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ORIGINAL RESEARCH

Behavioral and brain functional characteristics of children with Attention-Deficit/Hyperactivity disorder and anxiety trait

Zhao-Min Wu[1] · Peng Wang[2] · Juan Liu[1] · Lu Liu[3,4] · Xiao-Lan Cao[1] · Li Sun[3] · Qing-Jiu Cao[3,4] · Li Yang[3,4] · Yu-Feng Wang[3,4] · Bin-Rang Yang[1]

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Abstract

The current study aimed to explore the behavioral, daily-life executive functional, and brain functional connectivity patterns in children with attention-deficit/hyperactivity disorder (ADHD) and anxiety. A total of 246 children with non-comorbid ADHD and 91 healthy controls (HCs) participated in the current study, among whom 175 subjects went through resting-state functional magnetic resonance imaging (fMRI) scans. The ADHD participants were divided into two subgroups: ADHD with a high level of anxiety (ADHD + ANX) and ADHD with a low level of anxiety (ADHD-ANX). The Child Behavior Checklist (CBCL) and the Behavior Rating Inventory of Executive Function (BRIEF) were used to capture the behavioral and daily-life executive functional characteristics. Independent component analysis with dual regression models was applied to the fMRI data. All statistical models were estimated with age and sex as covariates. Compared with the ADHD-ANX group, the ADHD + ANX group showed more withdrawn, somatic, social, thought, attention, delinquent, and aggressive problems (all corrected $p < 0.05$). The ADHD + ANX group also displayed more impaired emotional control and working memory than the ADHD-ANX (all corrected $p < 0.05$). The ADHD-ANX group, but not the ADHD + ANX group, showed elevated functional connectivity within the default mode network compared with the HC group. The mean function connectivity within the default mode network significantly mediated the correlation between anxiety level and attention problems. In sum, anxiety in children with ADHD was associated with more social, emotional, and behavioral problems, more impaired daily-life executive function, and altered brain function. Our work provides important information on the heterogeneity of ADHD.

Keywords ADHD · Anxiety · Brain imaging · Behavior · Daily-life executive function

Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders, with an estimated prevalence of 6.2% among children and adolescents in China (Wang et al., 2017). ADHD is characterized by its core symptoms, including inattention, hyperactivity, and impulsivity. Individuals with ADHD have trouble focusing or concentrating on tasks. They tend to display excessive talking and physical movement behaviors, make careless mistakes, and dislike mentally demanding tasks (American Psychiatric Association, 2013). Moreover, about half of all patients with ADHD also have significant impairments in emotional regulation(Faraone et al., 2019). As ADHD is a heterogeneous disease, most patients with ADHD experience different conditions in addition to their core features, for example, emotional dysregulation or aggression. These

✉ Zhao-Min Wu
Zhaomin.Wu@foxmail.com

✉ Yu-Feng Wang
wangyf@bjmu.edu.cn

✉ Bin-Rang Yang
ybinrang@126.com

[1] Shenzhen Children's Hospital, 518000 Shenzhen, China

[2] Cardiac Rehabilitation Center, Fuwai Hospital, CAMS & PUMC, 100037 Beijing, China

[3] Peking University Sixth Hospital/Institute of Mental Health, National Clinical Research Center for Mental Disorders (Peking University Sixth Hospital), 100191 Beijing, China

[4] Key Laboratory of Mental Health, Ministry of Health, Peking University, 100191 Beijing, China

co-occurring conditions may cause a considerable burden for patients with ADHD and their families (Faraone et al., 2015). Evidence has shown that adults with ADHD comorbid with other conditions have a worse quality of life than ADHD patients without any comorbidities, and can experience increased levels of feeling overwhelmed, anxious, or fatigued, as well as a decreased ability to complete tasks and balance multiple projects simultaneously (Quintero et al., 2019).

There is evidence showing that subjects with ADHD have elevated levels of anxiety. A survey of college students demonstrated that subjects with ADHD endorsed more maladaptive beliefs about worry than healthy individuals, despite no increased rate of any current anxiety disorders observed (O'Rourke et al., 2020). An elevated level of anxiety was also observed in adolescents with ADHD (Liu et al., 2014). These patients were also found to have more impaired social functioning than those ADHD patients without anxiety symptoms (Bishop et al., 2019).

In addition to the clinical symptoms, subjects with ADHD also showed developmental cognitive deficits (Brown, 2008), which might be linked to individuals with ADHD experiencing greater difficulty in social functioning (Tseng & Gau, 2013). Some studies have investigated the impact of anxiety on cognitive function in adolescents and adults with ADHD. In a group of 98 adolescents with combined-subtype ADHD and 123 healthy controls (HCs, aged 12–18 years), ADHD adolescents with higher trait anxiety were found to perform better on indices of sustained attention, reaction time, and motor variability than both ADHD adolescents without trait anxiety and HCs (Ruf et al., 2017). This result was not replicated in another study (Adamo et al., 2021), which showed that adolescents and young adults with ADHD (aged 11–26 years) displayed impaired cognitive function irrespective of their levels of anxiety. To date, few studies have investigated the impact of anxiety on behavioral and cognitive function in children with ADHD.

Magnetic resonance imaging (MRI) is an in vivo technique that allows researchers to understand the biological mechanisms and pathophysiology underlying different brain disorders, including anxiety and ADHD. Altered brain activation and functional connectivity have commonly been identified in several brain networks in patients with ADHD or anxiety (Cortese et al., 2012; Lai, 2020). Few studies have explored the brain functional characteristics of patients with comorbid ADHD and anxiety. Compared with HCs, altered functional connectivity between the default mode network (DMN) and multiple brain regions were identified in patients with comorbid ADHD and social anxiety disorder (Ergul et al., 2019). Additionally, anxiety was revealed to affect the hemodynamic responses of adolescents with ADHD in the basal ganglia (Sorensen et al., 2016).

In summary, elevated anxiety symptoms are often present in people with ADHD. Potentially, these anxiety symptoms might affect behavioral, cognitive, and brain functional features in ADHD patients. To the best of our knowledge, more previous studies have focused on adolescents and adults with ADHD, and few studies have investigated the effect of anxiety on children with ADHD. Therefore, the current study aimed to explore the behavioral, daily-life executive functional, and brain functional characteristics of children with ADHD and their anxiety symptoms using a clinical cohort of 246 medication-naïve children with non-comorbid ADHD (i.e., with no comorbidity) and 91 HCs. We hypothesized that anxiety symptoms in children with ADHD would be associated with more social problems, more aggressive behaviors, more impaired daily-life executive function, and altered brain functional connectivity within ADHD-related brain networks.

Methods

Participants

The current study included a clinical sample of 246 children with ADHD (aged 6–14 years) recruited from Shenzhen Children's hospital and 91 HCs from elementary schools in Shenzhen. Among these participants, 94 subjects with ADHD and 81 healthy individuals (all right-hand dominant) went through a resting-state functional MRI scan. More information about the recruitment of participants can be found in the supplementary materials. This work was approved by the Ethics Committee of Shenzhen Children's Hospital. Informed consent was obtained from parents of children prior to the study.

Identification of anxiety level

The Conners' Parent Rating Scale (Revised) (CPRS) is widely used in clinical and scientific contexts. More details about the CPRS can be found in the supplementary material. According to their scores on the anxiety problem factor of the CPRS, the ADHD group was further divided into two subgroups, the ADHD with high anxiety level (ADHD + ANX, one standard deviation above the norm) and the ADHD with low anxiety level (ADHD-ANX) group. Details are provided in the supplementary material.

Behavioral Assessment

The Child Behavior Checklist (CBCL) was utilized to assess all participants' behavioral and emotional problems. According to the CBCL profile, these 113 items can be divided into

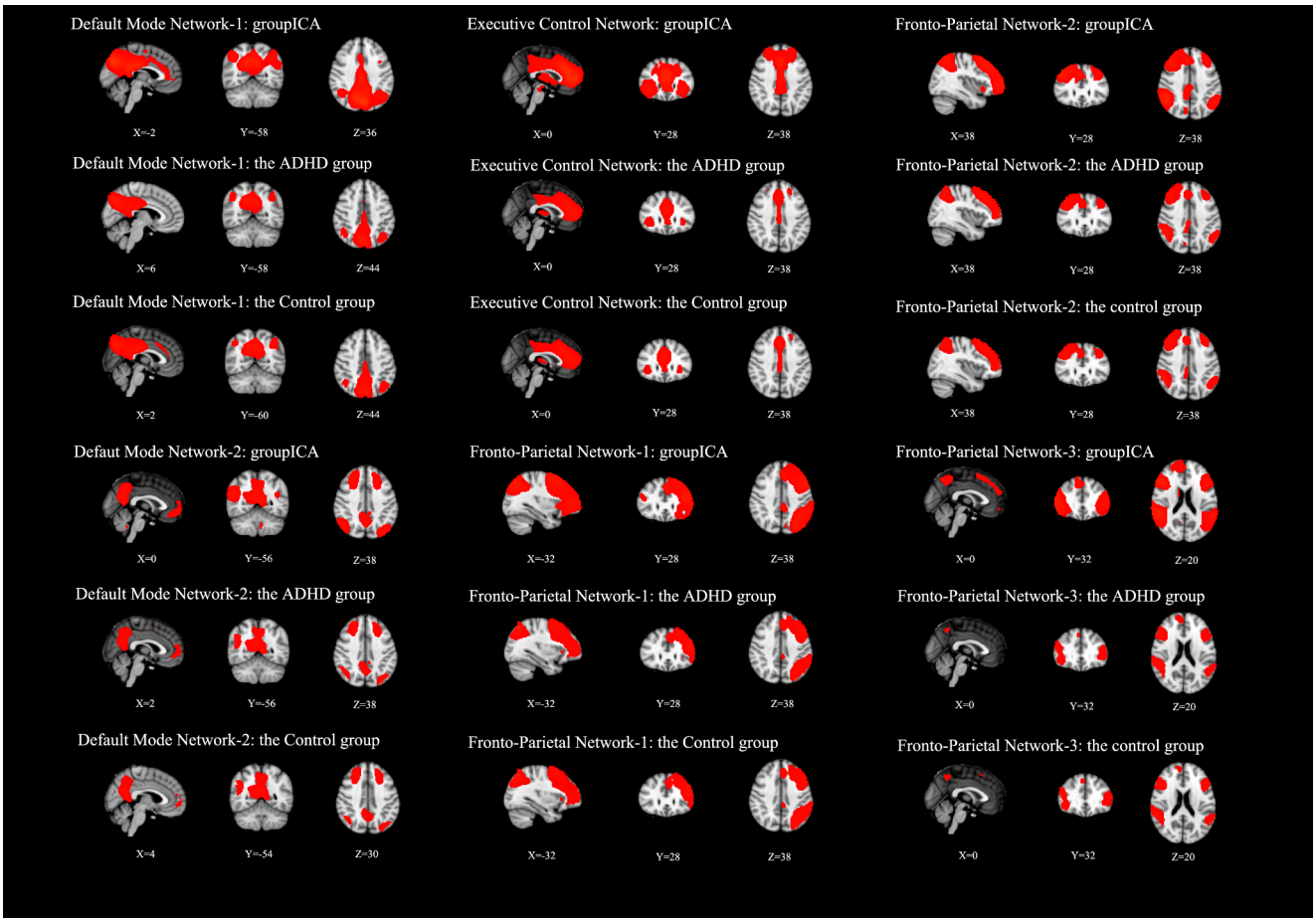

Fig. 1 The spatial maps of the six brain networks of interest extracted from group ICA, as well as the group-level networks for the ADHD group and the healthy control group. All networks were thresholded at $Z > 2.3$ and displayed on an MNI_T1_2mm_brain

eight factors: withdrawal, somatic complaints, anxiety/depression, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior. Details are provided in the supplementary material.

Daily-life executive function Assessment

The Behavior Rating Inventory of Executive Function (BRIEF) was used to assess everyday executive function in children (Gioia et al., 2002). This scale has eight subscales reflecting commonly described domains of executive function: inhibition, working memory, planning/organization, monitoring, initiation, shifting, organization of materials, and emotional control (Gioia et al., 2002). Details are provided in the supplementary material.

Processing of RS-fMRI images

Details of the acquisition and processing steps of the fMRI data can be found in the supplementary material. Independent component analysis (ICA) was performed in FSL to obtain functional connectivity networks. We decided to focus on a few networks that have been reported to play an important role in the pathophysiology of ADHD, including the executive control network, the default mode network, and the left and right frontoparietal networks. The selected brain networks are shown in Fig.1. The individual functional connectivity patterns were obtained using a dual-regression approach (Nickerson et al., 2017). Groupwise comparisons were conducted using the Randomise test in FSL. Cluster-wise statistical corrections were done using threshold-free cluster enhancement (TFCE), which provides *p*-values corrected for whole-skeleton family-wise error (FWE). In addition, only those significant clusters larger than 10 voxels were reported in the current study.

Statistical analysis

All statistical analyses were performed in R. Comparisons among the ADHD + ANX group, the ADHD-ANX group, and the HC group were performed on all eight factors from CBCL, as well as the eight factors from BRIEF, using

Table 1 Demographic and clinical characteristics of the ADHD and control groups

	ADHD + ANX (n = 63)	ADHD-ANX (n = 183)	Healthy Control (n = 91)	F value /ChiSq	*P* value	Pairwise*
Age	8.37 ± 1.69	8.20 ± 1.67	9.26 ± 1.32	14.09	< 0.001	A1/A2 < HC
Conners_Anxiety	4.17 ± 1.49	1.01 ± 0.91	0.18 ± 0.20	258.57	< 0.001	A1 > A2/HC
Sex(Male%)	79.37%	89.62%	59.34%	34.22	< 0.001	A2 > A1 > HC
Inattention	24.18 ± 2.35	24.29 ± 2.08	15.60 ± 1.51	80.41	< 0.001	A1/A2 > HC
Hyperactivity/Impulsivity	20.00 ± 4.22	20.46 ± 4.49	11.89 ± 1.27	10.32	< 0.001	A1/A2 > HC
Withdrawal	5.18 ± 2.81	2.40 ± 2.18	1.27 ± 1.66	46.05	< 0.001	A1 > A2 > HC
Somatic complaints	2.52 ± 2.34	1.30 ± 1.81	0.72 ± 1.50	14.16	< 0.001	A1 > A2/HC
Anxiety/Depression	6.10 ± 3.86	3.14 ± 3.02	1.18 ± 2.29	34.51	< 0.001	A1 > A2 > HC
Social problems	5.17 ± 3.06	3.77 ± 2.52	1.30 ± 1.55	28.86	< 0.001	A1 > A2 > HC
Thought problems	1.44 ± 1.42	1.00 ± 1.28	0.30 ± 1.06	10.00	< 0.001	A1 > A2 > HC
Attention problems	9.79 ± 3.29	7.91 ± 3.36	1.52 ± 1.88	102.06	< 0.001	A1 > A2 > HC
Delinquent behavior	5.04 ± 3.54	3.46 ± 2.22	1.32 ± 2.09	26.67	< 0.001	A1 > A2 > HC
Aggressive behavior	14.60 ± 7.07	10.28 ± 5.60	3.33 ± 3.68	51.30	< 0.001	A1 > A2 > HC

* A1 = ADHD + ANX, A2 = ADHD-ANX, HC = Healthy Control;

Table 2 Daily-life executive function of the ADHD and control groups

	ADHD + ANX (n = 63)	ADHD-ANX (n = 183)	Healthy Control (n = 91)	F value /ChiSq	*P* value	Pairwise*
Inhibition	18.38 ± 4.91	17.98 ± 4.35	11.83 ± 1.87	52.52	< 0.001	A1/A2 > HC
Shifting	13.31 ± 3.00	12.13 ± 2.73	9.70 ± 1.68	28.54	< 0.001	A1/A2 > HC
Emotional control	16.67 ± 4.14	14.65 ± 3.80	11.49 ± 1.97	26.52	< 0.001	A1 > A2 > HC
Initiation	16.00 ± 2.51	15.17 ± 3.12	10.39 ± 1.95	79.66	< 0.001	A1/A2 > HC
Working memory	23.80 ± 3.23	22.08 ± 3.81	13.77 ± 2.86	142.88	< 0.001	A1 > A2 > HC
Planning/Organization	25.69 ± 4.43	25.49 ± 4.80	17.39 ± 3.92	71.25	< 0.001	A1/A2 > HC
Organization of materials	13.73 ± 3.31	12.81 ± 3.11	9.33 ± 2.57	40.96	< 0.001	A1/A2 > HC
Monitoring	19.21 ± 3.18	18.58 ± 2.90	12.80 ± 2.79	79.74	< 0.001	A1/A2 > HC

* A1 = ADHD + ANX, A2 = ADHD-ANX, HC = Healthy Control

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ANX = anxiety

ANCOVA, with age and sex as covariates. Bonferroni correction was used to correct for multiple comparisons. Therefore, the significance level was set to 0.05/8 = 0.00625. Regression models were also built to test the brain–behavior association between the extracted mean functional connectivity strength of the clusters showing significant groupwise differences and the indicators from the CBCL and BRIEF. In addition, we also performed exploratory mediation analysis to further test the potential paths between brain imaging and behavioral measures. More details about the mediation models can be found in the supplementary material. The mediation models were estimated using the mediation package in R with the bootstrap approach, using linear regression fitted with least squares and the default 1000 simulations. Again, the Bonferroni correction was used to correct for multiple comparisons.

Results

Demographic and clinical characteristics

The control group was older than the ADHD groups on average (both $p < 0.05$). In addition, there were more male subjects in both ADHD groups compared with the control group. There was no significant difference in age or sex between the two ADHD groups. Within the ADHD group, those with or without MRI scans did not differ from each other significantly in terms of demographic characteristics and clinical symptoms, with the exception of the age of the ADHD-ANX group (details in supplementary material, Table S1). Among all the factors of the CBCL, except for the somatic complaints, both ADHD groups scored

Table 3 Clusters showing significant group-wise differences between the ADHD and control groups

	Network	No. of voxel	Cluster size (mm^3)	MNI coordinates (mm) of the peak voxel	Regions
ADHD – ANX > Control	DMN-1	35	280	0, -80, 40	bilateral precuneus cortex, bilateral cuneal cortex
		28	224	22, -64, 44	right lateral occipital cortex (superior division)
		21	168	10, -64, 34	right precuneus cortex
ADHD – ANX > Control	DMN-2	149	1192	18, -38, 38	right precuneus cortex, right precentral gyrus, right postcentral gyrus, right posterior cingulate gyrus
		102	816	44, -62, 28	right lateral occipital cortex (superior division), right angular gyrus
		33	264	38, -38, 46	right postcentral gyrus, right supramarginal gyrus, right superior parietal lobule
		19	152	14, -52, 8	right precuneus cortex, right posterior cingulate gyrus
		18	144	34, -76, -6	right occipital fusiform gyrus
		16	96	52, -34, 58	right postcentral gyrus, right supramarginal gyrus

Note: ADHD – ANX = ADHD patients with low anxiety level

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ANX = anxiety; DMN = default mode network

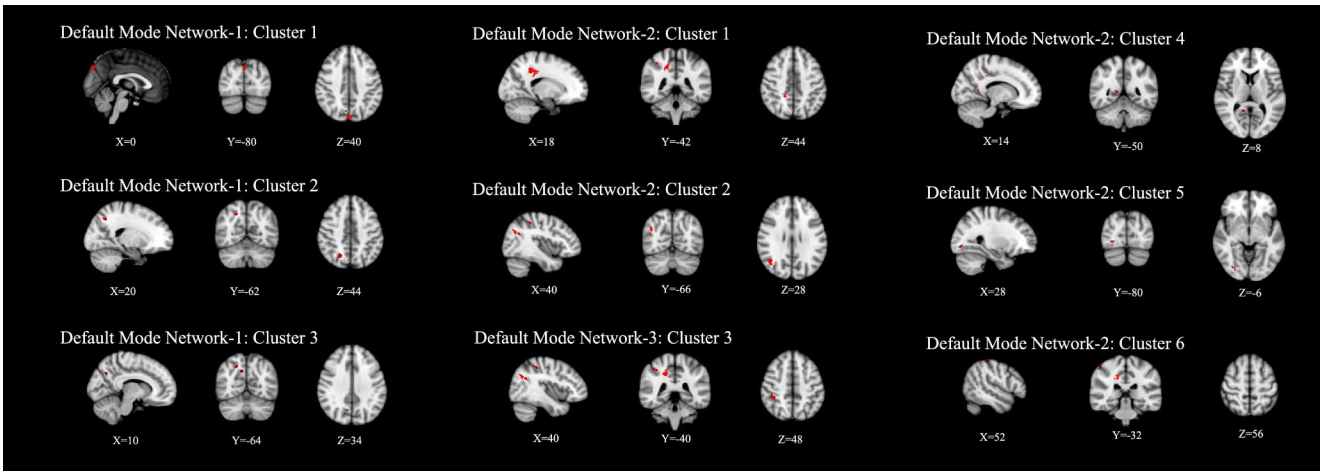

Fig. 2 Comparisons of the strength of functional connectivity among subjects with ADHD and trait anxiety, subjects with ADHD only, and healthy controls, displayed on an MNI_T1_2mm_brain

higher than the HC group (all corrected $p < 0.05$). Additionally, the ADHD + ANX group showed higher scores than the ADHD-ANX group on all eight factors (all corrected $p < 0.05$). On the somatic complaints factor indicated by the CBCL, the ADHD + ANX group scored higher than the ADHD-ANX group and the HC group ($p < 0.001$). In terms of daily-life executive function, both the ADHD + ANX and ADHD-ANX group scored higher than the HC group on all eight factors from BRIEF (all corrected $p < 0.05$). Furthermore, the ADHD + ANX group had higher scores on two of the factors, emotional control and working memory, than the ADHD-ANX group (all corrected $p < 0.05$). More descriptive statistical details on all demographic and clinical measurements can be found in the supplementary material in Tables S2 and S3. The estimated groupwise effect sizes of the CBCL and BRIEF measurements are summarized in the supplementary material, in Table S4.

Brain functional connectivity

Compared with the HC group, the ADHD-ANX group showed elevated functional connectivity within the default mode network, mainly in the precentral gyrus, postcentral gyrus, posterior cingulate gyrus, precuneus, and occipital cortex within the default mode network. The ADHD + ANX group, however, did not show any significantly altered

whole brain-wise functional connectivity within any of the brain networks. Direct comparisons between the ADHD-ANX and ADHD + ANX groups did not yield significant clusters. Details can be found in Table3; Fig.2. Significant brain–behavior correlations were detected between the functional connectivity (FC) strength within cluster 1 (shown in Table3, located mainly in the precuneus) and several indicators from the CBCL (e.g., attention and social), as well as indicators from BRIEF (e.g., working memory, initiation, planning, and monitoring). The correlation plots can be found in the supplementary materials in Figure S1.

Mediation models

In the mediation models, we identified potential mediating effects of anxiety, with the outcome measures being withdrawal (proportion mediated, 0.60; $p < 0.001$), somatic complaints (proportion mediated, 0.54, $p = 0.006$), anxiety–depression (proportion mediated, 0.62; $p < 0.001$), and social problems (proportion mediated, 0.37; $p = 0.004$) from the CBCL, as well as working memory from BRIEF (proportion mediated, − 0.132; $p = 0.022$). Mediating effects of the attention factor in CBCL on the mean functional connectivity of those clusters showing significant groupwise differences were also significant (proportion mediated, 0.924; $p < 0.001$). The detailed results of other paths of the mediation models are summarized in the supplementary material.

Discussion

In this study, we investigated the effect of anxiety on behavioral, cognitive, and brain functional characteristics in a clinical cohort of children with ADHD and HCs. Our results demonstrated that children with comorbid ADHD and high levels of anxiety presented more social, emotional, and aggressive problems than children with ADHD with a low level of anxiety and HCs. More impaired emotional control and working memory were also identified in children with ADHD and a high level of anxiety, compared to children with ADHD and a low level of anxiety and HCs. In terms of brain function, compared with the HC group, the ADHD-ANX group showed increased functional connectivity within the default mode network.

In our study, more anxiety in children with ADHD was linked to more internalized and externalized problems. Anxiety has been shown to attenuate aggressive behaviors in children and adolescents with ADHD (Falk et al., 2017). However, this was not consistent with the results of another study (Becker et al., 2012), which did not identify either the attenuation or exacerbation effect of anxiety on ADHD-related aggression. In a population-based study, children with both ADHD and anxiety symptoms displayed the highest levels of oppositional defiant disorder (ODD) and conduct disorder (CD), compared to those with ADHD only or anxiety only (Humphreys et al., 2012). Another study also showed a positive relationship between conduct disorder scores and anxiety scores in a cohort of treatment-naive children with ADHD (Bilgic et al., 2017). In line with this, our study showed that children with ADHD and a high level of anxiety had more aggressive and delinquent behaviors than those with ADHD and a low level of anxiety. In addition, our study also identified more social problems in children with ADHD and a high level of anxiety compared to those with ADHD and a low level of anxiety and HCs. This is consistent with the results of a systematic review (Bishop et al., 2019). Note that the positive relationship between anxiety and attention problems identified in the current study does not indicate a more severe attentional deficit in children with ADHD and a high level of anxiety compared to those with ADHD and a low level of anxiety. The attention factor of the CBCL includes items that overlap with the anxiety–depression factor and the social problems factor, which might explain this observed relationship.

Although laboratory-based cognitive tests have often generated inconsistent results, most studies using rating scales to assess daily-life executive function have provided consistent results for the damaging effects of anxiety in participants with ADHD. Anxiety symptoms appeared to be associated with self-rated executive functioning deficits beyond relationships with ADHD symptomatology in college studies (Jarrett, 2016). In particular, the ADHD + anxiety group showed greater difficulty with self-organization/problem solving and emotional control than the ADHD-only group. Previously, a study using BRIEF showed that both children with ADHD only and children with anxiety exhibited impaired emotional control compared to the control group (Kertz et al., 2016; Sorensen et al., 2011). The current study also used BRIEF to capture the daily-life executive function in a much larger sample size cohort. Our results demonstrated that both the ADHD + ANX and ADHD-ANX groups showed impaired daily-life executive function in all eight domains compared with HCs, with all effect sizes indexed by Cohen's *d*s larger than 0.5. In addition, the ADHD + ANX group displayed greater impairment in emotional control and working memory than the ADHD-ANX group. The mediation model also identified that anxiety level did mediate the working memory deficits.

Although there have been quite a few studies about how anxiety affects the clinical and cognitive characteristics of ADHD, few studies have investigated the underlying brain functional mechanisms. Brain functional alterations in large-scale networks have been proposed to underlie the neural mechanisms of multiple psychiatric disorders, including ADHD and anxiety. A recent meta-analysis of 20 studies with 944 ADHD patients and 1,121 controls revealed that

ADHD was associated with disrupted within-DMN connectivity (Sutcubasi et al., 2020). Another meta-analysis focusing on large-scale functional networks revealed hyperconnectivity between the frontoparietal network (FPN) and regions of the DMN in participants with ADHD compared with HCs (Gao et al., 2019). In terms of anxiety, frontoparietal and limbic–prefrontal function connectivity alterations have been shown to play a significant role in the pathophysiology of anxiety disorders (Lai, 2020). Co-occurring ADHD and anxiety were also shown to be related to altered brain function in DMN nodes. In a clinical cohort of children with autism spectrum disorder, brain function within the DMN was found to be related to the co-occurrence of anxiety and ADHD symptoms (Wan et al., 2019). Another study investigating the effects of ADHD diagnosis on brain function in a social anxiety disorder (SAD) sample found that, in comparison with HCs, hypoconnectivity between the fusiform gyrus and posterior DMN regions was present in children with SAD only, while hyperconnectivity of the same regions was detected in children with SAD and ADHD (Ergul et al., 2019). In line with these results, the current study also identified elevated functional connectivity within the default mode network in the ADHD with a low level of anxiety. However, in the ADHD with a high level of anxiety, we did not observe any function connectivity alterations in the DMN compared to the control group. Previously, reduced functional connectivity between the posterior lateral frontal regions, dorsal anterior cingulate cortex, and left fusiform gyrus was identified in highly anxious individuals compared to those with a low level of anxiety (Basten et al., 2011). This result might explain what we have observed in the current study, that is, the attenuated functional connectivity alterations in the ADHD + ANX group.

Limitations The current study explored the behavioral characteristics and neural correlates of children with ADHD and high anxiety levels. The significance level we utilized for the MRI data, the TFCE correction with a cluster extent threshold of 80 mm^3 (10 voxels of size $2 \times 2 \times 2$mm), seems lenient if we aimed at limiting the familywise error rate (Eklund et al., 2016). However, if we set a more stringent cluster extent, for example, 50 voxels, it might result in a low sensitivity (Noble et al., 2020). As there are few studies exploring the same topic as we did, a more lenient significance level can bring more insight into this area. In addition, we did not explore the potential confounding effects of depressive symptoms in children with ADHD. Future studies exploring the effects of anxiety and depression symptoms separately are warranted. Note that this study was conducted in a well-resourced city, and this result might not be generalizable to less well-developed areas.

Conclusion

In summary, in a clinical cohort of non-comorbid ADHD patients and controls, we found that anxiety in children with ADHD was associated with more aggression and social problems, as well as greater impairment in daily-life executive function. In addition, anxiety also altered the functional connectivity pattern in children with ADHD. The current study contributes to the ongoing exploration of the effects of anxiety on children with ADHD in a relatively large sample size of ADHD patients and HCs. By highlighting the effects of anxiety symptoms on ADHD in terms of clinical, daily-life executive functional, and brain functional connectivity characteristics, our work provides important information on the nature of the heterogeneity of ADHD.

Abbreviations

ADHD	attention-deficit/hyperactivity disorder.
ANX	anxiety.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11682-022-00722-w.

Author contributions Zhao-Min Wu and Peng Wang contributed significantly to the data collection, data analysis, and manuscript preparation. Juan Liu and Xiao-Lan Cao helped conduct the study. Lu Liu, Sun Li, and Qing-Jiu Cao helped with the data analysis, as well as the writing and reviewing of the manuscript. Li Yang, Bin-Rang Yang, and Yu-Feng Wang contributed to the design of the study, the data analysis, and the manuscript preparation.

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Data Availability Not applicable.

Declarations

Conflict of interest Zhao-Min Wu, Peng Wang, Juan Liu, Lu Liu, Xiao-Lan Cao, Li Sun, Qing-Jiu Cao, Li Yang, Yu-Feng Wang, and Bin-Rang Yang do not have any conflicts of interest.

Compliance with ethical standards This work was approved by the Ethics Committee of Shenzhen Children's Hospital (identification number: 202005702). Informed consent was obtained from parents of children prior to the study.

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