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Stimulant medications in children with ADHD normalize the structure of brain regions associated with attention and reward

Feifei Wu^{1,2,8}, Wenchao Zhang^{1,2,8}, Weibin Ji^{1,2}, Yaqi Zhang^{1,2}, Fukun Jiang^{1,2}, Guanya Li^{1,2}, Yang Hu^{1,2}, Xiaorong Wei³, Haoyi Wang⁴, Szu-Yung (Ariel) Wang⁵, Peter Manza⁵, Dardo Tomasi⁵, Nora D. Volkow⁵, Xinbo Gao⁵, Gene-Jack Wang⁵✉ and Yi Zhang^{1,2}✉

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Children with ADHD show abnormal brain function and structure. Neuroimaging studies found that stimulant medications may improve brain structural abnormalities in children with ADHD. However, prior studies on this topic were conducted with relatively small sample sizes and wide age ranges and showed inconsistent results. In this cross-sectional study, we employed latent class analysis and linear mixed-effects models to estimate the impact of stimulant medications using demographic, clinical measures, and brain structure in a large and diverse sample of children aged 9–11 from the Adolescent Brain and Cognitive Development Study. We studied 273 children with low ADHD symptoms and received stimulant medication (Stim Low-ADHD), 1002 children with high ADHD symptoms and received no medications (No-Med ADHD), and 5378 typically developing controls (TDC). After controlling for the covariates, compared to Stim Low-ADHD and TDC, No-Med ADHD showed lower cortical thickness in the right insula (INS, $d = 0.340$, $P_{FDR} = 0.003$) and subcortical volume in the left nucleus accumbens (NAc, $d = 0.371$, $P_{FDR} = 0.003$), indicating that high ADHD symptoms were associated with structural abnormalities in these brain regions. In addition, there was no difference in brain structural measures between Stim Low-ADHD and TDC children, suggesting that the stimulant effects improved both ADHD symptoms and ADHD-associated brain structural abnormalities. These findings together suggested that children with ADHD appear to have structural abnormalities in brain regions associated with saliency and reward processing, and treatment with stimulant medications not only improve the ADHD symptoms but also normalized these brain structural abnormalities.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder with a worldwide prevalence of approximately 5.3% in children [1]. Children and adolescents with ADHD are characterized by inattention, impulsivity, and hyperactivity. They are more likely to have numerous negative outcomes relative to healthy children, including impaired social functioning, increased risk of hospitalization and injuries, and substance use disorder [2, 3].

By 2018, the Centre for Disease Control reported approximately 3.3 million children with ADHD were taking ADHD medication in the United States [4]. Although ADHD medications consist of stimulant and non-stimulant compounds, stimulant medications (including methylphenidate (MPH)-based and amphetamine (AMP)-based agents) are considered the first-line therapy. The proposed mechanism of action of stimulant medications is that they can increase dopamine (DA) levels, a pharmacological effect that also underlies drug reward [5, 6]. These changes help to

reduce the core symptoms of ADHD, improving behavior and quality of life [7–9].

Previous structural magnetic resonance imaging (sMRI) studies revealed that ADHD is associated with brain structural abnormalities in regions involved with saliency detection (e.g., insula-INS, anterior cingulate cortex-ACC), reward (e.g., nucleus accumbens-NAc), memory (e.g., hippocampus), and emotion (e.g., amygdala) [10–12]. The volumes of the NAc, amygdala, caudate (CAU), hippocampus and ACC were smaller in individuals with ADHD compared with controls. There was a 3.5-year delay in peak thickness in prefrontal cortex maturation in children with ADHD relative to those without ADHD [13]. The delay indicates that cortical development in children with ADHD lagged behind that of typically developing children by several years. Since stimulant medications are commonly used to treat ADHD symptoms, an increasing number of sMRI studies have been conducted to assess their impact on brain structures. Most studies have compared neuroanatomy between children with ADHD who do not receive

¹Center for Brain Imaging, School of Life Science and Technology, Xidian University & Engineering Research Center of Molecular and Neuro Imaging, Ministry of Education, Xi'an, Shaanxi 710126, China. ²International Joint Research Center for Advanced Medical Imaging and Intelligent Diagnosis and Treatment & Xi'an Key Laboratory of Intelligent Sensing and Regulation of trans-Scale Life Information, School of Life Science and Technology, Xidian University, Xi'an, Shaanxi 710126, China. ³Kindergarten affiliated to Air Force Medical University, Xi'an, Shaanxi 710032, China. ⁴College of Westa, Southwest University, Chongqing 400715, China. ⁵Laboratory of Neuroimaging, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD 20892, USA. ⁶Chongqing Key Laboratory of Image Cognition, Chongqing University of Posts and Telecommunications, Chongqing 400065, China. ⁷Chongqing Institute for Brain and Intelligence, Guangyang Bay Laboratory, Chongqing 400064, China. ⁸These authors contributed equally: Feifei Wu, Wenchao Zhang.

✉email: gene-jack.wang@nih.gov; yizhang@xidian.edu.cn

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stimulant medications (No-Med ADHD), children with ADHD who are treated with stimulant medications (Stim-ADHD), and typically developing controls (TDC). Cross-sectional studies that assessed the impact of stimulant medications on brain structures and results showed larger gray matter/cortical volume in the INS, ACC, thalamus, cerebellum, NAc, CAU, and putamen in Stim-ADHD compared to No-Med ADHD and TDC [14–20]. One longitudinal study on No-Med ADHD (ages 9–11) showed excessive cortical thinning in the right motor strip, left middle/inferior frontal gyrus and right parieto-occipital region compared to TDC, but this effect was not observed in Stim-ADHD [11, 21]. An earlier study indicated smaller white matter volume in the frontal and temporal regions in No-Med ADHD relative to Stim-ADHD and TDC [22]. On the other hand, several studies did not observe stimulant medications-induced changes in brain structures, including total cortical gray matter volume [22] and white matter volume [23, 24].

Those aforementioned studies on children with ADHD included relatively small sample sizes (less than 100) and showed limited reproducibility [25]. In contrast, two recent studies with large cohorts ($N > 1000$) explored the impact of stimulants on surface-based morphometry in a sample of adolescents using the ENIGMA-ADHD study dataset and reported no significant stimulant medications-induced changes in brain structure [12, 26]. However, due to brain development, the large age range of children/adolescents in these studies might have impacted and biased the results of stimulant medications-induced changes [27, 28]. Several studies reported the congruent delay of changes in cortical thickness, surface area, and subcortical volume in individuals with ADHD, showing that the growth of the brain in individuals with ADHD is fundamentally different than in TDC individuals [13, 29]. In addition, those reports showed inconsistent findings where stimulant medications were considered as having either no impact or a normalizing impact on brain structure. Lastly, the different aims, methods and assessments may result in heterogeneity [26].

We employed the latent class analysis (LCA) method to identify distinct homogenous ADHD groups, using 18 symptoms in the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria. LCA, a model-based cluster analysis technique that combines the probability of reported symptoms (without using symptom number cutoffs) and overall symptom profiles, was designed to group individuals with similar symptom patterns into classes [30]. LCA explores numerous subgroups solutions that are compared on statistical and clinical parameters to obtain the “optimal” model [31]. In this manner, unobserved population heterogeneity can be captured by qualitatively or quantitatively differing subgroups, with additional advantages to the classical cluster analysis (CA) [32]. A strength of this method is that it permits quantification of the uncertainty of class membership and assessment of goodness of fit, compared to CA. Moreover, it allows for adjusting for covariates directly in the pattern identification [33]. This method has been shown to yield findings of clinical relevance and applied to ADHD data derived from U.S., Australian, and Dutch studies [34–36].

In the current study, we aimed to assess the impact of stimulant medications on brain structures after improvement of ADHD symptoms by investigating the differences in psychometric measures and brain morphometry among No-Med ADHD, Stim Low-ADHD (children with low ADHD symptoms and received stimulant medication) and TDC in the large dataset of ABCD. In addition, we analyzed the associations between differences in brain morphometry and psychometric measures among the three groups. Based on prior findings of brain structural improvement with stimulant medication treatment in ADHD, we hypothesized improvement of structural brain abnormalities in regions implicated in saliency detection (i.e., ACC and INS) and reward processing (i.e., NAc).

MATERIALS AND METHODS

Participants

The ABCD Study is an observational, multi-site (21 centers), longitudinal study of brain development and peri-adolescent health, including neuroimaging data, biometric data collection, and multidimensional measurement of behavioral and other assessments [37]. 11,877 participants aged 9–10 years old were enrolled for a ten-year follow-up study. The 21 centers obtained parents' full written informed consent and the children's assent, and research procedures and ethical guidelines were followed in accordance with the Institutional Review Boards. Baseline data from the ABCD Study Release 4.0 were used in the current study. Firstly, participants were excluded from the current study if they had not passed the quality criteria of MRI ($n = 613$), missing values of covariables ($n = 1121$), and head trauma with loss of consciousness (> 30 minutes, $n = 7$). Then, we excluded subjects that had prior or current psychiatric comorbidities ($n = 3009$) [38], including bipolar disorders and anxiety disorders, oppositional defiant disorder, obsessive-compulsive disorders, and conduct disorders according to the ABCD Parent Diagnostic Interview scale for DSM-V Full of K-SADS of the baseline for diagnosis (Supplementary Fig. S1). The final sample size was 7126 individuals.

Structural MRI acquisition

Children underwent 3T MRI (including Siemens, General Electric, or Phillips scanner) to obtain high-resolution T1-weighted structural MRI images (1 mm isotropic voxels) [39]. All structural MRI data were processed by the ABCD Study team using FreeSurfer version 7.1.1 to perform skull-stripping, white matter segmentation, initial mesh creation, correction of topological defects, and nonlinear registration to a spherical surface-based atlas [40]. MRI quality control was manually checked by trained MRI analysts from the ABCD Study team (0 = excluded, 1 = included). Morphometric measures (cortical thickness, area, volume, subcortical volume, and total intracranial volume-ICV) were included in the current analysis. Cortical regions-of-interest (ROIs) were those in the Desikan-Killiany atlas [41] and subcortical ROIs were those of the atlas-based segmentation [40, 41].

Clinical measures, medications, and demographics

Symptoms data used 18 symptoms from the ADHD individuals' questionnaires of the K-SADS from the ABCD Study (Table S1). The K-SADS has been used in numerous clinical, naturalistic follow-up, and epidemiological studies of affective and child psychiatric disorders [42]. The test-retest reliability of the K-SADS is moderate ($r = 0.63$) and in the good range for the present diagnosis of ADHD, comparable with other child psychiatric interviews [43].

The names and dosages of all medications taken by the child were extracted from the parents reported inventory. We identified children who were taking one or more stimulant medications such as methylphenidate (Ritalin, Concerta, Daytrana, Focalin, Metadate) and amphetamine (Adderall and Vyvanse) for ADHD, and who are taking non-stimulant medications such as atomoxetine (Strattera, Fluoride, Ranitidine, Guanfacine, and Clonidine) for ADHD.

We employed the child behavior checklist (CBCL) to assess psychiatric measures in children. The CBCL recorded the behavioral problems and competencies of children aged 4–18, as reported by their caregivers. With the responses provided, the software generates T-scores for clinical and functioning scales. It includes ten empirically-based syndrome scales related to psychiatric problems: anxious/depressed, withdrawn, somatic complaints, social, thought, attention, rule-breaking behavior, aggressive problems, internalizing problems, externalizing problems, and total score in psychiatric problems. Six DSM-V Scales and three 2007 Scales (including sluggish cognitive tempo, obsessive-compulsive problems, and stress problems) were obtained from the ABCD dataset. Also, the Brief Problem Monitor teacher (BPM-T) was performed to examine the psychometric properties. The BPM-T includes 18 items and the items are distributed on three subscales: attention/hyperactivity problems (6 items), externalizing problems (6 items), and internalizing problems (6 items). We also calculated the scores of attention and hyperactivity symptoms (ATT), internalizing (INT), and externalizing problems (EXT) [44].

In addition, we assessed children's age (in months), sex, and race/ethnicity (including white, black, Hispanic, Asian, and other) in the parents'/guardians' demographic questionnaire to control for these variables. We further controlled for socioeconomic factors, such as the caregiver's highest educational level (including $<$ general educational development (GED), college, Bachelor and postgraduate) and family income (including $< \$50K$, $\$50K - \$100K$ and $> \$100K$ per year), which have significant

effects on cognition and brain structure [45]. The body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared from the age- and sex-based growth charts.

Statistical analysis

Latent class analysis. Due to lacking diagnostic information for ADHD in the ABCD study, the LCA method was used to investigate an observed association and categorize a population into mutually exclusive and homogeneous subgroups according to a set of categorical variables [46, 47]. We identified latent subgroups to identify children with unobserved ADHD characteristics and with different ADHD symptom probability distributions, using the LCA method with the observed 18 ADHD symptoms extracted from the K-SADS. To determine the best fitting model, we first estimated the 1-class model and subsequently increased the number of classes by one until the value of the Bayesian Information Criteria (BIC) ceased to monotonically decrease or until the number of classes reached 10. The model selection criteria included Akaike Information Criterion (AIC), BIC, sample size adjust BIC (aBIC), entropy, Vuong-Lo-Mendell-Rubin (VLMR) likelihood ratio test, and theoretical implications [48, 49]. For AIC, BIC, and aBIC, a smaller value means a better model fit. The VLMR test provides a significant test of whether the number of classes (K) fits better than the number of K-1 classes, this test was critical in selecting the best model. We selected the final model based on the following criteria: the lowest value of the Information Criterion (AIC, BIC, and aBIC), high entropy [50], the *p*-value in the VLMR test, and practical application. All analyses were conducted using Mplus version 8.1 [51, 52].

Based on grouping results of LCA, we classified the non-clinical sample of ABCD as children with high/low ADHD symptoms at baseline. Then, all samples were further divided into children with high ADHD symptoms and received no medications (No-Med ADHD group), Stim-ADHD children with low ADHD symptoms and received stimulant medication (Stim Low-ADHD group whose ADHD symptoms were well-managed with stimulant medication), and children with low ADHD symptoms and received no medications (typically developing controls, TDC group) according to the medications survey inventory in children (Supplementary Fig. S2).

Linear mixed-effects modeling

Linear mixed-effects models (LMM) with random intercept parameters were used to account for sites for all analyses with the lme4 package in R version 4.0.5 [52]. The groups based on LCA results and medications survey inventory were chosen as outcomes of interest in the current analyses. All models included random effects for sites and family structure and fixed-effects covariates for the children's age, sex, race/ethnicity, the caregiver's highest educational level, BMI and family income.

Then, a one-way ANOVA contrast was implemented to assess group differences across three groups (TDC, Stim Low-ADHD and No-Med ADHD) in CBCL measures, BPM-T items and structural MRI measures. We further tested differences in outcomes using LMM with the following contrasts: (1) TDC group vs. No-Med ADHD group, (2) TDC group vs. Stim Low-ADHD group, and (3) No-Med ADHD group vs. Stim Low-ADHD group. Head size was associated with the cortical area and ROI volume but not cortical thickness [53]. Thus, in models of structural MRI measures, ICV was additionally added to the fixed-effects covariates for the cortical area, cortical volume, and subcortical volume, but not for cortical thickness. As in previous studies [54], Cohen's *d* effect size was calculated as a unitless index quantifying the group differences for all models [55, 56]. Cohen's *d* effect size was calculated as a unitless index quantifying the group differences for all models [57, 58]. False discovery rate (FDR) corrections were used to adjust for multiple group comparisons separately for CBCL measures, BPM-T items, and structural MRI measures (including 68 cortical thicknesses, 68 cortical areas, 68 cortical volumes, and 16 subcortical volumes).

To complement the significance testing and evaluate the morphometric similarity, we employed the two one-sided tests approach (TOST), a common method for equivalence testing, in the above contrasts (see Supplementary S1).

To ensure reliability and reproducibility, we underwent further analyses including, 1) conducting a longitudinal analysis using the data at the 2-year time point (see Supplementary S2); 2) exploring the stimulant effects in children with high ADHD symptoms and received stimulant medication (Stim High-ADHD) to verify the results (see Supplementary S3); and 3) exploring the stimulant effects in different ADHD subtypes (three subtypes in No-Med ADHD group, including No-Med ADHD-C/H/I subjects) (see Supplementary S4).

In addition, we performed the LMM to assess the effects on atomoxetine (ATX, including Strattera, Fluoride, Ranitidine, Guanfacine, and Clonidine, see Supplementary S5, Supplementary Table S17-S18).

Association between ADHD symptoms and the differences in brain structures

Pearson partial correlation with covariates for the children's age, sex, race/ethnicity, the caregiver's highest educational level, BMI, and family income was used to assess the association between structural MRI measures and CBCL measures including ADHD severity (attention problems and DSM-5 ADHD). FDR corrections for multiple comparisons were set to control for 2 regions (Fig. 2B) and all CBCL measures.

RESULTS

Sample characteristics and medications survey status in latent subgroups

The best fitting solution is the four-class model (AIC = 45592.83, BIC = 46761.74, aBIC = 46224.67, entropy = 0.99, VLMR likelihood ratio test $P < 0.001$, see Supplementary Table S1). The four class was labeled according to the levels of the conditional probabilities (Fig. 1A, see Supplementary Table S2). Class 1, the "ADHD combined presentation (ADHD-C)" (7.3% of the sample), contained participants with high items of response probability on all ADHD symptoms. Class 2, the "ADHD primary of hyperactive-impulsive presentation (ADHD-H)" (3.5% of the sample), contained participants with excessive hyperactivity/impulsivity. Class 3, the "ADHD primary of the inattentive presentation (ADHD-I)" (8.8% of the sample), contained participants with elevated inattention. Class 4, the "typically developing (TD)" (80.4% of the sample), contained participants with low ADHD symptoms (see Supplementary Table S3).

Comparisons of stimulant medications proportions across the latent subgroups indicated that three ADHD classes for ADHD had a higher prevalence of treatment with stimulant medications than the TD class ($\chi^2_{(3)} = 804.162$, $P < 0.001$). Children in the ADHD-C class had the highest proportion of treatment with stimulant medications in the three ADHD classes ($\chi^2_{(2)} = 990.547$, $P < 0.001$). The proportion of children treated with stimulant medications in the ADHD-H class was comparable to the ADHD-I class ($\chi^2_{(1)} = 7.086$, $P = 0.069$). Interestingly, in the TD class, there were children with low ADHD symptoms who reported taking medications for ADHD (6.2%), including stimulant medications (4.8%, Fig. 1B, see Supplementary Table S4).

Based on the medication statistics in the four latent subgroups, the No-Med ADHD group ($n = 1002$) included children from the 3 ADHD subgroups [$n = 305$ (ADHD-C), 512 (ADHD-I), and 185 (ADHD-H)]. The Stim Low-ADHD group contained children ($n = 273$) in the TD class who had low ADHD symptoms and received stimulant medications. The TDC group comprised children in the TD class ($n = 5378$) who had the lowest ADHD symptoms and were not taking medications. The fraction of boys was larger for the two ADHD groups than for the TDC group and was maximal for the Stim Low-ADHD group. Age was lowest in the No-Med ADHD group ($F = 11.533$, $P < 0.001$) and BMI was lowest in the Stim Low-ADHD group ($F = 7.045$, $P < 0.001$). The proportion of black children in the TDC group is the lowest. Children with family incomes between \$ 50K and \$ 100K are the highest in the TDC group. The proportions of caregivers' highest educational level at < GED and college were lower in the TDC group. (Table 1).

Alterations in psychiatry measures

One-way ANOVA showed significant differences on psychiatry measures in CBCL measures (all $P_{FDR} < 0.001$, Table 2). Post-hoc tests showed that increase psychiatry problems' scores in anxious/depressed problems, withdrawn problems and DSM-V depressive problems in Stim Low-ADHD and No-Med ADHD group as compared to the TDC group. There were lower psychiatry

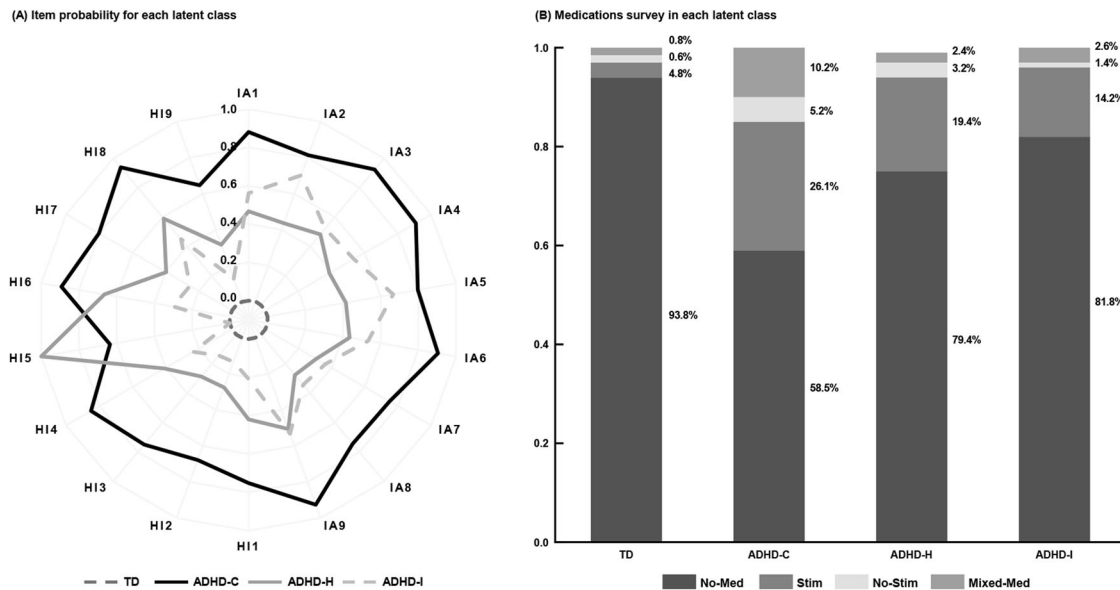


Fig. 1 Conditional probabilities are based on ADHD symptoms and statistics on ADHD medication in each latent class. **A** The visualization of item probabilities in ADHD symptoms for each latent class. ADHD symptoms were derived from the K-SADS. **B** The statistics information on ADHD medication by children. ADHD Attention deficit/hyperactivity disorder, ADHD-C ADHD combined presentation, ADHD-H ADHD primary of hyperactive-impulsive presentation, ADHD-I ADHD primary of the inattentive presentation, HI hyperactivity-impulsivity symptom, IA inattention symptoms, TD typically developing, No-Med without taking medications for ADHD, Stim psychostimulants [methylphenidate (Ritalin, Concerta, and Daytrana, Focalin, Metadate) and amphetamine (Adderall, and Vyvanse)], No-Stim no-psychostimulants [atomoxetine (Strattera, Fluoride, Ranitidine, Guanfacine, and Clonidine)], Mixed-Med combined medications (psychostimulants and non-psychostimulants) for ADHD.

problems' scores in somatic complaints and DSM-5_somatic problems in TDC and Stim Low-ADHD group as compared to No-Med ADHD. For other CBCL measures, post-hoc tests showed significant differences in pairwise among the three groups, with No-Med ADHD having the highest score, Stim Low-ADHD taking the second place, and TDC having the lowest score (Table 2). We also presented the K-SADS measures in the TDC, Stim Low-ADHD, and No-Med ADHD groups (Table 3). The CBCL and K-SADS measures in the No-Med ADHD group included children from the 3 subgroups (No-Med ADHD-C/I/H) were presented in Supplementary Table S5, S6.

The BPM-T data in 5042 (42.4%) subjects only are available in the ABCD 4.0 dataset. 2336 subjects are the same as this baseline study, including 107 subjects in the Stim Low-ADHD group, 397 in the No-Med ADHD group, and 1832 subjects in the TDC group (Supplementary S6, Supplementary Table S19). One-way ANOVA showed that significant differences on psychiatry measures in BPM-T items (all $P_{FDR} < 0.001$, Supplementary Table S20). Post-hoc tests showed that decreased scores in all attention and hyperactivity items in TDC and Stim Low-ADHD group as compared to No-Med ADHD group (Supplementary Table S20).

Alterations in brain structures

One-way ANOVA showed significant differences on brain structures in (1) cortical thickness [including left inferior parietal (IPL_L) and right INS], (2) cortical area [left pericalcarine (periCAL)], (3) cortical volume [including left entorhinal cortex (EC), left Pars triangularis (PTr), left periCAL and right inferior temporal (IT) cortex], and (4) subcortical volumes (including bilateral CAU left NAc, Fig. 2A, Supplementary Tables S7). Post-hoc tests showed increase scores on cortical thickness in the right INS and on subcortical volumes in left NAc in Stim Low-ADHD and TDC as compared to No-Med ADHD group (Fig. 2B, Supplementary Tables S7). When compared with TDC children, No-Med ADHD had significantly lower scores in 10 brain measures, including (1) cortical thickness in left IPL ($d = -0.162$, $P_{FDR} = 0.005$) and right INS ($d = -0.189$, $P_{FDR} = 0.0002$), and (2) cortical area in the left periCAL

cortex ($d = -0.178$, $P_{FDR} = 0.010$), and (3) cortical volumes in left EC ($d = -0.148$, $P_{FDR} = 0.014$), left PTr ($d = -0.126$, $P_{FDR} = 0.029$), periCAL_L cortex ($d = -0.156$, $P_{FDR} = 0.022$) and right IT cortex ($d = -0.134$, $P_{FDR} = 0.029$), and (4) subcortical volumes in bilateral CAU ($d = -0.167$, $P_{FDR} = 0.005$ and $d = -0.160$, $P_{FDR} = 0.005$, respectively) and left NAc ($d = -0.154$, $P_{FDR} < 0.001$, Fig. 2B, Supplementary Tables S7). There were no significant differences in brain measures (Fig. 2B, Supplementary Tables S7) between Stim Low-ADHD and TDC group.

The TOST results showed that those brain measures with no significant differences in the null hypothesis significance testing were statistically equivalent (all $P < 0.05$, see Supplementary Table S22–S24).

The difference in the left NAc was consistent in the longitudinal analysis (see Supplementary Table S8–S10), but the right INS was not. The different results in brain measures in the validation analysis were consistent with this study (see Supplementary Table S11–S13). The children in the No-Med ADHD-C and No-Med ADHD-H had significantly lower cortical thickness in the right INS relative to Stim Low-ADHD, but there were no significant differences between No-Med ADHD-I and Stim Low-ADHD groups. The results in the effects on stimulant medications in different ADHD subgroups are as follows: children in the No-Med ADHD-I had lower subcortical volume in the left NAc relative to Stim Low-ADHD, but there were no significant differences between No-Med ADHD-C/H and Stim Low-ADHD (see Supplementary Table S14–S16).

Association between ADHD symptoms and the differences in brain structures

There was no significant correlation between psychiatry measures including ADHD symptoms and brain structures in the Stim Low-ADHD group (see Supplementary Table S21).

DISCUSSION

In the current study, we adopted LCA and LMM to examine the impact of stimulant medications on brain structures after

Table 1. Demographic characteristics in three groups according to LCA and medication status.

	TDC (N = 5378)		Stim Low-ADHD (N = 273)		No-Med ADHD (N = 1002)		ANOVA		a		b		c	
	(Mean ± SE)	(Mean ± SE)	(Mean ± SE)	(Mean ± SE)	(Mean ± SE)	(Mean ± SE)	F	P	T	P	T	P	T	P
Age (mos)	119.4 ± 0.6	119.8 ± 0.4	118.5 ± 0.2	118.5 ± 0.2	11.553	< 0.001	11.553	< 0.001	-0.299	0.765	4.419	< 0.001	2.499	0.012
*Sex (F/M)	2609/2769	71/202	376/626	376/626	N/A	< 0.001	N/A	< 0.001	N/A	< 0.001	N/A	< 0.001	N/A	< 0.001
BMI (kg/m ²)	18.8 ± 0.1	18.0 ± 0.1	18.7 ± 0.1	18.7 ± 0.1	7.045	< 0.001	7.045	< 0.001	3.018	0.003	0.131	0.896	-2.676	0.007
*Race/Ethnicity														
White	73.5%	71.4%	65.1%	65.1%										
Black	13.0%	15.8%	20.1%	20.1%	N/A	< 0.001	N/A	< 0.001	N/A	0.411	N/A	< 0.001	N/A	0.260
Hispanic	5.7%	4.0%	5.7%	5.7%										
Asian	0.7%	0.4%	0.9%	0.9%										
Other	7.1%	8.4%	8.3%	8.3%										
*Household income, \$														
<50 K	27.1%	34.1%	31.9%	31.9%										
50 K–100 K	60.0%	53.8%	57.2%	57.2%	N/A	0.003	N/A	0.003	N/A	0.042	N/A	0.004	N/A	0.605
> 100 K	12.9%	12.1%	10.9%	10.9%										
*Parental education														
<GED	15.2%	17.2%	17.3%	17.3%										
College	28.9%	36.3%	31.4%	31.4%	N/A	0.002	N/A	0.002	N/A	0.009	N/A	0.012	N/A	0.448
Bachelor	29.7%	24.9%	28.4%	28.4%										
Postgraduate	25.8%	21.6%	22.9%	22.9%										

*Sex, Household income, Parental education: Chi-square test;

^a, group comparison between TDC and Stim Low-ADHD;^b, group comparison between TDC and No-Med ADHD;^c, group comparison between Stim Low-ADHD and No-Med ADHD.

ADHD Attention-deficit/hyperactivity disorder, mos Months, F female, M male, BMI Body mass index, GED General educational development, No-Med ADHD children with high ADHD symptoms and received no medications, Stim Low-ADHD children with low ADHD symptoms and received stimulant medication, TDC typical developing controls. Significant effects are indicated in bold.

Table 2. Differential group differences in CBCL measures between TDC, Stim Low-ADHD, and No-Med ADHD groups.

	1. TDC (N = 5378) (Mean ± SE)		2. Stim Low-ADHD (N = 273) (Mean ± SE)		3. No-Med ADHD (N = 1002) (Mean ± SE)		ANOVA		1 vs.2		1 vs.3		2 vs.3	
							F	P _{FDR}	d	P _{FDR}	d	P _{FDR}	d	P _{FDR}
Anxious/Depressed Problems	52.867 ± 0.075		54.668 ± 0.337		55.542 ± 0.175		110.615	< 0.001	−0.416	< 0.001	−0.633	< 0.001	−0.16	0.066
Withdrawn Problems	52.950 ± 0.073		55.257 ± 0.328		55.565 ± 0.170		110.259	< 0.001	−0.519	< 0.001	−0.571	< 0.001	−0.059	0.431
Somatic Complaints	54.532 ± 0.081		55.26 ± 0.362		56.865 ± 0.188		65.171	< 0.001	−0.144	0.077	−0.495	< 0.001	−0.269	0.002
Social Problems	52.169 ± 0.058		53.830 ± 0.258		55.596 ± 0.134		277.279	< 0.001	−0.55	< 0.001	−1.05	< 0.001	−0.331	< 0.001
Thought Problems	52.913 ± 0.073		56.032 ± 0.326		57.370 ± 0.169		307.361	< 0.001	−0.837	< 0.001	−1.09	< 0.001	−0.233	0.01
Attention Problems	52.566 ± 0.067		57.598 ± 0.301		60.714 ± 0.156		1183.588	< 0.001	−1.51	< 0.001	−1.96	< 0.001	−0.469	< 0.001
Rule-Breaking Behavior	52.169 ± 0.062		54.496 ± 0.275		55.730 ± 0.143		261.422	< 0.001	−0.707	< 0.001	−0.953	< 0.001	−0.26	0.011
Aggressive Behavior	52.090 ± 0.068		54.746 ± 0.304		56.012 ± 0.158		272.200	< 0.001	−0.72	< 0.001	−0.935	< 0.001	−0.253	0.014
Internalizing Problems	47.498 ± 0.137		51.224 ± 0.612		53.356 ± 0.318		152.575	< 0.001	−0.471	< 0.001	−0.786	< 0.001	−0.259	0.006
Externalizing Problems	44.506 ± 0.130		49.851 ± 0.581		52.542 ± 0.301		314.125	< 0.001	−0.761	< 0.001	−1.09	< 0.001	−0.383	0.001
Total Problems	44.316 ± 0.135		51.907 ± 0.604		55.080 ± 0.313		546.465	< 0.001	−1.2	< 0.001	−1.68	< 0.001	−0.478	< 0.001
DSM-5_Depressive Problems	52.770 ± 0.071		55.930 ± 0.317		56.387 ± 0.164		231.576	< 0.001	−0.823	< 0.001	−0.851	< 0.001	−0.09	0.305
DSM-5_Anxiety Problems	52.817 ± 0.076		54.459 ± 0.340		55.626 ± 0.176		116.392	< 0.001	−0.362	< 0.001	−0.656	< 0.001	−0.202	0.021
DSM-5_Somatic Problems	55.269 ± 0.090		55.611 ± 0.402		57.111 ± 0.209		32.143	< 0.001	−0.05	0.526	−0.343	< 0.001	−0.226	0.006
DSM-5_ADHD	51.982 ± 0.062		56.733 ± 0.275		59.254 ± 0.143		1136.717	< 0.001	−1.55	< 0.001	−1.98	< 0.001	−0.415	< 0.001
DSM-5_Oppositional Defiant	52.828 ± 0.068		55.493 ± 0.306		56.596 ± 0.159		251.799	< 0.001	−0.697	< 0.001	−0.878	< 0.001	−0.234	0.016
DSM-5_Conduct Problems	52.361 ± 0.069		54.983 ± 0.311		56.187 ± 0.161		239.759	< 0.001	−0.686	< 0.001	−0.902	< 0.001	−0.248	0.021
07_Sluggish Cognitive Tempo	52.310 ± 0.070		54.727 ± 0.314		56.886 ± 0.163		329.106	< 0.001	−0.613	< 0.001	−1.07	< 0.001	−0.325	< 0.001
07_Obsessive-Compulsive	53.013 ± 0.077		54.779 ± 0.346		56.210 ± 0.180		134.068	< 0.001	−0.397	< 0.001	−0.724	< 0.001	−0.272	0.01
07_Stress Problems	52.361 ± 0.072		55.183 ± 0.320		57.132 ± 0.166		369.276	< 0.001	−0.792	< 0.001	−1.26	< 0.001	−0.351	< 0.001

CBCL The child behavior checklist, DSM The diagnostic and statistical manual of mental disorders scales, 07 2007 version scales, *P_{FDR}* the false discovery rate corrections, No-Med ADHD children with high ADHD symptoms and received no medications, Stim Low-ADHD children with low ADHD symptoms and received stimulant medication, TDC typical developing controls. Significant effects are indicated in bold.

improvement of ADHD symptoms. Compared to TDC and Stim Low-ADHD children, there were significantly lower cortical thickness in the INS and smaller gray matter volume in the NAC in No-Med ADHD children, indicating that high ADHD symptoms were associated with structural abnormalities in these brain regions. In addition, there was no difference in brain structural measures between Stim Low-ADHD and TDC children, and further equivalence tests also showed no significant differences in those brain structures between Stim Low-ADHD and TDC children, suggesting that the stimulant effects improved both ADHD symptoms and ADHD-associated brain structural abnormalities. These findings together suggest that children with ADHD appear to have structural abnormalities in brain regions associated with saliency and reward processing, and treatment with stimulant medications not only improved the ADHD symptoms but also normalized these brain structural abnormalities. These findings are important for the treatment of children with ADHD using stimulant medication.

The INS and ACC are the core nodes of the salience network [59] and are often co-activated in functional imaging studies on goal-directed attention [60, 61]. The anterior insula is responsible for switching between default mode networks (DMN) and the central executive network (CEN) to facilitate access to attention and working memory resources when salient stimuli were detected [61–63]. Several sMRI studies reported deficits in the INS in people with ADHD [10, 64]. During the resting-state, ADHD children had INS hyperconnectivity [65], predominately with the substantia nigra and other reward regions [66], in association with hyperactivity/impulsivity [65]. These deficits may lead to an impaired attribution of salience to stimuli [67–69] and then possibly cause erroneous engagement/disengagement of DMN and CEN, which potentially results in the core ADHD symptom of inattention [10]. We found greater cortical thickness in the INS in Stim Low-ADHD relative to No-Med ADHD at baseline. However, the differences in the INS were not repeated in the longitudinal

analysis, we also found that the differences in the INS disappeared between No-Med ADHD and TDC at 2 years follow-up. One possible reason for this result is that the development of the INS cortex is complicated. One neurodevelopmental trajectories study reported that a lack of the phase of stabilization growth within the first three decades of life is presented in much of the INS [70]. Anterior INS has a linear developmental trajectory, the body of the INS has a complex quadratic fit trajectory, and the posterior INS has a cubic developmental trajectory [70]. Another possible reason might be the decreased number of subjects in ABCD dataset 4.0 release at 2-year time point, which may have biased the results. An additional possible reason may be that the No-Med group has delayed INS development at baseline which catches up to the other children at 2 years follow-up.

The NAC plays a prominent role in reward processing [71–73] and is crucial for motivation [74, 75]. The mesoaccumbens DA pathway projects from the ventral tegmental area (VTA) in the midbrain to the NAC and aberrant function in this pathway is thought to underlie the reward and motivation deficits observed in ADHD [76]. More and more studies suggest that ADHD core symptoms, such as hyperactivity/impulsivity, stem from a hypo-functioning mesolimbic DA branch, especially low DA levels in the NAC [77, 78]. Many studies have found that patients with ADHD have deficits in reward and motivation [76, 79]. Evidence of functional deficits in NAC also has been shown by fMRI studies documenting less NAC activation during reward processing in participants with ADHD relative to healthy controls [80–82]. sMRI studies showed reduced volume in the NAC among participants with ADHD [12, 56]. Positron Emission Tomography (PET) studies found that individuals with ADHD have reduced dopaminergic transmission in the NAC [83] and stimulant medications like MPH increase DA levels in striatum (including NAC) [83]. Brain-derived neurotrophic factor (BDNF), a member of the neurotrophins family of trophic factors [84], has been shown to modulate the release of DA through the activation of the tropomyosin-related kinase B

Table 3. The measures of ADHD symptoms in the K-SADS in TDC, Stim Low-ADHD, and No-Med ADHD groups.

		1. TDC (N = 5378)	2. Stim Low-ADHD (N = 273)	3. No-Med ADHD (N = 1002)
		(Mean ± SE)	(Mean ± SE)	(Mean ± SE)
IA1	Attention to detail	0 ± 0	0 ± 0	0.638 ± 0.015
IA2	Sustaining attention	0.003 ± 0.001	0.004 ± 0.004	0.663 ± 0.015
IA3	Fails to finish	0 ± 0	0 ± 0	0.626 ± 0.015
IA4	Can't organize	0 ± 0	0 ± 0	0.614 ± 0.015
IA5	Easily distracted	0 ± 0	0 ± 0	0.663 ± 0.015
IA6	Forgetful	0 ± 0	0 ± 0	0.629 ± 0.015
IA7	Loses things	0 ± 0	0 ± 0	0.475 ± 0.016
IA8	Concentration	0 ± 0	0 ± 0	0.436 ± 0.016
IA9	Does to listen	0 ± 0	0 ± 0	0.642 ± 0.015
HI1	Always on go	0 ± 0	0 ± 0	0.417 ± 0.016
HI2	Blurts out	0 ± 0	0 ± 0	0.321 ± 0.015
HI3	Can't wait to turn	0 ± 0	0 ± 0	0.343 ± 0.015
HI4	No quiet play	0 ± 0	0 ± 0	0.433 ± 0.016
HI5	Leaves seats	0 ± 0	0 ± 0	0.372 ± 0.015
HI6	Fidgets	0 ± 0	0 ± 0	0.548 ± 0.016
HI7	Talks excessively	0 ± 0	0 ± 0	0.434 ± 0.016
HI8	Interrupt	0 ± 0	0 ± 0	0.599 ± 0.015

ADHD Attention-deficit/hyperactivity disorder, HI hyperactivity-impulsivity symptom, IA inattention symptoms, No-Med ADHD children with high ADHD symptoms and received no medications, Stim Low-ADHD children with low ADHD symptoms and received stimulant medication, TDC typical developing controls.

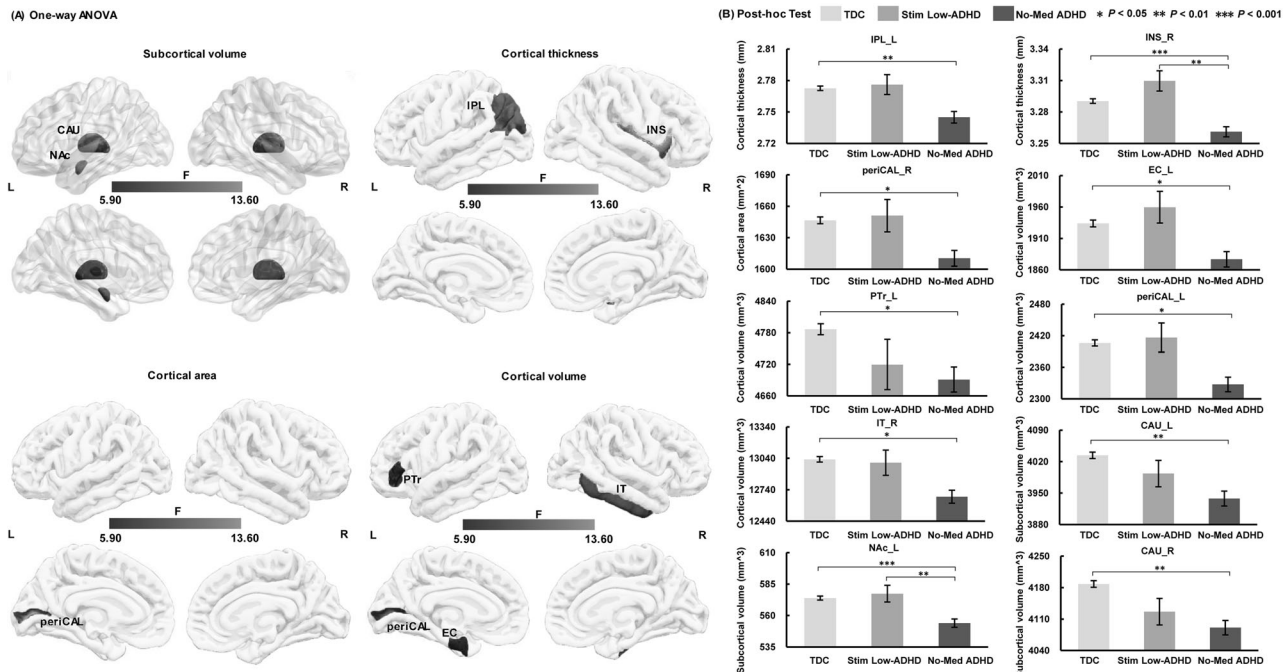


Fig. 2 One-way ANOVA analysis and post-hoc test. A One-way ANOVA analysis for brain structures. **B** Post-hoc test for brain structures. ADHD Attention-deficit/hyperactivity disorder, No-Med ADHD children with high ADHD symptoms and received no medications, Stim Low-ADHD children with low ADHD symptoms and received stimulant medication, TDC typically developing controls, L left hemisphere, R right hemisphere, IPL inferior parietal, INS insula, CUN cuneus, EC entorhinal cortex, PTR pars triangularis, pericAL pericalcarine, PCUN precuneus, IT inferior temporal, AMY Amygdala, CAU caudate, NAc nucleus accumbens.

(TrkB) receptors [85]. A decrease in midbrain BDNF activity may cause midbrain dopaminergic dysfunction resulting in ADHD [85]. An animal study of 20-day medication found that MPH increased BDNF expression in the NAc and caudate-putamen [86]. A clinical study observed that mean plasma BDNF levels after 6 weeks of treatment with MPH were significantly higher than before the treatment, and a significant correlation was reported between the increase in BDNF levels and improvement in hyperactivity symptoms with treatment [87]. One study reported that increases in BDNF expression were correlated with an increase in NAc volume [88]. PET studies have also shown that increases in DA in the ventral striatum where the NAc is located were associated with reduced ADHD symptoms with long-term treatment with stimulant medications in ADHD [83, 89]. Based on these findings, Volkow and collaborators proposed that the enhancement of DA by stimulant medications improves attention and decreases distractibility in part by enhancing saliency and motivation through the DA reward pathway centered in the NAc [89]. Several rats and human studies have reported increases in the NAc volume with chronic exposure to stimulant medications [90–93]. The enlarged NAc volume might also be associated with the neurotrophic effects of dopamine. A rodent study revealed increased dopamine neuron spine density in the NAc following stimulants administration [94]. Stimulant medications directly affect the limbic reward circuit and induced changes in the functional connectivity of the NAc [95]. Further, a number of studies have suggested a direct association between a region's brain structural changes (i.e., volume) and its functional connectivity with other regions [96, 97]. In line with previous studies, we found greater volume in the left NAc in the Stim Low-ADHD relative to the No-Med ADHD group. Thus, our findings corroborated our hypothesis that stimulant medications would improve structural abnormalities in NAc in children with ADHD.

Due to a lack of information about the mean dose and duration of stimulant treatment in children in the ABCD dataset, we cannot investigate the therapeutic effect of stimulant treatment in

medicated children with ADHD. Therefore, we only included the Stim Low-ADHD group in the current analysis to focus on the alteration in brain structures after improvement of ADHD symptoms. Moreover, improvement of certain brain structures (such as putamen, NAc, and ACC) by ADHD medication has been proposed [15, 19, 20]. Several studies reported positive correlations between treatment duration and volumes in the left NAc [15] and specific cerebellar subregions [98] and negative correlations in two subregions of the left hippocampus [99] and right lateral and medial posterior hemi-thalamic in medicated children with ADHD [17]. If an improvement effect in certain brain structures is occurring, the associations between treatment duration and these brain structures may help us to comprehend the time required to achieve this goal. Finally, the relatively smaller size in the Stim Low-ADHD group might also have impacted our findings.

No significant correlations were detected between the differences in brain structures (i.e., NAc or INS) and ADHD severity in the CBCL measures (i.e., attention problems or DSM 5 ADHD). These results might be due to the following reasons: (1) Brain function is based on large-scale functional networks that are defined as a collection of interconnected brain regions rather than a single brain region [100]. (2) Lacking data related to treatment duration and dose in the Stim Low-ADHD group, there were mixed situations in this group that could not be classified according to treatment duration and dose. Therefore, although our data showed a plausible association that the stimulant drugs improved both ADHD symptoms and ADHD-associated brain structural abnormalities, our findings should be interpreted with caution because this analysis may not be fully capturing potential associations between differences in brain structure and ADHD severity.

We found subcortical volume differences in the CAU and AMY between children in the No-Med ADHD group and TDC group, and no significant effects on stimulant medications in these regions. This result is consistent with previous studies. Reduced volume in children with ADHD in the CAU is one of the most replicated

findings in sMRI studies [15, 101, 102]. No effect of stimulant medications was found in the CAU in the participants with ADHD in several cross-sectional studies [19, 101]. Along the same lines, longitudinal studies on children pointed to the improvement of volumes in the CAU associated with age but not stimulant medications [22, 103]. A meta-analysis reported children with ADHD had a lower volume in the AMY relative to controls [12]. Two previous studies also pointed out there was no effect of stimulant medications on the AMY [15, 104].

We also found that there were differential effects of stimulant medication across ADHD subtypes. There was a significant difference between No-Med ADHD-C/H and Stim Low-ADHD in the INS. There was significantly greater left NAc volume in Stim Low-ADHD as compared to No-Med ADHD-I. In addition, we did not observe significant impacts of non-stimulant medications (such as ATX) on brain structures. An analysis reported that ATX and MPH have similar but not identical brain effects [105]. The null results might be due to small sample size ($N = 79$), which rendered us relatively underpowered to detect medication effects.

Limitations

There are several limitations. (1) Lacking of information as to the mean dose and duration of stimulant treatment in the ABCD dataset, precluded us from analyzing the association between brain measures and stimulant treatment in children with ADHD. (2) The current study included cross-sectional data and decreased number of sample size of children with ADHD, and future study with more longitudinal data are required to identify the long-term effect of stimulant medication on brain structures and ADHD symptoms.

CONCLUSIONS

The current study employed LCA and LMM to investigate the impact of stimulant medications on brain structures after improvement of ADHD symptoms. Results showed that high ADHD symptoms were associated with lower cortical thickness in the INS and smaller gray matter volume in the NAc, and the stimulant effects improved both ADHD symptoms and ADHD-associated brain structural abnormalities. These findings together suggest that children with ADHD appear to have structural abnormalities in brain regions associated with saliency and reward processing, and treatment with stimulant medications not only improved the ADHD symptoms but also normalized these brain structural abnormalities. Future studies could incorporate treatment duration, longitudinal data, and other MRI modalities for research aimed at employing the impact of stimulant medication on brain structures in children with ADHD.

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AUTHOR CONTRIBUTIONS

Conceptualization, Gene-Jack Wang, Yi Zhang; Data acquisition, Feifei Wu, Fukun Jiang, Weibin Ji, Yaqi Zhang, Wenchao Zhang, Szu-Yung Ariel Wang; Data analysis, Feifei Wu, Wenchao Zhang, Weibin Ji, Guanya Li, Yang Hu, Xiaorong Wei, Haoyi Wang; Writing-Original Draft, Feifei Wu, Weibin Ji, Yi Zhang, Gene-Jack Wang, Xinbo Gao; Writing-Review & Editing, Peter Manza, Dardo Tomasi, Nora D. Volkow. All authors critically reviewed the content and approved the final version for publication.

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The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Gene-Jack Wang or Yi Zhang.

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