



## RESEARCH ARTICLE

# Altered single-subject gray matter structural networks in drug-naïve attention deficit hyperactivity disorder children

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## Abstract

Altered topological organization of brain structural covariance networks has been observed in attention deficit hyperactivity disorder (ADHD). However, results have been inconsistent, potentially related to confounding medication effects. In addition, since structural networks are traditionally constructed at the group level, variabilities in individual structural features remain to be well characterized. Structural brain imaging with MRI was performed on 84 drug-naïve children with ADHD and 83 age-matched healthy controls. Single-subject gray matter (GM) networks were obtained based on areal similarities of GM, and network topological properties were analyzed using graph theory. Group differences in each topological metric were compared using nonparametric permutation testing. Compared with healthy subjects, GM networks in ADHD patients demonstrated significantly altered topological characteristics, including higher global and local efficiency and clustering coefficient, and shorter path length. In addition, ADHD patients exhibited abnormal centrality in corticostriatal circuitry including the superior frontal gyrus, orbitofrontal gyrus, medial superior frontal gyrus, precentral gyrus, middle temporal gyrus, and pallidum (all  $p < .05$ , false discovery rate [FDR] corrected). Altered global and nodal topological efficiencies were associated with the severity of hyperactivity symptoms and the performance on the Stroop and Wisconsin Card Sorting Test tests (all  $p < .05$ , FDR corrected). ADHD combined and inattention subtypes were differentiated by nodal attributes of amygdala ( $p < .05$ , FDR corrected). Alterations in GM network topologies were observed in drug-naïve ADHD patients, in particular in frontostriatal loops and amygdala. These alterations may contribute to impaired cognitive functioning and impulsive behavior in ADHD.

## KEYWORDS

attention deficit hyperactivity disorder, cognitive deficits, gray matter networks, psychoradiology, symptom severity

Ying Chen and Du Lei contributed equally to this work.

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## 1 | INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental condition affecting 2–7% of school-age children (Sayal, Prasad, Daley, Ford, & Coghill, 2018). Psychoradiology studies have documented structural brain alterations in patients, though typically at the level of individual regions rather than the whole brain connectome (Konrad & Eickhoff, 2010; Nakao, Radua, Rubia, & Mataix-Cols, 2011; Samea et al., 2019; Li et al., 2021; Gong, 2020; Sun, et al. 2015; Lui, et al. 2016). Further, inconsistencies in prior work may be related to differences in clinical variables such as comorbidity and medication history. Notably, evidence from both animal models and human studies has demonstrated altered synaptic plasticity in prefrontal, hippocampal, and striatal regions resulting from stimulant medication, as well as morphological deficits associated with psychostimulant use (Crowley, Cody, Davis, Lovinger, & Mateo, 2014; Jenson et al., 2015; Urban, Li, & Gao, 2013). Moreover, the gray matter (GM) morphometry of higher cortical regions crucial for cognitive and emotional processing is influenced by ADHD comorbidity (Bayard et al., 2020; Langer, Benjamin, Becker, & Gaab, 2019; Noordermeer et al., 2017; Yerys et al., 2019). Therefore, medication and comorbidity are potential confounds for MRI studies of ADHD.

To best control for these confounding factors, we have previously explored GM volume abnormalities in drug-naïve ADHD patients with limited comorbidities, and found altered GM volumes in orbitofrontal cortex and posterior mid-cingulate cortex, which were correlated with deficits of cognitive flexibility (He et al., 2015). These and other results provide initial evidence for morphological abnormalities in untreated ADHD patients. However, since the brain itself is a complex network of interconnected regions (Niu et al., 2018; Zhang et al., 2020), it is important to consider the role of regional alterations in brain volumes in the context of the whole brain network topology. The examination of the large-scale structural network in ADHD patients may thus provide a more comprehensive understanding of brain alterations in ADHD and their relationship to cognitive functioning, as it has in other disorders (Zhang et al., 2020).

To date, only two studies have reported altered GM organization in ADHD children (Griffiths et al., 2016; Saad et al., 2017). Both of these studies constructed brain networks at the group level using a structural covariance approach, which limits understanding of effects as the individual level such as their relationship with clinical variables. Moreover, patients in these studies were receiving medication and had multiple comorbidities, both of which may affect the organization of brain networks in ADHD patients.

Here, we computed single-subject GM networks based on the similarities of GM between brain regions (Tijms, Seriès, Willshaw, & Lawrie, 2012), and applied graph theoretical analysis to investigate the constructed networks in a large sample of drug-naïve ADHD children without psychiatric comorbidities. We also examined whether clinical phenotypes of ADHD were associated with changes in brain GM networks. The Stroop Color-Word Interference Test and

Wisconsin Card Sorting Test (WCST) were used to assess conflict monitoring and cognitive flexibility. We hypothesized that the topological organization of structural brain networks, for example, nodal centrality in frontostriatal loops, were altered in ADHD, and that alterations relate to symptom severity and cognitive deficits. Second, based on more impulsive symptoms in ADHD combined subtype (ADHD-C), we expected more widespread topological alterations in ADHD-C than ADHD inattentive subtype (ADHD-I).

## 2 | METHODS

### 2.1 | Participants

Then, 118 and 104 healthy control (HC) participants were included in the study. Children with ADHD (age range 7–16 years) who were drug-naïve and without psychiatric or significant medical comorbidities were recruited from the Mental Health Center of West China Hospital of Sichuan University. Diagnoses of ADHD were confirmed by two experienced clinical psychiatrists according to the DSM-IV criteria. Exclusion criteria included a history of conduct disorder, oppositional defiant disorder, Tourette's disorder, any major Axis I psychiatric disorder, head trauma, neurologic disorders or neurosurgery; current or past treatment with stimulants or other medications for symptoms of ADHD; left-handedness (assessed using Annett's Hand Preference Questionnaire); the scores of age-appropriate Wechsler Intelligence Scale for Children (IQ) lower than 90 points and any systemic illness that might affect brain anatomy and function. HCs were recruited from local communities and were matched for age and educational level with the ADHD patients. All HCs were screened using the Structured Clinical Interview for DSM-IV-Non-patient Edition to exclude any major Axis I psychiatric diagnosis. Individuals with a history of receiving psychotropic medications or having a known history of psychiatric illness in a first-degree relative were also excluded. Other exclusion criteria were the same as those for the ADHD group. All participants and their guardians provided written informed assent or consent as appropriate. The study was approved by the research ethics committee of West China Hospital of Sichuan University.

### 2.2 | Behavioral and cognitive assessments

The revised Conners' Parent Rating Scale and the Child Behavior Checklist (with ratings provided by participants' parents) were used to characterize clinical features of ADHD (Achenbach, 1991; Conners, 1999).

The Stroop Color Word Test was used to assess conflict processing. Participants were asked to name words presented in color congruent with word (e.g., word blue in blue print), then words with incongruent color. The color-word interference time was measured, which is addition time required to complete incongruent relative to congruent items.

The WCST (64-card version) was used to evaluate cognitive flexibility. Perseverative errors, nonperseverative errors, total errors, and categories achieved were recorded.

## 2.3 | MRI data acquisition

The scans were acquired using a 3-T MRI system (Trio; Siemens, Erlangen, Germany) with an eight-channel phased-array head coil. T1-weighted images were acquired using a magnetization prepared rapid gradient echo sequence (time of repetition = 1,900 ms; time of echo = 2.5 ms; flip angle = 9°) with  $256 \times 256$  matrix over a field of view of  $256 \times 256$  mm and 176 sagittal slices of 1 mm thickness.

## 2.4 | Data preprocessing

Structural image preprocessing was performed using Statistical Parametric Mapping (SPM) software (<http://www.fil.ion.ucl.ac.uk/spm/software/SPM8>). In brief, individual structural images were segmented into GM, white matter, and cerebrospinal fluid using the unified segmentation model. All automatic segmentations were then visually confirmed and spatially normalized to the Montreal Neurological Institute coordinate space, in which the template was defined using all participants in our study. Finally, the data were resliced to  $2 \times 2 \times 2$  mm<sup>3</sup> voxels and spatially smoothed (Gaussian kernel with a full width at half maximum of 6 mm). Of note, an experienced neuroradiologist inspected conventional MR imaging examinations of all participants to exclude individuals with excessive motion artifacts or vibration artifacts and gross neuroradiologic abnormalities. Then, 34 patients and 21 HC participants were excluded from statistical analysis due to excessive head motion artifacts, leaving a total of 84 drug-naïve ADHD participants (44 subjects with the combined subtype of ADHD and 40 subjects with the inattentive subtype) and 83 HC who were included in statistical analyses.

## 2.5 | Individual structural network construction

Single-subject GM networks were obtained based on interregional similarities using a completely automated and data-driven method that has been previously described in Tijms et al. (2012). Specifically, the GM segmentation of each individual was divided into a set of cubes, each containing  $3 \times 3 \times 3$  voxels. Each cube was defined as a node in the network, and edges were computed as the structural morphology similarities between two cubes using Pearson correlation coefficients. The maximum correlation coefficient over different rotations of the seed cube was identified to estimate cube similarity, because the angle of orientation of two cubes may reduce similarity values. Unweighted and undirected graphs were subsequently constructed by binarizing the similarity matrices, only keeping significant correlations after the false discovery rate (FDR) correction (Genovese, Lazar, & Nichols, 2002). Because the properties of the network vary

with the size of the network, it is crucial to normalize the derived GM networks in case-control studies to ensure all participants have the same number of nodes. For this reason, we followed the method proposed by Batalle et al. (2013) to normalize individual GM networks based on the unified automated anatomical labeling (AAL) atlas including a total of 90 nodes. In particular, each cube was assigned to the AAL region that encompassed the greatest number of the cube's voxels. The connectivity strength of two AAL regions was defined as the ratio of actual significant correlations to the total possible connections between nodes, thereby circumscribing the range between 0 and 1. This process established a  $90 \times 90$  weighted normalized network for each participant.

## 2.6 | Network properties

Network properties were calculated using GREYNET software (<http://www.nitrc.org/projects/gretna>) (Wang et al., 2015). A range of sparsity (S) thresholds ( $.10 < S < .34$  with an interval of .01) was applied to the correlation matrices. The sparsity range was selected to ensure the small-worldness nature of the thresholded networks. The area under the curve (AUC), which reflects measures across the sparsity parameter S, was calculated for each network metric to provide a summary scalar of the topological organization of the brain networks.

The topological properties of brain networks at both the global and nodal levels were calculated at each sparsity threshold. Small-world global parameters included the clustering coefficient (Cp), normalized clustering coefficient ( $\gamma$ ), characteristic path length (Lp), normalized characteristic path length ( $\lambda$ ), and small-world ( $\sigma$ ) parameters. Network efficiency parameters included global efficiency (Eglob) and local efficiency (Eloc). The nodal-level properties included nodal efficiency, nodal degree, and betweenness centrality.

## 2.7 | Statistical analysis

Using SPSS software, a two-sample *t* test was used to test for group differences in age, IQ, Stroop test scores and WSCT performance, and a chi-square test was used to test for sex differences between the two groups.

The network-based statistics (NBS) method ([www.nitrc.org/projects/nbs/](http://www.nitrc.org/projects/nbs/)) was used to identify the specific pairs of region pairs that exhibited between-group differences in nodal characteristics. First, nodes that exhibited significant between-group differences in at least one of the three nodal centralities (node degree, efficiency, and betweenness) were chosen. A subnetwork connection matrix for each participant was then created. Finally, a set of suprathreshold links between connected components were identified using NBS metrics (threshold = 2.5,  $p < .05$ ) (Zalesky, Fornito, & Bullmore, 2010).

The AUCs of network parameters between the ADHD and control groups for each metric (small-world, network efficiency and regional centrality measures) were compared using nonparametric

permutation tests (Lei et al., 2015). The Benjamin–Hochberg FDR was used to adjust for multiple comparisons (Genovese et al., 2002).

After significant between-group differences were identified in the network metrics, exploratory partial correlation analysis was used to assess associations of these metrics with clinical symptoms and cognitive performance using age and sex as covariates. To further identify the significant predictors of clinical symptoms and cognitive performance, significant correlations with clinical symptoms and cognitive performance network metrics were substituted subsequently into multiple stepwise regression analysis (FDR  $q$  value selected to maintain false positive error rate  $< .05$ ).

The same statistical approach was applied to identify possible demographic, clinical characteristic, network metrics differences between ADHD-C and ADHD-I subtypes.

### 3 | RESULTS

#### 3.1 | Participant characteristics

Demographic variables, including age sex, and IQ, did not significantly differ between the ADHD and control groups (both  $p > .05$ ) (Table 1). Compared with control participants, children with ADHD had longer color interference time on the Stroop test (all  $p < .001$ ). In WCST, ADHD participants had more total errors, perseverative errors and nonperseverative errors, and fewer categories achieved than control participants (all  $p < .001$ ) (Table 1). The combined (ADHD-C) and inattentive (ADHD-I) subtypes of ADHD were not significantly different

between demographic variables and cognitive variables, but the ADHD combined subtype has higher hyperactivity index and attention problem scores than the inattentive subtype (Table 1).

#### 3.2 | Difference between ADHD and HC subjects

Compared with controls, children with ADHD exhibited decreased characteristic path length  $L_p$  ( $p = .004$ ) and increased clustering coefficient  $C_p$  ( $p = .002$ ). No significant differences were observed in normalized clustering coefficient  $\gamma$ , normalized characteristic path length  $\lambda$ , or small-worldness. With respect to network efficiency, both global efficiency ( $p = .004$ ) and local efficiency ( $p = .001$ ) were higher in the ADHD group (Figure 1).

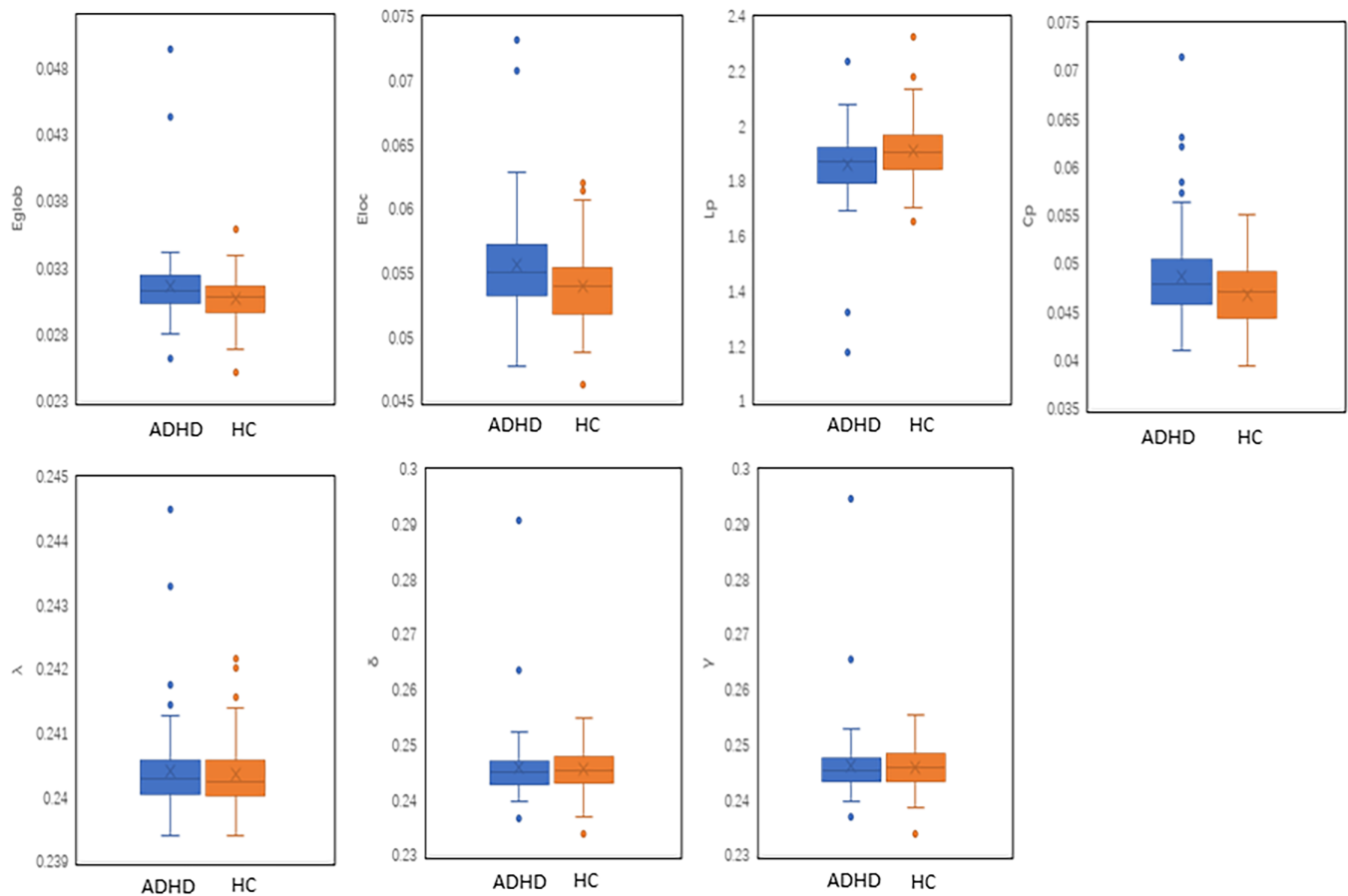
For nodal metrics, compared with controls, the ADHD group exhibited increased nodal degree in the right precentral gyrus, left superior frontal gyrus and right pallidum, increased nodal efficiency in the left middle frontal gyrus, left superior frontal gyrus, right pallidum, and left middle temporal gyrus, increased nodal betweenness centrality in the right pallidum, and decreased nodal betweenness centrality in the left superior frontal gyrus (all  $p < .05$ , FDR corrected) (Figure 2, Table S2).

A network with 6 nodes and 10 edges was identified that was significantly altered in ADHD using NBS (Figure 3). The nodes included components of dorsolateral corticostriatal circuitry (including dorsolateral superior frontal gyrus, medial superior frontal gyrus, middle temporal gyrus, precentral gyrus, and pallidum) extending to orbitofrontal–striatal circuits. Connectivity between

**TABLE 1** Demographic and clinical characteristics of the participants

|  | All participants ( $n = 187$ ) |                               | $p$   | ADHD participants          |   | $p$   |
|--|--------------------------------|-------------------------------|-------|----------------------------|---|-------|
|  | ADHD ( $n = 84$ )              | Control subjects ( $n = 83$ ) |       | Combined (Li et al., 2014) | Inattentive (Cubillo, Halari, Smith, Taylor, & Rubia, 2012) |       |
| Age (years)  | 10.01 $\pm$ 2.34               | 10.39 $\pm$ 2.18              | .293  | 9.74 $\pm$ 2.45            | 10.06 $\pm$ 2.35  | .537  |
| Gender   | 12/72                          | 14/69                         | .645  | 7/37                       | 5/35  | .66   |
| IQ   | 103.27 $\pm$ 7.7               | 106.57 $\pm$ 7.86             | .53   | 101.67 $\pm$ 5.95          | 102.79 $\pm$ 8.19   | .659  |
| Revised Conners' Parent Rating Scale hyperactivity index | 13.68 $\pm$ 6.13               | 4.98 $\pm$ 4.44               | <.001 | 16.57 $\pm$ 5.18           | 10.18 $\pm$ 5.36  | <.001 |
| Child behavior checklist attention problem scores        | 9.53 $\pm$ 3.49                | 3.69 $\pm$ 3.20               | <.001 | 10.37 $\pm$ 3.17           | 8.47 $\pm$ 3.64   | .017  |
| Color-Word interference time (s) of Stroop test          | 168.13 $\pm$ 86.73             | 98.33 $\pm$ 35.89             | <.001 | 184.34 $\pm$ 100.13        | 149.37 $\pm$ 64.35  | .068  |
| WCST   |                                |                               |       |                            |   |       |
| Total correct  | 29.12 $\pm$ 10.06              | 34.63 $\pm$ 6.67              | <.001 | 28.33 $\pm$ 9.85           | 30.05 $\pm$ 10.36   | .441  |
| Total errors   | 17.13 $\pm$ 11.75              | 10.34 $\pm$ 8.22              | <.001 | 17.67 $\pm$ 11.95          | 16.5 $\pm$ 11.64  | .654  |
| Perseverative errors                                     | 5.36 $\pm$ 6.08                | 2.51 $\pm$ 3.17               | <.001 | 4.98 $\pm$ 5.31            | 5.82 $\pm$ 6.94   | .535  |
| Nonperseverative errors                                  | 11.77 $\pm$ 7.49               | 7.84 $\pm$ 5.71               | <.001 | 12.69 $\pm$ 8.01           | 10.68 $\pm$ 6.78  | .227  |
| Categories completed                                     | 4.16 $\pm$ 1.87                | 5.16 $\pm$ 1.62               | <.001 | 4.04 $\pm$ 1.85            | 4.29 $\pm$ 1.92   | .555  |

Abbreviations: ADHD, attention deficit/hyperactivity disorder; IQ, Wechsler Intelligence Scale; WCST, Wisconsin Card Sorting Test.



**FIGURE 1** Graphs show differences global metrics between the attention deficit hyperactivity disorder (ADHD) and healthy controls (HCs). Compared with the controls, ADHD exhibited an increased global efficiency (Eglob) ( $p = .004$ ), local efficiency (Eloc) ( $p = .001$ ), and clustering coefficient (Cp) ( $p = .002$ ) and a decreased characteristic path length (Lp) ( $p = .004$ ), but no significant differences in normalized clustering coefficient ( $\gamma$ ), normalized characteristic path length ( $\lambda$ ), or small-worldness ( $\sigma$ )

these nodes in ADHD was higher than in controls (all  $p < .001$ , FDR corrected).

Stepwise regression models examining relations between topological structures of structural brain networks and cognitive function in ADHD revealed that global efficiency was related to Color-Word interference time on the Stroop test. Clustering coefficient and nodal degree of left medial superior frontal gyrus were related to perseverative errors of WCST. Nodal efficiency of left orbital cortex was related to hyperactivity symptoms of ADHD (all  $p < .05$ , FDR corrected) (Table S4, Figure 4).

### 3.3 | Differences between combined and inattentive subtypes

ADHD-C children and ADHD-I children were not significantly different in small-world properties. For nodal metrics, ADHD-C children exhibited increases in all nodal metrics of left amygdala (all  $p < .05$ , FDR corrected) (Figure 2). When subsequent stepwise regression analyses were performed in both ADHD-C children and

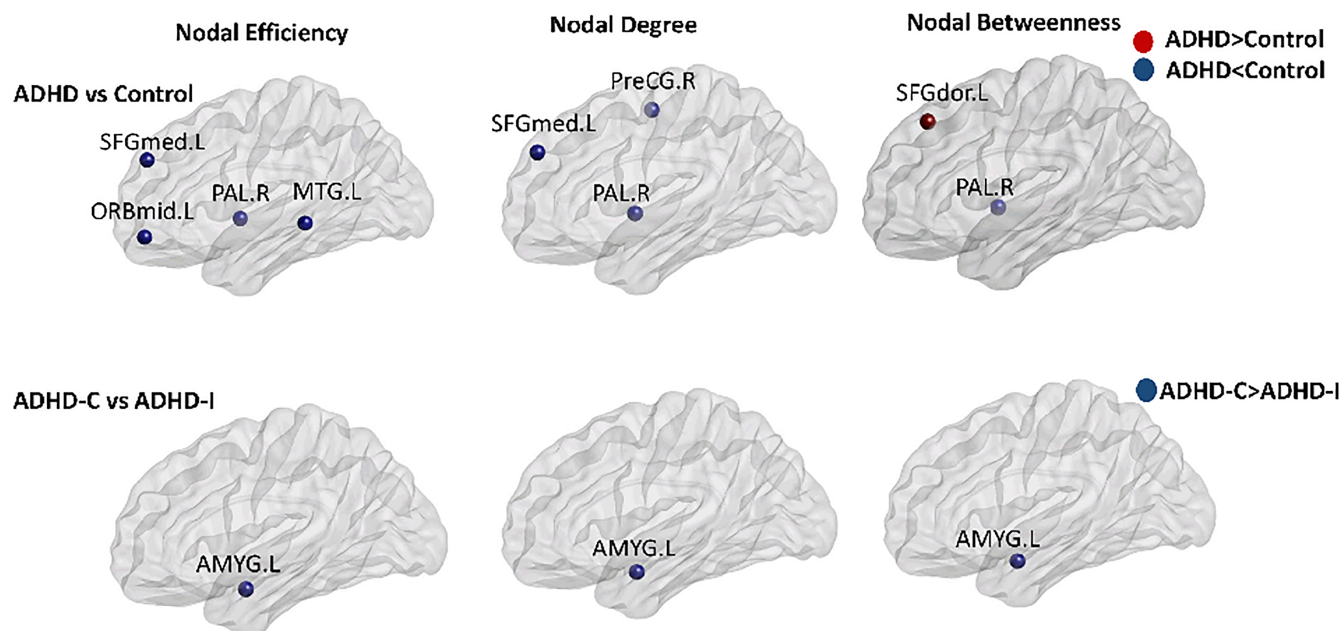
ADHD-I children separately, we observed no differences in correlations between network metrics and cognitive impairment or symptoms of ADHD.

## 4 | DISCUSSION

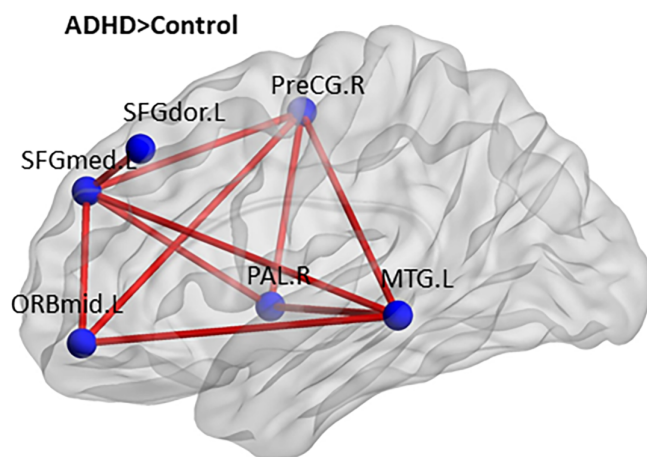
The present study investigated changes in GM networks in drug-naïve ADHD children. Compared with healthy subjects, ADHD patients demonstrated altered large-scale brain network topologies characterized by significantly shorter path length and higher clustering. The alterations were identified in dorsal and orbital frontal cortex, temporal cortex and striatum, and were associated with impulsive behaviors and cognitive impairment. Overall, the individual network-level abnormalities identified in the present study highlight clinically relevant alterations in the brain network organization which provide new neurobiological insights into the pathophysiology of ADHD importantly in patients prior to lifetime ADHD medication exposure.

Our findings of abnormal global organization of the GM network in ADHD children were partly consistent with previous graph





**FIGURE 2** Brain regions with abnormal nodal centralities in the brain gray matter network compared between the ADHD patients and controls, the ADHD-C and ADHD-I groups. ADHD, attention deficit hyperactivity disorder; ADHD-C, ADHD combined subtype; ADHD-I, inattentive subtype; AMYG, amygdala; L, left; MTG, middle temporal gyrus; ORBmid, orbital middle frontal gyrus; PAL, lenticular nucleus, pallidum; PreCG, precentral gyrus; R, right; SFGdor, dorsolateral superior frontal gyrus; SFGmed, medial superior frontal gyrus

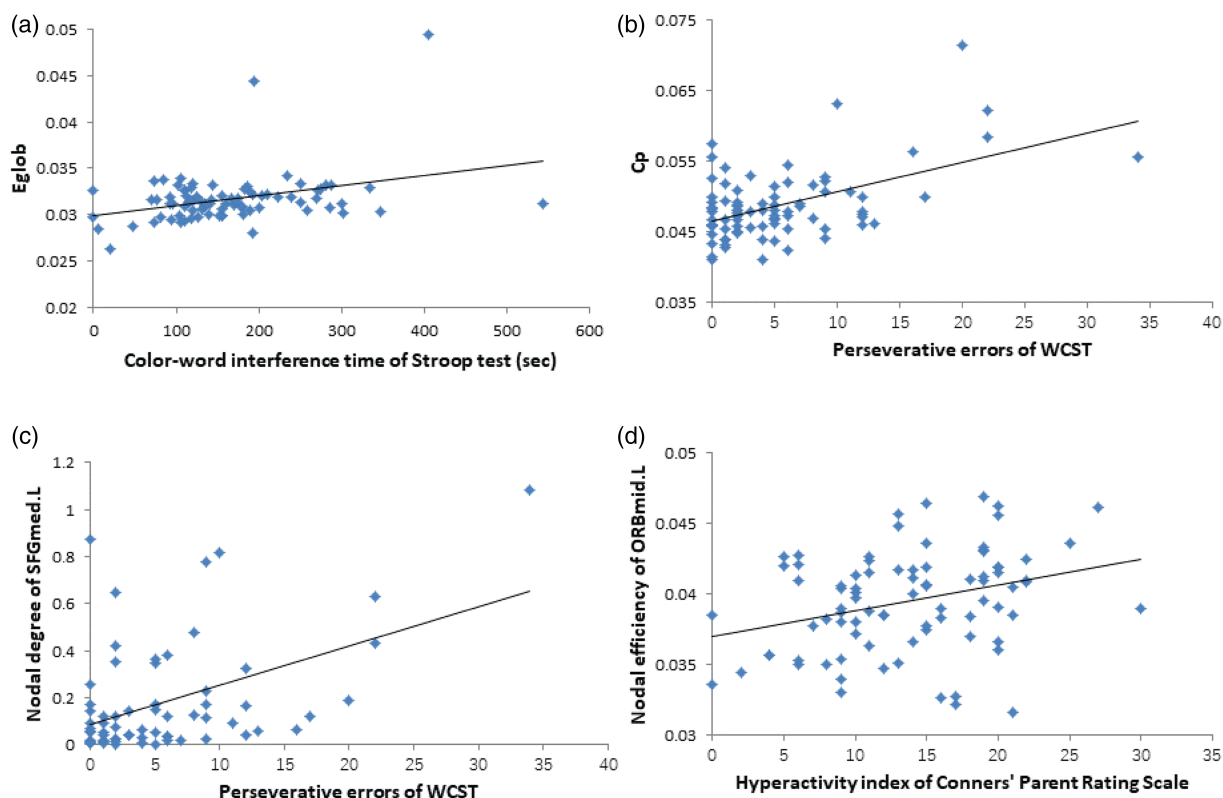


**FIGURE 3** The networks showing abnormal connections in the brain networks compared between ADHD patients and controls. Every node denotes a brain region and every line denotes a connection. Red color represents increased connections in ADHD groups than controls. ADHD, attention deficit hyperactivity disorder; L, left; MTG, middle temporal gyrus; ORBmid, orbital middle frontal gyrus; PAL, lenticular nucleus, pallidum; PreCG, precentral gyrus; R, right; SFGdor, dorsolateral superior frontal gyrus; SFGmed, medial superior frontal gyrus

analytical studies of GM organization in ADHD in medicated patients (Griffiths et al., 2016; Saad et al., 2017). Notably, while one study showed increased clustering of GM networks in ADHD patients (Griffiths et al., 2016), another study failed to find any significant

results (Saad et al., 2017). Medication effects may contribute to the inconsistency of previous findings. Psychostimulant medication has been shown to normalize reductions in local GM volume of the anterior cingulate cortex in ADHD (Semrud-Clikeman, Plińska, Lancaster, & Liotti, 2006; Sobel et al., 2010), and the ADHD-associated excess cortical thinning during adolescence may also be moderated by psychostimulant treatment (Nakao et al., 2011; Shaw et al., 2009). The comorbidity of psychiatric disorders may also influence results of ADHD case-control studies. Volumetric reductions in GM have been shown to be more pronounced in ADHD patients with comorbidity, and abnormalities in brain regions affected by different comorbidities vary which can confound and weaken brain-illness relations (Mizuno et al., 2019; Paraskevopoulou et al., 2020). Furthermore, when looking at group level data, some subtle individual structural differences which are of particular interest in clinical populations may be underestimated or unidentified (Tijms et al., 2012).

The findings of shorter path length and higher clustering in drug-naïve ADHD patients indicate higher integration and segregation of brain structural networks in patients, consistent with excessive transmission of brain information (Bullmore & Sporns, 2012; Deco, Tononi, Boly, & Kringelbach, 2015). ADHD is strongly heritable and linked to mutations that interfere with dopaminergic or noradrenergic signaling which is crucial in regulating synaptic activity and plasticity (Cortese et al., 2012). Altered synaptic pruning and neuropil volume, and the distribution and/or density of cell bodies, may contribute to our findings of altered anatomic network organization. From a functional perspective, when dopamine or norepinephrine neurotransmitter



**FIGURE 4** The stepwise regression models examining relations between topological structures of gray matter (GM) brain networks and cognitive function in attention deficit hyperactivity disorder (ADHD) revealed that the global efficiency (Eglob) was independent risk factor for Color-Word interference time of Stroop test. Clustering coefficient (Cp) and Nodal degree of left medial superior frontal gyrus (SFGmed.L) were independent risk factors for perseverative errors of Wisconsin Card Sorting Test (WCST). And nodal efficiency of left orbital middle frontal gyrus (ORBmid.L) was independent risk factor for hyperactivity symptoms of ADHD (all  $p < .05$ , false discovery rate [FDR] corrected)

modulation is excessive, it can result in decreased signal to noise levels in neural connectivity (Madadi Asl, Vahabie, & Valizadeh, 2019). This may contribute to excessive brain arousal and to symptoms and cognitive features of ADHD.

This possibility is consistent with the observed associations of network metrics with poorer performance on the Stroop and WCST tests in ADHD, indicating that the observed network changes are associated with impairments in cognition. Consistent with these findings, several investigators have demonstrated that ADHD children exhibit anomalous patterns of neural connectivity when engaging in cognitive tasks (Collins & Frank, 2016; Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012). Our study extends this literature by showing that cognitive alterations are related to abnormalities in anatomic network configuration.

In terms of nodal properties, higher nodal degree, efficiency and betweenness were mainly distributed in the dorsolateral frontal cortex, orbitofrontal cortex, medial superior frontal gyrus, middle temporal gyrus, precentral gyrus, and pallidum, suggesting greater connectivity and interactions especially in frontal cortical regions (Liao, Vasilakos, & He, 2017; Sporns, 2011). Dorsolateral frontal cortex is critical for response selection under conditions of response conflict (Carter & van Veen, 2007; Cubillo et al., 2012). Orbitofrontal alterations have been associated with impulsivity and aggression in

human brain lesion, animal models, and functional imaging studies (Knutson & Cooper, 2005; Kringelbach, 2005). The globus pallidus, a core component of the striatum which receives robust neural input from frontal cortex, is important in modulating behavioral inhibition and thus is believed to be a contributing factor to the pathophysiology of ADHD (Li et al., 2014; Tomasi & Volkow, 2012). The present study demonstrated that increased nodal degree, efficiency, and betweenness of medial superior frontal gyrus was associated with poorer performance of WCST in ADHD, and increased nodal degree of left orbitofrontal gyrus in ADHD patients was related to more severe impulsive behaviors. These findings together support dual-pathway models of ADHD including dorsolateral prefrontostriatal and orbitofrontal-striatal circuits in ADHD.

This study also demonstrated that different ADHD subtypes exhibited some differences in nodal properties. Specifically, we found that nodal attributes (degree, efficiency, and betweenness) of amygdala were different between the two subtypes. Amygdala is considered to play a crucial role in the control of emotion and impulsive behavior (Vazquez-Sanroman, Arlington Wilson, & Bardo, 2021; Venniro et al., 2018). Previous studies of ADHD have demonstrated that significantly altered volumes of amygdala, implicating anatomic disruption of amygdala in the pathogenesis of this disorder (Van Dessel et al., 2018; Van Dessel et al., 2020). The present findings add

to this model by demonstrating increased connections between the amygdala and other brain regions which were associated with hyperactivity/impulsivity.

The present study has some limitations. First, the brain atlas and processing pipeline we selected for constructing brain networks may affect the network analysis results. Second, while the construction of individual structural networks was based on the similarity of GM, the physiological correlates of these anatomic network alterations are still unclear and need to be investigated in the future. Third, this study excluded ADHD subjects with comorbidities, which generalize the findings to ADHD patients with more diverse and complicated.

In conclusion, the current study revealed excessive brain connectivity in individual similarity-based GM networks in drug-naïve ADHD children and adolescents, especially in the frontal striatal loop and amygdala. These alterations were related to cognitive dysfunction and impulsive behavior in ADHD, pointing to a potential network-based neural mechanism underlying the pathophysiology of ADHD.

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## CONFLICT OF INTEREST

Dr J. A. S. reports support from VeraSci and Yao the Bard.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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## REFERENCES

- Achenbach, T. (1991). *Manual for the child behavior checklist/4-18 and 1991 profile*. Burlington, VT: Department of Psychiatry, University of Vermont.
- Batalle, D., Muñoz-Moreno, E., Figueras, F., Bargallo, N., Eixarch, E., & Gratacos, E. (2013). Normalization of similarity-based individual brain networks from gray matter MRI and its association with neurodevelopment in infants with intrauterine growth restriction. *NeuroImage*, 83, 901–911.
- Bayard, F., Nymberg Thunell, C., Abé, C., Almeida, R., Banaschewski, T., Barker, G., ... Petrovic, P. (2020). Distinct brain structure and behavior related to ADHD and conduct disorder traits. *Molecular Psychiatry*, 25(11), 3020–3033.
- Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. *Nature Reviews Neuroscience*, 13(5), 336–349.
- Carter, C. S., & van Veen, V. (2007). Anterior cingulate cortex and conflict detection: An update of theory and data. *Cognitive, Affective, & Behavioral Neuroscience*, 7(4), 367–379.
- Collins, A. G., & Frank, M. J. (2016). Surprise! Dopamine signals mix action, value and error. *Nature Neuroscience*, 19(1), 3–5.
- Conners, C. K. (1999). Clinical use of rating scales in diagnosis and treatment of attention-deficit/hyperactivity disorder. *Pediatric Clinics of North America*, 46, 857–870.
- Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M. P., & Castellanos, F. X. (2012). Toward systems neuroscience of ADHD: A meta-analysis of 55 fMRI studies. *The American Journal of Psychiatry*, 169(10), 1038–1055.
- Crowley, N. A., Cody, P. A., Davis, M. I., Lovinger, D. M., & Mateo, Y. (2014). Chronic methylphenidate exposure during adolescence reduces striatal synaptic responses to ethanol. *The European Journal of Neuroscience*, 39(4), 548–556.
- Cubillo, A., Halari, R., Smith, A., Taylor, E., & Rubia, K. (2012). A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with attention deficit hyperactivity disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. *Cortex*, 48(2), 194–215.
- Deco, G., Tononi, G., Boly, M., & Kringelbach, M. L. (2015). Rethinking segregation and integration: Contributions of whole-brain modelling. *Nature Reviews Neuroscience*, 16(7), 430–439.
- Genovese, C. R., Lazar, N. A., & Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage*, 15(4), 870–878.
- Gong, Q. (2020). *Psychoradiology. Neuroimaging Clinics of North America*. (Vol. 30, pp.1–123). New York: Elsevier Inc.
- Griffiths, K. R., Grieve, S. M., Kohn, M. R., Clarke, S., Williams, L. M., & Korgaonkar, M. S. (2016). Altered gray matter organization in children and adolescents with ADHD: A structural covariance connectome study. *Translational Psychiatry*, 6(11), e947.
- He, N., Li, F., Li, Y., Guo, L., Chen, L., Huang, X., ... Gong, Q. (2015). Neuroanatomical deficits correlate with executive dysfunction in boys with attention deficit hyperactivity disorder. *Neuroscience Letters*, 600, 45–49.
- Jenson, D., Yang, K., Acevedo-Rodriguez, A., Levine, A., Broussard, J. I., Tang, J., & Dani, J. A. (2015). Dopamine and norepinephrine receptors participate in methylphenidate enhancement of in vivo hippocampal synaptic plasticity. *Neuropharmacology*, 90, 23–32.
- Knutson, B., & Cooper, J. C. (2005). Functional magnetic resonance imaging of reward prediction. *Current Opinion in Neurology*, 18, 411–417.
- Konrad, K., & Eickhoff, S. B. (2010). Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. *Human Brain Mapping*, 31(6), 904–916.
- Kringelbach, M. L. (2005). The human orbitofrontal cortex: Linking reward to hedonic experience. *Nature Reviews Neuroscience*, 6(9), 691e702.
- Langer, N., Benjamin, C., Becker, B. L. C., & Gaab, N. (2019). Comorbidity of reading disabilities and ADHD: Structural and functional brain characteristics. *Human Brain Mapping*, 40(9), 2677–2698.
- Lei, D., Li, K., Li, L., Chen, F., Huang, X., Lui, S., ... Gong, Q. (2015). Disrupted functional brain connectome in patients with posttraumatic stress disorder. *Radiology*, 276(3), 818–827.
- Li, F., Su, H., Biswal, B. B., Sweeney, J. A., & Gong, Q. (2021). Artificial intelligence applications in psychoradiology. *Psychoradiology*, 1(2), 94–107.
- Li, Y., Li, F., He, N., Guo, L., Huang, X., Lui, S., & Gong, Q. (2014). Neural hyperactivity related to working memory in drug-naïve boys with attention deficit hyperactivity disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 53, 116–122.
- Liao, X., Vasilakos, A. V., & He, Y. (2017). Small-world human brain networks: Perspectives and challenges. *Neuroscience and Biobehavioral Reviews*, 77, 286–300.
- Lui, S., Zhou, X. J., Sweeney, J., & Gong, Q. (2016). Psychoradiology: the frontier of neuroimaging in psychiatry. *Radiology*, 281(2), 357–372.
- Madadi Asl, M., Vahabie, A. H., & Valizadeh, A. (2019). Dopaminergic modulation of synaptic plasticity, its role in neuropsychiatric disorders, and its computational modeling. *Basic and Clinical Neuroscience*, 10(1), 1–12.



- Metin, B., Roeyers, H., Wiersema, J. R., van der Meere, J., & Sonuga-Barke, E. (2012). A meta-analytic study of event rate effects on go/no-go performance in attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 72(12), 990–996.
- Mizuno, Y., Kagitani-Shimono, K., Jung, M., Makita, K., Takiguchi, S., Fujisawa, T. X., ... Tomoda, A. (2019). Structural brain abnormalities in children and adolescents with comorbid autism spectrum disorder and attention-deficit/hyperactivity disorder. *Translational Psychiatry*, 9(1), 332.
- Nakao, T., Radua, J., Rubia, K., & Mataix-Cols, D. (2011). Gray matter volume abnormalities in ADHD: Voxel-based meta-analysis exploring the effects of age and stimulant medication. *The American Journal of Psychiatry*, 168(11), 1154–1163.
- Niu, R., Lei, D., Chen, F., Chen, Y., Suo, X., Li, L., ... Gong, Q. (2018). Reduced local segregation of single-subject gray matter networks in adult PTSD. *Human Brain Mapping*, 39(12), 4884–4892.
- Noordermeer, S. D. S., Luman, M., Greven, C. U., Veroude, K., Faraone, S. V., Hartman, C. A., ... Oosterlaan, J. (2017). Structural brain abnormalities of attention-deficit/hyperactivity disorder with oppositional defiant disorder. *Biological Psychiatry*, 82(9), 642–650.
- Paraskevopoulou, M., van Rooij, D., Batalla, A., Chauvin, R., Luijten, M., Schene, A. H., ... Schellekens, A. F. A. (2020). Effects of substance misuse on reward-processing in patients with attention-deficit/hyperactivity disorder. *Neuropsychopharmacology*, 46, 622–631. <https://doi.org/10.1038/s41386-020-00896-1>
- Saad, J. F., Griffiths, K. R., Kohn, M. R., Clarke, S., Williams, L. M., & Korgaonkar, M. S. (2017). Regional brain network organization distinguishes the combined and inattentive subtypes of attention deficit hyperactivity disorder. *NeuroImage. Clinical*, 15, 383–390.
- Samea, F., Soluki, S., Nejati, V., Zarei, M., Cortese, S., Eickhoff, S. B., ... Eickhoff, C. R. (2019). Brain alterations in children/adolescents with ADHD revisited: A neuroimaging meta-analysis of 96 structural and functional studies. *Neuroscience and Biobehavioral Reviews*, 100, 1–8.
- Sayal, K., Prasad, V., Daley, D., Ford, T., & Coghill, D. (2018). ADHD in children and young people: Prevalence, care pathways, and service provision. *Lancet Psychiatry*, 5(2), 175–186.
- Semrud-Clikeman, M., Pliszka, S. R., Lancaster, J., & Liotti, M. (2006). Volumetric MRI differences in treatment-naïve vs chronically treated children with ADHD. *Neurology*, 67(6), 1023–1027.
- Shaw, P., Sharp, W. S., Morrison, M., Eckstrand, K., Greenstein, D. K., Clasen, L. S., ... Rapoport, J. L. (2009). Psychostimulant treatment and the developing cortex in attention deficit hyperactivity disorder. *The American Journal of Psychiatry*, 166(1), 58–63.
- Sobel, L. J., Bansal, R., Maia, T. V., Sanchez, J., Mazzone, L., Durkin, K., ... Peterson, B. S. (2010). Basal ganglia surface morphology and the effects of stimulant medications in youth with attention deficit hyperactivity disorder. *The American Journal of Psychiatry*, 167(8), 977–986.
- Sporns, O. (2011). The human connectome: A complex network. *Annals of the New York Academy of Sciences*, 1224, 109–125.
- Sun, H., Lui, S., Yao, L., Deng, W., Xiao, Y., Zhang, W., ... Gong, Q. (2015). Two patterns of white matter abnormalities in medication-naïve patients with first-episode schizophrenia revealed by diffusion tensor imaging and cluster analysis. *JAMA Psychiatry*, 72(7), 678–686.
- Tijms, B. M., Serié, P., Willshaw, D. J., & Lawrie, S. M. (2012). Similarity-based extraction of individual networks from gray matter MRI scans. *Cerebral Cortex*, 22(7), 1530–1541.
- Tomasi, D., & Volkow, N. D. (2012). Abnormal functional connectivity in children with attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 71(5), 443–450.
- Urban, K. R., Li, Y. C., & Gao, W. J. (2013). Treatment with a clinically-relevant dose of methylphenidate alters NMDA receptor composition and synaptic plasticity in the juvenile rat prefrontal cortex. *Neurobiology of Learning and Memory*, 101, 65–74.
- Van Dessel, J., Sonuga-Barke, E., Mies, G., Lemiere, J., Van der Oord, S., Morsink, S., & Danckaerts, M. (2018). Delay aversion in attention deficit/hyperactivity disorder is mediated by amygdala and prefrontal cortex hyper-activation. *Journal of Child Psychology and Psychiatry*, 59(8), 888–899.
- Van Dessel, J., Sonuga-Barke, E., Moerkerke, M., Van der Oord, S., Lemiere, J., Morsink, S., & Danckaerts, M. (2020). The amygdala in adolescents with attention-deficit/hyperactivity disorder: Structural and functional correlates of delay aversion. *The World Journal of Biological Psychiatry*, 21(9), 673–684.
- Vazquez-Sanroman, D. B., Arlington Wilson, G., & Bardo, M. T. (2021). Effects of social isolation on perineuronal nets in the amygdala following a reward omission task in female rats. *Molecular Neurobiology*, 58(1), 348–361.
- Venniro, M., Zhang, M., Caprioli, D., Hoots, J. K., Golden, S. A., Heins, C., ... Shaham, Y. (2018). Volitional social interaction prevents drug addiction in rat models. *Nature Neuroscience*, 21(11), 1520–1529.
- Wang, J., Wang, X., Xia, M., Liao, X., Evans, A., & He, Y. (2015). GREYNA: A graph theoretical network analysis toolbox for imaging connectomics. *Frontiers in Human Neuroscience*, 30(9), 386.
- Yerys, B. E., Tunç, B., Satterthwaite, T. D., Antezana, L., Mosner, M. G., Bertollo, J. R., ... Herrington, J. D. (2019). Functional connectivity of frontoparietal and salience/ventral attention networks have independent associations with co-occurring attention-deficit/hyperactivity disorder symptoms in children with autism. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 4(4), 343–351.
- Zalesky, A., Fornito, A., & Bullmore, E. T. (2010). Network-based statistic: Identifying differences in brain networks. *NeuroImage*, 53(4), 1197–1207.
- Zhang, W., Lei, D., Keedy, S. K., Ivleva, E. I., Eum, S., Yao, L., ... Sweeney, J. A. (2020). Brain gray matter network organization in psychotic disorders. *Neuropsychopharmacology*, 45(4), 666–674.

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