

## REGULAR RESEARCH ARTICLE

# Shared and Unique Effects of Long-Term Administration of Methylphenidate and Atomoxetine on Degree Centrality in Medication-Naïve Children With Attention-Deficit/Hyperactive Disorder

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## Abstract

**Background:** Although methylphenidate (MPH) and atomoxetine (ATX) can improve clinical symptoms and functional impairments in attention deficit/hyperactive disorder (ADHD), the underlying psychopharmacological mechanisms have not been clearly elucidated. Therefore, we aimed to explore the shared and unique neurologic basis of these 2 medications in alleviating the clinical symptoms and functional impairments observed in ADHD.

**Methods:** Sixty-seven ADHD and 44 age-matched children with typical development were included and underwent resting-state functional magnetic resonance imaging scans at baseline. Then patients were assigned to MPH, ATX, or untreated subgroups, based on the patients' and their parents' choice, for a 12-week follow-up and underwent a second functional magnetic resonance imaging scan. The treatment effect on degree centrality (DC) was identified and correlated with clinical symptoms and functional impairments in the ADHD group.

**Results:** Both MPH and ATX normalized the DC value in extensive brain regions mainly involving fronto-cingulo-parieto-cerebellum circuits. However, ATX showed limited significant effects on the cerebellum compared with ADHD at baseline. The improvements in clinical symptoms were correlated with increased DC in the right inferior temporal gyrus in both MPH and ATX subgroups but showed opposite effects. The alleviation of functional impairments in the school/learning domain negatively correlated with decreased DC in the bilateral cerebellum after MPH treatment, and the family functional domain positively correlated with decreased DC in the cerebellum and negatively correlated with decreased DC in the postcentral gyrus after ATX treatment.

**Conclusions:** Both MPH and ATX can normalize abnormal brain functions that mainly involve the fronto-cingulo-parieto-cerebellum circuit in ADHD. Furthermore, the 2 medications showed shared and unique effects on brain functions to alleviate clinical symptoms and functional impairment.

**Keywords:** Attention-deficit/hyperactivity disorder, methylphenidate, atomoxetine, degree centrality, functional impairments

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## Significance Statement

This naturalistic cohort study examined the shared and unique psychopharmacological mechanisms underlying methylphenidate (MPH) and atomoxetine (ATX) treatment in children with attention deficit/hyperactive disorder (ADHD). We used degree centrality (DC), a measurement quantified via resting-state functional magnetic resonance imaging (rs-fMRI), to evaluate the importance of specific regions in the whole brain at the voxel level and to investigate the neural correlates of improvements in clinical symptoms and functional impairments after 12 weeks of medications for ADHD. To our knowledge, this is the first study to explore the neural correlates of the improvements in functional impairments and included ADHD children who did not undergo any treatment during a 12-week follow-up to exclude the confounding effects of brain development in children with ADHD. We found that both MPH and ATX could normalize abnormal brain functions that involve the fronto-cingulo-parieto-cerebellum circuit in ADHD and that shared and specific brain regions exhibited correlations of improvements in clinical symptoms and functional impairments. These results may provide evidence for novel therapeutic targets for non-pharmacological therapy.

## Introduction

Attention deficit hyperactive disorder (ADHD) is a common neurodevelopmental disorder that occurs in early childhood and may persist into adolescence and even adulthood. Its characteristics include developmentally inappropriate levels of inattention (IA) and/or hyperactivity/impulsivity (HI) (Posner et al., 2020). Patients with ADHD exhibit functional impairments predominantly in the domains of academic functioning, peer relationships, and family functioning (Pelham et al., 2005) in school, family, and society settings (Johnston and Mash, 2001; DuPaul, 2007; Hoza, 2007). The prevalence of the disorder among children and adolescents in 6 continents was estimated to be 5.29% (95% CI=5.01–5.56) (Polanczyk et al., 2014). Methylphenidate (MPH) and atomoxetine (ATX) are the most prescribed medication for clinical administration (Cortese, 2020), and they have partly overlapping pharmacological effects. For example, MPH can increase extracellular synaptic levels of dopamine and norepinephrine by blocking dopamine transporters and norepinephrine transporters (NET) in the brain (Han and Gu, 2006). However, ATX can selectively inhibit NET in the brain and increase the extracellular synaptic levels of norepinephrine and dopamine in the prefrontal cortex (Yu et al., 2016). After long-term administration, both medications can improve clinical symptoms (Cortese et al., 2018) and reduce the functional impairments, including those of cognitive functions (Coghill et al., 2014), executive function (Yang et al., 2012), and other various domains evaluated by the Weiss Functional Impairment Rating Scales-Parent Form (WFIRS-P) (Fuentes et al., 2013; Nagy et al., 2016).

However, the psychopharmacological mechanism of MPH and ATX in ADHD require further clarification. Previous magnetic resonance imaging (MRI) studies have shown the dissociable and common effects of MPH and ATX during different cognitive or executive tasks on the brain activity of children and adolescents with ADHD (Smith et al., 2013; Cubillo et al., 2014; Kowalczyk et al., 2019). Moreover, changes in brain functional activity may be related to the improvements of clinical symptoms (Schulz et al., 2012). The frontal lobes and the cerebellum are highly sensitive to MPH, which can “normalize” the activation of these areas in the brain even to levels observed in typically developed children (Czerniak et al., 2013). In resting-state functional MRI (fMRI) studies, single-dose MPH decreased resting-state functional connectivity in executive and default-mode networks (DMN) (Silk et al., 2017) and normalized fronto-parieto-cerebellar dysfunctions in boys with ADHD (An et al., 2013b). In addition, long-term MPH administration can affect the same regions as a single dose in children with ADHD (Shang et al., 2016; Yoo et al., 2018) and can influence the interactions between the frontoparietal network, insular cortex, and DMN (Battel et al., 2016; Yoo et al., 2018). Nevertheless, research on the effects of ATX on the resting brain of children with ADHD

remains insufficient. Lin and Gau found that an 8-week ATX administration could strengthen the anti-correlation between the DMN and the task-positive network among adults with ADHD (Lin and Gau, 2015). To our knowledge, only 1 study has simultaneously compared the effects of MPH and ATX on intrinsic brain activity of children with ADHD (Shang et al., 2016). This study found that improvements in HI correlated with changes in fractional amplitude of low-frequency fluctuation in the bilateral precentral and postcentral gyrus after either MPH or ATX treatment, but the effects of the 2 medications on these regions were opposite. Furthermore, correlations between the reduction in IA symptoms and intrinsic brain activity showed different effects after MPH or ATX administration.

However, all the aforementioned studies mostly focused on clinical symptoms or executive functions but ignored the overall improvements of social functional impairments after medication administration in children with ADHD. Social function is a “real-world consequence” of ADHD symptoms and reflects the difficulties children face in reality (Barkley et al., 2006). Both MPH and ATX can improve functional impairments measured by the WFIRS-P in children with ADHD (Yang et al., 2012; Fuentes et al., 2013). These improvements were associated with a reduction in clinical symptoms (Coghill et al., 2017). However, to our knowledge, there have been no studies on the correlation between improvements in social functional impairments and alterations in brain activity or function. Such studies may be helpful in understanding the potential pathological mechanisms for treating functional impairment and in identifying novel targets for future non-pharmacological treatment. In addition, the brain development trajectories of children with ADHD differ from those of typically developing children (Soman et al., 2022). Previous studies on the effects of long-term medication administration on brain function may neglect the influence of the natural development of ADHD on brain function (Friedman and Rapoport, 2015). The effects of brain development in children with ADHD may confound the effects of medication on brain activity or function.

Degree centrality (DC) is a method based on graph theory that is used to explore global connectivity, measuring the functional connectivity of a given voxel to the rest of the brain and mapping the importance of brain regions (Yang et al., 2015). A previous study reported that medication-naïve boys with ADHD showed decreased DC values in the left superior temporal gyrus and increased DC values in the left superior occipital lobe and right inferior parietal lobe compared with normal controls (Zhou et al., 2019), which indicates a pathophysiological process driven by the cognitive and affective cortico-striatal-thalamic-cortical loops and attention network in children with ADHD.

In this study, we explored the common and unique effects of long-term MPH and ATX administration on the brain functions

of children and adolescents with ADHD as well as the correlation between the treatment effects of MPH and ATX on DC and the improvements in clinical symptoms and functional impairments in the ADHD group. To further exclude the influences of natural brain development in children with ADHD, the study included patients who did not use any medication during the 12-week follow-up. Based on previous studies, we hypothesized that MPH and ATX may have shared and unique effects on ADHD brain function, normalizing fronto-parieto-cerebellar dysfunction, and that the changes in DC in these regions correlated with improvements of clinical symptoms and functional impairments.

## METHODS

### Participants

Seventy-six medication-naïve children and adolescents (age range: 86–193 months, mean = 124 ± 26.0 months) with clinically diagnosed ADHD based on the DSM-IV were recruited from the outpatient department of Peking University Sixth Hospital (Beijing, China). The patients and their parents were interviewed by a child psychiatrist using the Kiddie Schedule for Affective Disorder and Schizophrenia for School-Aged Children – Lifetime Version to ensure the diagnosis of ADHD. Another 46 age-matched typically developed children (TDC) (age range: 88–160 months, mean = 119.9 ± 49.1 months) were recruited from schools or nearby communities using recruitment advertisements. All participants met the following criteria: (1) full-scale IQ score >80 as measured by the Wechsler Child Intelligence Scale, Third Edition; (2) no history of head trauma with loss of consciousness; (3) no history of any psychotic medication use; (4) no current diagnosis of schizophrenia, bipolar disorder, major depressive disorder, anxiety disorder, obsessive-compulsive disorder and other axis I disorders other than offensive/defiant disorder, or tic disorder; (5) no history of neurological disorders or other severe diseases; and (6) no contraindications to MRI scans. Moreover, participants in TDC group were required to have no history of psychiatric disorder.

Informed consent was approved by the Ethics Committee at Peking University Sixth Hospital before the study was conducted. All participants provided written informed consent and were fully informed of the study.

Children with ADHD underwent an MRI scan, and their parents reported the scores for clinical symptoms using ADHD-rating scales (ADHD-RS) and for functional impairments using the WFIRS-P at baseline. The WFIRS-P consists of 50 questions in which parents evaluate their children's functional impairment over the past month. The items of the WFIRS-P are scored on a 4-point Likert-type rating scale: 0 (never or not at all), 1 (sometimes or somewhat), 2 (often or much), or 3 (very often or very much) and aggregated to produce 6 domain scores (family, learning and school, life skills, child's self-concept, social activities, and risky activities). An overall score (summary index) was also computed for all WFIRS-P items. A higher score on each WFIRS-P domain and summary index indicate greater functional impairment (Ying et al., 2011).

After the MRI scan in the baseline, children with ADHD were treated with MPH, ATX, or no medication treatment according to the parent's choices after consultations with a professional child psychiatrist (C.Q.J. or Y.L.).

Children in both medication groups received 12 weeks of treatment and began medication in the morning after the first visit. The initial dosage was 18 mg/d for MPH and 10 mg/d for ATX. Drug dosage was titrated every week for MPH and every 2

to 4 days for ATX, depending on clinical response and adverse effects (MPH maximum daily dosage, 54 mg/d; ATX maximum daily dosage, 1.2 mg/kg or 100 mg/d). The untreated subgroups did not receive any systematic therapy during the follow-up period. After 12 weeks, all children in each ADHD subgroup underwent a second MRI scan for following-up states and assessment of clinical symptoms and functional impairments. Participants with medication administration underwent the second MRI scan after taking medications as usual in the morning to map the maximum efficacy of the medication. At the follow-up, the average dosage for MPH was 30.92 ± 13.2 mg/d, and the dosage-weight ratio for ATX was 1.07 ± 0.46 mg/kg·d, with an average dose of 41.9 ± 13.3 mg/d.

The TDC only acquired 1 MRI scan at baseline.

Improvement in clinical symptoms and functional impairments were evaluated by the decreased rate for each subscale or domain and the total score.

$$\Delta \text{scores} = \text{Decreased rate (\%)} = \frac{S_2 - S_1}{S_1} \times 100\%$$

( $S_2$  is the score at follow-up, and  $S_1$  is the score at baseline)

### MRI Data Acquisition

Images were acquired on a GE Discovery 3.0 T MR750 system at the Centre for Neuroimaging Sciences, Peking University Sixth Hospital. Participants were asked to keep their eyes closed during scanning but not fall asleep. The imaging parameters were as follows: 240 echo planar imaging volumes; TR=2000 ms; TE=30 ms; flip angle=90°; field of view=220 mm × 220 mm; matrix size=64 × 64; 43 axial slices acquired in an interleaved descending order; slice thickness=3.2 mm, slice gap=0 mm, and the imaging plane being parallel to the anterior commissure–posterior commissure image plane. A high-resolution T1-weighted anatomical image was acquired for spatial normalization. The parameters of T1 image were as follows: TR=6.7 s, TE=Min Full, flip angle=8°, 180 slices, slice thickness=1.0 mm, slice gap=0 mm, field of view=256 mm × 256 mm, and matrix size=256 × 256.

### Data Preprocessing

Imaging preprocessing was performed using MATLAB R2017b and the Data Processing and Analysis for (resting-state) Brain Imaging software (Yan et al., 2016) according to standard procedure (Chao-Gan and Yu-Feng, 2010). The preprocessing pipeline was as follows. The first 10 time points were removed to allow for scanner calibration and participants' adaptation to the scanning environment. For each participant, the functional images were slice-timing corrected and realigned. Head motion was indexed by the mean frame-wise displacement (FD) derived using Jenkinson's relative root mean square algorithm (Jenkinson et al., 2002). Participants with a mean FD exceeding 2 SDs (Yan et al., 2013) above the sample mean (0.10 ± 0.13 mm) were excluded from further analysis. Subsequent steps included spatial normalization to the Montreal Neurological Institute template using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra, resampling to 3 × 3 × 3 mm<sup>3</sup>, temporal band-pass filtering (0.01–0.1 Hz), nuisance signal regression (including Friston-24 model motion parameters, white matter, cerebrospinal fluid, and global signals), and detrending.

After the preprocessing, 1 participant in the TDC group and 8 participants in the ADHD group (one of whom took MPH, 6 who

took ATX, and 1 who did not take either medication) were excluded due to excessive head motion either at baseline or during follow-up. Another child in the TDC group and 1 in the untreated group were excluded due to abnormal structural images, such as a severe ghost or mild ventriculomegaly. Finally, 44 participants in the TDC group and 67 children with ADHD (24 who took MPH, 20 who took ATX, and 23 who did not take any medication) were included in the next stage of analysis, but only some of them completed the WFIRS-P both at baseline and follow-up: 21 in the MPH group, 15 in the ATX group, and 21 in the untreated group.

## DC Analysis

Each voxel in the brain can be thought of as a node, with an edge indicating the functional connectivity between any 2 voxels (Zuo et al., 2012). Based on preprocessed data, voxel-wise DC value calculations were performed using the RESTPLUS software (Jia et al., 2019). The time series in each voxel was extracted to compute the Pearson's correlation coefficients ( $r$ ) between any pair of voxels within the whole-brain grey matter mask. Fisher's  $r$ -to- $z$  transformation was performed on Pearson's correlation data to obtain a normalized  $Z$ -score DC value map, and the whole-brain functional network was mapped with a threshold  $r > 0.25$ . After normalization, a 6-mm  $\times$  6-mm  $\times$  6-mm full width at half maximum Gaussian kernel was applied to the functional connectivity map for further statistical analysis. To ensure the robustness of the results, different correlation thresholds (0.2, 0.3) of DC were applied, and the procedure was repeated. Furthermore, to exclude the influence of handedness on brain function, left-handed participants were excluded from the [supplementary analysis](#).

## Statistical Analysis

The demographic and clinical data were compared using SPSS 22.0, and the Shapiro-Wilk test was applied to assess data normality and the Levene test for homogeneity of variance. For normally distributed variables with homogeneity of variance, 2-tailed independent-samples  $t$  tests and ANOVA were used, with the Bonferroni test used for post-hoc analysis. A chi-squared test was used to compare categorical data distribution between groups. The paired  $t$  test was conducted for clinical symptoms assessed by the ADHD-RS, social functional impairments assessed by the WFIRS-P, and head motions assessed by the FD at baseline and follow-up in each ADHD subgroup. The significance level was set at  $P < .05$ .

A 2-sample  $t$  test analysis with age, gender, mean FD (ADHD group at baseline), IQ, and handedness as covariates was performed to explore the differences in DC between the ADHD and TDC groups. Next, the paired  $t$  test was performed among the 3 ADHD subgroups, with the mean FD at baseline and follow-up as covariates. To determine the effects of medications in the aberrant areas specifically for ADHD at the same time, excluding the confounds arising from brain development in patients with ADHD, the paired  $t$  test in the MPH and ATX subgroups and the following correlation analysis were all restricted within a mask. The mask, which includes the areas, showed a significant difference (2-sample  $t$  tests,  $P < .05$ , uncorrected) in DC between the ADHD group at baseline and the TDC group, and excluded the voxels showing significant differences (paired  $t$  test,  $P < .05$ , uncorrected) in DC among the untreated subgroup between baseline and follow-up. Moreover, the voxels in the mask were constrained in the grey matter. Furthermore, we performed a correlation analysis between changes in the mean  $z$ -DC value and the decreased rate of ADHD-RS and WFIRS-P in each ADHD

subgroup. In the correlation analysis, the mean FD at baseline and follow-up as well as sex were set as covariates.

For all these imaging results, we applied Gaussian Random Field for the correction of multiple comparisons, voxel-level  $P < .005$ , and cluster-level  $P < .05$  (Chen et al., 2018).

In addition, the DC maps acquired using different thresholds were reanalyzed as described previously. After excluding left-handed participants, we repeated the aforementioned imaging analysis procedure.

## RESULTS

### Demographics

For the TDC and ADHD groups at baseline, there was no significant difference in age ( $P = .336$ ) and handedness ( $P = .826$ ), but there was a significant difference in IQ ( $P = .002$ ) and sex ( $P = .005$ ) (Table 1).

Within the 3 ADHD subgroups, there was no significance difference in age ( $P = .254$ ), IQ ( $P = .709$ ), sex ( $P = .810$ ), handedness ( $P = .171$ ), comorbidity with offensive/defiant disorder ( $P = .545$ ) or other disorders ( $P = .660$ ), and ADHD subtypes ( $P = .213$ ). With regard to the severity of clinical symptoms at baseline, there was no significant difference in the total score ( $P = .075$ ) and IA score ( $P = .555$ ) within 3 subgroups, but the HI score showed statistical significance ( $P = .032$ ). Bonferroni post-hoc analysis showed that the HI scores in the ATX subgroups were significantly higher than those in the untreated subgroups (Table 2).

### Improvements in Clinical Symptoms and Function Impairments

After MPH treatment, ADHD-RS scores in children with ADHD showed a significant decreased compared with baseline, including total score ( $P < .001$ ), IA score ( $P < .001$ ), and HI scores ( $P < .001$ ). Furthermore, the WFIRS-P total scores ( $P = .035$ ) and Domain B (learning and school) scores ( $P = .004$ ) also significantly decreased. After ATX treatment, ADHD-RS scores in children with ADHD showed a significant decrease compared with baseline, including the total score ( $P < .001$ ), IA scores ( $P = .002$ ), and HI scores ( $P < .001$ ), but WFIRS-P scores did not. In untreated patients, only HI scores significantly decreased after 12 weeks ( $P = .035$ ) ([supplementary Table 1](#)).

### Baseline and Follow-up Comparison of DC

Compared with TDC, ADHD showed a decreased DC in the parietal, occipital, and frontal lobes, but increased DC in the temporal lobe and cerebellum at baseline. All these areas that showed differences ( $P < .05$ , uncorrected) were included in a mask. After 12 weeks of follow-up, children with ADHD in the

**Table 1.** Demographics of TDC and Patients with ADHD

	TDC (n=44)	ADHD (n=67)	P
Age, mo	119.86 $\pm$ 23.39	124.86 $\pm$ 28.52	.336
IQ	110.11 $\pm$ 2.50	102.07 $\pm$ 13.41	.002*
Gender (M/F)	28/16	58/9	.005*
Handness (R/L)	42/2	62/5	.826

Abbreviations: ADHD, attention deficit/hyperactive disorder; IQ, intelligence quotient; M/F, males/females; R/L, right/left; TDC, typically development children.

\* $P < .05$ .

**Table 2.** Demographics of ADHD Subgroups

	ATX (n=20)	MPH (n=24)	Untreated (n=23)	P
Age, mo	131.82 ± 34.00	126.10 ± 18.23	117.50 ± 31.50	.254
IQ	103.00 ± 15.37	103.13 ± 11.79	100.17 ± 13.57	.709
Gender (M/F)	18/2	20/4	20/3	.810
Handness (R/L)	17/3	22/2	23/0	.171
Comorbidity				
ODD (yes/no)	5/15	3/21	5/18	.545
Others (yes/no)	4/16	5/19	7/16	.660
ADHD subtypes, (C/IA/HI)	12/7/1	15/9/0	8/14/1	.213
ADHD scores				
IA	27.80 ± 4.75	26.88 ± 3.92	26.26 ± 5.18	.555
HI	23.10 ± 7.79	22.08 ± 5.63	18.13 ± 6.02	.032 <sup>a</sup>
Total	50.09 ± 11.33	48.96 ± 8.34	44.39 ± 8.95	.075

Abbreviations: ATX, atomoxetine; C, combined subtype; HI, hyperactivity/impulsivity; IA, inattention; IQ, intelligence quotient; M/F, males/females; MPH, methylphenidate; ODD, offensive/defiant disorder; R/L, right/left.

<sup>a</sup>P < 0.05.

<sup>b</sup>Bonferroni post-hoc analysis showed ATX > untreated. One patient in MPH subgroups, 3 in ATX subgroups, and 1 in the untreated group comorbid with ODD and other disorders at the same time. Other comorbidities include: tic disorder and nocturnal enuresis.

untreated subgroups showed decreased DC in regions of the temporal lobes and cerebellum and increased in parietal, occipital, and frontal lobes; these areas were excluded from the mask. Subsequent analysis was confined to this mask.

After 12-week MPH administration, the bilateral inferior temporal gyrus (Bi-ITG) and fusiform gyrus showed decreased DC, while the right postcentral gyrus (R-PocG), bilateral middle frontal gyrus (Bi-MFG), right superior frontal gyrus, left inferior parietal lobule, and left supplementary motor area (L-SMA) had increased DC values. The left cerebellum (L-Cbl) showed a decrease in DC after 12-week ATX administration (Table 3; Figure 1). However, the 2 medications had no overlapping region that exhibited a change after treatment. Most of these results could be reproduced at different DC thresholds ( $r=0.2$ ;  $r=0.3$ ), and under the DC threshold of 0.2, the L-SMA showed increased DC values after ATX treatment (supplementary Tables 2 and 3; supplementary Figure 1). After excluding left-handed participants, most results were replicated. Furthermore, MPH and ATX normalized the abnormal DC in the SMA, and ATX normalized DC in the bilateral frontal lobes (supplementary Table 4).

### Correlation Between Improvements in ADHD Symptoms and DC Changes in Each Subgroup

After 12-week MPH administration, the ADHD-RS-total  $\Delta$ scores were negatively correlated with changes in DC in the right fusiform gyrus/inferior temporal gyrus (R-ITG) and L-Cbl (Table 4; Figure 2A). The  $\Delta$ ADHD-RS-IA scores were negatively correlated with decreased DC in the L-Cbl (Figure 2B). The  $\Delta$ scores of ADHD-RS-HI were negatively correlated with changes in DC in the bilateral fusiform gyrus/Bi-ITG (Figure 2C). After 12-week ATX treatment, the ADHD-RS-total  $\Delta$ scores positively correlated with decreased DC in the right fusiform gyrus/R-ITG (Figure 2D). After excluding left-handed participants, most results were replicated. However, the ADHD-RS-HI  $\Delta$ scores were positively correlated with DC changes in the right middle temporal pole after ATX treatment (supplementary Table 5).

### Correlation Between Improvements in Functional Impairments and DC Changes in Each Subgroup

Improvement in domain B after MPH administration was negatively correlated with decreased DC in the bilateral cerebellum

in the MPH subgroup (Table 5; Figure 3A). As for the ATX subgroup, although there were no significant improvements of function impairments, there appeared to be a correlation between the alleviation of functional impairments and alteration of DC in the different brain regions. Specifically, the improvement in domain A (family) was negatively correlated with the alteration of DC in the cerebellum and R-PoCG (Figure 3B). After excluding left-handed participants, only the results of the ATX subgroup could be replicated, whereas the results of MPH could not (supplementary Table 6).

## Discussion

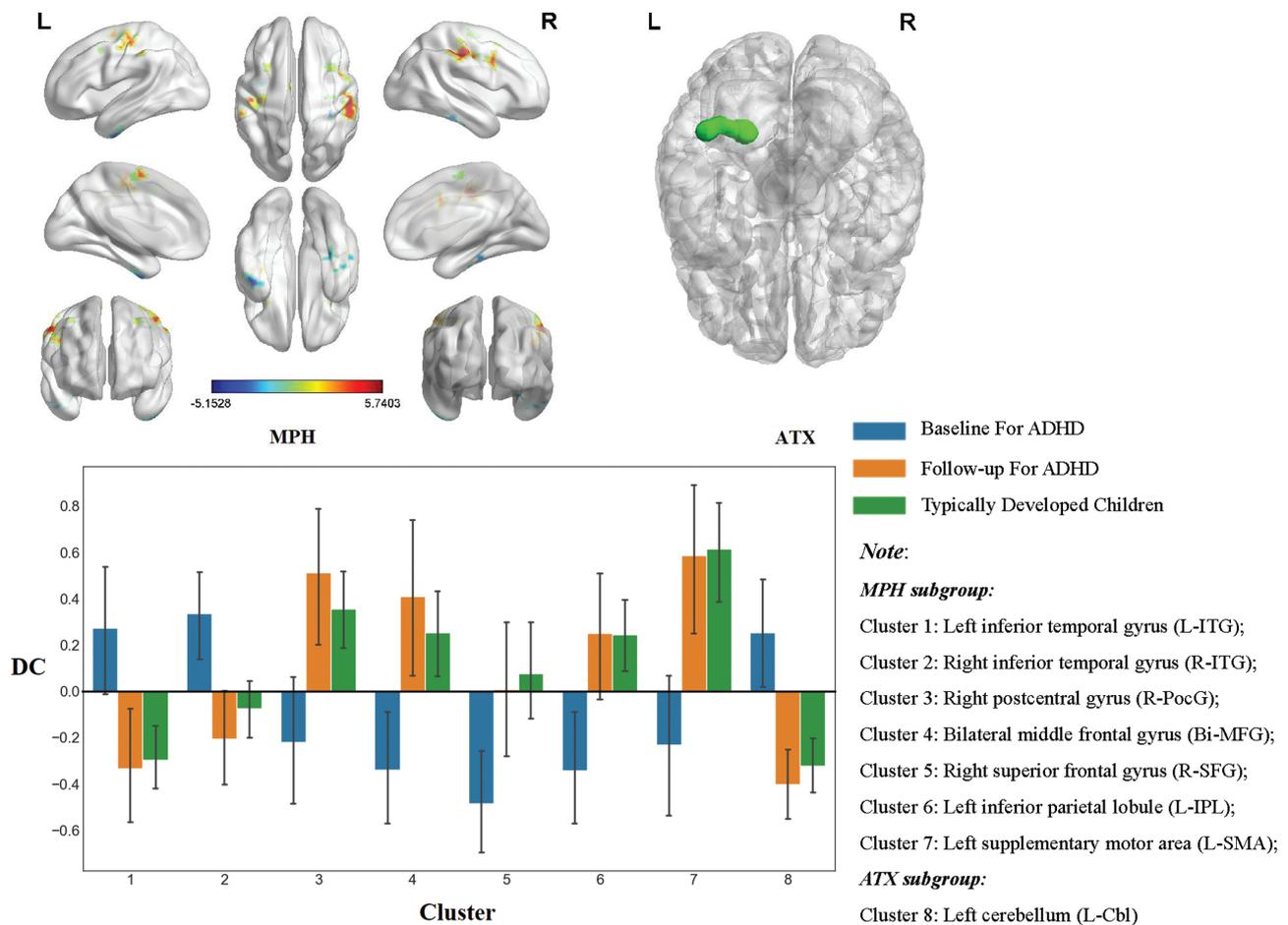
This study adopted DC to characterize the shared and unique effects of MPH and ATX on brain functions of medication-naïve children with ADHD. This study was a real-world observational cohort and might better reflect actual clinical practice. We found that both MPH and ATX could improve clinical symptoms and normalize the function of extensive brain regions that mainly constitute the fronto-cingulo-parieto-cerebellum circuits and that are primarily located in the ITG. Meanwhile, improvements in clinical symptoms and functional impairments were correlated with alterations in the DC value, mainly in the temporal lobe and cerebellum after medication treatment. Although the 2 medications simultaneously acted on the R-ITG, they showed an opposite correlation with improvements in clinical symptoms. To our knowledge, this is the first study to explore the treatment effects of MPH and ATX on relationships between changes in brain function and improvements in social functional impairments among medication-naïve children and adolescents with ADHD.

Compared with baseline, a 12-week administration of MPH and ATX resulted in patients in both medicated subgroups showing improvements in clinical symptoms, which was consistent with the results of a previous study (Cortese et al., 2018). However, the untreated subgroup also showed a significant reduction in HI symptoms, suggesting that HI symptoms decrease with age and may not be attributed to the effect of medication (Larsson et al., 2011). However, for functional impairments, only the children taking MPH showed a reduction in the total score and domain B. This finding was partly similar to those of previous studies that showed that MPH has an impact on improvements in school setting (Stein et al., 2011) and that the stimulants outperformed ATX in improving the total score and

Table 3. Regions Showing Significant Differences After MPH and ATX Treatment

Treatments	R/L	Regions	Peak MNI coordinates			Cluster size (voxels)	Peak t value
			X	Y	Z		
MPH	L	Inferior temporal gyrus	-45	-6	-42	51	-4.86
	R	Inferior temporal gyrus	42	-27	-36	33	-5.15
	R	Postcentral gyrus	51	-24	42	247	5.74
	R	Middle frontal gyrus	33	12	48	23	4.46
	R	Superior frontal gyrus	33	-12	69	21	4.55
	L	Inferior parietal gyrus	-57	-33	48	108	5.50
	L	Supplementary motor area	0	-9	60	36	4.64
ATX	L	Cerebellum	-21	-51	-27	50	-0.63

Abbreviations: ATX, atomoxetine; MNI, Montreal Neurological Institute; MPH, methylphenidate; R/L, left/right.



**Abbreviations:** ATX, atomoxetine; DC, degree centrality; MPH, methylphenidate; R/L, right/left

Figure 1. Changes in DC between baseline and follow-up in MPH and ATX subgroups.

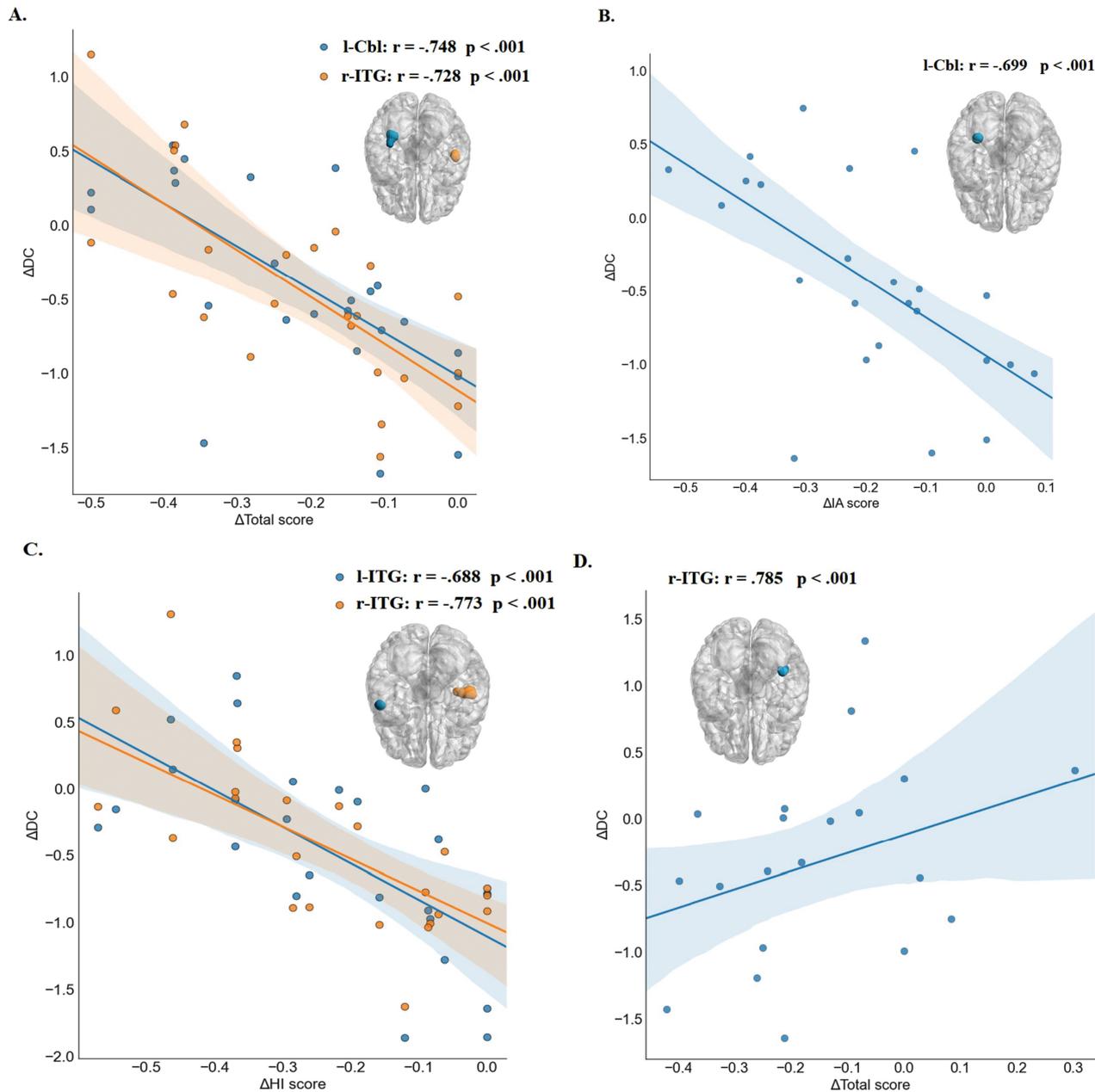
learning on the WFIRS-P (Nagy et al., 2016). The lack of improvements in functional impairment with ATX treatment may be due to insufficient dosage. Previous studies have shown a reduction in WFIRS-P scores after at least 9 weeks of ATX treatment, and the patients were administered a maximum ATX dose of 1.4 mg/kg·d and 100 mg/d (Hervas et al., 2014; Nagy et al., 2016). In our study, the average dose was  $1.07 \pm 0.46$  mg/kg·d and  $41.9 \pm 13.3$  mg/d ultimately, which was much lower than that of the previous study. Therefore, the overall alleviation of functional impairments after treatment with MPH and ATX may require a longer duration and higher dose.

In the present study, compared with TDC, brain regions in children with ADHD, including the R-PocG, Bi-MFG, right superior frontal gyrus, left inferior parietal lobule, and L-SMA, which are included in the fronto-cingulo-parieto-cerebellum cognitive-attention circuit and which underpin high-order brain functions such as executive control function (Bush, 2010; Castellanos and Proal, 2012), showed normalization effects after MPH treatment. These results were consistent with the previous studies (Cao et al., 2006; An et al., 2013a, 2013b). In addition, aberrant DC in the ITG was found to have normalization effects after MPH treatment, and the DC changes in these regions were correlated

**Table 4.** Correlation Between Changes in ADHD-RS and Changes in DC After MPH and ATX Treatment

Treatment	$\Delta$ Scores	R/L	Regions	Peak MNI Coordinates			Cluster size (voxels)	Peak t value
				X	Y	Z		
MPH	IA	L	Cerebellum	-33	-45	-33	25	-0.73
	HI	L	inferior temporal gyrus	-57	-6	-33	58	-0.69
		R	inferior temporal gyrus	48	-21	-24	35	-0.71
	Total	L	Cerebellum	-33	-45	-33	54	-0.74
		R	inferior temporal gyrus	51	-21	-21	24	-0.74
ATX	Total	R	inferior temporal gyrus	45	-39	-15	36	0.80

Abbreviations:  $\Delta$ Scores, decreased rate of ADHD-Rating Scales (ADHD-RS); ATX, atomoxetine; HI, hyperactivity/impulsivity; IA, inattention; MNI, Montreal Neurological Institute; MPH, methylphenidate; R/L, left/right.



**Abbreviations:**  $\Delta$ Score, decreased rate of ADHD-Rating Scales (ADHD-RS); r-/l-, right-/left-; ITG, inferior temporal gyrus; Cbl, cerebellum; IA, ADHD-RS-Inattention score; HI, ADHD-RS-Hyperactivity/impulsivity scores.

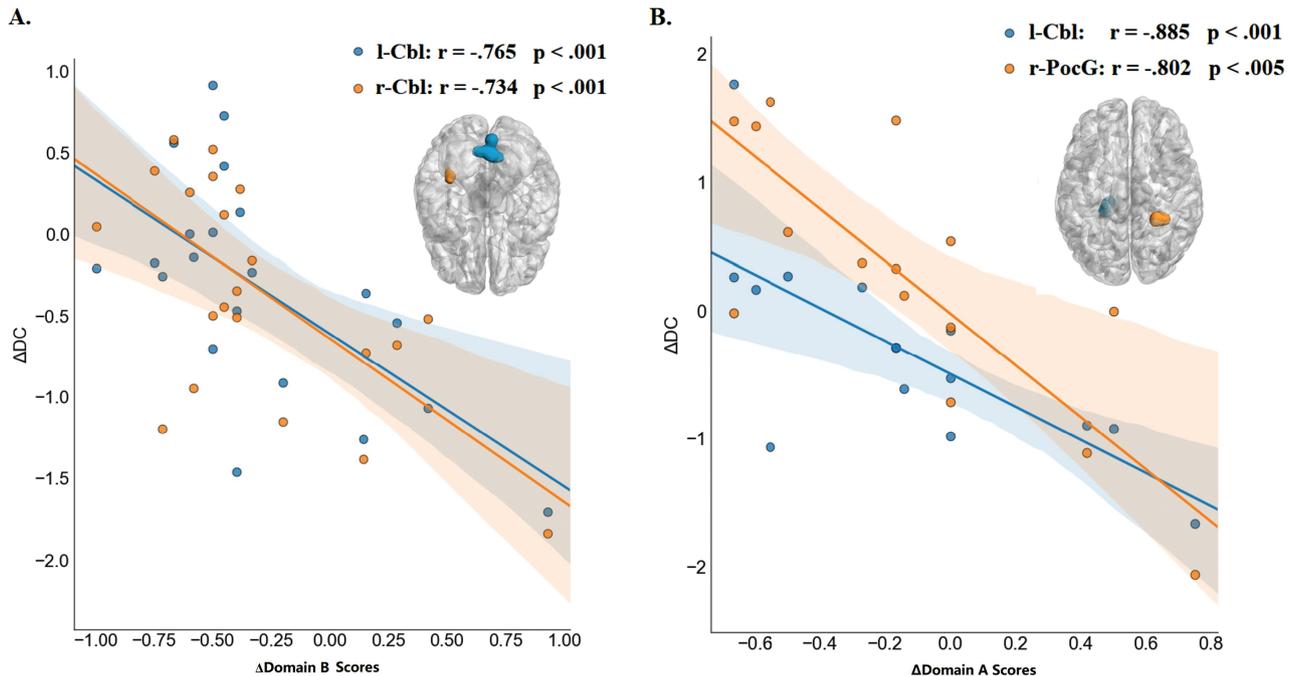
**Note:** MPH subgroup: **Figure 2A, 2B, 2C**; ATX subgroup: **Figure 2D**;

**Figure 2.** Correlation between changes in symptoms and changes in DC in MPH and ATX subgroups.

**Table 5.** Correlation Between Changes in the WFIRS-P and Changes in DC After MPH and ATX Treatment

Treatment	$\Delta$ Scores	R/L	Regions	Peak MNI Coordinates			Cluster size (voxels)	Peak r value
				X	Y	Z		
MPH	Domain B	R	Cerebellum	9	-63	-36	69	-0.75
		L	Cerebellum	-33	-45	-33	30	-0.67
ATX	Domain A	R	Cerebellum	45	-39	-15	36	0.80
		R	Postcentral gyrus	36	-42	60	44	-0.83

Abbreviations:  $\Delta$ Scores, decreased rate of Weiss Functional Impairments Rating Scales-Parent Report (WFIRS-P); ATX, atomoxetine; Domain A, family; Domain B, school and learning; MNI, Montreal Neurological Institute; MPH, methylphenidate; R/L, left/right.



**Abbreviations:**  $\Delta$ Scores, decreased rate of Weiss Functional Impairments Rating Scales-Parent Report (WFIRS-P); r-/l-, right-/left-; PocG, postcentral gyrus; Cbl, cerebellum; Domain A, family; Domain B, school and learning.

**Note:** MPH subgroup: **Figure 3A** ATX subgroup: **Figure 3B**;

**Figure 3.** Correlation between changes in the WFIRS-P and changes in DC in MPH and ATX subgroups.

with improvements in clinical symptoms. Furthermore, the DC value decreased in the L-Cbl of the ATX group, which was also normalized in our study. After excluding left-handed individuals, most of the results were replicated and showed robustness. Twelve weeks of ATX administration can upregulate cerebellar activation when ADHD adults perform cognitive tasks, and it also plays a key role in the fronto-cingulo-parieto-cerebellar circuit (Bush et al., 2013). Taking all these findings into account, we suggest that the normalization effect of MPH and ATX on the fronto-cingulo-parieto-cerebellar cognitive-attention circuit is associated with the recovery of cognitive and attentional processing in children with ADHD. However, the effects of MPH and ATX showed opposite directions and had no overlapping changing regions, which underlie the specific treatment effects of the 2 medications.

Previous studies have shown that children with ADHD exhibited increased regional homogeneity and decreased functional connectivity density in the (De Celis Alonso et al., 2014), which correlates with ADHD symptoms (Tomasi and Volkow,

2012). Moreover, the cerebellum is involved in planning, organization, and execution, and MPH can inhibit NET and dopamine transporters, which are widespread in the cortex, subcortex, and cerebellum (Rubia et al., 2014). Therefore, the effects of MPH on the cerebellum are associated with improvements in ADHD symptoms, which also involve fronto-cingulo-parieto-cerebellar circuit.

In the present study, MPH showed a normalization effect on the DC value in the bilateral fusiform gyrus/Bi-ITG. In addition, the DC changes in the ITG correlated with clinical symptoms in both medication subgroups, implicating the involvement of the fusiform gyrus/ITG in ADHD pathology and therapeutic effects. These regions are considered to be involved in emotion regulation (Frank et al., 2014) and showed abnormality on regional homogeneity (Cao et al., 2006), suggesting that the dysregulation of emotion processing may underpin the pathopsychological mechanism underlying ADHD (Castellanos et al., 2006). Emotional dysregulation in children with ADHD may lead to emotional impulsivity and externalizing symptoms

(Shaw et al., 2014; Faraone et al., 2019). Previous studies found increased amplitude of low frequency fluctuation in the ITG after MPH treatment in ADHD children (Yoo et al., 2018) and observed changes in the interactions between the ITG and affective and cognitive control networks after ATX treatment (Lin and Gau, 2015; Faraone et al., 2019), further supporting the results of this study. However, in our study, the 2 medications showed opposite effects on the correlation between reductions in symptoms and DC changes in the ITG. A previous study also showed different therapeutic effects of long-term administration of the 2 medications, demonstrating a different correlation between improvements in HI and low-frequency fluctuation changes in bilateral precentral and postcentral gyri during a resting-state fMRI study (Shang et al., 2016). The effect of MPH on negative correlation between decreased DC in fusiform/ITG and improvements in HI symptoms and total symptoms may be a compensatory effect, indicating that the lower DC value showed less importance of the region and more severe clinical symptoms. However, the overall symptoms were reduced by modulating the fronto-cingulo-parieto-cerebellum circuit, which normalized after MPH treatment. ATX could strengthen the anti-correlation between the DMN and ITG, and this effect may be due to the decreased connection between the 2 regions and is relevant to modulating emotional dysregulation and the HI symptoms (Lin and Gau, 2015). Moreover, the interpretation of the results should be done with caution because of the complex relationships between fMRI blood oxygen level depend signals and brain function. The different effects of the 2 medications may be associated with their effects on the signal-to-noise ratio, which could be increased by both MPH and ATX in non-human primates, but through a complementary effect in which the MPH suppressed non-specific information while ATX increases a specific signal (Gamo et al., 2010). Due to the complex characteristics of the blood oxygen level depend signal, the specific meanings of the results need to be further interpreted in future study.

MPH could also improve functional impairments in domain B in children with ADHD. Higher scores in domain B reflect more severe functional impairments in children with ADHD for learning and schoolwork, and the domain B score significantly correlated with executive functions among Chinese children (Ying et al., 2011). As mentioned above, the cerebellum is involved in the fronto-cingulo-parieto-cerebellum cognitive-attention circuit, which underpins higher-order functions in the brain (Bush, 2010; Castellanos and Proal, 2012). Furthermore, the normalization effects on the cerebellum after MPH treatment were associated with  $\Delta$ scores of ADHD-RS-IA in this study. Improvements in clinical symptoms may further improve performance in school and learning, reducing the functional impairment in domain B. For ATX treatment, although there was no significant improvement in functional impairments, the  $\Delta$ scores in the WFIRS-P showed some correlation trends, such as a correlation between a reduction in the WFIRS-P domain A (family) scores and DC changes in the R-PocG. Domain A scores are associated with HI symptoms among Chinese children with ADHD (Ying et al., 2011). A study on long-term ATX administration in children with ADHD found that improvements in HI correlated with changes in intrinsic activity in bilateral precentral and postcentral gyri (Shang et al., 2016), further proving the effect of long-term ATX administration on the sensorimotor system (Schulz et al., 2012). However, the reason why most of the WFIRS-P results were not replicated may be small sample size for right-handed individuals who finished WFIRS-P assessment. These results require larger samples

to validate the effects of ATX on the improvements in functional impairments.

Nevertheless, this study had several limitations. First, the sample size was relatively small, which may have caused the study to be statistically underpowered and may be one of the reasons for unstable results of correlations between improvements in social functional impairments and changes in DC. Second, the sexes of the ADHD and TDC groups were not matched. Although we treated sex as a covariate in the analysis, some results should be treated with caution and may require a larger and sex-matched sample for validation. Moreover, some results in the study may show several differences when various thresholds are adopted for DC calculations. These differences can be explained by the strength of functional connectivity across separate brain regions. When a lenient threshold is adopted, some weak connections may increase the DC to a certain region and vice versa (Zuo et al., 2012). Finally, MPH treatment improved function involved in learning and school performance, but ATX treatment did not result in any improvements in functional impairments, which can be attributed to the duration and relatively lower dose for ATX. Therefore, future research should include a longer duration of MPH and a higher dose of ATX to focus on the relationship between improvements in functional impairments and brain function.

## CONCLUSION

In conclusion, this was a real-world study and reflected real clinical conditions. We found that both MPH and ATX could improve clinical symptoms and normalize the function of the fronto-cingulo-parieto-cerebellum cognitive-attention circuit. They have a shared effective brain area (i.e., R-ITG), but showed opposite effects. They also involved other specific brain regions (e.g., Bi-Cbl for MPH and R-PocG for ATX) to improve functional impairments. This study helps us further understand the therapeutic effects of MPH and ATX and the pathological mechanism of ADHD.

## Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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## Interest Statement

The authors declare that they have no conflict of interest.

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