disorder. These works might also have important implications on the development of imaging-based biomarkers for clinical diagnosis and treatment evaluation in ADHD.

Keywords ADHD · Connectome · Graph theory · Small-world · Functional connectivity · Structural connectivity

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed neurodevelopment disorders in childhood, which could continue through adulthood for some people. It is clinically characterized by developmentally inappropriate symptoms of inattention, hyperactivity, and impulsivity, resulting in substantial educational and social burdens [1, 2]. Via the diagnostic and statistical manual of mental disorders (DSM-5) diagnostic criteria, the disorder is estimated to affect 5 % in children or adolescents and 2.5 % in adults [1].

Previous studies have documented that besides these behavior disturbances, patients with ADHD exhibit functional and structural abnormalities in distributed neural systems that are mainly linked with cognitive control, attention, and

motivation/reward functions [3–9]. For instance, ADHD-related regional dysfunction and morphological changes have been reported in the dorsal frontoparietal cortex, orbitofrontal cortex, and ventral striatum structures [10–14]. Disrupted functional and structural associations between these regions have been also reported in ADHD [15–17]. It was commonly contended in these studies that ADHD is not only involved in regional brain abnormalities but also associated with disruptions of neuronal circuits.

Recently, the development of noninvasive neurophysiological and neuroimaging techniques as well as graphic network analysis tools allows to model the brain as a complex network and to further explore topological organization of the resultant networks (i.e., connectomes) [18, 19]. Using these approaches, researchers have consistently found that the human brain functional and structural networks exhibit many nontrivial topological properties such as small-worldness, modularity, and highly connected hub regions [20–24]. Several recent studies have utilized these connectome-based approaches to demonstrate topological organization disruption in both functional and structural brain networks in children with ADHD [25–35], providing novel insights into the core pathophysiological mechanism of network dysfunction.

In this review, we aim to summarize these connectome-based studies in ADHD, focusing specifically on the topological alterations in the large-scale brain networks. First, we briefly introduce some basic concepts regarding connectomics and graph theory. Next, we review recent findings of functional and structural brain networks in ADHD based on multimodal neurophysiological and neuroimaging data (electroencephalograph (EEG), resting-state functional MRI (R-fMRI), and diffusion MRI (dMRI)). Finally, we discuss the limitations and future research directions of connectome-based network analysis in ADHD.

Human Connectomics and Graph Theory

Connectomics and Brain Connectivity

Human connectomics is an emerging scientific concept that refers to a comprehensive description of the structural and functional connectivity patterns of the human brain [18, 19]. With the progression of advanced neurophysiological and neuroimaging techniques, researchers can map the brain as a complex network at the macro-scale level, consisting of a set of nodes (representing voxels, regions, or sensors) and a set of connections between the nodes (representing white matter pathways, structural, or functional pair-wise relationships). Specifically, structural connections can be calculated by estimating the brain's morphological (e.g., gray matter volume or cortical thickness) correlations in structural MRI data [36–38] or tracing the white matter projections linking cortical and subcortical regions in dMRI data [39–42]. Functional connections estimate the synchronizations of neural activity by computing the statistical dependence (e.g., cross-correlation, mutual information, or spectral coherence) of the time series among different sites, which can be obtained from fMRI, EEG/magnetoencephalography, and functional near-infrared spectroscopy [25, 43, 44]. After computing internode connectivity matrices, a network threshold (e.g., correlation coefficient, fiber numbers, or network density) is usually applied to eliminate weak connectivities possibly arising from signal noise. To this end, brain networks (usually sparse) are obtained and can be further characterized by using graph theoretical approaches. Figure 1 shows a brief flowchart about construction and analysis of the brain networks in ADHD studies.

Graph Theory Approaches

In the graph theory context, a brain network can be represented as a graph $G(N, K)$, with N denoting the number of nodes and K denoting the number of edges in graph G. Accordingly, an $N \times N$ adjacency matrix can be generated to indicate the existence or strength of edges between each pair of nodes in the graph G. A network can be classified as directed or undirected depending on whether its edges have a sense of direction and unweighted (binary) or weighted depending on whether the edges are assigned with different strengths. To date, no studies have explored the directed brain networks in ADHD. Thus, we focused on the undirected ones. Several key network metrics are illustrated below. For more details of graph theory methods, please refer to previous studies [24, 45, 46].

Small-World and Network Efficiency The small-world [47] is an attractive model to capture the organization principles that govern a variety of social, economic, and biological networks. Small-world structure reflects an optimal balance between information segregation and integration, which is essential for high synchronizabilty and fast information transmission in a complex network. Here, we first introduced two key metrics relevant to this model: the characteristic shortest path length and clustering coefficient (Fig. 2). Path is any unique sequence of edges that connects two nodes with one another, and its length is given by the number of steps (in a binary graph) or the sum of the edge lengths (in a weighted graph), with the shortest one referred to as the distance. The characteristic path length of a network is the global average of the distances between all pairs of nodes. This measure quantifies the capability for parallel or distributed information propagation of a network. The clustering coefficient of a network is the average of the clustering coefficients over all nodes in the network, where the clustering coefficient of a node is defined as the number of existing connections among the node's neighbors divided by all their possible connections. This measure quantifies the extent of local interconnectivity or cliquishness of information transfer

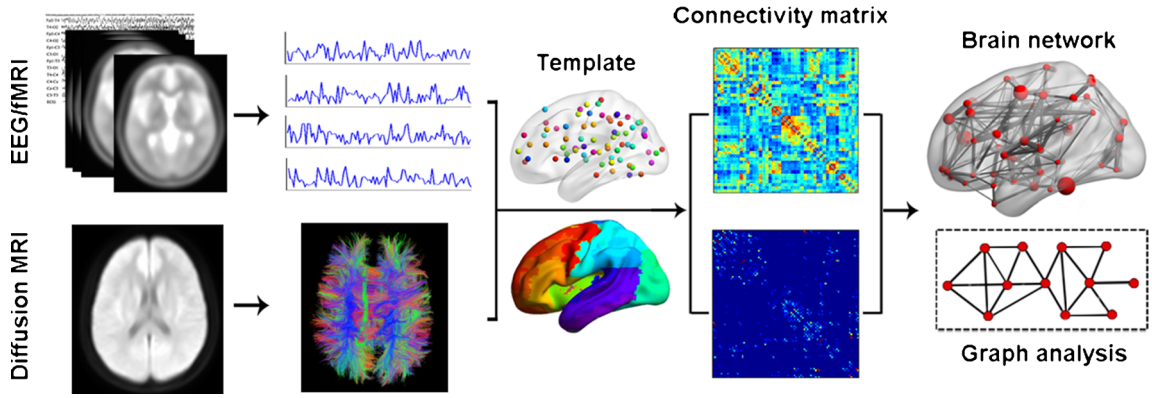

Fig. 1 A flowchart of construction and analysis functional and structural brain networks used in the ADHD studies. Briefly, the time courses from the EEG/fMRI data or the fiber pathways from diffusion MRI data are first extracted. The brain regions were then parcellated by structurally or functionally defined templates. The individual connectivity matrices are generated by considering the pair-wise functional or structural associations between brain regions. To the end, the brain network is obtained and further visualized as a graph and its topological properties can be calculated with graph theoretical approaches

of a network. The two metrics of a real network can be compared with those in benchmark networks such as random and regular networks. A small-world network possesses higher local interconnectivity than a random network (low clustering coefficient and short characteristic path length) and higher global integrity than a regular network (high clustering coefficient and long path lengths).

Network efficiency is a more biologically relevant metric to describe brain networks from the perspective of information flow. The global efficiency of a network is defined as the mean of the inverse of shortest path length in the network. The local efficiency of a network is measured as the averaged global efficiency of the subgraph composed of the neighbors of all nodes. Global efficiency and local efficiency measure how efficiently information is exchanged at the global and local levels, respectively [48, 49]. Using these efficiency measurements, networks with high global and local efficiencies are also considered to be small-world [48–50].

Nodal Centrality Several graphic metrics can be used to measure nodal centrality such as degree, efficiency, and eigenvector. These measures can quantify the roles of a node within a network from different perspectives (Fig. 2). The degree of a node is the number (in a binary graph) or the total connectivity strength (in a weighted graph) of all edges that link to the node, reflecting the most directly quantifiable measure of centrality. The nodal efficiency is calculated as the averaged reciprocal shortest path length between the node and the other nodes, representing the ability of information transfer from itself to other nodes in the entire network [50]. The eigenvector centrality is defined as the first eigenvector of the adjacent matrix corresponding to the largest eigenvalue [51], and with its recursive property, it is able to capture the global prominence of a node [52]. In the brain networks, regions with high nodal centrality are usually referred as hubs.

Human Connectomics Based on Graph Theory

Using the abovementioned graph theory metrics, recent studies have consistently demonstrated that both human brain functional and structural networks exhibit many nontrivial topological properties such as small-worldness structure, high efficiency of information transfer, and highly connected hub regions located predominantly in the medial prefrontal and

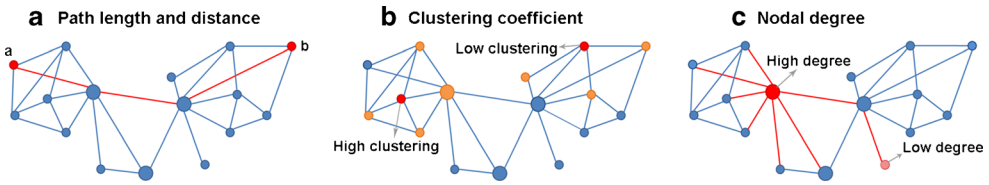

Fig. 2 Illustrations of basic network metrics. As an example, we showed a binary network with 16 nodes and 29 edges. **a** The length of the shortest path between two nodes corresponds to the distance between them. Here, the two nodes, **a** and **b**, connect to each other by three steps indicated by the *red lines*. **b** The clustering coefficient of a node represents the extent of local interconnectivity among its neighbors. The node labeled with "high clustering" (*red*) has in total of four neighbors (*yellow*) that are linked by four existing edges of six possible edges. Thus, the clustering coefficient of the labeled node is 4/6 (i.e., 0.67). Another node labeled with "low clustering" (*red*) has a clustering coefficient value of 0 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 node labeled with "high degree" (*red*) has a degree of seven and the node labeled with "low degree" (*pink*) has a degree of 1

parietal cortices and lateral temporal and parietal cortices [36, 38, 40, 50, 53–55]. Moreover, these important network characteristics are highly heritable [56–58] and exhibit remarkable changes in the course of normal development [59–62] and aging [50, 63, 64]. Recently, aberrant network topological configurations have been found to be associated with various neuropsychiatric disorders such as Alzheimer's disease [65–67], schizophrenia [68–70], and ADHD [25–35].

Brain Connectomics in ADHD

In this review, we provide an overview of graph-based brain network studies in ADHD. The databases of PubMed/MEDLINE were searched, with the latest search conducted in January 2014. To the end, there are 11 published brain network studies in ADHD employing the noninvasive neurophysiological and neuroimaging data (e.g., EEG, R-fMRI, and dMRI) and graph-based network analysis methods (Table 1). Notably, all of the studies were conducted on child populations except for one, which studied adults with ADHD. In this section, we summarize the findings of both functional and structural brain networks in ADHD and further discuss how they enrich our understanding of the pathophysiology of ADHD.

Functional Connectomics in ADHD

Using EEG and R-fMRI, several studies have demonstrated abnormal topological properties in the functional brain networks in ADHD.

EEG Networks EEG measures the electric field changes caused by the neuronal activities with a high temporal resolution (milliseconds). Functional connectomic analysis based on EEG data in healthy people has revealed a small-world structure [71, 72]. In ADHD, Ahmadlou and colleagues [25] firstly used EEG to built brain networks in 12 children with ADHD and 12 typically developing controls. Whole-brain, left, and right hemispheric network analyses were separately performed at both frequency full-band (0–60 HZ) and multiple subbands (delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (30–60 Hz)). They found that compared with the healthy children, ADHD children had significantly higher clustering coefficient and lower characteristic path length in their left brain networks only at delta band, suggesting higher local and global information processing in the left hemisphere. They did not detect any significant group differences in topological properties of either whole-brain or right hemispheric networks. In their later study [26], however, they observed that the whole-brain network properties were significantly different between the ADHD patients showing positive (n=15) and negative (n=15) responses toward neurofeedback training. Specifically, the characteristic path length of the whole-brain networks at beta band was significantly greater in ADHD children with positive response as compared to those resistant to training. Interestingly, the characteristic path length of the brain networks in ADHD children with positive response significantly decreased after cognitive therapy, while those with negative response showed no significant changes. These findings indicate that the neurofeedback therapies could elevate the global information integration capacity of whole-brain functional networks in specific ADHD children.

Functional MRI Networks In contrast to EEG, which measures electrophysiology signal, fMRI detects neuronal activities utilizing changes in cerebral blood flow and oxygen consumption with relatively poorer temporal resolution (~2 s) but higher spatial resolution (~2 mm). R-fMRI reflects the spontaneous or intrinsic brain activity as low-frequency fluctuations in blood oxygen level-dependent (BOLD) signals [73]. Recently, R-fMRI has been widely used to study the human brain functional networks in healthy populations [53, 74].

In ADHD research, Wang et al. [33] were the first to use R-fMRI to investigate functional connectivity patterns of whole-brain functional network in 19 boys with ADHD and 19 healthy controls. The networks consisted of 90 nodes as regions of interest (ROIs), deriving from the automated anatomical labeling (AAL) template. The authors reported that the functional brain networks of both groups exhibited an economical small-world topology. However, children with ADHD showed abnormal small-world architecture characterized by higher local efficiencies (associated with local or segregated processing) combined with a tendency of lower global efficiencies (associated with distributed or integrated processing), suggesting a shift toward the configuration of regular networks (Fig. 3). Previous studies have suggested that the maturation of the healthy human brain follows a "local to distributed" principle [59, 60, 75]. Thus, Wang et al.'s results point to a developmental delay of whole-brain functional networks in ADHD children. Also observed in this study was significantly decreased nodal efficiency in the orbitofrontal cortex, which is classically implicated in the executive function, and in several temporal and occipital regions. Increased nodal efficiency was found in the inferior frontal gyrus, a region critical for response inhibition. These nodal efficiency alterations suggest that the roles of these nodes in the brain functional networks are profoundly affected by the disorder. Delayed maturation in ADHD has further been reported in a specific functional subnetwork-default-mode network (DMN) [31]. The DMN is primarily composed of the medial prefrontal and parietal cortices as well as the

Table 1 Neurophysiological and neuroimaging studies on brain connectomics in patients with ADHD

Studies	Subjects		Modality	Node definition	Edge definition	Network type
	ADHD	Controls				
Ahmadlou et al. [25]	*N*=12 (M/F 9/3) 8–13 years	*N*=12 (M/F 9/3) 8–13 years	EEG	19-channel (*N*=19)	Synchronization likelihood	W
Ahmadlou et al. [25]	ADHD positive *N*=15 (M/F 11/4) 8–13 years ADHD negative *N*=15 (M/F 12/3) 8–13 years	—	EEG	19-channel (*N*=19)	Synchronization likelihood	W
Wang et al. [33]	*N*=19 boys 13.59±1.52 years	*N*=20 boys 13.32±0.97 years	fMRI	AAL atlas (*N*=90)	Pearson' s correlation	B
Fair et al. [31]	*N*=23 (M/F 12/11) 10.04±2.58 years	*N*=23 (M/F 16/7) 10.57±2.86 years	fMRI	DMN regions (*N*=12)	Pearson's correlation	W
Fair et al. [30][a]	ADHD I *N*=80 (M/F 58/22) 11.45 years ADHD C *N*=112 (M/F 91/21) 10.31 years	*N*=455 (M/F 229/226) 14.39 years	fMRI	Dosenbach-160 (*N*=160)	Pearson's correlation	W
Tomasi and Volkow [32][a]	*N*=255 (M/F 204/51) 10.68 years	*N*=316 (M/F 168/148) 10.76 years	fMRI	Voxel-wise	Pearson's correlation	W
Di Martino et al. [29]	ADHD *N*=45 (M/F 37/8) 9.9±1.8 years ASD *N*=56 (M/F 49/7) 10.1±1.8 years	*N*=50 (M/F 37/13) 10.7±1.8 years	fMRI	Voxel-wise	Pearson's correlation	B
Colby et al. [35][a]	*N*=285 (M/F 215/58)	*N*=491(M/F 181/160)	fMRI	(1) Voxel-wise; (2) Harvard-Oxford atlas (*N*=110); (3) CC400 atlas (*N*=400); (4) Stanford FIND atlas (*N*=90)	Pearson's correlation	W
Cocchi et al. [28]	*N*=16 (M/F 9/7) Male 23.0±1.8 years Female 23.8±1.0 years	*N*=15 (M/F 7/8) Male 22.4±0.9 years Female 23.3±1.0 years	fMRI	AAL atlas (*N*=90)	Pearson's correlation	B
Cao et al. [27]	*N*=30 boys 10.3±1.9 years	*N*=30 boys 10.3±1.6 years	DTI	(1) AAL atlas (*N*=90); (2) H-1024 template (*N*=1,024)	Probabilistic tractography	W
Hong et al. [34]	ADHD I *N*=26 (M/F 20/6) 9.78±2.81 years ADHD C *N*=39 (M/F 33/6) 9.30±2.47 years	*N*=26 (M/F 13/13) 10.04±2.47 years	DTI	AAL atlas (*N*=116)	Deterministic tractography	W

ADHD I inattentive ADHD subtype; *ADHD C* combined ADHD subtype, *ASD* autism spectrum disorders, *ADHD positive* ADHD children with positive response to neurofeedback therapy, *ADHD negative* ADHD children resistant to neurofeedback therapy

[a] Data from the ADHD-200 database

lateral temporal and parietal cortices. It is generally thought to support internally oriented processing [76] and exhibits functional abnormalities in ADHD [5]. Using R-fMRI, Fair et al. [31] specifically examined functional connectivity networks of the 12 predefined DMN ROIs in 23 children with ADHD and 23 controls. They conducted interregional functional connectivity analysis within DMN and observed decreased anterior-posterior connectivity in children with ADHD

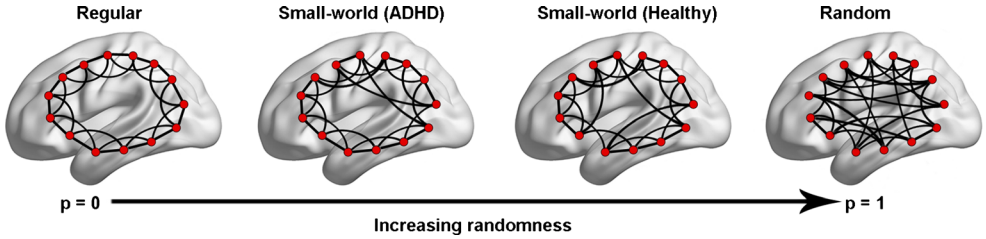

Fig. 3 Small-world models for ADHD and healthy brain networks. The regular network has a high local clustering (high local efficiency) and a long characteristic shortest path length (low global efficiency) [47]. The random network has a low local clustering (low local efficiency) and a small characteristic shortest path length (high global efficiency) [47]. The clustering coefficients and characteristic path length of small-world networks are located at the middle between the regular and random networks [47]. As reviewed here, Wang et al. [33] and Cao et al. [27] found that, although both patients with ADHD and healthy children exhibited small-world structure in their functional and structural networks, the patients were associated with higher local efficiency and lower global efficiency as compared to healthy controls. This suggests a shift of topology toward regular configurations in ADHD networks. Notably, Ahmadlou et al. [25] did not observe the pattern in EEG-based ADHD brain networks, which could be due to the heterogeneity of their samples in response to cognitive training [26]

relative to healthy controls. This pattern greatly overlaps with that showing developmental dynamics in healthy populations. Combining the findings of these two studies [31, 33], we speculate that ADHD children are associated with a developmental delay in functional connectivity patterns of both whole-brain and subnetworks. Very recently, Fair and colleagues [30] analyzed the R-fMRI data from the ADHD-200 database [77] and reported different changing connectivity patterns in the whole-brain network between ADHD subtypes. According to DSM-5, ADHD children are clinically heterogeneous and can be divided into three subtypes: hyperactive/impulsive (relatively infrequent), inattentive, and combined. Fair et al. [30] constructed the functional brain networks with 160 nodes from predefined functional ROIs [78] in 80 children with inattentive ADHD subtype, 112 children with combined ADHD subtype, and 455 healthy controls, and investigated regional nodal connectivity using the degree metric. While the two groups of ADHD patients showed similar abnormalities in the sensorimotor system, some unique patterns were also observed: the inattention ADHD group exhibited atypical patterns in the dorsal lateral prefrontal cortex and cerebellum and the combined ADHD group in the midline components of DMN. After controlling for the influences of micro-movements using multiple motion-correction strategies [79–82], these findings were largely preserved.

Besides these region-wise network analyses, there were two R-fMRI studies performing voxel-wise network analysis to examine regional alterations in ADHD children from a centrality perspective. In the first study, Tomasi and Volkow [32] calculated the Pearson's correlations between any pairs of the brain voxels in 255 ADHD children and 316 healthy children from the ADHD-200 database [77]. After considering the physical distance information, they divided all correlations into long-range and short-range ones and then calculated the corresponding functional connectivity density (i.e., weighted degree). They found that the children with ADHD had lower connectivity (both short- and long-range) in regions of the dorsal attention (superior parietal cortex), default-mode (precuneus) networks and cerebellum, and higher short-range connectivity in reward-motivation regions (ventral striatum and orbitofrontal cortex) (Fig. 4). Furthermore, the magnitude of such changes significantly correlated with scores of inattention and hyperactivity/impulsivity in patients with ADHD. Further seed-based analysis revealed that the orbitofrontal cortex had stronger connectivity with striatum and anterior cingulate and lower connectivity with superior parietal cortex in ADHD children. Also using a voxel-wise centrality analysis approach, Di Martino et al. [29] reported common and distinct modes of functional brain network in 56 patients with autism spectrum disorders and 45 patients with ADHD. They observed abnormal degree centrality in the precuneus in both patient groups. Changes in some other regions were disorder specific, including higher-degree centrality in the right striatum/pallidum in ADHD and higher-degree centrality in the bilateral temporolimbic areas in autism. Further analysis revealed that like ADHD patients, autism children with ADHD-like comorbidity showed degree connectivity abnormalities in the basal ganglia. By contrast, autism children without ADHD-like comorbidity had higher degree centrality in the temporolimbic areas than ADHD children. Notably, they also used the eigenvector centrality metric but did not find any significant group differences. These voxel-wise analyses further extended the findings of region-wise brain network studies. Very interestingly, Colby and colleagues [35] proposed a machine learning approach, which combined regional- and voxel-based structural and functional features as well as demographic information, to predict diagnostic status of individuals with ADHD from typically developing children in the ADHD-200 database [77]. Structural features included nine quantitative metrics (e.g., surface area, gray matter volume, cortical thickness, and cortical curvature) from 113 cortical and noncortical ROIs. Functional features included Pearson's correlation functional connectivity matrices, nodal and global graph theoretical measures, nodal power spectra, voxel-wise global degree

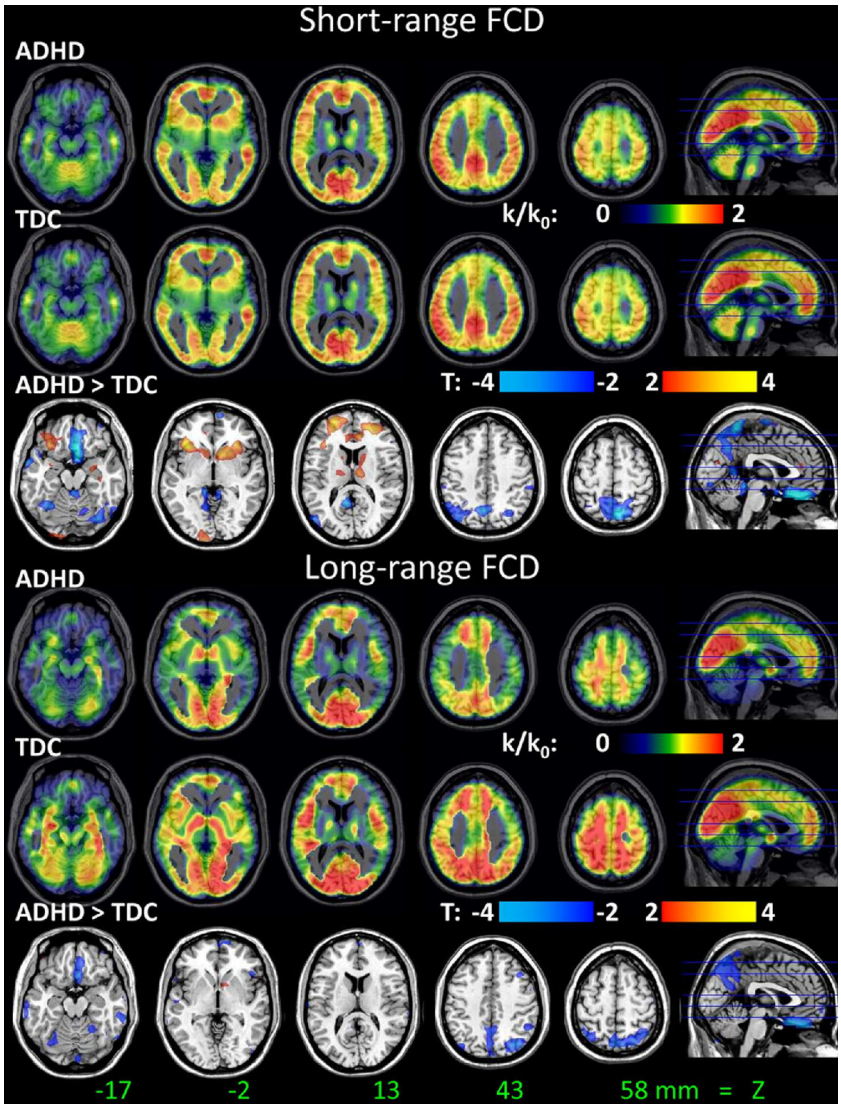

Fig. 4 Distribution of short-range (*top panel*) and long-range (*bottom panel*) functional connectivity density for ADHD children and typically developing children (*TDC*) and the statistical differences between the groups. A threshold of functional connectivity density (>0.6) was used to compute short- and long-range functional connectivity density (*FCD*) maps. One-way analysis of variance with three covariates (age, gender, and mean motion) was used to contrast short- and long-range FCD maps between groups. The figure was adapted from [32]

connectivity, and voxel-wise regional homogeneity. With this methodology, they were able to predict individuals with ADHD from healthy children with 55 % accuracy (versus a 39 % chance level in this sample), 33 % sensitivity, and 80 % specificity.

So far, only one R-fMRI study explored the ADHD-related alterations in whole-brain functional network in adults. Cocchi et al. [28] investigated topological organization of the whole-brain functional networks with 90 ROIs from the AAL template in 16 adults with ADHD and 15 comparable controls. Different from the findings with ADHD children, they did not observe any significant alterations in global network properties. However, disturbed nodal properties were detected in ADHD adults: the nodal characteristic path length was significantly lower in the right medial frontal and right superior occipital cortices; nodal clustering coefficient was significantly higher in the left orbitofrontal and right superior temporal cortices and lower in the left superior occipital cortex. Using the network-based-statistic (NBS) approach [83], they found abnormal interregional connectivity involving a frontal amygdale-occipital subnetwork and a frontal temporal-occipital subnetwork, which significantly correlated with symptoms of inattention and hyperactivity/impulsivity in patients with ADHD.

Taken together, both EEG and R-fMRI network analyses suggested disrupted functional topology in ADHD. From a global perspective, children with ADHD showed a shift of topology toward regular configurations in the functional brain networks [33] (Fig. 3), while the adults patients showed little differences compared with healthy controls [28]. Redistribution of regional nodes and connectivity was commonly detected in both children and adults, involving the sensorimotor, attention, default-mode, striatum, and cerebellum systems [25, 26, 28–33]. These network disruptions significantly correlated with behavior disturbances (e.g., inattention and hyperactivity/impulsivity symptoms) in ADHD

patients [28, 32] and exhibit differential patterns between clinical subtypes [30]. These less-optimized topological configurations of functional brain networks might imply the neuronal basis of cognitive deficits in ADHD.

Structural connectomics in ADHD

Recent advances in dMRI and tractography methods have greatly facilitated the noninvasive mapping of structural networks in the human brain. Specifically, white matter pathways can be mapped through inferring the spatial orientations and trajectories of bundles of myelinated axons traversing the brain, on the basis of measurements of diffusion anisotropy of water or other small molecules within biological tissue [84, 85]. To date, there are only two studies employing dMRI data to explore the white matter network abnormalities in ADHD [27, 34]. In the first study, Cao and colleagues [27] reported abnormal structural connectivity in the white matter networks in 30 drug-naïve boys with ADHD as compared to 30 age- and gender-matched healthy controls. By employing the probabilistic tractography method [85], they constructed the weighted structural networks with 90 nodes from the AAL template. Although efficient small-world organization was observed in both groups, boys with ADHD exhibited lower global efficiency and higher local efficiency than healthy boys. It should be noted that this pattern of topological changes (Fig. 3) has been reported in the brain functional network analysis [33], indicating the existence of structural basis underlying the functional abnormalities in this disorder. Furthermore, using NBS analysis, they detected significantly decreased structural connectivity in the prefrontal-dominant circuitry and increased connectivity in the orbitofrontal-striatal circuitry, which significantly correlated with inattention and hyperactivity/impulsivity symptoms, respectively (Fig. 5). Additionally, they showed ADHD-related decreases in nodal efficiency in several frontal, parietal, and occipital regions. In the second study, Hong and colleagues [34] examined the white matter structural networks comprising 112 nodes from the AAL template (including all cortex and cerebellum regions) in 26 children with the inattentive ADHD subtype, 39 children with the combined ADHD subtype, and 26 healthy controls. Using NBS, they observed abnormal structural connectivity between frontal and striatal regions in ADHD, which was compatible with the finding of Cao et al [27]. They further observed abnormal connectivity component in the cerebellar regions. The fractional anisotropy values in some of these fiber bundles significantly correlated with attentional performance in ADHD patients. Notably, the authors also reported the connectivity differences between ADHD subtypes: Compared with the inattentive ADHD group, the combined ADHD group showed a lower connectivity of a right-

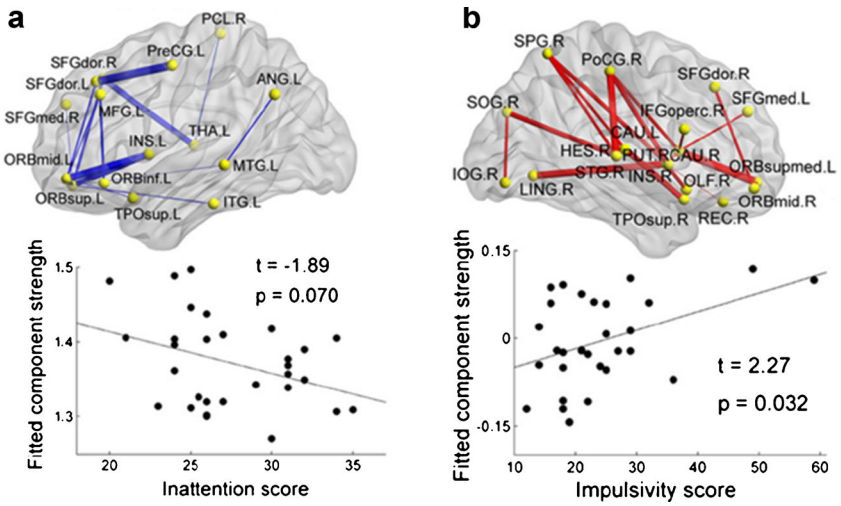

Fig. 5 The decreased or increased white matter connections in ADHD boys compared with healthy controls and their relationships with clinical characteristics in patients. **a** The significantly decreased network-based-statistic (*NBS*) component (*blue curve*) in ADHD patients compared with healthy controls. These connections formed a single connected network, primarily involving prefrontal and insula regions, and the strength of the component negatively correlated with the inattention scores in ADHD patients. **b** The significantly increased (*red curve*) NBS component in ADHD patients compared with healthy controls. These connections formed a single connected network, primarily involving striatum structures and orbitofrontal regions, and the strength of the component positively correlated with the impulsivity scores in ADHD patients. *PreCG* precental gyrus; *SFGdor* superior frontal gyrus, dorsolateral; *ORBsup* superior frontal gyrus, orbital part; *MFG* middle frontal gyrus; *ORBmid* middle frontal gyrus, orbital part; *IFGoperc* inferior frontal gyrus, opercular part; *ORBinf* inferior frontal gyrus, orbital part; *SFGmed* superior frontal gyrus, medial; *ORBsupmed* superior frontal gyrus, medial orbital; *INS* insula; *LING* lingual gyrus; *SOG* superior occipital gyrus; *IOG* inferior occipital gyrus; *PoCG* postcentral gyrus; *SPG* superior parietal gyrus; *PCL* paracentral lobule; *CAU* caudate nucleus; *PUT* lenticular nucleus, putamen; *THA* thalamus; *HES* Heschl gyrus; *STG* superior temporal gyrus; *TPOsup* temporal pole: superior temporal gyrus; *MTG* middle temporal gyrus; *ITG* inferior temporal gyrus. The figure was adapted from [27]

lateralized network predominantly linking frontal, cingulate, and supplementary motor areas.

In summary, the two dMRI studies highlighted disruptions of the white matter structural connectivity networks in children with ADHD. At the global level, Cao et al., [27] showed a less-optimized and regular-toward small-world structure in the structural networks in ADHD patients, being consistent with the functional brain network analysis [33] (Fig. 3). At the nodal level, aberrant regional changes were found mainly in frontal, striatal, and cerebellar regions [27, 34]. Disrupted structural connections mainly involved the orbitofrontal-striatal, prefrontal-dominant, and cerebellum-relevant circuitries [27, 34]. Moreover, these network abnormalities were associated with cognitive declines in patients with ADHD and were different between ADHD subtypes [27, 34]. Collectively, these results suggest a pathologically wiring in white matter networks in ADHD, thus providing crucial structural substrates underlying the functional and behavior deficits in ADHD.

Conclusions and Future Perspectives

In this review, we summarized recent findings of brain connectomics in ADHD using EEG, R-fMRI, and dMRI data. Convergent evidence from these multi-modal neuroimaging studies demonstrated that both functional and structural brain networks in ADHD were topologically disrupted at both global and local levels. Moreover, these disruptions are likely to explain behavior symptoms in ADHD patients. These findings provided empirical evidence for network dysfunction of ADHD and thus greatly added our understanding of the pathophysiological mechanisms of this disorder. However, it should be realized that the studies of brain networks in ADHD are at their infant stages. There are still many important questions, which are outlined below and are needed to be elucidated in the future.

First, how do the structural and functional brain connectomes of ADHD change gradually as the disease progresses? Previous longitudinal work of Shaw et al. [10] found that the development of gray matter thickness especially in the prefrontal cortex was significantly slower in ADHD patients compared with healthy children. However, no work has directly explored the differences of developmental trajectories in network architecture between ADHD children and typical development children. Further studies combing continuous longitudinal data of ADHD are crucial to address these questions.

Second, what are the differences and similarities in terms of network topology across different subtypes of ADHD? Patients with ADHD can be clinically divided into three subtypes according to their symptoms. The works reviewed here [30, 34] suggest distinct functional and structural connectivity patterns for combined and inattentive subtypes. Moreover, there could be mechanistic heterogeneity that potentially underlies the existing classification scheme [86]. Using neurocognitive profiles, both ADHD children and typical developmental children can be successfully identified into distinct categories. Thus, further works combining extensive cognitive profiling and connectomic analysis are of great interest to uncover the neuronal circuitries underlying specific cognitive deficits in ADHD subtypes.

Third, what is the physiological basis of disrupted network topology in ADHD? The connectome-based studies reviewed here suggest that the aberrant regional changes in ADHD were primarily distributed in the sensorimotor, attention, default-mode, striatum, and cerebellum regions. Previous positron emission tomography studies have showed that the dopamine synaptic markers including dopamine transporters and D(2)/D(3) receptors in the striatum and the midbrain were significantly reduced in patients with ADHD [87, 88]. Furthermore, poor attentional performers exhibited reduced dopamine activity in the left caudate in either ADHD patients or healthy controls [89]. Evidence from MR spectroscopy studies revealed ADHD-related glutamatergic alterations happened in the prefrontal cortex, striatum, and frontal lobes (for a review, see [90]). Rodent models in ADHD also showed low dopamine D5 receptor density in the hippocampus [91] and bioenergetic metabolites changes in the striatum [90, 92]. Recently, the regional centrality measures of the brain networks (e.g., regional nodal degree and betweenness centrality) exhibited significant correlations with the brain's metabolism demands such as aerobic glycolysis [23], regional cerebral blood flow [93], and regional cerebral metabolic rate of glucose [94]. All of these studies indicate a physiological basis underlying the network dysfunctions shown in ADHD, but further studies are needed to clarify the issues.

Fourth, what are the effects of clinical treatment (e.g., cognitive training, pharmacological interventions, and brain stimulus techniques) on the brain networks for ADHD? The EEG work of Ahmadlou and colleagues [26] revealed significant effects of neurofeedback therapy on the brain functional networks. Previous R-fMRI study reported significant effects of dopamine antagonism on brain functional networks in healthy people [50]. Recently, An et al. [95] used R-fMRI to demonstrate that an acute dose of methylphenidate hydrochloride, the first-line treatment of ADHD for more than 50 years, can significantly normalize fronto-parieto-cerebellar dysfunctions in the boys with ADHD. Several positron emission tomography studies in ADHD subjects also detected significant methylphenidate-elicited dopamine increases in regions including the ventral striatum, midbrain, and prefrontal and temporal cortices, which contribute to the improvement of attention performances [89, 96]. However, studies about drug therapy effects on ADHD brain networks are still in lack. Nonetheless, these previous works suggest that the

pathological neuronal circuitries in ADHD could be selectively modulated by treatment. Further studies employing various clinical treatment approaches in combination with multimodal neuroimaging and connectome-based analysis are important to evaluate biological mechanisms underlying ADHD therapeutic effects from a network perspective.

Fifth, what is the relationship between brain network patterns and environmental or genetic factors in ADHD? Both environmental and genetic factors play important roles in ADHD [5]. For example, environmental factors like the low birth weight [97] and perinatal exposure to teratogens [98] have been shown to correlate with ADHD. Genes for neurotrophic factors and nerve growth factors have also been shown to be involved in ADHD development [99–101]. Moreover, previous studies have reported genetic effects on the organization of human functional networks in both children [58] and adults [56]. Further brain network studies considering environmental and genetic information in ADHD are of great interest and will advance our knowledge about the pathological mechanisms of this disorder.

Finally, some methodological issues involving the brain conectome analysis should be addressed. It is well acknowledged that it is currently challenging to map the human brain networks appropriately and precisely [102]. Given the lack of gold standard for regional parcellation in the brain, the definition of network nodes is relatively arbitrary at present. The nodes are usually defined using templates employing random, anatomical, or functional parcellation criteria. Recent works suggest that different node choices have remarkable influences on the properties of resulting networks [69, 103]. In parallel with the definition of nodes, the procedure to determine the edges in brain networks is another important issue. Multiple choices are currently available for estimating interregional functional connectivity such as partial correlation, Pearson's correlation, and mutual information and structural connectivity such as determined or probabilistic tractography. These connectivity metrics and relevant imaging pre-processing procedures often affect resulting network topological properties and exhibit different test-retest reliability patterns across scanning time [104–106]. Therefore, caution should be taken in choosing the analytical schemes in brain network studies. Besides, multi-modal imaging analysis represents one potential avenue for future research on ADHD connectomics. So far, most of brain connectome studies in ADHD have utilized the data of EEG, R-fMRI, and dMRI for network construction. Other imaging techniques such as structural MRI [36] and functional near-infrared spectroscopy [44] can also be used to reconstruct the brain's structural and functional networks with complimentary connectivity information. Therefore, the multi-modal brain network analysis would give a fuller view of the structural and functional connectomes in ADHD, which are still lacking at present.

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