



Reduced hemispheric asymmetry of brain anatomical networks in attention deficit hyperactivity disorder

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Abstract

Despite many studies reporting a variety of alterations in brain networks in patients with attention deficit hyperactivity disorder (ADHD), alterations in hemispheric anatomical networks are still unclear. In this study, we investigated topology alterations in hemispheric white matter in patients with ADHD and the relationship between these alterations and clinical features of the illness. Weighted hemispheric brain anatomical networks were first constructed for each of 40 right-handed patients with ADHD and 53 matched normal controls. Then, graph theoretical approaches were utilized to compute hemispheric topological properties. The small-world property was preserved in the hemispheric network. Furthermore, a significant group-by-hemisphere interaction was revealed in global efficiency, local efficiency and characteristic path length, attributed to the significantly reduced hemispheric asymmetry of global and local integration in patients with ADHD compared with normal controls. Specifically, reduced asymmetric regional efficiency was found in three regions. Finally, we found that the abnormal asymmetry of hemispheric brain anatomical network topology and regional efficiency were both associated with clinical features (the Adult ADHD Self-Report Scale and Wechsler Adult Intelligence Scale) in patients. Our findings provide new insights into the lateralized nature of hemispheric dysconnectivity and highlight the potential for using brain network measures of hemispheric asymmetry as neural biomarkers for ADHD and its clinical features.

Keywords Attention deficit hyperactivity disorder · Hemispheric asymmetry · Diffusion tensor imaging · Structural connectivity · Graph theoretical approaches

Introduction

Hemispheric structural asymmetry of the brain has been well investigated in healthy controls (Arthur and Paul 2003; Good et al. 2001; Watkins et al. 2001), and shows a clear relationship with hemispheric functions such as language, motor, cognitive and visual-spatial processing (Arthur and Paul 2003; Pujol et al. 2002; Wu et al. 2012; Yan et al. 2011). Moreover, research on structural asymmetry shows the well-

known rightward predilection in frontal and leftward predilection in occipital lobes (Hamilton et al. 2007; Lancaster et al. 2003; Watkins et al. 2001). Traditional research on brain structural asymmetries has focused on gray matter (GM) asymmetries. Moreover, asymmetries of brain volume have been demonstrated in focal regions that show varying degrees of correspondence to nervous system functions, including auditory perception (Sigalovsky et al. 2006), language processing (Galaburda et al. 1978), learning (Sailer et al. 2003) and attention (Casey et al. 1997). For instance, volume asymmetries have been observed in the caudate (CAU), which is considered to be related with motor activity and to play a key role in attention deficit hyperactivity disorder (ADHD) (Hynd et al. 1993). Recent studies have shown that structural asymmetry was not only observed in GM but also in white matter (WM) fibers that connect cortical brain regions (Cao et al. 2003; Takao et al. 2011). For example, diffusion tensor imaging (DTI) has been used to investigate healthy subjects and has shown a variety of WM asymmetries in the arcuate fasciculus and the anterior cingulum (Buchel et al. 2004;

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Parker et al. 2005; Song et al. 2014; Thiebaut et al. 2011). Convergent studies have shown that DTI is a promising non-invasive technique for investigating WM organization and the underlying connectivity of the brain region (Barrick et al. 2007; Lawes et al. 2008; Mori et al. 2002). It can reconstruct the major WM tracts faithfully to the known WM anatomy, allowing the mapping of the brain's structural connectivity in vivo (Conturo et al. 1999), which provides a new anatomical insight into lateralized brain functions.

Studies have shown that atypical lateralization of brain structure is associated with gender (Kulynych et al. 1994; Shaywitz et al. 1995; Thiebaut et al. 2011; Tian et al. 2011), aging (Cabeza 2002), handedness (Amunts et al. 2000; Barrick et al. 2005; Castellanos et al. 1996) and several neuropsychiatric disorders, such as Schizophrenia (Kubicki et al. 2002; Kubicki et al. 2003; Park et al. 2004), Alzheimer's disease (Derflinger et al. 2011; Thompson et al. 1998), Autism (Chandana et al. 2005; Joseph et al. 2014) and ADHD (Filipek et al. 1997). Among these neuropsychiatric disorders, alterations of atypical lateralization might play a role in the pathogenesis of childhood neurodevelopmental disorders, specifically ADHD (Team 2000). ADHD is the most common childhood neuropsychiatric disorder, and it can continue through adolescence and adulthood (Konrad and Eickhoff 2010). It is characterized by developmentally inappropriate symptoms of excessive inattention and impulsivity as well as hyperactivity with the attentional deficit (Barkley 2003). Neuroimaging investigations have shown that the ADHD is related to atypical lateralization, with reports that the pathophysiology of ADHD exhibits abnormalities in brain functions that are mainly linked with cognitive control, attention and motor functions (Langleben et al. 2001; Rubia et al. 2005; Team 2000). Furthermore, the pathophysiology of ADHD has also been documented to be associated with cortical asymmetry (Castellanos et al. 1996; Shaw et al. 2009; Sowell et al. 2003). The search for causes of disrupted lateralization in ADHD is ongoing and inconclusive. One theory proposed by Barkley et al. (Barkley 1994) suggests that the core deficit in ADHD is a failure to inhibit or delay motor responses. As an important structure of the striatum, the putamen has anatomical connection with cortical motor areas and is involved in high-level cognitive functions such as working memory (Chang et al. 2007) and language processing (Booth et al. 2007). It has been suggested that structural and functional abnormalities in the putamen are key to understanding ADHD due to the interconnected nature of the putamen neural networks that subservise language and memory (Cao et al. 2009). Recently, research on ADHD has shifted from examining GM lateralization to examining WM lateralization with the prevalence of the non-invasive DTI technique (Ashtari et al. 2005; Casey et al. 2007; Makris et al. 2008). In one recent study using the tractography applying constrained spherical deconvolution to investigate a total of 43 patients

with ADHD, Silk et al. (2016) found a significant lateralization to the left for fractional anisotropy (FA, a DTI measurement) in the putamen tracts. To date, few magnetic resonance imaging (MRI) studies have focused on aberrant WM lateralization in patients with ADHD and have not been as informative or conclusive as studies of GM abnormalities. Moreover, most previous studies have mainly investigated specific inter-regional asymmetries in a pairwise manner, specifically identifying which connections were more coherent or stronger in one hemisphere relative to the other, whereas the effects of these laterality changes on wider neural network asymmetry have yet to be determined.

A recent conceptualization suggests that the human brain forms a large-scale network of interconnected regions within the human connectome that provides the anatomical substrate for neural communication, functional processing, and information integration in the brain (Sporns 2011; Yan et al. 2015). Graph theoretical approaches provide a powerful tool to characterize the topological organization of complex networks and have been widely applied to the study of human brain networks in healthy controls and subjects with diseases (Bullmore and Sporns 2009; Griffa et al. 2013; He and Evans 2010; Lo et al. 2010; Rudie et al. 2012). Using graph theoretical approaches, studies have shown that the structural networks determined by a variety of neuroimaging modalities (e.g., structural MRI and diffusion MRI) in patients with ADHD existed topological properties such as the small-world property (Beare et al. 2017; Sidlauskaite et al. 2015). Moreover, correlations between intelligence quotient (IQ) and network properties have also been demonstrated (Wang et al. 2009). ADHD is becoming seen as a disorder of brain dysconnectivity or brain network organization because of the heterogeneous clinical presentation of ADHD (e.g., verbal and performance impairments and impulsivity/hyperactivity scores), which may arise from variability in abnormalities of the volumes of the whole brain and specific regions (Castellanos et al. 1996; Giedd et al. 1994; Hynd et al. 1993). Researchers have also found that specific regional efficiency was associated with higher ADHD symptom scores (Sidlauskaite et al. 2015).

It is noteworthy that the reported aberrations in the structural networks of patients with ADHD are revealed exclusively at a "whole-brain" level. Recently, a few studies have investigated alterations in network topological organization at the hemispheric level in either healthy adults or subjects with mental diseases (Ahmadlou et al. 2012; Iturria-Medina et al. 2011; Ratnarajah et al. 2013; Sun et al. 2017; Tian et al. 2011). For instance, Tian et al. (2011) utilized resting-state functional MRI (R-fMRI) to investigate hemisphere- and gender-related differences in the functional networks of healthy controls. They found that the hemispheric networks exhibited the small-world property and there were hemisphere-related differences in regional nodal characteristics. Using DTI

tractography (a technique to reconstruct WM fiber pathways) and a graph theory framework, Sun et al. (2017) investigated the hemispheric asymmetries of structural brain networks in patients with schizophrenia. They found the small-world property was preserved in the hemispheric networks and a significant group-by-hemisphere interaction was revealed in both the characteristic path length and global efficiency, contributing to a significantly reduced hemispheric asymmetry in global integration in patients compared with healthy controls. Electroencephalograph (EEG) recordings are known to be divided into 5 sub-bands: delta, theta, alpha, beta, and gamma (Yan et al. 2018, 2017). To study the effect of the 5 sub-bands in patients with ADHD, Ahmadlou et al. (2012) adopted graph theoretical approaches to investigate organization of the overall and hemispheric brain networks of patients with ADHD. They found that the clustering coefficient and characteristic path length in the left-hemisphere brain network in the delta EEG sub-band of patients with ADHD were significantly different from those of the non-ADHD patients.

To date, few studies have examined hemispheric differences in the topological organization of structural brain networks in patients with ADHD. Given that converging evidence shows aberrant hemispheric asymmetries in various brain regions and WM tracts (Castellanos et al. 1996; McAlonan et al. 2007; Overmeyer et al. 2001) and as well as altered structural connectivity in patients with ADHD (Beare et al. 2017; Konrad et al. 2010; Qiu et al. 2011), it may be helpful for us to understand the underlying nature of the altered laterality and the pathophysiology of the disorder when determining the hemispheric asymmetries of anatomical networks in patients with ADHD. In the current study, we investigated the hemispheric asymmetries of brain anatomical networks in patients with ADHD by adopting the DTI deterministic tractography method and standard graph theoretical

approaches. In particular, we focused on the graph measures of the small-world property, global and local network efficiency, and relative nodal centrality to examine (1) the aberrant hemispheric asymmetry of the brain connectome in patients with ADHD and (2) whether the abnormal hemispheric asymmetries of the network organization were associated with clinical variables.

Materials and methods

Subjects

This neuroimaging dataset was shared from the UCLA Consortium for Neuropsychiatric Phenomics LA5c Study and approved by the UCLA Institutional Review Board. The data were obtained via the public database openfMRI (Poldrack et al. 2013; Poldrack and Gorgolewski 2017). In this study, 40 patients with ADHD (male/female = 21/19, age = 32.10 ± 10.40 years) and 53 age- and gender-matched normal subjects (male/female = 28/25, age = 32.50 ± 9.20 years) were recruited from the LA2k study; more details available in the openfMRI database (ds000030). In Table 1, we present detailed demographic and clinical characteristics of the normal controls and participants with ADHD. The Adult ADHD Self-Report Scale (ASRS) was used to assess the symptom severity of ADHD. The Wechsler Adult Intelligence Scale (WAIS) is an IQ test designed to measure intelligence and cognitive abilities in adults and older adolescents. The Letter-Number Sequencing task in WAIS (WAIS_LNS) is designed to measure the ability of working memory, attention and mental control. The Matrix Reasoning task in WAIS (WAIS_MR) is designed to measure the

Table 1 Demographic and clinical characteristics of the samples

Characteristic	Group (patients/controls = 40/53)		Statistical test	
	Patients with ADHD	Normal controls		
Age (years)	21–50(32.10 ± 10.40)	21–49(32.50 ± 9.20)	$t_{91} = 0.212$	$p = 0.833^a$
Male/Female	19/21	25/28	$\chi^2_1 = 0.527$	$p = 0.468^b$
Education (years)	12–19 (14.70 ± 1.80)	12–19 (15.10 ± 1.70)	$t_{91} = 1.319$	$p = 0.191^a$
ASRS ^c	8–23(15.43 ± 3.85)	4–14(8.98 ± 2.84)	$t_{91} = -9.365$	$p < 0.001^a$
WAIS_LNS ^d	15–24(19.98 ± 2.70)	14–28(20.88 ± 3.07)	$t_{91} = 1.530$	$p = 0.219$
WAIS_MR ^d	10–26(20.50 ± 3.92)	7–24(20.07 ± 4.36)	$t_{91} = -0.422$	$p = 0.674$
WAIS_VOC ^d	23–56(43.20 ± 9.58)	24–54(44.53 ± 7.91)	$t_{91} = 0.735$	$p = 0.464$

Unless otherwise indicated, data are expressed as a range of minimum–maximum (mean \pm SD)

^a The P -value was obtained using a two-sample two-tailed t -test

^b The P -value was obtained using a two-tail Pearson χ^2 test

^c The Adult ADHD Self-Report Scale (ASRS) was used to assess the symptom severity of ADHD

^d The WAIS_LNS, WAIS_MR, WAIS_VOC scores were used to assess the intelligence and cognitive ability in adults and older adolescents

inductive reasoning abilities. The Vocabulary task is designed to measure verbal comprehension and expression ability.

Data acquisition

Structural MRI data were acquired on one of two 3 T Siemens Trio scanners, located at the AhmansonLovelace Brain Mapping Center (Siemens version syngo MRB15) and the Staglin Center for Cognitive Neuroscience (Siemens version syngo MRB17) at UCLA. The 152 MRI volume images were collected using a T2weighted echoplanar imaging (EPI) sequence with the following parameters: slice thickness = 4 mm, 34 slices, TR = 2 s, TE = 30 ms, flip angle = 90°, matrix 64 × 64, FOV = 192 mm, oblique slice orientation. Additionally, one highresolution anatomical scan MPRAGE were collected. The parameters for MPRAGE were the following: TR = 1.9 s, TE = 2.26 ms, FOV = 250 mm, matrix = 256 × 256, sagittal plane, slice thickness = 1 mm, 176 slices. For each participant, the diffusion sequences were scanned 3 times to improve the signal-to-noise ratio (SNR).

Data preprocessing and network construction

Before data preprocessing, the recorded images were visually inspected by experienced radiologists. No subject had head motions with more than 1.0 mm maximum displacement in any direction (x, y, or z) or 1° of any angular motion throughout the scan. Data preprocessing and brain network constructions were performed using the MATLAB toolbox named PANDA (Cui et al. 2013). Specifically, data preprocessing approaches included correcting for simple head movements and eddy current distortions using affine transformation to the b0 image (Jenkinson et al. 2002). After data preprocessing, 6 independent components of the diffusion tensor were estimated from which FA was calculated. Subsequently, whole-brain fiber tractography was obtained by performing deterministic fiber tracking algorithms (Mori et al. 1999). The fiber tracking procedure started from the deep WM regions and terminated if two consecutive moving directions had a crossing angle above 35° or the FA was out of the threshold range (0.1~1).

The method for constructing the structural brain network in this study referred to the procedure used in Gong et al. (2009). The fundamental components in the construction of brain networks are nodes. According to the automated anatomical labeling (AAL) parcellation scheme (Tzouriomazoyer et al. 2002), the respective network nodes were defined as 90 regions (45 in each hemisphere) in this study. A linear transformation was applied locally within each subject's DTI image correlated with the T1-weighted image to coregister the image to the b0 image in DTI space, followed by the application of a nonlinear transformation to map the image to the ICBM152 T1 template [Montreal Neurological Institute (MNI)]. Then, a

subject-specific AAL mask was weaved from the MNI space to the DTI native space with the corresponding inverse transformation, such that separate labeling values were maintained via nearest-neighbor interpolations (Cui et al. 2013; Gong et al. 2009). The network edge was defined as the number of fiber (FN) connecting 2 regions (Bai et al. 2012; Shu et al. 2011), and the fiber connecting 2 regions was considered to exist if two consecutive moving directions had a crossing angle under 35° or the FA fell within the threshold range (0.1~1). To reduce the influence from pseudo-connections caused by possible noise effects on the whole-brain tractography, a predefined threshold was identified; if the FN between the 2 regions was larger than 3, a connection between these 2 regions was considered to exist (Shu et al. 2011). For each subject, two 45 × 45 hemispheric brain networks were obtained by eliminating the inter-hemispheric connections, one network for the left hemisphere and another for the right hemisphere. Further network analysis was based on these 2 sets of 45 × 45 weighted networks for each subject.

Network analysis

Watts and Strogatz (1998) proposed the small-world property, which means that the network has a higher clustering coefficient and equivalent characteristic path length compared with random networks. At the global and regional levels, this work investigated eight network properties to analyze the topological organization of the constructed WM networks. The seven global properties included the global efficiency (E_g), the local efficiency (E_{loc}), the weighted clustering coefficient (C_p), the weighted characteristic path length (L_p), the normalized clustering coefficients (γ), the normalized characteristic path length (λ) and the small-world property (σ). The nodal efficiency, $E_{nodal}(i)$, was used to assess the regional characteristics of the brain (Achard and Bullmore 2007). The definitions and brief interpretations of the network properties are shown in Table 2. Moreover, detailed descriptions of the graph theoretical parameters can be seen in previous work (Boccaletti et al. 2006; Bullmore and Sporns 2009; Rubinov and Sporns 2010). The graph theoretical analysis was performed using the GRETNA software (<http://www.nitrc.org/projects/gretna/>).

Asymmetry score

The asymmetry score (Iturria-Medina et al. 2011; Ratnarajah et al. 2013) of the abovementioned hemispheric network was calculated according to the following formulation: $AS(X) = 100 \times (X(R) - X(L)) / (X(R) + X(L))$, where $X(R)$ and $X(L)$ represent the network property of the right and left hemispheres, respectively. The asymmetry score $AS(X)$ is helpful for us to find the differences between the right and left hemispheres. The range of $AS(X)$ is from +100 to -100. When $AS(X)$ is positive, this indicates that the brain network showed

Table 2 Formulations and descriptions of network topological properties applied in this work

Network properties	Definitions	Measurement and interpretation
Global efficiency (E_g)	$E_g = \frac{1}{N(N-1)} \sum_{i,j \in N, i \neq j} \frac{1}{N(N-1)}$	E_g reflects the efficiency of the whole network information transmission.
Local efficiency (E_{loc})	$E_{loc} = \frac{1}{N} \sum_{i \in N} E_g(i)$	E_{loc} is a measure of the mean local efficiency of the network.
Clustering coefficient (C_p)	$C_p = \frac{1}{N} \sum_{i \in N} \frac{\sum_{j,l} a_{ij} a_{jl} a_{li}}{k_i(k_i-1)}$	C_p measures the extent of the local density of a network G with N nodes ($N = 45$ in this work). Here, k_i is the number of edges connecting to node i and a_{ij} is the edge between region i and j .
Characteristic path length (L_p)	$L_p = \frac{1}{N(N-1)} \sum_{i,j \in N, i \neq j} d_{ij}$	N is the number of nodes in the network G . d_{ij} is the shortest path length between node i and j . L_p is the inverse relation of E_g .
Normalized clustering coefficient (γ)	$\gamma = C_p / C_{random}$	C_{random} represents the clustering coefficient of the random network.
Normalized characteristic path length (λ)	$\lambda = L_p / L_{random}$	L_{random} represents the characteristic path length of the random network.
Small-world property (σ)	$\sigma = \gamma / \lambda$	σ is a measure of the small-world property.
Nodal efficiency (E_{nodal})	$E_{nodal}(i) = \frac{1}{N} \sum_{i,j \in N, i \neq j} \frac{1}{N}$	$E_{nodal}(i)$ measures the information transmission ability of node i in the network G . It is the inverse of the mean of the shortest path length between node i and all other nodes.

prominent rightward asymmetry. When $AS(X)$ is negative, this indicates that the brain network showed prominent leftward asymmetry. (For example, E_g reflects the efficiency of the whole network information transmission. For a network, the higher E_g , the more efficient of the global integration. Therefore, a positive $AS(E_g)$ indicates that the global integration of the right hemispheres was more efficient than that of the left hemispheres. A negative $AS(E_g)$ shows that the global integration of the left hemispheres was more efficient than that of the right hemispheres.)

Statistical analysis

Between-group differences

This work analyzed data by using separate two-tailed t-tests to reveal group differences in age, education and a χ^2 test to find group differences in gender. Considering hemisphere as a within-subject factor, group as a between-subject factor, and group-by-hemisphere as an interaction, this work used a general linear model (GLM) of the obtained network metrics to assess differences in hemispheric effects on network properties between patients with ADHD and normal controls. Studies have shown that hemispheric asymmetry is related to age (Cabeza 2002; Dolcos et al. 2002) and gender (Good et al. 2001; McGlone, and Jeannette 1980). Hence, we set age, gender, and the age-by-gender interaction as covariates in the GLM. If any difference was significant, further post hoc tests, including paired t-tests for hemispheric differences and two-sample two-tailed t-tests for group differences, were performed. For the asymmetry score, a two-tailed one-sample t-test was performed to determine whether the AS of the eight network properties within each group was significantly different from zero. Meanwhile, a univariate analysis of covariance (ANCOVA) was performed on the AS values to assess group

differences. The factors of age, gender, and the age-by-gender interaction were also controlled. A value of $P < 0.05$ was considered to be a significant difference. To evaluate differences in regional properties, similar statistical analysis methods as those used for the global properties were used in this work. In particular, the FDR correction was performed on the threshold ($P < 0.05$) for all tests. All statistical analyses were performed using the SPSS 19 software.

Relationship between network properties and clinical variables

This work explored the relationships between hemispheric asymmetry scores and clinical variables in patients with ADHD. Considering age, gender and age-by-gender as covariates, the current work employed multiple linear regression methods using the statistical analyses software SPSS 19. The significant hemispheric asymmetry of network property E_g was chosen as an independent variable in order to reduce the number of calculations for the regional properties. It was unnecessary to correct for multiple comparisons because the aforementioned analyses were exploratory in nature. Hence, a relationship was considered significant with an uncorrected P -value of 0.05.

Results

Global properties of hemispheric networks

Hemispheric and group differences

The aim of this study was to investigate the structural organization of hemispheric networks rather than the whole brain. We found that all four hemispheric brain anatomical networks

(2 hemispheres \times 2 groups) exhibited prominent features of the small-world property, as expressed by a larger γ ($\gamma > 1$) and a smaller λ ($\lambda \approx 1$). The statistical analyses revealed significant topological changes in the global properties between both groups and hemispheres. As shown in Table 3, the network properties with significant group differences included the normalized clustering coefficients (γ , NC > ADHD, $F_{1, 89} = 8.405$, $P = 0.005$), the normalized characteristic path length (λ , NC > ADHD, $F_{1, 89} = 8.583$, $P = 0.004$) and the small-world property (σ , NC > ADHD, $F_{1, 89} = 7.045$, $P = 0.009$), indicating a hemispheric-independent small-world property surplus in patients with ADHD. Furthermore, the hemispheric difference was highly significant for global efficiency E_g (left < right, $F_{1, 89} = 6.722$, $P = 0.010$), characteristic path length L_p (right < left, $F_{1, 89} = 6.837$, $P = 0.010$), γ (right < left, $F_{1, 89} = 17.669$, $P < 0.001$), λ (right < left, $F_{1, 89} = 4.636$, $P = 0.034$) and σ (right < left, $F_{1, 89} = 17.287$, $P < 0.001$). These results indicated that the right hemisphere exhibited better global efficiency of information transmission, whereas the left hemisphere showed better small-world characteristic. More importantly, a significant group-by-hemisphere interaction was revealed in E_g ($F_{1, 89} = 8.636$, $P = 0.004$), E_{loc} ($F_{1, 89} = 7.861$, $P = 0.006$) and L_p ($F_{1, 89} = 8.636$, $P = 0.004$). Post hoc analyses indicated that this interaction resulted from a significant rightward predilection of global integration ($P < 0.001$) and local integration ($P = 0.034$), and a significant leftward predilection of the characteristic path length ($P < 0.001$) in normal controls, with a symmetrical trend seen in patients with ADHD, as shown in Fig. 1.

For normal controls, hemispheric differences were observed in the other network properties except for the clustering coefficient. The right hemisphere showed more efficient global integration ($P < 0.001$) and local integration ($P = 0.034$) than the left hemisphere, whereas the left hemisphere exhibited longer characteristic path length ($P < 0.001$) and better

small-world architecture ($P < 0.001$) than the right hemisphere. However, no hemispheric differences were found in the network properties of patients with ADHD.

The asymmetry score

Statistical analysis results of the asymmetry scores for the global properties are shown in Table 4. Hemispheric asymmetry was only observed in normal controls and absent in patients with ADHD. For normal controls, the right hemisphere tended to be more globally [positive $AS(E_g)$, $P < 0.001$] and locally [positive $AS(E_{loc})$, $P = 0.029$] efficient. Additionally, left hemispheric advantages in the characteristic path length [negative $AS(L_p)$, $P < 0.001$], the normalized clustering coefficients [negative $AS(\gamma)$, $P < 0.001$], the normalized characteristic path length [negative $AS(\lambda)$, $P = 0.023$] and the small-world property [negative $AS(\sigma)$, $P < 0.001$] were also observed in normal controls. Comparing the asymmetry scores for the seven global properties between 2 groups, we found significant group differences in E_g ($F_{1, 89} = 8.900$, $P = 0.004$), E_{loc} ($F_{1, 89} = 8.409$, $P = 0.005$) and L_p ($F_{1, 89} = 8.900$, $P = 0.004$), which were in accordance with the significant group-by-hemisphere interaction in E_g , E_{loc} and L_p revealed by a GLM model. This result further indicated that the rightward asymmetries in global and local integration were only observed in normal controls and disappeared in patients with ADHD.

Regional nodal properties of hemispheric networks

Hemispheric and group differences

To localize regions, a GLM statistical analyses was used to find the statistical hemispheric differences between patients and normal controls (Fig. 2). Using the FDR-correction, 10

Table 3 Group and hemispheric difference on the network properties

Properties	General linear mixed model		
	Group difference $F_{1, 89}$ (P-value)	Hemisphere difference $F_{1, 89}$ (P-value)	Interaction $F_{1, 89}$ (P-value)
E_g	1.341(0.250)	6.722(0.010) [▲]	8.636(0.004)
E_{loc}	0.136(0.713)	0.206(0.651)	7.861(0.006)
C_p	2.999(0.087)	0.193(0.622)	0.051(0.822)
L_p	1.141(0.238)	6.837(0.010) [▼]	8.994(0.004)
γ	8.405(0.005) [↑]	17.669(< 0.001) [▼]	2.191(0.142)
λ	8.583(0.004) [↑]	4.636(0.034) [▼]	3.689(0.058)
σ	7.045(0.009) [↑]	17.287(< 0.001) [▼]	1.617(0.207)

The statistical results were computed with a GLM considering hemisphere as a within-subject factor, group as a between-subject factor, and group-by-hemisphere as interaction. For all analyses, the effects of age, gender, and age-by-gender interaction were controlled. Significant effects ($P < 0.05$) were portrayed by the bold text

ADHD, Attention-deficit/hyperactivity disorder; NC, normal control; ↓, NC < ADHD; ↑, NC > ADHD; ▼, right < left; ▲, right > left

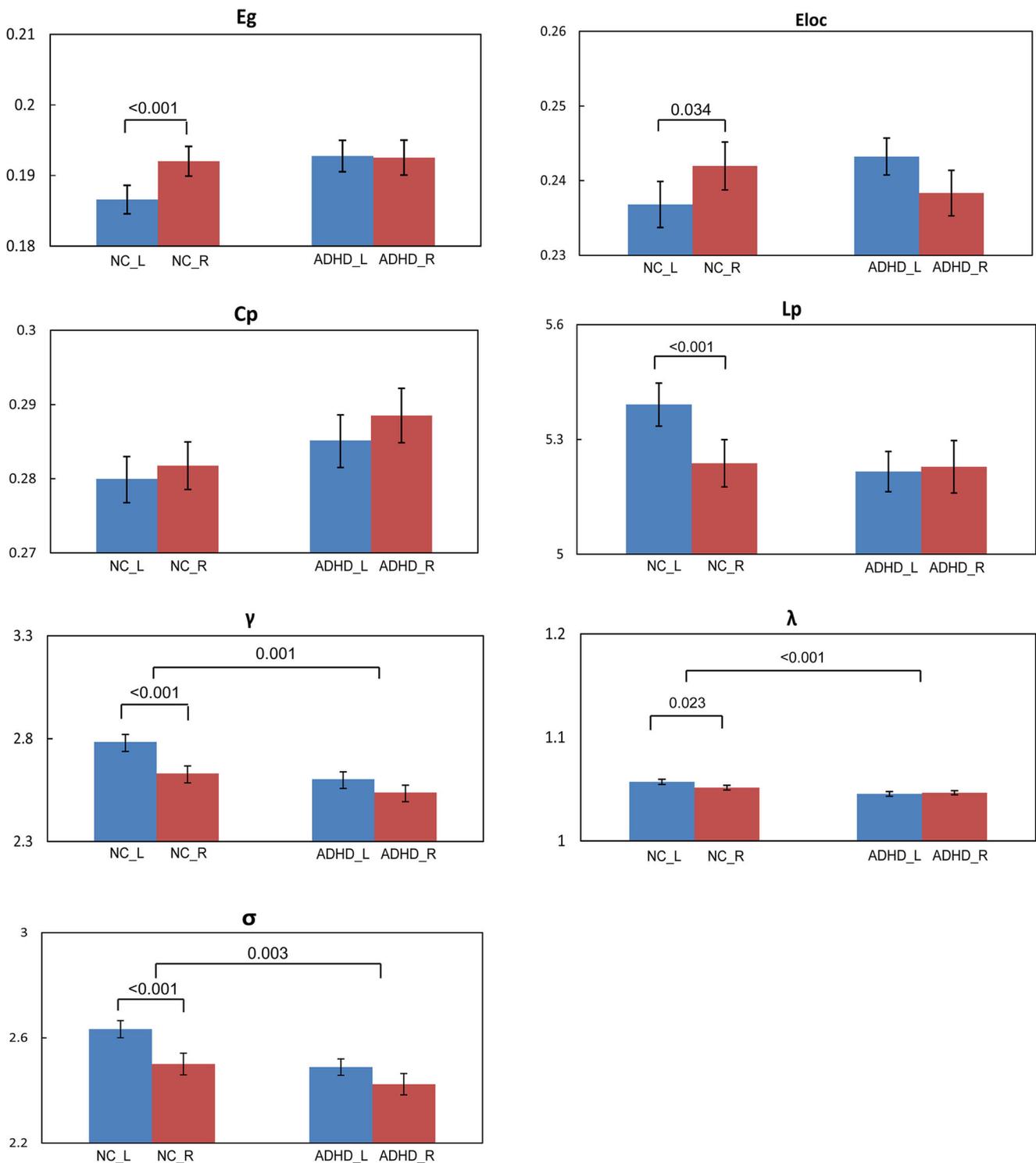


Fig. 1 Further statistical analysis of network properties. Bars represent mean \pm standard deviation. Each horizontal line and associated number represent the P-value of a t-test (paired t-test for hemispheric difference at each group and two-sample t-test for group difference). NC_L, left

hemisphere in normal controls; NC_R, right hemisphere in normal controls; ADHD_L, left hemisphere in attention deficit hyperactivity disorder; ADHD_R, right hemisphere in attention deficit hyperactivity disorder

regions with significant hemispheric differences ($P < 0.05$) were observed (Fig. 2a). Among these 10 brain regions, the orbitofrontal gyrus (middle) [ORBmid], the calcarine fissure

[CAL], the lingual gyrus [LING], the superior occipital gyrus [SOG], the supramarginal gyrus [SMG], the angular gyrus [ANG], the precuneus [PCUN] and the temporal pole

Table 4 Group differences on the asymmetry scores of the global properties

Properties	Patients with ADHD t_{39} (P-value)	NC subjects t_{52} (P-value)	ADHD versus NC $F_{1, 89}$ (P-value)
$AS(E_g)$	-1.118(0.269)	4.902(<0.001)	8.900(0.004)
$AS(E_{loc})$	-1.901(0.065)	2.243(0.029)	8.409(0.005)
$AS(C_p)$	0.730(0.470)	0.396(0.694)	0.049(0.825)
$AS(L_p)$	0.201(0.842)	-4.902(<0.001)	8.900(0.004)
$AS(\gamma)$	-1.453(0.154)	-3.895(<0.001)	2.000(0.161)
$AS(\lambda)$	0.446(0.658)	-2.339(0.023)	3.681(0.058)
$AS(\sigma)$	-1.636(0.110)	-3.747(<0.001)	1.441(0.223)

A one-sample two-tailed t-test was used to evaluate the statistical results within each group. The between-group differences were computed via a univariate ANCOVA, and the effects of age, gender, and age by-gender interaction were controlled for all of these analyses. A negative t -value within each group shows a leftward asymmetry and vice versa. The significant effect ($P < 0.05$) of network property was expressed in Bold

ADHD, attention deficit hyperactivity disorder; NC, normal control

(middle) [TPOmid] exhibited more advantageous nodal efficiency in the right regions than the left regions, whereas 2

regions, the supplementary motor area [SMA] and the anterior cingulate gyrus [ACG], showed significant left-greater-than-

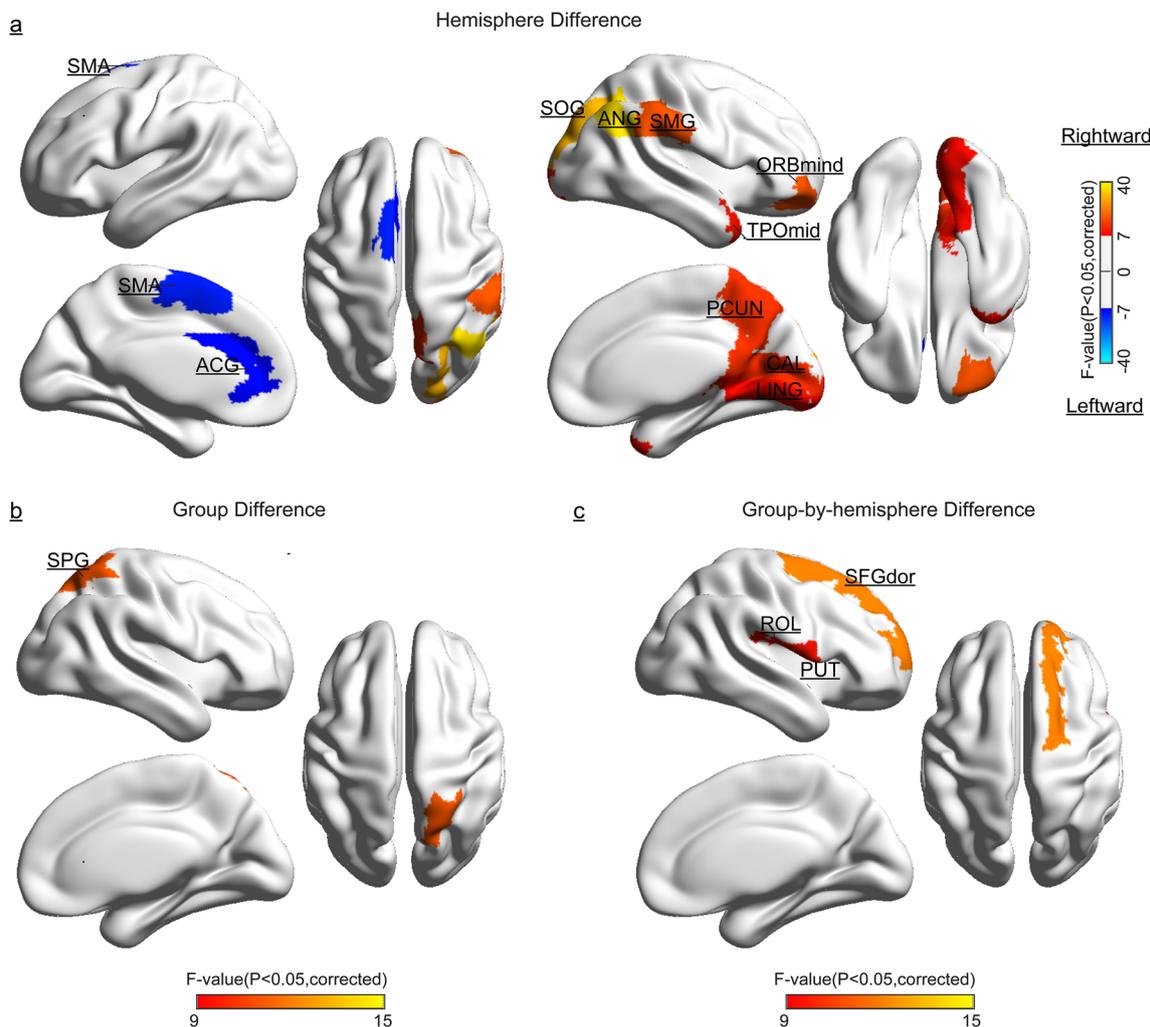


Fig. 2 Cortical regions with significant differences (a) hemispheric difference, (b) group difference, and (c) group-by-hemispheric interaction on the nodal efficiency. The color bar denotes F-values.

Significant difference was identified with a threshold value of $P < 0.05$ (FDR-corrected). Significantly different regions were overlaid on surface maps provided by BrainNet Viewer software (Xia et al. 2013)

right asymmetries in nodal efficiency. Moreover, the superior parietal gyrus [SPG] exhibited a significant group effect (NC < ADHD, $P < 0.05$, FDR-corrected) on the nodal efficiency (Fig. 2b). Furthermore, regions with significant group-by-hemisphere interactions were the superior frontal gyrus (dorsal) [SFGdor] ($F_{1, 89} = 12.003$, $P = 0.001$), the rolandic operculum [ROL] ($F_{1, 89} = 9.560$, $P = 0.003$), and the putamen [PUT] ($F_{1, 89} = 14.932$, $P < 0.001$; Fig. 2c). Three regions showed trend-wise group-by-hemisphere interactions, which were the CAL ($F_{1, 89} = 6.025$, $P = 0.012$), the LING ($F_{1, 89} = 7.072$, $P = 0.009$) and the ANG ($F_{1, 89} = 7.364$, $P = 0.008$). Post hoc analyses (Fig. 3) showed that a significantly reduction in the hemispheric asymmetry of nodal efficiency in patients with ADHD led to the interaction effects. The PUT, ROL and SFGdor region in ADHD patients showed left-greater-than-right asymmetries in nodal efficiency, while the three regions in normal controls showed right-greater-than-left asymmetries.

The asymmetry score

Significant ($P < 0.05$, FDR-corrected) asymmetries were observed in 18 nodes in the hemispheric networks of normal controls (Fig. 4a) and 12 nodes in the hemispheric networks of patients with ADHD (Fig. 4b). The results were consistent with the above GLM hemispheric results, including the distribution and asymmetries direction of these cortical regions. For patients with ADHD, we observed significant leftward asymmetries in regional efficiency in the SMA, middle occipital gyrus [MOG], postcentral gyrus [PoCG], thalamus [THA], heschl gyrus [HES] and temporal pole (superior) [TPOsup] regions. Significant rightward asymmetries in regional efficiency were revealed in the cuneus [CUN], superior occipital gyrus [SOG], inferior occipital gyrus [IOG], PCUN, SMG and ANG. When comparing patients with ADHD and normal controls, significant group differences ($P < 0.05$, FDR-corrected) in the asymmetry scores for the regional efficiency were observed in the SFGdor, the ROL and the PUT. The SFGdor, the ROL and the PUT region in normal controls

showed significant rightward hemispheric asymmetries while the three regions in patients with ADHD did not show any significant hemispheric asymmetries. Additionally, trends in differences were revealed in three regions, including the CAL (22) ($F_{1, 89} = 7.052$, $P = 0.009$), the LING (24) ($F_{1, 89} = 7.958$, $P = 0.006$) and the ANG (33) ($F_{1, 89} = 7.564$, $P = 0.007$). These results were line with the significant group-by-hemisphere interaction in the nodal efficiency observed in the previous linear mixed model.

Relationship between hemispheric asymmetry and clinical features

For the ADHD group, we found that the asymmetry scores in three global properties were significant positively correlated with scores on the (WAIS). Among the three network properties, the asymmetry scores in local efficiency were positively correlated with matrix reasoning task scores in the WAIS (WAIS_MR) ($AS(E_{loc})$, $r = 0.328$, $p = 0.045$). The asymmetry scores in the normalized clustering coefficients and the small-world property exhibited positive correlations with the vocabulary task in the WAIS (WAIS_VOC) ($AS(\gamma)$, $r = 0.335$, $p = 0.040$; $AS(\sigma)$, $r = 0.323$, $p = 0.048$). For the regional properties, the asymmetry scores for six nodes (including the OLF, the REC, the PoCG, the CAU, the PUT, and the PAL) were significantly ($P < 0.05$) correlated with clinical characteristics (Table 5). Among these six regions, two regions, including the REC ($AS(REC)$, $r = -0.348$, $p = 0.032$) and PUT ($AS(PUT)$, $r = -0.361$, $p = 0.026$), exhibited significant negative correlations with the ASRS. Only the CAU region exhibited a significant positive correlation [$AS(CAU)$, $r = 0.438$, $p = 0.006$] with the WAIS_LNS. For the WAIS_MR, two regions including the CAU [$AS(CAU)$, $r = 0.386$, $p = 0.017$] and the PAL [$AS(PAL)$, $r = -0.330$, $p = 0.043$], showed significant correlations. For the WAIS_VOC, significant correlations were found between the asymmetry scores in nodal efficiency in the OLF [$AS(OLF)$, $r = -0.330$, $p = 0.043$] and the PoCG [$AS(OLF)$, $r = 0.342$, $p = 0.036$].

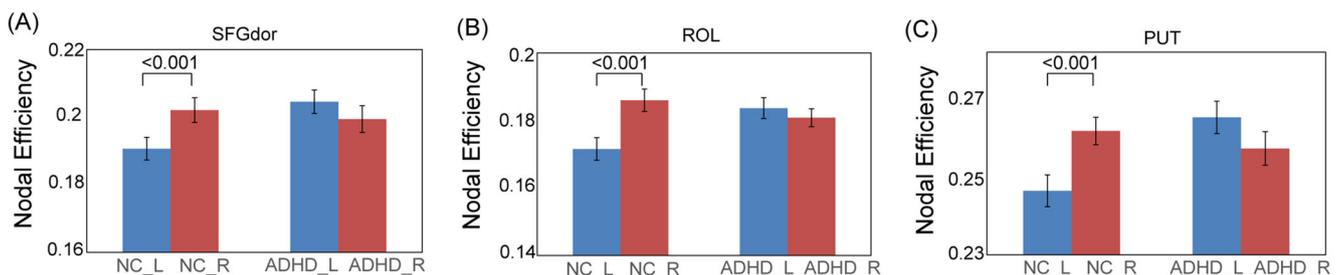


Fig. 3 The nodal efficiency for PUT, ROL and SFGdor in both groups of normal controls and attention deficit hyperactivity disorder. Each bar indicates the mean nodal efficiency. NC_L, left region in normal

controls; NC_R, right region in normal controls; ADHD_L, left region in attention deficit hyperactivity disorder; ADHD_R, right region in attention deficit hyperactivity disorder

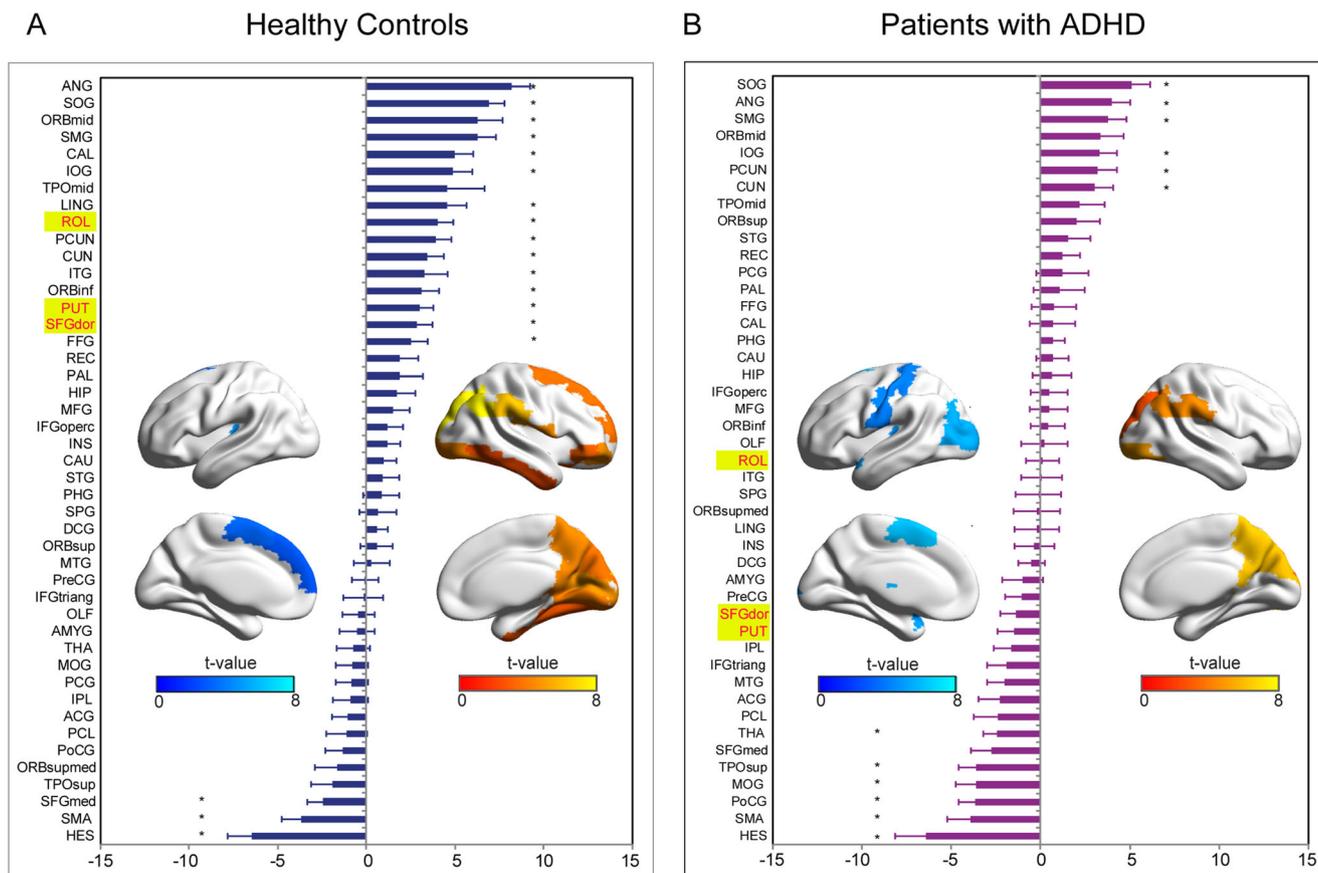


Fig. 4 The asymmetry scores of nodal efficiency for the hemispheric network with 45 nodes. Each bar indicates the mean asymmetry scores (AS). Error bars represent standard error. For both groups of (a) normal controls and (b) patients with ADHD, regions with significant AS are marked with asterisk (* $P < 0.05$, FDR-corrected). All the regions in each group were ascending sorted according to the statistical t-values.

Similarly, the color bar indicated the statistical t-values. The spatial distributions of cortical regions with significant AS in both groups were also presented with BrainNet Viewer software (Xia et al. 2013). Cortical regions with significant group difference were presented with yellow background

Discussion

In this study, we utilized DTI technology and graph theoretical approaches to investigate the hemispheric asymmetry in brain WM structural networks in patients with ADHD. The main

findings are as follows: 1) the small-world property was seen in the hemispheric networks of patients with ADHD; 2) the global efficiency, local efficiency and the characteristic path length exhibited significant group-by-hemisphere interactions as a result of significantly reduced hemispheric asymmetry in

Table 5 Partial correlation coefficients between the global and nodal asymmetry scores and clinical characteristics of patients with ADHD

Properties	Partial correlation coefficients (P-value)			
	ASRS	WAIS_LNS	WAIS_MR	WAIS_VOC
$AS(E_{loc})$	0.057(0.732)	-0.144(0.388)	0.328(0.045)	0.062(0.713)
$AS(\gamma)$	0.013(0.939)	0.184(0.269)	0.102(0.544)	0.335(0.040)
$AS(\sigma)$	-0.033(0.843)	0.191(0.250)	0.084(0.618)	0.323(0.048)
$AS(OLF)$	-0.077(0.647)	-0.166(0.318)	-0.229(0.168)	-0.330(0.043)
$AS(REC)$	-0.348(0.032)	-0.077(0.645)	-0.208(0.210)	-0.209(0.207)
$AS(PoCG)$	0.083(0.620)	-0.054(0.749)	0.104(0.535)	0.342(0.036)
$AS(CAU)$	-0.102(0.541)	0.438(0.006)	0.386(0.017)	0.148(0.374)
$AS(PUT)$	-0.361(0.026)	-0.209(0.209)	-0.038(0.819)	-0.239(0.148)
$AS(PAL)$	0.167(0.316)	-0.218(0.189)	-0.374(0.021)	-0.317(0.052)

global integration and local integration in patients with ADHD compared with normal controls; 3) the three regions of the SFGdor, ROL, and PUT showed reduced asymmetry in nodal efficiency in patients with ADHD; and 4) several hemispheric network properties and regional efficiency exhibited significant correlations with clinical characteristics of ADHD.

Small-world property of hemispheric structural networks of human brain

The identification of the small-world property proposed by Watts and Strogatz (1998) has been a great help in understanding the topological organization of brain networks (Bullmore and Sporns 2009; Sporns 2011). For a network with small-world characteristic, the normalized characteristic length λ should be close to 1 ($\lambda = L_p/L_{random} \approx 1$, indicating that the L_p of the actual network should be close to that of the matched random network), and the normalized clustering coefficient γ should be much larger than 1 ($\gamma = C_p/C_{random} \gg 1$, indicating that the C_p of the actual network should be larger than that of the matched random network). The small-world property value can be represented by a scalar ($\sigma = \gamma/\lambda$). When the small-world property value is larger than 1, this indicates that the network has a small-world characteristic, indicating a balance between global integration and local specialization/necessities (fault tolerance) of brain functional activity. Convergent studies have proved that the whole-brain networks in normal controls and in patients with ADHD possess the small-world characteristic (Cao et al. 2013; Wang et al. 2009). This study constructed anatomical hemispheric networks rather than whole-brain networks in normal controls and patients with ADHD. For the four anatomical networks (2 hemispheres \times 2 groups), we observed that all network property values of γ were larger than 1 and those of λ were nearly 1 (Fig. 1). When evaluating the small-world property of the hemispheric networks, we found that the σ of the four anatomical networks were larger than 2.2 (Fig. 1). This indicated that the hemispheric networks in both groups of normal controls and patients with ADHD exhibited significant small-world characteristics, which is in accordance with previous studies on whole-brain structural networks (Puetz et al. 2017; Xia et al. 2014) and functional networks (Liu et al. 2015; Wang et al. 2009). Our findings extend earlier observations and prove that the small-world characteristic exists in hemispheric networks of both normal controls and patients with ADHD. This finding demonstrates that the small-world characteristic is also a basic topological feature of hemispheric structural networks.

For the network properties of global efficiency, local efficiency, clustering coefficient and characteristic path length, no differences were observed between the ADHD group and the normal control group in the current study. Consistent with our results, Sidlauskaite et al. (2015) reported no group differences in any of the global properties of whole-brain structural

networks constructed by the DTI technology. In addition, they found no group differences in the small-world property between patients with ADHD and normal controls. Interestingly, we found significant group differences in the normalized clustering coefficients (γ), the normalized path length (λ) and the small-world property (σ), that is, normal controls had larger γ , λ and σ values independent of hemisphere, indicating a reduced small-world characteristic in patients with ADHD. The apparent discrepancies between the present results and the Sidlauskaite et al. (2015) results could stem from the following two aspects. First, their study focused on whole-brain networks rather than hemispheric networks. Second, the number of participants in the current study (53 normal controls and 40 adults with ADHD) was significant larger than that of the Sidlauskaite et al. study (21 normal controls and 18 adults with ADHD). Prior observations from functional networks (Liu et al. 2015) are compatible with our findings of a smaller small-world property value, which showed that the small-world property for normal controls was more efficient than that of participants with ADHD. Along this line, our findings of “hemispheric-independent” significantly smaller small-world property values could provide further evidence for the notion of ADHD as a psychopathological feature. In addition, we found hemispheric differences in five network properties for normal controls, including the E_g , L_p , γ , λ and σ . Among these five global properties, the value of E_g in the right hemisphere was significantly larger than that of the left hemisphere, which indicated that the global integration in the right hemisphere was more efficient than that of the left hemisphere. The values of L_p , γ , λ and σ in the left hemisphere were larger than those in the right hemisphere, which showed more of a balance between fault tolerance and global integration in the left hemisphere than in the right.

For the asymmetry scores, we found that normal controls exhibited a significantly positive asymmetry in global efficiency and local efficiency, and a negative asymmetry in characteristic path length. This demonstrates that the right hemisphere tended to be more globally and locally efficient than the left hemisphere. Consistent with our results, a study of healthy humans by Iturria-Medina et al. (2011) showed a significant positive asymmetry in global and local efficiency of structural networks. However, this rightward advantage in global and local integration in normal controls was absent in patients with ADHD. These results may be attributed to a significant increase of global integration in the left hemisphere and a decrease of the local integration in the right hemisphere. According to Iturria-Medina’s et al. notion (2011), the left hemisphere is mainly responsible for specific cognitive functions such as language and motor skills. In addition, convergent studies (Langleben et al. 2001; Rubia et al. 2005; Silk et al. 2016; Team 2000) have reported that the pathophysiology of ADHD exhibits abnormalities in neural systems that are mainly related to cognitive control and motor functions.

Along with these ideas, our finding of increased global efficiency in the left hemisphere provides further pathophysiological evidence for ADHD as a syndrome. In addition, Makris et al. (Makris et al. 2008) investigated the cingulum bundle (CB) and superior longitudinal fascicle (SLF) as parts of the attentional and executive system. They found lower fiber connectivity in the right CB and SLF in adult patients with ADHD. This result indicated that the local efficiency was decreased in the right hemisphere, which is consistent with our observations, suggesting that a reduction in local efficiency in right hemisphere may be considered a syndrome of ADHD. Moreover, we observed significant left-greater-than-right asymmetry of γ , λ , σ only in the normal control group. Our findings supplemented earlier studies, suggesting that hemispheric asymmetry may be an underlying psychotic psychopathology in patients with ADHD.

Hemisphere-related differences in regional nodal parameters

Previous studies mainly focused on investigating the morphological or activation differences between 2 regions. Regional asymmetry of the hemispheric anatomical networks was evaluated by comparing regional efficiency in this study.

In line with the abnormalities seen in whole-brain structural and functional networks in cognitive, affective, and motor functions in patients with ADHD (Angelica et al. 2013), significant leftward asymmetries in regional efficiency were revealed in several regions (including the SMA, the MOG, the PoCG, the THA, the HES and the TPOsup). Three regions including the MOG, the PoCG and the TPOsup were shown to exhibit increased activation in the left region in previous studies (Cortese et al. 2012; Schneider et al. 2010; Suskauer et al. 2008). The SMA and the THA were shown to exhibit reduced activation in the right hemisphere in earlier studies (Hart et al. 2013; Smith et al. 2008). These studies provide convergent evidence for our findings. Rightward asymmetries in regional efficiency were found in visual regions mainly located in the CUN, the SOG, the IOG and the PCUN, corresponding to the rightward advantage in emotion and in visual-spatial processing (Jones et al. 2008). Additionally, we found two rightward regions of linguistic function, including the SMG and the ANG. Our findings were consistent with those of Hale et al. (2005), who reported a left hemisphere deficit in linguistic dysfunction in patients with ADHD. Moreover, Schneider et al. (2010) found that decreased activation in the left SMG region was correlated with higher scores in inattention. This result further proves our findings of rightward asymmetry in the SMG region. Hence, aberrations in brain regional characteristics are increasingly implicated and thought to underlie the neurobiological basis of ADHD. Interestingly, we found that ADHD was associated with reduced nodal efficiency in the SPG. This is in contrast to previous brain connectome studies (Cherkasova and Hechtman 2009; Tamm et al.

2006), that they reported that ADHD subjects showed reduced activity in the SPG during cognitive tasks. The main reason for this apparent discrepancy is that previous studies focused on investigating functional connectivity, and our study focused on investigating structural connectivity. In addition, a significant group-by-hemisphere interaction in nodal efficiency was found in three regions (the SFGdor, the ROL and the PUT). All three regions showed a pattern of hemispheric asymmetry reduction in patients with ADHD. This finding of an interaction agrees with the above results of regional asymmetry.

Relationship between hemispheric asymmetry and clinical features

An interesting finding of the current study is that within patients with ADHD, the topological properties of hemispheric networks were related to the intelligence and cognitive abilities assessed by the WAIS_MR and WAIS_VOC. Specifically, we found that the asymmetry scores for local efficiency showed a positive correlation with WAIS_MR score; this means that the larger the WAIS_MR, the lower the local efficiency in the left hemisphere. This tendency to show lower left lateralized nodal efficiency has been previously reported by Sidlauskaite et al. (2015). For the WAIS_VOC, the asymmetry score for the normalized clustering coefficients and the small-world property revealed a significant positive relation; that is, the larger WAIS_VOC score, the larger the asymmetry in the normalized clustering coefficients and the small-world property. Consistent with our observations, a previous imaging study (Hale et al. 2010) noted that ADHD is associated with impaired left hemisphere function during lateralized language tasks.

For nodal efficiency, we found the asymmetry scores for both the REC and the PUT were negative related with the ASRS. This means both the REC and the PUT regions showed an increased leftward predilection with increased ASRS scores. Compatible with our findings, Silk et al. (2016) found that FA values that were more strongly lateralized to the left in the PUT WM were associated with greater symptom severity in patients with ADHD. For the WAIS_LNS, only the asymmetry of the CAU region exhibited a significant positive relation. This indicated that the better the memory, the higher the activity in the right CAU region. A previous study by Olesen et al. (2004) provides evidence for our result. They found the right CAU region exhibited more activity after working memory training. For the WAIS_MR score, the asymmetry scores for the CAU showed a significant positive correlation. Consistent with this finding, Castellanos et al. (1996) reported that the volume of the CAU was significantly correlated with ratings of ADHD severity and cognitive performance. Rubia et al. (1999) reported that the CAU in ADHD showed right-greater-than-left response

during the control task. This indicated the hemispheric asymmetry of CAU region was positively related to the ability of task solving and the WAIS_MR measures the ability of task solving. In addition, we found that the PAL region showed a significant negative correlation of the WAIS_MR. This negative correlation may be result form an increased nodal efficiency in the left PAL. One study reported that the left PAL region showed an increased nodal efficiency in ADHD children (Wang et al. 2009). For the WAIS_VOC, the asymmetry scores for the OLF showed a significant negative correlation, and those of the PoCG showed a positive correlation. These results indicated that the better intelligence and cognitive abilities, the lower the activity in the OLF and the higher activity in the right PoCG. Our findings are in line with previous studies by Murphy et al. (2001) and Schweitzer et al. (2004). Murphy et al. (2001) found the OLF region was impaired in adults with ADHD compared to normal controls. The studies of Schweitzer et al. (2004) reported that the right PoCG showed increased normalized regional cerebral blood flow activity, which was related to short-memory. Notably, the statistical significance in this study was not determined after performing corrections for multiple comparisons. In future studies, we will investigate the progressive disruptions in brain structural networks and their relationship with clinical features that are of particular interest in revealing the illness progression of ADHD.

In conclusion, the main focus of the current work was to investigate the hemispheric differences in the brain anatomical networks in the patients with ADHD. A computationally inexpensive deterministic tractography method was used to reconstruct the brain networks. Graph theoretical analysis was used to analyze the brain anatomical networks at the “whole-hemisphere”. We found that beyond a dysconnectivity pattern, there was a reduced hemispheric asymmetry in WM topological properties including the global, local and regional efficiency in patients with ADHD. In addition, we found that the asymmetry of local and regional properties exhibited correlations with clinical features of ADHD. These observations support the view that altered hemispheric asymmetries in brain anatomical networks may emphasize aberrant brain functions and clinical symptoms observed in patients with ADHD. In subsequent studies, we will try to utilize the probabilistic diffusion tractography methods to reconstruct the brain anatomical networks in order to confirm our above observations. Additionally, we will examine the effects of age and gender on hemispheric asymmetries in brain anatomical networks.

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Compliance with ethical standards

Conflict of interest The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval The study was carried out in strict accordance with the University of California, Los Angeles Institutional Review Board.

Informed consent After receiving a thorough explanation, all participants gave written informed consent according to the procedures approved by the University of California Los Angeles Institutional Review Board.

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