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Distinct topological properties of cue-evoked attention processing network in persisters and remitters of childhood ADHD

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Abstract

Attention deficit/hyperactivity disorder (ADHD) is a highly prevalent and impairing neurodevelopmental disorder that persists into adulthood in a sizeable portion of afflicted children. The persistence of ADHD elevates the risk for adverse outcomes that result in substantial individual and societal burden. The objective of this study is to assess neurobiological substrates associated with variability of clinical outcomes in childhood ADHD, which has considerable value for the development of novel interventions that target mechanisms associated with recovery. A total of 36 young adults who were diagnosed with ADHD combined-type during childhood and 33 group-matched controls were involved in the study. Adults with childhood ADHD were further divided into 17 persisters and 19 remitters based on DSM-5 criteria. Functional magnetic resonance imaging data during a cue-evoked attention task were collected from each subject. The cue-evoked attention processing network was constructed using graph theoretic techniques. Network properties, including global-, local-, and nodal-efficiency, and network hubs were computed. Group comparisons of the network properties were conducted. Significantly lower nodal efficiency in right inferior frontal gyrus and reduced left side frontal-parietal functional interactions were observed in both remitters and persisters relative to the controls. The ADHD persisters showed a unique pattern of significantly lower nodal efficiency in right middle frontal gyrus (MFG) and hyper-interactions between bilateral MFG. This study suggests that right MFG functional impairments may relate to inactive fronto-parietal functional interactions for sensory

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

and cognitive information processing and symptom persistence in young adults with childhood ADHD.

Keywords

ADHD; Remission; Persistence; Graph Theoretic Techniques; Attention Processing Network

1. INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed neurodevelopmental disorders, impacting approximately 9.5% of school-age children in the United States (Pastor, Reuben, Duran, & Hawkins, 2015). Symptoms of ADHD persist into adulthood in up to 60% of patients, and cause substantial impairment and suffering in patients, their families, and the community (Faraone, Biederman, & Mick, 2006). Neural determinants of the diverse developmental trajectories of childhood ADHD remain unknown. Elucidation of these mechanisms could set the stage for the development of novel interventions that yield enduring benefits and improve long-term outcomes.

Cortico-striato-thalamo-cortical (CSTC) loops that support attention and cognitive processing have been implicated in both the etiology (Casey, Nigg, & Durston, 2007) and developmental remission of ADHD (Halperin & Schulz, 2006). Abnormal functional activation and connectivity in thalamic, striatal, and prefrontal areas have been reported in children and adults with ADHD, suggesting that they reflect a core pathophysiology that remains static over the lifespan (Cortese et al., 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013). Abnormalities in prefrontal anatomy, activation, and connectivity associated with ADHD have been found to vary as a function of adult outcome (Francx et al., 2015; Li et al., 2007; Mattfeld et al., 2014; Schulz et al., 2017; Shaw et al., 2006; Shaw et al., 2013; Shaw et al., 2015). Persistence of ADHD into adulthood has been linked to increased prefrontal cortical thinning (Shaw et al., 2006; Shaw et al., 2013), lower prefrontal white matter fractional anisotropy (Shaw et al., 2015), and reduced prefrontal activation and connectivity within the caudal and subcortical regions (Francx et al., 2015; Mattfeld et al., 2014; Schulz et al., 2017). Symptomatic remission of ADHD has been linked to the normalization of the prefrontal structure (Shaw et al., 2006; Shaw et al., 2013) and function (Francx et al., 2015; Mattfeld et al., 2014; Schulz et al., 2017).

Our existing studies in young adults with childhood ADHD suggested a double dissociation of functional anomalies linked to childhood onset and adult outcome. Childhood ADHD was associated with reduced cue-related thalamic activation and connectivity with the brainstem regardless of adult outcome, while symptom remission was linked to enhanced cue-related thalamo-prefrontal connectivity (Clerkin et al., 2013). However, these basic measures of regional activation and connectivity have limited capacity to characterize the functional human brain as a high performance parallel information processing system.

From multiple lines of evidence, it is known that the human brain exhibits both locally specialized processing units within relatively circumscribed regions or clusters (Bartels & Zeki, 2000), as well as distributed interregional interactions [e.g. the frontal-parietal

attention network (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008)]. The functional brain networks are small-world and economical in the sense of providing high global and local efficiencies of parallel information processing with low rewiring cost (Achard & Bullmore, 2007). The development of graph theoretic techniques (GTT) provided powerful methods to characterize the nodal (regional) and global topological properties of such functional brain networks, which has been implemented in ADHD studies. Multiple resting-state fMRI studies have reported abnormal global and regional topological properties in children with ADHD when compared with typically developing children (TDC), such as lower global efficiency, reduced nodal efficiency in frontal areas (Cao, Wang, et al., 2014; Fair et al., 2009; Supekar, Musen, & Menon, 2009; Wang et al., 2009); delayed maturation of the default mode network (DMN) (Fair et al., 2009; Fair et al., 2010); and different connectivity patterns among nodes of the entire resting-state functional brain network in children with ADHD-inattentive, -hyperactive/impulsive, and - combined subtypes (Fair et al., 2012). Resting-state GTT studies in adults with ADHD reported increased coherence in the DMN when comparing to children with ADHD (Fair et al., 2008); no significant alterations in global network properties, but significantly lower nodal path length of right medial frontal and right superior occipital cortices, and significantly higher nodal clustering coefficient in left orbitofrontal and right superior temporal cortices, relative to group-matched control adults (Cocchi et al., 2012). A few task-based GTT studies have also been conducted in children with ADHD. A multi-source interference task-based electroencephalography (EEG) study showed increased local characteristics combined with decreased global characteristics in children with ADHD compared to the group-matched TDC (Liu, Chen, Lin, & Wang, 2015). A visual sustained attention task-based fMRI study observed significantly reduced nodal efficiency in frontal and occipital regions in children with ADHD, and a hyperactive network hub in anterior cingulate cortex (Xia, Foxe, Sroubek, Branch, & Li, 2014). These existing GTT studies in resting-state and task-based functional neuroimaging data demonstrated altered global and regional topological patterns of the functional brain networks in children and adults with ADHD (Cao, Shu, Cao, Wang, & He, 2014). However, systems-level functional brain characteristics associated with the diverse adult outcomes of childhood ADHD have not yet been investigated.

The current study utilized GTT to examine the systems-level neurophysiological mechanisms associated with symptom persistence and remission of childhood ADHD in young adults diagnosed with the disorder during childhood and matched comparison subjects. Within the 69 participants of this study, 67 overlapped with those in a previous study which reported that greater frontal-thalamo functional connectivity during *response preparation* stage of attention processing significantly linked to ADHD symptom remission (Clerkin et al., 2013). Both the current and the previous studies used fMRI data acquired during the same cued attention task, but focused on different components of attention that were represented by different contrasts of the task. The current study focused on the *cue-evoked attention* stage defined by the cue vs. baseline contrast, while the previous study focused on the *response preparation* stage defined by the cue minus non-cue contrast. During cued attention processing, the *cue-evoked attention* component occurs prior to the *response preparation* component. Existing clinical studies have found a delayed pattern of attention development in children with ADHD, especially on the *cue-evoked attention*

component (Suades-Gonzalez et al., 2017). We hypothesized that optimal topological organization of the functional brain network for *cue-evoked attention* processing may be associated with symptom remission in adults with childhood ADHD.

2. METHODS

2.1. Participants

Neuroimaging and clinical data from 69 young adults were included in analyses of this study, including 36 probands who were diagnosed with ADHD combined-type (ADHD-C) in childhood and 33 matched comparison subjects who had no history of ADHD. Initially, a total of 60 ADHD probands, who were diagnosed with ADHD-C at their 7 – 11 years of age, were screened during their young adulthood. Thirty-six of them met the strict inclusion criteria for the ADHD-P (persisters) or ADHD-R (remitters) groups, and were able to provide usable magnetic resonance imaging (MRI) data. Of these 36 adults with childhood ADHD, 17 were classified as ADHD-P, who endorsed at least three inattentive and three hyperactive/impulsive symptoms. In these 17 ADHD-P, 14 were diagnosed with ADHD-C, 1 met criteria for ADHD-inattentive presentation, and 2 met criteria for ADHD-hyperactive/impulsive presentation, based on DSM-5 criteria for adult ADHD. Those classified as ADHD-R (N=19) endorsed no more than 3 inattentive or 3 hyperactive/impulsive symptoms in adulthood, and had no more than 5 symptoms in total to allow separation from the ADHD-P group.

A total of 46 young adults, who were evaluated as non-ADHD in childhood, were re-evaluated for the current study. Thirty-six of them met the inclusion criteria for controls (had no more than three inattentive or hyperactive/impulsive symptoms) and provided usable data.

For both groups, childhood evaluations were based on the IOWA Conners' Teachers Rating Scale (Loney & Milich, 1982), and diagnosed with childhood ADHD-C via a parent interview using the Diagnostic Interview Schedule for Children version 2 (Shaffer et al., 1996; Shaffer, Fisher, Piacentini, Schwab-Stone, & Wicks, 1989), while adulthood evaluations used the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 2002), supplemented by a semi-structured interview for ADHD that was adapted from the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) (Kaufman et al., 1997) and the Conners' Adult ADHD Diagnostic Interview for DSM-IV (Epstein, Johnson, & Conners, 2006). Exclusion criteria for the study included chronic medical illness; neurological disorder; diagnosis of schizophrenia, autism spectrum disorder, or chronic tic disorder; Full Scale IQ < 70; and not speaking English. Clinical and demographic characteristics are summarized in Table 1.

Thirty-four probands had been treated with short-acting psychostimulants. Mean duration of treatment was 2.5 years (SD = 3.85) for ADHD-R and 4.8 years (SD = 4.19) for ADHD-P sub-groups ($t = -1.65$, $p = 0.108$). Two subjects in the ADHD-P sub-group were taking psychostimulants at the time of this study, and underwent a 48-hour medication wash-out period before MRI acquisition.

The study was approved by the institutional review boards of Queens College of the City University of New York, the Icahn School of Medicine at Mount Sinai, and New Jersey Institute of Technology. Participants provided signed informed consent and were reimbursed for their time and travel expenses.

2.2. Cued Attention Task for fMRI

This event-related task consisted of four 300 seconds runs that each began and ended with a 30-second fixation cross. Each run consisted of a series of 120 letters containing 24 targets (“X”), half preceded by a cue (“A”), and the other half preceded by a non-cue letter (“B” through “H”). Participants were told that the letter “A” (the Cue) was always followed by the target letter “X”; but not all targets (i.e., “X”) were preceded by an “A”. The stimuli were presented for 200 ms with a pseudorandom inter-stimulus interval which ranged from 1550 to 2050 ms (mean=1800 ms per run). The task was described in more detail in (Clerkin et al., 2009). Participants were instructed to respond as rapidly as possible using their right index finger to every target. A practice trial on a laptop prior to the scan was performed by each subject to ensure comprehension of the instructions.

2.3. Imaging Data Acquisition Parameters

All participants were scanned using the same 3.0T Siemens Allegra (Siemens, Erlangen, Germany) whole body MRI scanner. For each of the four runs, a total of 120 T2*-weighted volumes were acquired in the axial plane using a gradient-echo echo-planar sequence (TR=2500 ms, TE=27 ms, flip angle=82°, matrix=64×64, slice thickness=4 mm, 40 slices, in-plane resolution=3.75 mm²). Stimuli were projected onto a rear projection screen mounted at the head of the magnet bore that was viewed through a mirror on the head coil. For the purpose of co-registration, a high resolution T2-weighted anatomical volume of the brain was acquired at the same 40 slice locations with a turbo spin-echo pulse sequence (TR=4050 ms, TE=99 ms, flip angle=170°, field of view=240 mm, matrix=512×336, slice thickness=4mm, in-plane resolution=0.41 mm²).

2.4. Individual-level fMRI Data Preprocessing and Seed Regions (Nodes) Detection

fMRI data were preprocessed using the Statistical Parametric Mapping 8 software (Wellcome Trust Centre for Neuroimaging, London, UK). The fMRI data were slice timing corrected, realigned to the first volume, coregistered to the T2 structural image, normalized to the Montreal Neurological Institute (MNI) template with a voxel size of $2 \times 2 \times 2$ mm³, and spatially smoothed with an 8-mm full-width at half maximum Gaussian kernel. Additional frame-wise head motion analyses were conducted by calculating the mean absolute displacement of each brain volume compared with the previous volume from the translation parameters (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). No participant was excluded for excessive head motion detected by frame-wise analyses (Mean Motion < 0.2 mm in all data). The six basic motion parameters created during realignment and three frame-based motion parameters were regressed out from each fMRI data. The residual time series were analyzed to generate the cues (“A”), targets (“X”), and non-cues (letters other than “A” and “X”)-related activation maps by FMRIB improved linear regression model (FILM), which uses a nonparametric estimation of time series autocorrelation to prewritten

each voxel's time series (Smith et al., 2004). The average activation map responding to the cues was generated for each group. Multiple comparisons were controlled in both individual-level and group-level analyses by applying family-wise error rate (FWER), i.e. Gaussian random-field theory at a cluster corrected significance threshold of $p < 0.05$.

A total of 52 cortical and subcortical seed regions (nodes of the functional brain network for cue-evoked attention processing) were determined based on the combination of the activation maps of the groups of ADHD probands and controls. The combined activation map was parceled according to the structural and functional connectivity-based Brainnetome atlas (Fan et al., 2016). The seed regions were spheres (radius = 4mm) identified from the coordinates of the local activation peaks containing at least 50 contiguous voxels surrounding the peak voxel (See from Figure 1A and 1B, and Supplementary Table 1 for details of seed region determination). The size of the seed regions was determined based on the estimation of average cortical thickness of adult human brain (Power et al., 2011; Wig et al., 2014).

2.5. Network Analysis

To construct the cue-evoked attention processing network, the single-trial beta value maps from the total of 48 cue-related events in the preprocessed data from each subject was first extracted (technical details see from (Rissman, Gazzaley, & D'Esposito, 2004)). These 48 maps were sequentially combined to form the whole brain single-trial beta value series. The average beta value series in each of the 52 seed regions was then calculated. Pearson correlation of the average beta value series in each pair of the seed regions was calculated. The functional connectivity matrix was constructed using the absolute values of the correlation coefficients, and was converted into a binary graph, by using the network cost as threshold. The network cost was defined as:

$$C_G = \frac{K}{N(N-1)/2}$$

where N and K were the total number of nodes and edges respectively; $N(N-1)/2$ was the number of all possible sub-networks in the graph G (Latora & Marchiori, 2001).

Resting-state fMRI studies often use only positive or only negative values in the correlation coefficient matrices to construct brain networks, with concerns that positive and negative functional connectivities in brain regions may have different physiological substrates during resting-state (Di, Kim, Chen, & Biswal, 2014; Shehzad et al., 2009). The current study chose to use the absolute values of the functional correlation coefficients, which is consistent with the majority of existing task-based functional brain network studies, with an understanding that strong functional connections of brain regions in both positive and negative ways represent strong regional interactions for sensory and cognitive information transferring during the task (Meunier et al., 2014; Wang, Ren, & Zhang, 2017). Again, consistent with existing task-based functional network studies, we chose to use the binarized, instead of weighted connectivity matrix that were often implemented in resting-state studies (Iraji et al., 2016; Tomasi, Wang, Wang, & Volkow, 2014).

We investigated the network topological properties over a wide range of the cost values from 0.1 to 0.5 (with increments of 0.01). This selected cost value interval was widely suggested to allow the small-world properties to be properly estimated and the sub-networks to be connected with enough discriminatory power in functional connectivity (Bullmore & Sporns, 2009; Watts & Strogatz, 1998; Xia et al., 2014). Global-efficiency, $E_{glob}(G)$ and local-efficiency, $E_{loc}(G)$, were defined using the following:

$$E_{glob}(G) = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{l_{ij}}, \text{ and } E_{loc}(G) = \frac{1}{N} \sum_{i \in G} E_{glob}(G_i)$$

where l_{ij} was the shortest path length between node i and j , $E_{glob}(G_i)$ the global efficiency of the sub-network G_i that was constructed by the set of nodes that were immediate neighbors of node i (Latora & Marchiori, 2001). The graph is considered a small-world network if it met the criteria: $E_{glob}(G_{regular}) < E_{glob}(G) < E_{glob}(G_{random})$ and $E_{loc}(G_{random}) < E_{loc}(G) < E_{loc}(G_{regular})$, where $E_{glob}(G_{regular})$, $E_{glob}(G_{random})$, $E_{loc}(G_{regular})$ and $E_{loc}(G_{random})$ represent the global- and local-efficiency of the node- and edge-matched regular and random networks, respectively (Achard & Bullmore, 2007). In this study, the network cost range from 0.15 to 0.3 was determined based on these criteria (Figure 1C and 1D).

Nodal-efficiency, $E_{nodal}(G, i)$, was defined as following:

$$E_{nodal}(G, i) = \frac{1}{N-1} \sum_{j \in G} \frac{1}{l_{ij}}$$

Where l_{ij} was the shortest path length between node i and j . It was a local measurement to evaluate the communication efficiency between a node i and all other nodes in the network G (Latora & Marchiori, 2001).

Network hubs in each diagnostic group were also investigated. Degree (D) and betweenness centrality (BC) were utilized to determine whether a node acts as a network hub. The definition of degree (D_i) of node i was the number of edges connected to that node, while the betweenness centrality (BC_i) of node i was defined by the number of all the shortest paths between two nodes (other than node i) that pass through node i (Sporns, Honey, & Kotter, 2007). In each individual, the average values of the degree and betweenness centrality measures of each node over the network cost range of 0.15 – 0.3 were calculated and then normalized by converting into z scores using a normal distribution. The network hubs in each group were identified by estimating the grand sample means of D and BC in each diagnostic group. These standardized values were then tested with a normal distribution. A node i was defined as an **acting network hub** if $1 - \Phi(z_i) < \alpha$, where $\Phi(\cdot)$ was the standard normal cumulative distribution function, and $\alpha = 0.05$ was the level of significance (Li, Xia, Bertisch, Branch, & Delisi, 2012).

2.6. Group Statistic Analyses

Group comparisons of clinical, behavioral and demographical characteristics and fMRI task performance measures were carried out using chi-square tests for discrete variables, and / or

unpaired two-sample t-tests for continuous variables between the controls and ADHD probands, and further between the two ADHD sub-groups (i.e., ADHD-R and ADHD-P).

Group comparisons of the functional brain network topological measures, including efficiency measures $E_{glob}(G)$, $E_{loc}(G)$, and $E_{nodal}(G,i)$ at each i , and network hub measures D_i and BC_i at each i , were carried out using the one-way analysis of covariance (ANCOVA) and post-hoc t-tests among the three groups; controls, ADHD-R and ADHD-P, with gender as a fixed-effect covariate and age as a random-effect covariate. Bonferroni correction was used to control multiple comparisons at $\alpha=0.05$.

Pearson's correlation analyses were applied in the ADHD-R and ADHD-P groups, respectively, to determine associations between the ADHD symptoms (measured using the T scores of the DSM-IV Inattentive and Hyperactive-Impulsive Indices and the fMRI task performance measures) and the brain network measures that showed significant alterations in either ADHD-R or ADHD-P relative to controls. Again, Bonferroni correction was applied to control multiple comparisons at $\alpha=0.05$.

3. RESULTS

3.1. Clinical, Behavioral and Demographic Measures

Demographic measures did not show significant between-group differences (Table 1). All participants achieved a $> 85\%$ rate for response accuracy when performing the fMRI task. Task performance measures, including response accuracy rate, omission error rate, commission error rate, did not show between-group differences. Compared to the controls, the ADHD probands showed significantly larger standard deviation of the reaction time for the cued targets ($p=0.005$) and all targets ($p=0.006$), and significantly longer mean reaction time for the cued targets ($p=0.048$).

3.2. Brain Network Topological Measures

The network global- and local-efficiency measures did not significantly differ among the controls, ADHD-R and ADHD-P. Relative to the ADHD-P, the group of ADHD-R showed significantly higher nodal-efficiency in both right ($p=0.027$) and left MFG ($p=0.029$).

Group comparisons of the network hub measures showed that compared to the controls, the group of ADHD-P had significantly lower degree (D) in right MEG ($p=0.045$), and significantly lower betweenness centrality (BC) in left SFG ($p=0.016$), left MFG ($p=0.002$), right IFG ($p=0.004$) and left precentral nodes ($p=0.003$).

Figure 2 and Table 2 showed the anatomical regions and locations of the acting network hubs (see definition in Section 2.5), which were significantly more active than the average of all the nodes within each of the three diagnostic groups. Distinct patterns of acting network hub distribution were observed among these groups. The group of controls showed acting network hubs in bilateral IPL and functional connections between the left IPL and left SFG hubs, that were not found in the groups of ADHD-R and ADHD-P. The right MFG, and right globus pallidus and putamen were shown as acting network hubs only in the ADHD-R, while left MFG and left precentral gyrus were shown as acting network hubs only in the

ADHD-P. In addition, a unique pattern of significant bilateral MFG functional connectivity in the sub-group of ADHD-P ($p = 0.005$) was observed when compared to controls and the ADHD-R.

3.3 Associations between Brain and Behavioral Measures

As shown in Figure 3, right IFG, right IPL, and bilateral MFG played different roles in ADHD symptom manifestation in the ADHD-R and ADHD-P. Specifically, higher nodal efficiency of right IFG were significantly associated with lower inattentive ($r = -0.592$, $p = 0.01$) and hyperactive/impulsive ($r = -0.544$, $p = 0.02$) symptom severity scores in ADHD-R, but significantly associated with higher inattentive ($r = 0.614$, $p = 0.026$) and hyperactive/impulsive ($r = 0.62$, $p = 0.024$) symptom severity scores in the ADHD-P. Stronger bilateral MFG functional connectivity was significantly associated with increased inattentive symptoms ($r = 0.484$, $p = 0.042$) in the ADHD-R but not in the ADHD-P. Higher nodal efficiencies of right IPL was strongly associated with increased inattentive symptoms in the ADHD-P ($r = 0.56$, $p = 0.046$).

In addition, reduced average reaction time for cued targets was significantly associated with higher right IPL nodal efficiency in the group of ADHD-R ($r = -0.583$, $p = 0.011$).

4. DISCUSSION

To our knowledge, this is the first study in the field to report distinct topological properties of the cue-evoked attention processing brain network in persisters and remitters who were diagnosed with ADHD during childhood. Specifically, missing network hubs in IPL, and lacking fronto-parietal functional communications were observed in the ADHD probands (both ADHD-R and ADHD-P) relative to the controls. Furthermore, the ADHD-P showed even lower nodal efficiency in bilateral MFG relative to the ADHD-R, and a unique pattern of hyper-interactions between bilateral MFG during the cue-evoked attention processing.

A variety of existing clinical and neuroimaging studies have suggested that functional and structural abnormalities in the frontal and parietal areas (especially MFG and IPL) are associated with the onset of childhood ADHD. Both task-based and resting-state fMRI studies have reported functional alterations in MFG in children with ADHD (Li, Branch, De La Fuente, & Xia, 2013; Li, Sroubek, et al., 2012; Posner, Park, & Wang, 2014; Schulz et al., 2017; Yang et al., 2011). Decreased MFG cortical thickness has also been frequently reported in children with ADHD (Batty et al., 2010; Li et al., 2007; Shaw et al., 2006), and was found to be associated with the persistence of more severe childhood ADHD into adulthood (Rajendran et al., 2013; Shaw et al., 2006; Shaw et al., 2013). On the other hand, improved MFG activation and connectivity with other brain regions were found to be associated with the reduction of ADHD symptoms over development (Shaw, Gogtay, & Rapoport, 2010; Shaw et al., 2006). The parietal lobe is another critical component of the attention network, which has been frequently reported in studies of ADHD (Bush, 2011). One of our previous fMRI studies showed significantly decreased right IPL activation for cognitive and motor control in adults with childhood ADHD that has persisted relative to the ADHD-R and healthy controls (Schulz et al., 2017). DTI studies suggested that disrupted white matter integrity in tracts connecting IPL and prefrontal cortices significantly

contribute to the persistence of childhood ADHD into adulthood (Cortese et al., 2013; Makris et al., 2008). Together with these existing results, our findings suggest that severe functional impairments of right hemisphere frontal areas, especially right MFG, may impact normal fronto-parietal functional interactions for sensory and cognitive information processing, and play an important role for the persistence of ADHD symptoms in young adults.

We further found that the nodal efficiency of right IFG was significantly negatively correlated with the ADHD symptom severity scores and reduced mean reaction time for cued targets in ADHD-R, while significantly positively correlated with the ADHD symptom severity scores in the ADHD-P. And nodal efficiency of right IPL was significantly positively correlated with increased inattentive symptoms in the ADHD-P. These findings depict distinct roles of the right frontal lobes for the remission or persistence of ADHD symptoms, respectively; and further suggest the significant involvement of right frontal and parietal lobes for symptom persistence of childhood ADHD.

In the results of this study, the putamen nucleus of the right striatum acted as a network hub for cue-evoked attention processing in ADHD-R. Based on the nature of the Degree and Between-centrality measures, a network hub has significantly more connections with other nodes in the network, but not necessarily has higher nodal efficiency for transferring functional information in the network (Li, Xia, et al., 2012). Structural and functional alterations in the striatum have been widely reported in children (Xia et al., 2012) and adults (Wang, Jiao, Tang, Wang, & Lu, 2013) with ADHD. The super active putamen hub for cue-evoked attention processing in the ADHD-R may suggest the importance of optimal putamen function for symptom remission of childhood ADHD.

Some limitations of the study need to be considered. First, the study included both male and female subjects. Although it is unclear yet whether the neuropathological underpinnings of ADHD have gender differences, clinical studies have observed different symptoms and comorbidity profiles in male and female patients (Quinn & Madhoo, 2014). To partially remove gender-related effect, we added sex as a fixed effect covariate in the group-level analyses. We further compared the network property measures between the 16 male ADHD-R and 13 male ADHD-P and found a pattern of between-group differences similar with the primary results reported in the results section. Female-specific tests were not conducted due to the very limited number of female participants in the study. Second, the sample size of this study is relatively small. Therefore, the findings may have the preliminary nature. Our future research will focus on investigating the neuroanatomical bases of the functional and behavioral aberrances associated with symptom persistence of childhood ADHD, in a much larger sample that improves the statistic power.

5. CONCLUSION

In conclusion, this study found that right frontal lobe functional impairments that may relate to inefficient fronto-parietal functional interactions for sensory and cognitive information processing and symptom persistence in young adults with childhood ADHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- Achard S, & Bullmore E (2007). Efficiency and cost of economical brain functional networks. *PLoS Comput Biol*, 3(2), e17. doi:10.1371/journal.pcbi.0030017 [PubMed: 17274684]
- Bartels A, & Zeki S (2000). The architecture of the colour centre in the human visual brain: new results and a review. *Eur J Neurosci*, 12(1), 172–193. [PubMed: 10651872]
- Batty MJ, Liddle EB, Pitiot A, Toro R, Groom MJ, Scerif G, ... Hollis C (2010). Cortical gray matter in attention-deficit/hyperactivity disorder: a structural magnetic resonance imaging study. *J Am Acad Child Adolesc Psychiatry*, 49(3), 229–238. [PubMed: 20410712]
- Beare R, Adamson C, Bellgrove MA, Vilgis V, Vance A, Seal ML, & Silk TJ (2017). Altered structural connectivity in ADHD: a network based analysis. *Brain Imaging Behav*, 11(3), 846–858. doi:10.1007/s11682-016-9559-9 [PubMed: 27289356]
- Bullmore E, & Sporns O (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci*, 10(3), 186–198. doi:10.1038/nrn2575 [PubMed: 19190637]
- Bush G (2011). Cingulate, frontal, and parietal cortical dysfunction in attention-deficit/hyperactivity disorder. *Biol Psychiatry*, 69(12), 1160–1167. doi:10.1016/j.biopsych.2011.01.022 [PubMed: 21489409]
- Cao M, Shu N, Cao Q, Wang Y, & He Y (2014). Imaging functional and structural brain connectomics in attention-deficit/hyperactivity disorder. *Mol Neurobiol*, 50(3), 1111–1123. doi:10.1007/s12035-014-8685-x [PubMed: 24705817]
- Cao M, Wang JH, Dai ZJ, Cao XY, Jiang LL, Fan FM, ... He Y (2014). Topological organization of the human brain functional connectome across the lifespan. *Dev Cogn Neurosci*, 7, 76–93. doi:10.1016/j.dcn.2013.11.004 [PubMed: 24333927]
- Cao Q, Shu N, An L, Wang P, Sun L, Xia MR, ... He Y (2013). Probabilistic diffusion tractography and graph theory analysis reveal abnormal white matter structural connectivity networks in drug-naïve boys with attention deficit/hyperactivity disorder. *J Neurosci*, 33(26), 10676–10687. doi:10.1523/JNEUROSCI.4793-12.2013 [PubMed: 23804091]
- Casey BJ, Nigg JT, & Durston S (2007). New potential leads in the biology and treatment of attention deficit-hyperactivity disorder. *Curr Opin Neurol*, 20(2), 119–124. doi:10.1097/WCO.0b013e3280a02f78 [PubMed: 17351480]
- Clerkin SM, Schulz KP, Berwid OG, Fan J, Newcorn JH, Tang CY, & Halperin JM (2013). Thalamo-cortical activation and connectivity during response preparation in adults with persistent and remitted ADHD. *Am J Psychiatry*, 170(9), 1011–1019. doi:10.1176/appi.ajp.2013.12070880 [PubMed: 24030612]
- Clerkin SM, Schulz KP, Halperin JM, Newcorn JH, Ivanov I, Tang CY, & Fan J (2009). Guanfacine potentiates the activation of prefrontal cortex evoked by warning signals. *Biol Psychiatry*, 66(4), 307–312. doi:10.1016/j.biopsych.2009.04.013 [PubMed: 19520360]
- Cocchi L, Bramati IE, Zalesky A, Furukawa E, Fontenelle LF, Moll J, ... Mattos P (2012). Altered functional brain connectivity in a non-clinical sample of young adults with attention-deficit/hyperactivity disorder. *J Neurosci*, 32(49), 17753–17761. doi:10.1523/JNEUROSCI.3272-12.2012 [PubMed: 23223295]

- Cortese S, Imperati D, Zhou J, Proal E, Klein RG, Mannuzza S, ... Castellanos FX (2013). White matter alterations at 33-year follow-up in adults with childhood attention-deficit/hyperactivity disorder. *Biol Psychiatry*, 74(8), 591–598. doi:10.1016/j.biopsych.2013.02.025 [PubMed: 23566821]
- Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, & Castellanos FX (2012). Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. *Am J Psychiatry*, 169(10), 1038–1055. doi:10.1176/appi.ajp.2012.11101521 [PubMed: 22983386]
- Di X, Kim EH, Chen P, & Biswal BB (2014). Lateralized resting-state functional connectivity in the task-positive and task-negative networks. *Brain Connect*, 4(9), 641–648. doi:10.1089/brain.2013.0215 [PubMed: 25327308]
- Dosenbach NU, Fair DA, Cohen AL, Schlaggar BL, & Petersen SE (2008). A dual-networks architecture of top-down control. *Trends Cogn Sci*, 12(3), 99–105. doi:10.1016/j.tics.2008.01.001 [PubMed: 18262825]
- Epstein JN, Johnson D, & Conners CK (2006). *Conners' Adult ADHD Diagnostic Interview for DSM-IV*. (North Tonawanda, NY: Multi-Health Systems.).
- Fair DA, Cohen AL, Dosenbach NU, Church JA, Miezin FM, Barch DM, ... Schlaggar BL (2008). The maturing architecture of the brain's default network. *Proc Natl Acad Sci U S A*, 105(10), 4028–4032. doi:10.1073/pnas.0800376105 [PubMed: 18322013]
- Fair DA, Cohen AL, Power JD, Dosenbach NU, Church JA, Miezin FM, ... Petersen SE (2009). Functional brain networks develop from a “local to distributed” organization. *PLoS Comput Biol*, 5(5), e1000381. doi:10.1371/journal.pcbi.1000381 [PubMed: 19412534]
- Fair DA, Nigg JT, Iyer S, Bathula D, Mills KL, Dosenbach NU, ... Milham MP (2012). Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. *Front Syst Neurosci*, 6, 80. doi:10.3389/fnsys.2012.00080 [PubMed: 23382713]
- Fair DA, Posner J, Nagel BJ, Bathula D, Dias TG, Mills KL, ... Nigg JT (2010). Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. *Biol Psychiatry*, 68(12), 1084–1091. doi:10.1016/j.biopsych.2010.07.003 [PubMed: 20728873]
- Fan L, Li H, Zhuo J, Zhang Y, Wang J, Chen L, ... Jiang T (2016). The Human Brainnetome Atlas: A New Brain Atlas Based on Connectional Architecture. *Cereb Cortex*, 26(8), 3508–3526. doi:10.1093/cercor/bhw157 [PubMed: 27230218]
- Faraone SV, Biederman J, & Mick E (2006). The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol Med*, 36(2), 159–165. doi:10.1017/S003329170500471X [PubMed: 16420712]
- First MB, Spitzer RL, Gibbon M, & Williams JBW (2002). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/NP)*. (New York: Biometrics Institute, New York State Psychiatric Institute.).
- Franx W, Oldehinkel M, Oosterlaan J, Heslenfeld D, Hartman CA, Hoekstra PJ, ... Mennes M (2015). The executive control network and symptomatic improvement in attention-deficit/hyperactivity disorder. *Cortex*, 73, 62–72. doi:10.1016/j.cortex.2015.08.012 [PubMed: 26363140]
- Halperin JM, & Schulz KP (2006). Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. *Psychol Bull*, 132(4), 560–581. doi:10.1037/0033-2909.132.4.560 [PubMed: 16822167]
- Hart H, Radua J, Nakao T, Mataix-Cols D, & Rubia K (2013). Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry*, 70(2), 185–198. doi:10.1001/jamapsychiatry.2013.277 [PubMed: 23247506]
- Hong SB, Zalesky A, Fornito A, Park S, Yang YH, Park MH, ... Kim JW (2014). Connectomic disturbances in attention-deficit/hyperactivity disorder: a whole-brain tractography analysis. *Biol Psychiatry*, 76(8), 656–663. doi:10.1016/j.biopsych.2013.12.013 [PubMed: 24503470]
- Iraji A, Calhoun VD, Wiseman NM, Davoodi-Bojd E, Avanaki MRN, Haacke EM, & Kou Z (2016). The connectivity domain: Analyzing resting state fMRI data using feature-based data-driven and model-based methods. *Neuroimage*, 134, 494–507. doi:10.1016/j.neuroimage.2016.04.006 [PubMed: 27079528]

- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, ... Ryan N (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*, 36(7), 980–988. doi:10.1097/00004583-199707000-00021 [PubMed: 9204677]
- Latora V, & Marchiori M (2001). Efficient behavior of small-world networks. *Phys Rev Lett*, 87(19), 198701. doi:10.1103/PhysRevLett.87.198701 [PubMed: 11690461]
- Li X, Branch C, De La Fuente A, & Xia S (2013). Role of pulvinar-cortical functional brain pathways in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*, 52(7), 756–758. doi:10.1016/j.jaac.2013.04.016 [PubMed: 23800489]
- Li X, Jiang J, Zhu W, Yu C, Sui M, Wang Y, & Jiang T (2007). Asymmetry of prefrontal cortical convolution complexity in males with attention-deficit/hyperactivity disorder using fractal information dimension. *Brain Dev*, 29(10), 649–655. doi:10.1016/j.braindev.2007.04.008 [PubMed: 17573219]
- Li X, Sroubek A, Kelly MS, Lesser I, Sussman E, He Y, ... Foxe JJ (2012). Atypical pulvinar-cortical pathways during sustained attention performance in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*, 51(11), 1197–1207 e1194. doi:10.1016/j.jaac.2012.08.013 [PubMed: 23101745]
- Li X, Xia S, Bertisch HC, Branch CA, & Delisi LE (2012). Unique topology of language processing brain network: a systems-level biomarker of schizophrenia. *Schizophr Res*, 141(2–3), 128–136. doi:10.1016/j.schres.2012.07.026 [PubMed: 22917951]
- Liu T, Chen Y, Lin P, & Wang J (2015). Small-World Brain Functional Networks in Children With Attention-Deficit/Hyperactivity Disorder Revealed by EEG Synchrony. *Clin EEG Neurosci*, 46(3), 183–191. doi:10.1177/1550059414523959 [PubMed: 24699437]
- Loney J, & Milich R (1982). Hyperactivity, inattention, and aggression in clinical practice,. In Wolraich M & R. D. (Eds.). *Advances in Developmental and Behavioral Pediatrics*(Greenwich, CT: JAI Press), pp. 113–147.
- Makris N, Buka SL, Biederman J, Papadimitriou GM, Hodge SM, Valera EM, ... Seidman LJ (2008). Attention and executive systems abnormalities in adults with childhood ADHD: A DT-MRI study of connections. *Cereb Cortex*, 18(5), 1210–1220. doi:10.1093/cercor/bhm156 [PubMed: 17906338]
- Mattfeld AT, Gabrieli JD, Biederman J, Spencer T, Brown A, Kotte A, ... Whitfield-Gabrieli S (2014). Brain differences between persistent and remitted attention deficit hyperactivity disorder. *Brain*, 137(Pt 9), 2423–2428. doi:10.1093/brain/awu137 [PubMed: 24916335]
- Meunier D, Fonlupt P, Saïve AL, Plailly J, Ravel N, & Royet JP (2014). Modular structure of functional networks in olfactory memory. *Neuroimage*, 95, 264–275. doi:10.1016/j.neuroimage.2014.03.041 [PubMed: 24662576]
- Pastor P, Reuben C, Duran C, & Hawkins L (2015). Association between diagnosed ADHD and selected characteristics among children aged 4–17 years: United States, 2011–2013. *NCHS Data Brief*(201), 201. [PubMed: 25974000]
- Posner J, Park C, & Wang Z (2014). Connecting the dots: a review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder. *Neuropsychol Rev*, 24(1), 3–15. doi:10.1007/s11065-014-9251-z [PubMed: 24496902]
- Power JD, Barnes KA, Snyder AZ, Schlaggar BL, & Petersen SE (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage*, 59(3), 2142–2154. doi:10.1016/j.neuroimage.2011.10.018 [PubMed: 22019881]
- Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, ... Petersen SE (2011). Functional network organization of the human brain. *Neuron*, 72(4), 665–678. doi:10.1016/j.neuron.2011.09.006 [PubMed: 22099467]
- Quinn PO, & Madhoo M (2014). A review of attention-deficit/hyperactivity disorder in women and girls: uncovering this hidden diagnosis. *Prim Care Companion CNS Disord*, 16(3). doi:10.4088/PCC.13r01596
- Rajendran K, Trampush JW, Rindskopf D, Marks DJ, O'Neill S, & Halperin JM (2013). Association between variation in neuropsychological development and trajectory of ADHD severity in early

- childhood. *Am J Psychiatry*, 170(10), 1205–1211. doi:10.1176/appi.ajp.2012.12101360 [PubMed: 23897408]
- Rissman J, Gazzaley A, & D'Esposito M (2004). Measuring functional connectivity during distinct stages of a cognitive task. *Neuroimage*, 23(2), 752–763. doi:10.1016/j.neuroimage.2004.06.035 [PubMed: 15488425]
- Schulz KP, Li X, Clerkin SM, Fan J, Berwid OG, Newcorn JH, & Halperin JM (2017). Prefrontal and parietal correlates of cognitive control related to the adult outcome of attention-deficit/hyperactivity disorder diagnosed in childhood. *Cortex*, 90, 1–11. doi:10.1016/j.cortex.2017.01.019 [PubMed: 28292705]
- Shaffer D, Fisher P, Dulcan MK, Davies M, Piacentini J, Schwab-Stone ME, ... Regier DA (1996). The NIMH Diagnostic Interview Schedule for Children Version 2.3 (DISC-2.3): description, acceptability, prevalence rates, and performance in the MECA Study. *Methods for the Epidemiology of Child and Adolescent Mental Disorders Study*. *J Am Acad Child Adolesc Psychiatry*, 35(7), 865–877. [PubMed: 8768346]
- Shaffer D, Fisher P, Piacentini J, Schwab-Stone M, & Wicks J (1989). *Diagnostic Interview Schedule for Children-Parent Version (DISC-2.1P)*. (New York: New York Psychiatric Institute.).
- Shaw P, Gogtay N, & Rapoport J (2010). Childhood psychiatric disorders as anomalies in neurodevelopmental trajectories. *Hum Brain Mapp*, 31(6), 917–925. doi:10.1002/hbm.21028 [PubMed: 20496382]
- Shaw P, Lerch J, Greenstein D, Sharp W, Clasen L, Evans A, ... Rapoport J (2006). Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry*, 63(5), 540–549. doi:10.1001/archpsyc.63.5.540 [PubMed: 16651511]
- Shaw P, Malek M, Watson B, Greenstein D, de Rossi P, & Sharp W (2013). Trajectories of cerebral cortical development in childhood and adolescence and adult attention-deficit/hyperactivity disorder. *Biol Psychiatry*, 74(8), 599–606. doi:10.1016/j.biopsych.2013.04.007 [PubMed: 23726514]
- Shaw P, Sudre G, Wharton A, Weingart D, Sharp W, & Sarlls J (2015). White matter microstructure and the variable adult outcome of childhood attention deficit hyperactivity disorder. *Neuropsychopharmacology*, 40(3), 746–754. doi:10.1038/npp.2014.241 [PubMed: 25241803]
- Shehzad Z, Kelly AM, Reiss PT, Gee DG, Gotimer K, Uddin LQ, ... Milham MP (2009). The resting brain: unconstrained yet reliable. *Cereb Cortex*, 19(10), 2209–2229. doi:10.1093/cercor/bhn256 [PubMed: 19221144]
- Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, ... Matthews PM (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, 23 Suppl 1, S208–219. doi:10.1016/j.neuroimage.2004.07.051 [PubMed: 15501092]
- Sporns O, Honey CJ, & Kotter R (2007). Identification and classification of hubs in brain networks. *PLoS One*, 2(10), e1049. doi:10.1371/journal.pone.0001049 [PubMed: 17940613]
- Suades-Gonzalez E, Forns J, Garcia-Esteban R, Lopez-Vicente M, Esnaola M, Alvarez-Pedrerol M, ... Sunyer J (2017). A Longitudinal Study on Attention Development in Primary School Children with and without Teacher-Reported Symptoms of ADHD. *Front Psychol*, 8, 655. doi:10.3389/fpsyg.2017.00655 [PubMed: 28559855]
- Supekar K, Musen M, & Menon V (2009). Development of large-scale functional brain networks in children. *PLoS Biol*, 7(7), e1000157. doi:10.1371/journal.pbio.1000157 [PubMed: 19621066]
- Tomasi D, Wang R, Wang GJ, & Volkow ND (2014). Functional connectivity and brain activation: a synergistic approach. *Cereb Cortex*, 24(10), 2619–2629. doi:10.1093/cercor/bht119 [PubMed: 23645721]
- Wang L, Zhu C, He Y, Zang Y, Cao Q, Zhang H, ... Wang Y (2009). Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. *Hum Brain Mapp*, 30(2), 638–649. doi:10.1002/hbm.20530 [PubMed: 18219621]
- Wang X, Jiao Y, Tang T, Wang H, & Lu Z (2013). Altered regional homogeneity patterns in adults with attention-deficit hyperactivity disorder. *Eur J Radiol*, 82(9), 1552–1557. doi:10.1016/j.ejrad.2013.04.009 [PubMed: 23684384]

- Wang X, Ren Y, & Zhang W (2017). Depression Disorder Classification of fMRI Data Using Sparse Low-Rank Functional Brain Network and Graph-Based Features. *Comput Math Methods Med*, 2017, 3609821. doi:10.1155/2017/3609821 [PubMed: 28487746]
- Watts DJ, & Strogatz SH (1998). Collective dynamics of ‘small-world’ networks. *Nature*, 393(6684), 440–442. doi:10.1038/30918 [PubMed: 9623998]
- Wig GS, Laumann TO, Cohen AL, Power JD, Nelson SM, Glasser MF, ... Petersen SE (2014). Parcellating an individual subject’s cortical and subcortical brain structures using snowball sampling of resting-state correlations. *Cereb Cortex*, 24(8), 2036–2054. doi:10.1093/cercor/bht056 [PubMed: 23476025]
- Xia S, Foxe JJ, Sroubek AE, Branch C, & Li X (2014). Topological organization of the “small-world” visual attention network in children with attention deficit/hyperactivity disorder (ADHD). *Front Hum Neurosci*, 8, 162. doi:10.3389/fnhum.2014.00162 [PubMed: 24688465]
- Xia S, Li X, Kimball AE, Kelly MS, Lesser I, & Branch C (2012). Thalamic shape and connectivity abnormalities in children with attention-deficit/hyperactivity disorder. *Psychiatry Res*, 204(2–3), 161–167. doi:10.1016/j.psychres.2012.04.011 [PubMed: 23149038]
- Yang H, Wu QZ, Guo LT, Li QQ, Long XY, Huang XQ, ... Gong QY (2011). Abnormal spontaneous brain activity in medication-naïve ADHD children: a resting state fMRI study. *Neurosci Lett*, 502(2), 89–93. doi:10.1016/j.neulet.2011.07.028 [PubMed: 21810451]

Figure 1:

Node locations and small-world properties of the functional brain networks. (A): cue-evoked attention processing-related activation map in the group of controls; (B): locations of the seeds determined from the combination of activation maps in controls and ADHD probands; (C): the 52 × 52 functional connectivity matrices in controls and probands; and (D): the small-world properties of the functional brain networks. The global and local efficiency curves of both controls and probands showed small world pattern over a range of 0.15 – cost 0.3. The Degree distribution curves fitted by an exponentially truncated power of the form, $P(k) \sim k^{\alpha-1} e^{-k/k_c}$, showed the estimated $\alpha = 1.618$, $k_c = 5.092$ for the control group and $\alpha = 1.558$, $k_c = 5.438$ for the probands group. (CON: controls; PRO: ADHD probands; L: left and R: right hemisphere.)

Figure 3:

Regions that showed significant correlations between their nodal efficiency and the clinical symptom measures, including the T scores of inattentive and hyperactive/impulsive symptoms, in the remitters and persisters. (E_Nodal: nodal efficiency; C_Functional: functional connectivity; T_I: T score of the inattentive symptoms; T_H: T score of the hyperactive/impulsive symptoms).

Table 1:

Demographic and clinical characteristics in groups of controls and ADHD probands (and further in the sub-groups of remitters and persisters of the ADHD probands).

	Controls (N = 33)	ADHD (N = 36)		Remitted (N=19)	Persistent (N=17)	
	Mean (SD)	Mean (SD)	<i>p</i>	Mean (SD)	Mean (SD)	<i>p</i>
Age	24.27 (2.2)	24.69 (2.1)	<i>0.44</i>	24.79 (2.2)	24.55 (2.2)	<i>0.77</i>
Full-scale IQ	102.81(15.5)	99.11 (14.5)	<i>0.33</i>	99.57 (14.9)	98.46 (14.9)	<i>0.84</i>
Socioeconomic status	50.28 (14.1)	42.46 (16.9)	<i>0.05</i>	43.53 (15.2)	41.19 (19.2)	<i>0.69</i>
Conners' Adult ADHD Rating Scale (T score)						
Inattentive	45.19 (8.3)	55.29 (12.6)	<i><0.001</i>	49.94 (10.9)	62.69 (11.1)	<i><0.01</i>
Hyperactive/impulsive	42.73 (6.1)	52.36 (12.3)	<i><0.001</i>	46.06 (9.0)	61.08 (11.0)	<i><0.001</i>
ADHD Total	43.42 (7.7)	55.48 (14.2)	<i><0.001</i>	48.44 (11.2)	65.23 (12.1)	<i><0.001</i>
ADHD semi-structured interview (number of symptoms)	0.81(1.3)	6.26 (4.8)	<i><0.001</i>	2.52 (1.8)	10.69 (3.2)	<i><0.01</i>
	N (%)	N (%)	<i>p</i>	N (%)	N (%)	<i>p</i>
Male	28 (84.8)	29 (80.6)	<i>0.64</i>	16 (84.2)	13 (76.5)	<i>0.56</i>
Right-handed	31 (93.9)	32 (88.9)	<i>0.46</i>	17 (89.5)	15 (88.2)	<i>0.91</i>
Race			<i>0.21</i>			<i>0.42</i>
Caucasian	12 (36.4)	17 (47.2)		9 (47.4)	8 (47.1)	
African American	12 (36.4)	5 (13.9)		4 (21.1)	1 (5.9)	
More than one race	6 (18.2)	6 (16.7)		4 (21.1)	2 (11.8)	
Asian	2 (6.1)	0		0	0	
Ethnicity			<i>0.33</i>			<i>0.96</i>
Hispanic/Latino	10 (30.3)	15 (41.7)		8 (42.1)	7 (41.2)	
Current mood disorder	4 (12.1)	6 (16.7)	<i>0.59</i>	3 (15.8)	3 (17.6)	<i>0.88</i>
Current anxiety disorder	8 (24.2)	10 (27.8)	<i>0.74</i>	3 (15.8)	7 (41.2)	<i>0.09</i>
Current substance disorder	7 (21.2)	13(36.1)	<i>0.17</i>	8 (42.1)	5 (29.4)	<i>0.43</i>

Table 2:

Acting network hubs in each of the groups of controls, ADHD remitters, and ADHD persisters (L. = left side; R. = right side).

		Controls			Remitters		Persisters	
Node ID	Anatomical Region	BA	Dg	BC	Dg	BC	Dg	BC
1	L. Superior frontal gyrus	8						
3	L. Middle frontal gyrus	9/46						
7	R. Middle frontal gyrus	9/46						
9	R. Inferior frontal gyrus	45						
10	L. Inferior frontal gyrus	44						
11	R. Inferior frontal gyrus	44						
13	R. Inferior frontal gyrus	4						
15	L. Precentral gyrus (tongue and larynx region)	4						
16	R. Precentral gyrus (tongue and larynx region)	4						
26	R. Inferior parietal lobule	40						
28	L. Inferior parietal gyrus	40						
35	L. Insula							
36	R. Insula							
37	L. Cingulate gyrus	24						
38	R. Cingulate gyrus	24						
40	R. Globus pallidus							
45	R. Dorsolateral putamen							
49	L. Thalamus							
50	R. Thalamus							

BA=Brodmann's Area; Dg=Degree; BC=Between-centrality.

BOLD fonts indicate the nodes that showed different roles in the three clinical groups.