Research Paper

Subcortical volumetric alterations as potential predictors of methylphenidate treatment response in youth with attention-deficit/hyperactivity disorder

Ji-Sahn Kim; Kyung Hwa Lee, PhD; Chan-Sop Hwang; Jae-Won Kim, MD, PhD

Background: Patients with attention-deficit/hyperactivity disorder (ADHD) show structural alterations in the subcortical and dopaminergic regions of the brain. Methylphenidate is a first-line treatment for ADHD, and it is known to affect the subcortical and dopaminergic systems. The degree of pretreatment structural alterations in patients with ADHD may be an important factor in predicting methylphenidate treatment outcomes. The present study examined whether pretreatment volumetric alterations in the subcortical and dopaminergic regions predicted treatment response in youth with ADHD. **Methods:** This study included 67 youth with ADHD and 25 healthy controls. Youth with ADHD received 8 weeks of methylphenidate treatment. They completed baseline (pretreatment) T_1-weighted structural MRI scans and underwent clinical assessments before and after methylphenidate treatment. The healthy controls also completed baseline structural MRI scans. We assessed volumetric alterations using relative volumes (volume of each region of interest/intracranial volume). **Results:** Among 67 youth with ADHD, 44 were treatment responders and 23 were nonresponders based on post-treatment scores on the Clinical Global Impression Scale–Improvement. Nonresponders had larger volumes in the bilateral amygdala and right thalamus than responders. Nonresponders also had larger volumes in amygdalar subregions (i.e., the bilateral lateral nucleus and right basal nucleus) and hippocampal subregions (i.e., the right hippocampal head and right molecular layer) relative to responders. **Limitations:** We did not collect post-treatment structural T_1-weighted images, so volumetric changes related to methylphenidate treatment in youth with ADHD were undetermined. **Conclusion:** These findings suggest that pretreatment volumetric alterations in subcortical regions may serve as biomarkers for predicting methylphenidate treatment response in youth with ADHD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children and adolescents that often continues until adulthood.[1] Youth with ADHD commonly show hyperactivity, inattentiveness and impulsivity, frequently expressed as behavioural problems and decreased concentration during school activities. Proper treatment of ADHD could promote social adjustment and normal daily performance in youth with ADHD. Stimulants such as methylphenidate have been used widely to treat youth with ADHD and are reported to be effective in 70% to 80% of those who receive them.[2] However, because some youth with ADHD do not respond to methylphenidate treatment, identifying factors that can predict treatment response is important to aid in accurate prescribing. As a neurodevelopmental disorder, ADHD is known to be associated with neurobiological alterations in both brain structure and function.[3] This study focused on identifying neurobiological factors that could predict treatment response to medication in youth with ADHD.

The mechanisms of action of methylphenidate are associated with dopamine active transporter, which is widely expressed in the thalamus[4] and striatum areas such as the nucleus accumbens.[5] Previous studies using positron emission tomography have reported that methylphenidate works as an antagonist against active dopamine active transporter, hindering the reuptake of dopamine in the synapses.[6] This results in increased dopamine concentrations in the synaptic clefts that is proportional to the degree of dopamine active transporter blockage.[6] Increased dopamine in the neural circuit strengthens attentiveness to tasks in patients with ADHD who are treated with methylphenidate.[6] Moreover, animal studies have reported that methylphenidate amplifies intercellular concentrations of dopamine and norepinephrine in the prefrontal cortex[7] and

Correspondence to: J.-W. Kim and K.H. Lee, Division of Child and Adolescent Psychiatry, Department of Psychiatry, Seoul National University College of Medicine, 101 Daehak-Ro, Chongno-Gu, Seoul, 03080, Republic of Korea; kimjw412@snu.ac.kr, kyunghwalee365@gmail.com

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enhances hippocampal synaptic plasticity.[8] Methylphenidate has also been reported to promote learning-induced amygdala plasticity in rats[9] and normalize amygdala function in children with ADHD.[10] These results suggest that methylphenidate may modify function and structure in the striatum, prefrontal cortex, thalamus, hippocampus and amygdala, eventually improving the symptoms of ADHD. The findings also indicate that brain regions modified by methylphenidate may be altered in youth with ADHD before treatment. This study examined whether pretreatment structural alterations predicted methylphenidate treatment response in youth with ADHD.

Several studies have observed volume differences in the subcortical and dopaminergic brain regions in patients with ADHD compared to healthy controls. A previous meta-analysis showed that compared to healthy controls, children and adults with ADHD had smaller volumes in the nucleus accumbens, amygdala, caudate nucleus, hippocampus and putamen.[11] Preschoolers with ADHD also displayed smaller thalamus volumes compared to healthy controls.[12] Previous findings for hippocampal volumes in people with ADHD have been contradictory. For example, unlike the meta-analysis described above,[11] 1 study showed increased hippocampal volumes in children and adolescents with ADHD compared to controls.[13]

Previous research has shown that subregions of the hippocampus and amygdala were distinguished both anatomically and functionally,[14,15] and that they responded differently in psychiatric disorders.[16–18] The hippocampus and amygdala include several subregions that serve different roles, and those subregions have been reported to show altered volumes in youth with ADHD. In children and adolescents with ADHD, volumetric alterations have been observed in the hippocampal tail, subiculum, cornu ammonis 1 (CA1), cornu ammonis 4 (CA4), presubiculum, molecular layer, granule cell layers of the dentate gyrus, fimbria[19] and hippocampal head[13] of the hippocampus, and in the basal and lateral nuclei of the amygdala.[13] Overall, these findings provide evidence for volumetric alterations related to ADHD in the subcortical and dopaminergic brain regions that may predict treatment outcomes in youth with ADHD.

Importantly, previous studies have predicted treatment response using pretreatment brain structural alterations. One of these studies reported that treatment responders had larger pretreatment volumes in the bilateral head of the caudate nuclei and the right nucleus accumbens compared to nonresponders.[20] There is also evidence that stimulant treatment is associated with structural alterations in brain regions, demonstrating smaller or larger volumes in treated versus untreated youth and adults with ADHD. Stimulant-treated youth with ADHD showed a larger post-treatment thalamus than untreated youth with ADHD.[21] Stimulant-treated adults with ADHD had smaller post-treatment volumes in the right hippocampus than both treatment-naive adults and healthy controls.[22] Stimulant-treated children with ADHD also showed larger post-treatment volumes in the anterior cingulate cortex than treatment-naive children.[23]

Taken together, these findings suggest that subcortical regions and dopaminergic brain systems may serve as target regions for predicting ADHD treatment response. Therefore, this study focused on volumetric alterations in the caudate nucleus, nucleus accumbens, thalamus, hippocampus and anterior cingulate cortex as regions of interest (ROIs). Although the relationship between amygdalar volumes and methylphenidate treatment has been rarely studied, we also included the amygdala as an extra ROI, considering the reported biomolecular effects of methylphenidate on the amygdala.[9]

As mentioned earlier, only a few studies have predicted treatment response to stimulants using pretreatment brain structural alterations. However, when we conceived the present work, we found that these studies focused only on the caudate and nucleus accumbens as their ROIs to predict stimulant treatment outcomes.[20] Given that youth with ADHD have shown volumetric alterations in subcortical and dopaminergic regions, and that stimulants affect structures in these regions, we broadened our ROIs to the 6 regions described above. Structural MRI has several advantages, including accessibility in psychiatric clinical practice and convenience.[24] It may be clinically important to ascertain whether pretreatment brain structural alterations can predict treatment response.

We acquired pretreatment T_1-weighted structural MRIs from youth with ADHD and healthy controls, and we compared volumetric alterations in our ROIs between responders, nonresponders and healthy controls using relative volumes (volume of each ROI/intracranial volume). Given that patients with ADHD who were treated with methylphenidate had larger volumes in these ROIs than treatment-naive patients and that larger pretreatment volumes predicted treatment effects, we hypothesized that volumes in the ROIs would be larger in responders than in nonresponders. Given that volume alterations have been observed in the subregions of the amygdala and hippocampus,[13,19] we also explored whether volumetric alterations in the amygdala and hippocampal subregions predicted treatment response in youth with ADHD.

Methods

Participants

For this study, we recruited 94 youth with ADHD who visited Seoul National University Children's Hospital outpatient clinic and 30 healthy controls. All ADHD participants were aged 6 to 17 years; had an IQ above 70; and had no history of treatment with methylphenidate, or had received methylphenidate treatment for less than 6 months and had not been treated for 4 weeks before entering the study.[25–27] Patients with ADHD were excluded if they had an intellectual disability; a congenital genetic disorder; an acquired brain injury; a developmental disability, such as autism spectrum disorder; juvenile psychoses, such as schizophrenia; Tourette syndrome or obsessive–compulsive disorder; or a language or severe learning disability. Healthy controls were recruited based on the criteria above, but those with previous or current ADHD were excluded.

Among the patients with ADHD, 9 dropped out before the baseline MRI data had been acquired, 13 had problematic brain MRIs and 5 were missing clinical information (unobtainable). Among the healthy controls, 2 dropped out and 3 had problematic brain MRIs. Thus, our final sample included 67 youth with ADHD (mean age ± standard deviation 9.76 ± 2.51 years; 13 girls) and 25 healthy controls (mean age ± standard deviation 10.00 ± 2.50 years; 14 girls). This study was approved by the institutional review board of Seoul National University Hospital. Written informed consent was obtained from all participants and their parents.

Diagnostic and clinical assessment

Patients with ADHD were diagnosed based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision,[28] and the Korean version of the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL-K).[29] Participants' clinical inattentiveness and hyperactivity-impulsivity were measured using the ADHD rating scale (ADHD-RS), which was completed by their parents.[30] Patients' inattentiveness and impulsivity were assessed by omission and commission errors, respectively, on the standardized visual version of the computerized Continuous Performance Test (CPT).[25,31] Healthy controls were also assessed using the K-SADS-PL-K criteria, the ADHD-RS and the CPT. Healthy controls were confirmed not to have ADHD based on K-SADS-PL-K criteria.

Methylphenidate treatment and clinical assessment of response

In patients with ADHD, we assessed baseline clinical performance using the Clinical Global Impression Scale–Severity before initiating methylphenidate treatment. After clinical assessment, patients began 8 weeks of methylphenidate treatment. Doses were adjusted every 2 weeks until patients showed sufficient therapeutic effect, and then doses were maintained for the remaining treatment sessions (ClinicalTrials.gov; NCT01912352). After treatment ended, we assessed patients' treatment response and clinical performance using the Clinical Global Impression Scale–Improvement (CGI-I), which consists of a numeric scale from 1 (ADHD symptoms highly improved) to 7 (ADHD symptoms highly aggravated). The CGI-I scale has been used frequently as a sole criterion for analyzing treatment response in patients with ADHD.[25,32–34] Patients with a CGI-I score of 2 or less were grouped as responders (44 patients; mean age 9.5 years; 9 girls) and the others were grouped as nonresponders (23 patients; mean age 10.4 years; 4 girls). The CGI-I scale was administered by the psychiatrist who treated the patients (J.-W.K.). Four patients with ADHD who did not complete an 8-week treatment session were classified as nonresponders for the intention-to-treat analysis. Their methylphenidate dose and weight at the time of dropout were considered to be their final methylphenidate dose and weight.

MRI data acquisition and processing

We acquired high-resolution, T_1-weighted brain MRIs using a 3 T scanner (Trio Tim; Siemens) and a 12-channel birdcage head coil. We used a T_1-weighted 3-dimensional gradient echo pulse sequence with magnetization-prepared rapid gradient echo sequencing to obtain the images (repetition time 1900 ms; echo time 3.13 ms; slice thickness 0.9 mm; flip angle 9°; matrix size 256 × 224 × 176). Two evaluators (J.-S.K., C.-S.H.) visually inspected the T_1-weighted images ($\kappa = 0.64$, $p < 0.001$ for head motion; $\kappa = 0.71$, $p < 0.001$ for partial signal loss). Images with structural abnormalities such as large humps (1 patient), severe head movement (5 patients and 3 controls) and partial signal loss (7 patients) were excluded from the final analysis.

All T_1 images were processed using the recon-all pipeline (https://surfer.nmr.mgh.harvard.edu/fswiki/recon-all/) in Freesurfer 6.0 (https://surfer.nmr.mgh.harvard.edu/). Movement correction, intensity normalization, Talairach transformation and skull stripping were included in the recon-all pipeline. Details of the preprocessing of T_1-weighted images and analysis procedures have been described in previous research.[35] We inspected the processed images and corrected erroneous white matter segmentation near the parietal cortex areas using "control points" (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/ControlPoints_freeview/). During image processing through recon-all, cortical and subcortical regions were automatically segmented, and the volumes of these regions were calculated. Figure 1 shows examples of segmented ROIs.

As mentioned previously, we analyzed the volumes of the hippocampal and amygdalar subregions in addition to the ROIs. For further analysis of the hippocampal and amygdalar subregions, we performed segmentation of the hippocampal subfield and the nuclei of the amygdala and made volumetric measurements using automatic procedures implemented in Freesurfer 6.0.[36,37] Based on the literature, we set the hippocampal head, hippocampal tail, subiculum, CA1, CA4, presubiculum and molecular layer of the hippocampus and the basal and lateral nuclei of the amygdala as additional ROIs. For each participant, we divided the volume of each ROI by the participant's intracranial volume to calculate relative volumes.[20,38,39] We used relative volume to strictly control for intracranial volume, because the volumes of developing brains vary widely.[40]

Statistical analysis

We used SPSS 25.0 for Windows (SPSS Inc.) for all statistical analyses. For participant demographic and clinical characteristics, we analyzed continuous variables such as age and ADHD-RS using Student t tests, and categorical variables such as sex using χ^2 tests. To examine whether volumes in responders differed from those in nonresponders, we conducted analyses of covariance, controlling for age, sex and IQ for each ROI. We set the relative volumes of the ROIs as dependent variables. We checked for outliers (3 × interquartile range, as defined in SPSS) before all statistical analyses, but we found none. Because we used multiple ROIs in this study, we used Benjamini–Hochberg false discovery rate (FDR) to correct for multiple tests.[41]

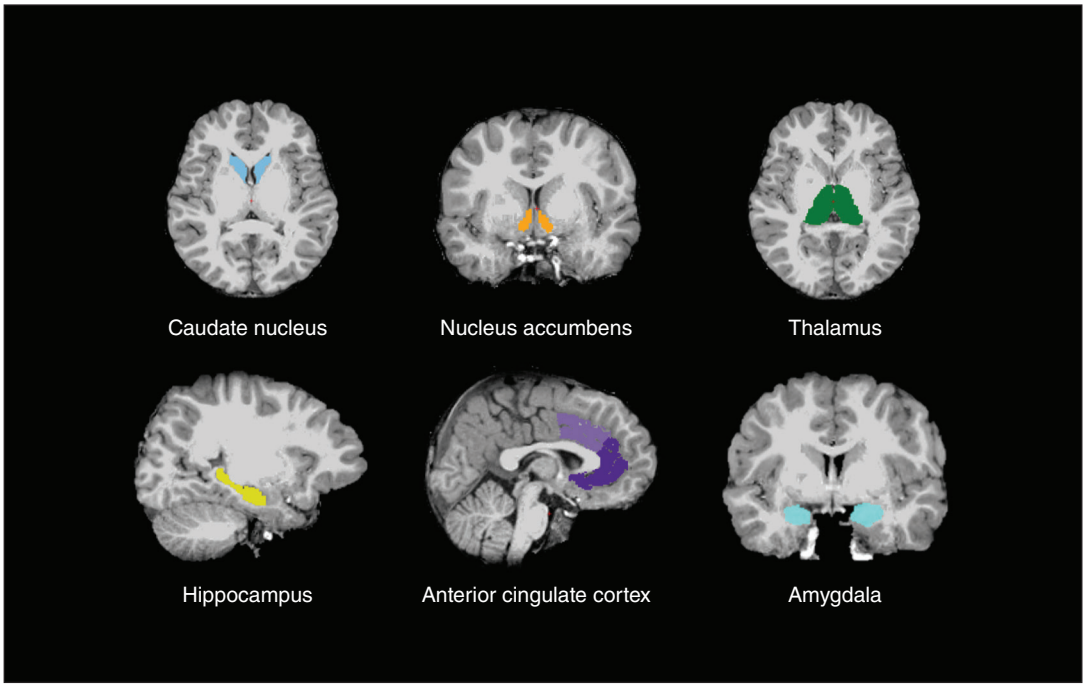

Figure 1: Regions of interest.

Results

Demographic and clinical characteristics

Table 1 summarizes participants' demographic and clinical characteristics. The group of youth with ADHD had more male participants and a lower average IQ than the control group. To control for the effects of these variables, we set sex and IQ as covariates in the analyses that follow. Given the wide range of ages among participants, we also included age as a covariate. Compared to healthy controls, youth with ADHD showed higher inattentiveness and hyperactivity-impulsivity scores on the ADHD-RS. Youth with ADHD also had higher CPT omission scores than healthy controls.

As noted above, 44 of the 67 youth with ADHD were responders and 23 were nonresponders. We found no significant demographic differences (including age, sex and IQ) between responders and nonresponders. We also found no differences between the 2 groups in terms of pretreatment ADHD-RS and CPT scores. Responders and nonresponders did not show significant differences in final methylphenidate treatment dose or dose per weight.

Table 1: Participant demographic and clinical characteristics

	All participants $n = 92$			Methylphenidate response $n = 67$		
Characteristic	ADHD $n = 67$	Control $n = 25$	p value	Responders $n = 44$	Nonresponders $n = 23$	p value
Age, yr	9.76 ± 2.51	10.00 ± 2.50	0.69	9.45 ± 2.37	10.35 ± 2.72	0.17
Female, *n* (%)	13 (19.4)	14 (56)	0.002	9 (20.5)	4 (17.4)	0.76
IQ	107.79 ± 13.22	116.92 ± 10.80	0.003	107.52 ± 12.33	108.30 ± 15.07	0.82
ADHD rating scale (pretreatment)						
Inattentive	15.03 ± 5.61	3.04 ± 3.97	< 0.001	15.68 ± 5.94	13.78 ± 4.80	0.19
Hyperactive–impulsive	10.87 ± 5.42	1.36 ± 1.63	< 0.001	11.20 ± 5.69	10.22 ± 4.93	0.48
Continuous Performance Test (pretreatment)						
Omission error	65.21 ± 20.79	50.80 ± 6.89	0.001	64.57 ± 20.25	66.43 ± 22.21	0.73
Commission error	63.85 ± 17.32	57.56 ± 14.64	0.11	64.00 ± 17.52	63.57 ± 17.32	0.92
Final methylphenidate dose, mg	32.45 ± 11.97	—	—	32.61 ± 11.24	32.13 ± 13.54	0.88
Final methylphenidate dose, mg/kg	0.92 ± 0.25	—	—	0.98 ± 0.25	0.81 ± 0.22	0.01

ADHD = attention-deficit/hyperactivity disorder.
Values are mean ± standard deviation unless otherwise specified.

Volumetric differences in the subcortical regions: responders versus nonresponders

The volumes of the ROIs between groups are described in Appendix 1, Table S1, available at www.jpn.ca/lookup/doi/10.1503/jpn.210074/tab-related-content. Nonresponders had significantly larger volumes in the bilateral amygdala (right: $F_{1,62} = 12.07$, $p = 0.001$, $\eta_p^2 = 0.163$; left: $F_{1,62} = 10.27$, $p = 0.002$, $\eta_p^2 = 0.142$) and right thalamus ($F_{1,62} = 8.02$, $p = 0.006$, $\eta_p^2 = 0.115$) than responders (Figure 2). These differences remained significant after we applied Benjamini–Hochberg FDR correction.

Nonresponders also had marginally larger volumes in the left thalamus ($F_{1,62} = 5.31$, $p = 0.025$, $\eta_p^2 = 0.079$) and right hippocampus ($F_{1,62} = 5.45$, $p = 0.023$, $\eta_p^2 = 0.081$) than responders, but these differences were nonsignificant after we applied Benjamini–Hochberg FDR correction.

We found no significant differences in the other ROIs, including the caudate, the anterior cingulate cortex and the nucleus accumbens.

Volumetric differences in the amygdalar and hippocampal subregions: responders versus nonresponders

Given the heterogeneous roles of the amygdalar and hippocampal subregions, we examined group volumetric differences in the preselected subregions of each. In the amygdalar subregions, nonresponders had significantly larger volumes in the bilateral lateral nucleus (right: $F_{1,62} = 11.52$, $p = 0.001$, $\eta_p^2 = 0.157$; left: $F_{1,62} = 8.35$, $p = 0.005$, $\eta_p^2 = 0.119$) and the right basal nucleus ($F_{1,62} = 13.74$, $p < 0.001$, $\eta_p^2 = 0.181$) than responders (Figure 3 and Appendix 1, Table S2). These differences remained significant after we applied Benjamini–Hochberg FDR correction. We found no significant differences for the left basal nucleus.

In the hippocampal subregions, nonresponders had significantly larger volumes in the right molecular layer ($F_{1,62} = 12.95$, $p = 0.001$, $\eta_p^2 = 0.173$), right hippocampal head ($F_{1,62} = 9.93$, $p = 0.003$, $\eta_p^2 = 0.138$) and right CA1 ($F_{1,62} = 7.73$, $p = 0.007$, $\eta_p^2 = 0.111$) than responders (Figure 4 and Appendix 1, Table S3). These differences remained significant after we applied Benjamini–Hochberg FDR correction. We observed no significant differences in the other subregions, including the CA4, hippocampal tail, presubiculum and subiculum.

Additional analyses

Comparison with healthy controls

To examine volumetric differences between responders, nonresponders and healthy controls, we also conducted 3-group comparisons. We found significant volumetric differences in the bilateral amygdala (right: $F_{2,86} = 5.73$, $p = 0.005$, $\eta_p^2 = 0.118$; left: $F_{2,86} = 5.70$, $p = 0.005$, $\eta_p^2 = 0.117$) and the right thalamus ($F_{2,86} = 5.24$, $p = 0.007$, $\eta_p^2 = 0.109$) among responders, nonresponders and healthy controls. Post hoc tests showed that nonresponders had significantly larger volumes in the bilateral amygdala (right: $p = 0.003$, left: $p = 0.003$) and right thalamus ($p = 0.011$) than responders (Appendix 1, Figure S1). However, we found no significant volumetric differences in the amygdala between responders and controls or between nonresponders and controls.

In the amygdalar subregions, we found significant volumetric differences in the bilateral lateral nucleus (right: $F_{2,86} = 6.08$, $p = 0.003$, $\eta_p^2 = 0.124$; left: $F_{2,86} = 5.15$, $p = 0.008$, $\eta_p^2 = 0.107$) and right basal nucleus ($F_{2,86} = 7.38$, $p = 0.001$, $\eta_p^2 = 0.146$) among responders, nonresponders and controls. Post hoc tests showed that nonresponders had significantly larger volumes in the bilateral lateral nuclei (right: $p = 0.003$; left: $p = 0.009$) and right basal nucleus ($p = 0.001$) than responders (Appendix 1, Figure S2). Nonresponders also had significantly larger volumes in the left lateral nucleus ($p = 0.049$) and right basal nucleus ($p = 0.010$) than controls (Appendix 1, Figure S2). We found no significant differences between responders and controls.

In the hippocampal subregions, we found significant volumetric differences in the right molecular layer ($F_{2,86} = 6.70$, $p = 0.002$, $\eta_p^2 = 0.135$) and right hippocampal head ($F_{2,86} = 5.23$, $p = 0.007$, $\eta_p^2 = 0.109$) among responders, nonresponders and controls. Post hoc tests showed that nonresponders had significantly larger volumes in the right molecular layer of the hippocampus ($p = 0.002$) and right hippocampal head ($p = 0.009$) than responders (Appendix 1, Figure S3). Nonresponders also had significantly larger volumes in the right molecular layer of the hippocampus ($p = 0.019$) and right hippocampal head ($p = 0.039$) than controls (Appendix 1, Figure S3). We found no significant differences between responders and controls.

Group differences in subcortical volume using absolute volumes

In the main analyses, we used relative volumes to strictly control for intracranial volume, but we conducted the same analyses using absolute volumes. Similar to the results for relative volumes, nonresponders had larger volumes in the subcortical ROIs (bilateral amygdala), amygdalar subregions (bilateral lateral nuclei and right basal nucleus) and hippocampal subregions (right molecular layer, right hippocampal head and right CA1) compared to responders. More detailed results are reported in Appendix 1.

Group differences in subcortical volume using methylphenidate response criteria based on the CGI-I and ADHD-RS

In the main analyses, we classified responders and nonresponders based on 1 item of the CGI-I. Although CGI-I scores have been reported to be reliable in detecting treatment response,[42] some studies have defined treatment response based on a combination of CGI-I and ADHD-RS scores.[43,44] Therefore, we also classified methylphenidate treatment response based on criteria defined by combining CGI-I and ADHD-RS scores. Responders were defined as participants who met both of the following standards: post-treatment ADHD-RS scores of 18 or under and post-treatment CGI-I scores of 2 or under.[43,44] The correspondence between classification using the combined criteria and original classification using only CGI-I scores was excellent ($\kappa = 0.843$, $p < 0.001$).

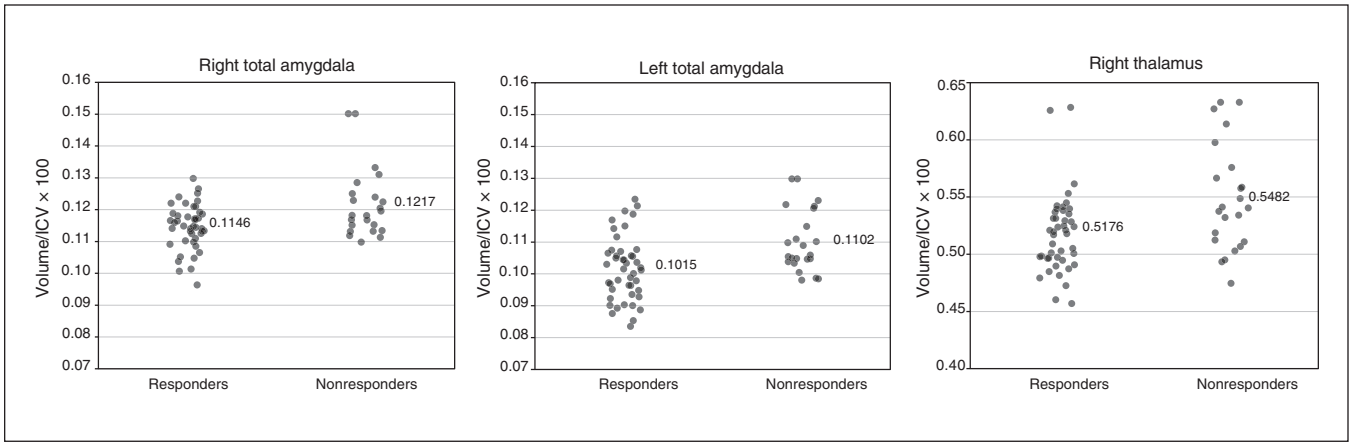

Figure 2: Scatter plots of volumes in the bilateral total amygdala and right thalamus for responders and nonresponders. Average values for each group are displayed. ICV = intracranial volume.

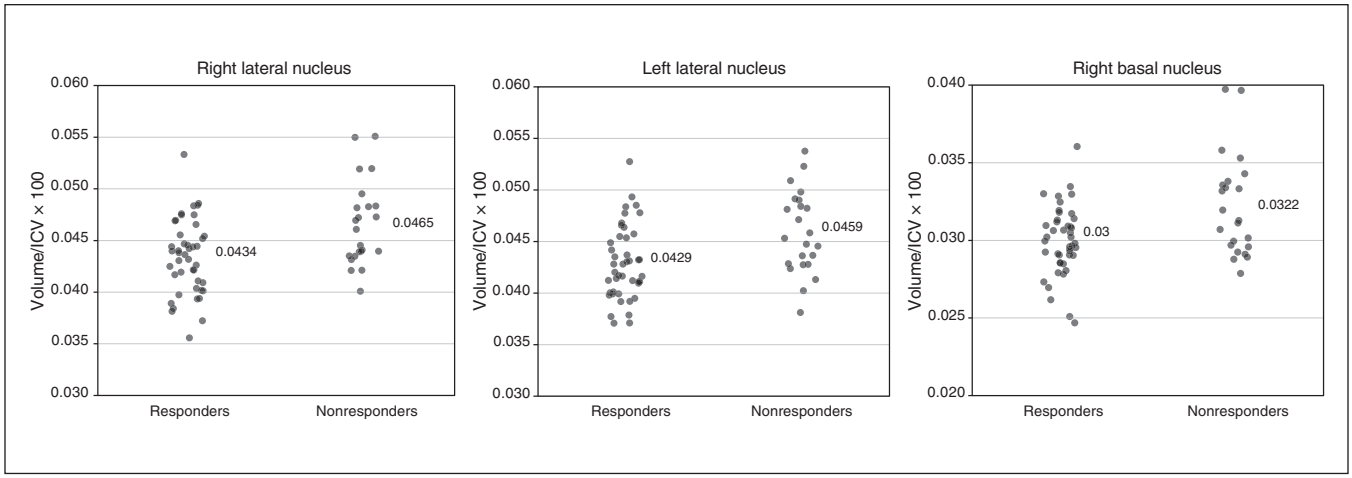

Figure 3: Scatter plots of volumes in the bilateral lateral nuclei and right basal nucleus of the amygdala for responders and nonresponders. Average values for each group are displayed. ICV = intracranial volume.

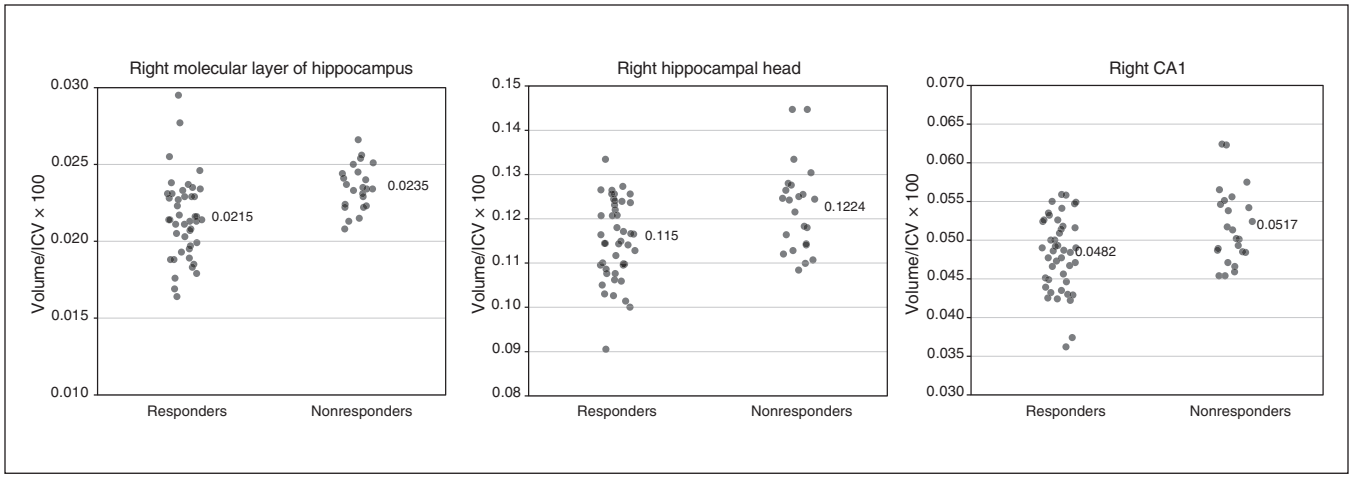

Figure 4: Scatter plots of volumes in the right molecular layer of the hippocampus, the right hippocampal head and the right hippocampal CA1 for responders and nonresponders. Average values for each group are displayed. CA1 = cornu ammonis 1; ICV = intracranial volume.

We also examined whether volumetric differences remained unchanged when responders and nonresponders were defined based on the combined criteria, and we found similar results. Nonresponders had enlarged volumes in the subcortical ROIs (right thalamus and bilateral amygdala), the amygdalar subregions (right lateral nucleus and right basal nucleus) and a hippocampal subregion (right molecular layer) compared to responders. Specific results are reported in Appendix 1.

Group differences in subcortical volume controlling for methylphenidate treatment history before enrolment

Eight participants had received methylphenidate medication before they were enrolled in the study. Given that previous methylphenidate treatment history may be associated with brain volumetric alterations at baseline, we conducted the same analyses controlling for whether or not participants had received methylphenidate treatment before enrolment. Our main results remained unchanged. For example, nonresponders had enlarged volumes in the subcortical ROIs (bilateral amygdala and right thalamus), the amygdalar subregions (bilateral lateral nuclei and right basal nucleus) and the hippocampal subregions (right molecular layer and right hippocampal head) compared to responders. More detailed results are reported in Appendix 1.

Group differences in subcortical volume controlling for final methylphenidate dose by weight

We found a significant difference between responders and nonresponders in final methylphenidate dose by weight. To rule out the possible effect of methylphenidate dose by weight on volumetric alterations, we conducted the same analyses controlling for this factor. Similar to the main results, nonresponders had enlarged volumes in the subcortical ROIs (bilateral amygdala and right thalamus), the amygdalar subregions (bilateral lateral nuclei and right basal nucleus) and the hippocampal subregions (right molecular layer and right hippocampal head) compared to responders. More detailed results are reported in Appendix 1.

Correlation between volumetric alterations and clinical measures

Given the significant correlations between the volumes of the caudate and nucleus accumbens and the degree of improvement on the CPT and the Conner's Parent Rating Scale,[20] we investigated the relationships between ROI volumes and improvement on the CPT and ADHD-RS in youth with ADHD. In this additional analysis, we focused on ROIs that predicted significant methylphenidate treatment outcomes, such as the thalamus, amygdala, molecular layer of the hippocampus, hippocampal head, lateral nucleus and basal nucleus of the amygdala. We calculated differences between pretreatment and post-treatment scores on the CPT and ADHD-RS to assess improvement. We performed regression analyses to examine whether pretreatment volumes predicted improvements in ADHD symptoms and behaviours, controlling for age, sex and IQ. However, pretreatment volumes did not predict improvement on the CPT or ADHD-RS.

Discussion

We investigated pretreatment brain structural alterations and their potential to predict methylphenidate treatment response in youth with ADHD. We compared pretreatment volumes in subcortical regions and dopaminergic regions between responders and nonresponders. Nonresponders consistently showed larger volumes in subcortical areas (bilateral amygdala and right thalamus), amygdalar subregions (right and left lateral nuclei and right basal nucleus) and hippocampal subregions (right molecular layer, right head and right CA1) compared to responders. Nonresponders also showed larger volumes in the amygdalar subregions (left lateral nucleus and right basal nucleus) and hippocampal subregions (right molecular layer and right hippocampal head) than controls. However, responders did not show significant volumetric differences in these regions compared to controls. We found no significant group differences in other ROIs, including the anterior cingulate cortex, caudate nucleus, nucleus accumbens and total hippocampus. Pretreatment volumes in the regions that predicted methylphenidate treatment response did not predict improvement in CPT or ADHD-RS scores.

As hypothesized, our study revealed structural differences in subcortical regions (thalamus, hippocampal subregions and amygdala subregions) between responders and nonresponders. These results suggest that pretreatment structural alterations in ADHD may play an important role in predicting methylphenidate treatment outcomes. In general, structural alterations in nonresponders may be associated with functional alterations. These 3 regions are known to be closely connected as part of the subcortical regions. For example, impairments in hippocampal and amygdalar function may attenuate their modulation of the thalamus,[45] leading to a deficit in thalamocortical information processing that may result in impulsivity symptoms in with ADHD.[46]

However, our findings related to the direction of group differences were inconsistent with our hypotheses. Unlike our hypotheses, nonresponders showed larger volumes than responders in the thalamus, amygdala and its subregions, and hippocampal subregions. One possible reason for these findings may have been a compensatory plastic hypertrophic response to functional deficits in these regions. Neuronal hypertrophy could be associated with the normalizing mechanisms of the defective brain regions that contribute to ADHD symptoms.[13] Functional deficits may be trivial in responders, preserving brain regional volumes, similar to controls. However, functional impairment may be substantial in nonresponders to enforce compensatory hypertrophic response. For example, compensatory hyperactivity and collateral sprouting of axons in partially damaged hippocampi have been reported previously.[47] This mechanism may explain why nonresponders in the present study showed enlarged volumes in the anterior hippocampus that could compensate for its functional deficit, known to be associated with impulsivity and waiting problems in patients with ADHD.[13,48,49] Compensatory volumetric enlargement has also been reported in the thalamus in other neurodevelopmental disorders related to hyperactivity symptoms.[50] Therefore,

compensatory hypertrophy in the brains of nonresponders may be associated with functional deficits that are refractory to methylphenidate treatment. Further research is needed to assess brain activity and volume after treatment to confirm compensatory hypertrophy in these regions in nonresponders.

Another possible reason for our findings may be related to abnormal hyperactivity of the brain regions in nonresponders. Nonresponders may have more hyperactive brain regions related to ADHD pathogenesis than responders and controls, and this may be expressed as neuronal hypertrophy and enlarged volume in the subcortical regions. For example, amygdala hyperactivity in ADHD patients,[51] normalized by methylphenidate treatment,[10,52] was reported to be accompanied by volume enlargement in the amygdala.[53] However, we did not measure brain activity in this study. Further research is required to examine how neural activity and volumes (or their combination) predict methylphenidate treatment response in youth with ADHD.

Although we found significant volumetric differences between responders and nonresponders, the 2 groups did not show significant differences in pretreatment clinical measurements of ADHD, such as CPT and ADHD-RS scores. These findings could be in line with previous studies that reported significant brain function and structure differences but no significant differences in clinically observable performance.[54–56] Moreover, lack of difference in rating and test scores between responders and nonresponders may be explained using our compensation model: compensation could have prevented functional deficits from being expressed at a clinical level. The finding that some neurobiological deficits are not expressed as deficits in clinical performance also add importance to studies that predict treatment response using neurobiological factors such as volumetric alteration. Overall, our findings may emphasize the importance of predicting methylphenidate treatment response using neurobiological factors, especially in situations where it is difficult to detect pretreatment clinical and behavioural manifestations in youth with ADHD.

Limitations

The present study had some limitations that should be noted. We did not collect structural T_1 images after methylphenidate treatment, limiting our ability to examine volume changes after treatment. Future research is needed to verify whether responders and nonresponders show volumetric alterations in the thalamus, amygdala and hippocampal subregions after methylphenidate treatment. Because we interpreted enlarged ROIs as markers associated with functional deficits, any volume changes in the brain after methylphenidate treatment could add another possible explanation of functional improvements.

We did not measure functional changes (e.g., neural activation) in the ROIs or directly measure the connectivity between the ROIs. As mentioned above, structural alteration in nonresponders may be related to functional deficits. Thus, it is important to measure neural activation and functional connectivity between regions. Given that our ROIs (e.g., thalamus, amygdala and hippocampus) and the subregions of the amygdala and hippocampus were interconnected,[45,57] it may be particularly important to examine alteration in their function and connectivity and how structural alteration is associated with functional deficits. Functional connectivity during the resting state and when performing tasks has been reported to effectively explain the pathogenesis of ADHD.[25,58,59] To confirm our explanation of volumetric alterations by functions and connectivity of the ROIs, further research using functional MRI is needed to demonstrate differences in the function and connectivity of the ROIs between groups.

Our study included patients with a methylphenidate treatment history of less than 6 months. These patients had not been treated with methylphenidate for at least 4 weeks before participating in the present study, so we assumed that any persisting pharmacological effects could be ruled out. Our additional analyses showed that methylphenidate treatment history did not affect our main findings. However, some effects of methylphenidate treatment history on structural alterations (e.g., other regions outside our ROIs) may have remained. To rule out any remaining possibilities of structural alterations induced by previous methylphenidate treatment, future research is needed that includes only medication-naive patients with ADHD, exploring whether structural alterations at pretreatment can predict methylphenidate treatment response.

Conclusion

This study found that methylphenidate treatment outcomes in youth with ADHD were predicted by altered pretreatment volumes in the thalamus, the amygdala and its subregions, and the hippocampal subregions. These findings suggest that structural alterations, such as volumes in subcortical regions, may be an important factor for predicting treatment response in ADHD. Given the advantages of MRI measurement as noted above, measuring brain structure before treatment is practical for clinical use, especially when predicting methylphenidate treatment outcomes in youth with ADHD. For further practical applications, calculating the accuracy of volumetric-based predictions using machine-learning techniques would be useful for future ADHD treatment research.[60] Our findings also suggest that more attention should be paid to patients who do not respond to methylphenidate treatment in clinical practice. For example, in youth with ADHD who show a higher degree of pretreatment structural alterations in the subcortical regions, alternative pharmacological treatment may be considered when establishing a treatment plan.

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Affiliations: From the Department of Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea (J.-S. Kim, Hwang); and the Division of Child and Adolescent Psychiatry, Department of Psychiatry, Seoul National University Hospital, Seoul, Republic of Korea (Lee, J.-W. Kim).

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References

1. Polanczyk G, de Lima MS, Horta BL, et al. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry* 2007;164:942-8.
2. Chan E, Fogler JM, Hammerness PG. Treatment of attention-deficit/hyperactivity disorder in adolescents: a systematic review. *JAMA* 2016;315:1997-2008.
3. Mehta TR, Monegro A, Nene Y, et al. Neurobiology of ADHD: a review. *Curr Dev Disord Rep* 2019;6:235-40.
4. Garcia-Cabezas MA, Rico B, Sanchez-Gonzalez MA, et al. Distribution of the dopamine innervation in the macaque and human thalamus. *Neuroimage* 2007;34:965-84.
5. Banaschewski T, Becker K, Scherag S, et al. Molecular genetics of attention-deficit/hyperactivity disorder: an overview. *Eur Child Adolesc Psychiatry* 2010;19:237-57.
6. Curatolo P, D'Agati E, Moavero R. The neurobiological basis of ADHD. *Ital J Pediatr* 2010;36:79.
7. Arnsten AF. Stimulants: therapeutic actions in ADHD. *Neuropsychopharmacology* 2006;31:2376-83.
8. Jenson D, Yang K, Acevedo-Rodriguez A, et al. Dopamine and norepinephrine receptors participate in methylphenidate enhancement of in vivo hippocampal synaptic plasticity. *Neuropharmacology* 2015;90:23-32.
9. Tye KM, Tye LD, Cone JJ, et al. Methylphenidate facilitates learning-induced amygdala plasticity. *Nat Neurosci* 2010;13:475-81.
10. Bottelier MA, Schrantee A, Ferguson B, et al. Age-dependent effects of acute methylphenidate on amygdala reactivity in stimulant treatment-naive patients with attention deficit/hyperactivity disorder. *Psychiatry Res Neuroimaging* 2017;269:36-42.
11. Hoogman M, Bralten J, Hibar DP, et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. *Lancet Psychiatry* 2017;4:310-9.
12. Rosch KS, Crocetti D, Hirabayashi K, et al. Reduced subcortical volumes among preschool-age girls and boys with ADHD. *Psychiatry Res Neuroimaging* 2018;271:67-74.
13. Plessen KJ, Bansal R, Zhu H, et al. Hippocampus and amygdala morphology in attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 2006;63:795-807.
14. Duvernoy HM, Cattin E, Naidich T, et al. *The human hippocampus.* Berlin: Springer Verlag; 2005.
15. Michely J, Rigoli F, Rutledge RB, et al. Distinct processing of aversive experience in amygdala subregions. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2020;5:291-300.
16. Malykhin NV, Coupland NJ. Hippocampal neuroplasticity in major depressive disorder. *Neuroscience* 2015;309:200-13.
17. Yao Z, Fu Y, Wu J, et al. Morphological changes in subregions of hippocampus and amygdala in major depressive disorder patients. *Brain Imaging Behav* 2020;14:653-67.
18. Brown SSG, Rutland JW, Verma G, et al. Structural MRI at 7T reveals amygdala nuclei and hippocampal subfield volumetric association with major depressive disorder symptom severity. *Sci Rep* 2019;9:10166.
19. Al-Amin M, Zinchenko A, Geyer T. Hippocampal subfield volume changes in subtypes of attention deficit hyperactivity disorder. *Brain Res* 2018;1685:1-8.
20. Moreno A, Duno L, Hoekzema E, et al. Striatal volume deficits in children with ADHD who present a poor response to methylphenidate. *Eur Child Adolesc Psychiatry* 2014;23:805-12.
21. Ivanov I, Bansal R, Hao X, et al. Morphological abnormalities of the thalamus in youths with attention deficit hyperactivity disorder. *Am J Psychiatry* 2010;167:397-408.
22. Onnink AM, Zwiers MP, Hoogman M, et al. Brain alterations in adult ADHD: effects of gender, treatment and comorbid depression. *Eur Neuropsychopharmacol* 2014;24:397-409.
23. Semrud-Clikeman M, Pliszka SR, Lancaster J, et al. Volumetric MRI differences in treatment-naive vs chronically treated children with ADHD. *Neurology* 2006;67:1023-7.
24. Enneking V, Leehr EJ, Dannlowski U, et al. Brain structural effects of treatments for depression and biomarkers of response: a systematic review of neuroimaging studies. *Psychol Med* 2020;50:187-209.
25. Hong SB, Harrison BJ, Fornito A, et al. Functional dysconnectivity of corticostriatal circuitry and differential response to methylphenidate in youth with attention-deficit/hyperactivity disorder. *J Psychiatry Neurosci* 2015;40:46-57.
26. Quinn D, Bode T, Reiz JL, et al. Single-dose pharmacokinetics of multilayer-release methylphenidate and immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. *J Clin Pharmacol* 2007;47:760-6.
27. Espay AJ, Dwivedi AK, Payne M, et al. Methylphenidate for gait impairment in Parkinson disease: a randomized clinical trial. *Neurology* 2011;76:1256-62.
28. *Diagnostic and statistical manual of mental disorders.* 4th ed. Washington (DC): American Psychiatric Association; 1994.
29. Kim YS, Cheon KA, Kim BN, et al. The reliability and validity of Kiddie-Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version–Korean version (K-SADS-PL-K). *Yonsei Med J* 2004;45:81-9.
30. So YKNJ, Kim YS, Ko SG, et al. The reliability and validity of Korean parent and teacher ADHD rating scale. *J Korean Neuropsychiatr Assoc* 2002;41:283-9.
31. Greenberg LM, Waldman ID. Developmental normative data on the test of variables of attention (T.O.V.A.). *J Child Psychol Psychiatry* 1993;34:1019-30.
32. Green T, Avda S, Dotan I, et al. Phenotypic psychiatric characterization of children with Williams syndrome and response of those with ADHD to methylphenidate treatment. *Am J Med Genet B Neuropsychiatr Genet* 2012;159B:13-20.
33. Kim BN, Kim JW, Hong SB, et al. Possible association of norepinephrine transporter-3081(A/T) polymorphism with methylphenidate response in attention deficit hyperactivity disorder. *Behav Brain Funct* 2010;6:57.
34. Krause J, la Fougere C, Krause KH, et al. Influence of striatal dopamine transporter availability on the response to methylphenidate in adult patients with ADHD. *Eur Arch Psychiatry Clin Neurosci* 2005;255:428-31.
35. Fischl B. FreeSurfer. *Neuroimage* 2012;62:774-81.
36. Iglesias JE, Augustinack JC, Nguyen K, et al. A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: application to adaptive segmentation of in vivo MRI. *Neuroimage* 2015;115:117-37.
37. Saygin ZM, Kliemann D, Iglesias JE, et al. High-resolution magnetic resonance imaging reveals nuclei of the human amygdala: manual segmentation to automatic atlas. *Neuroimage* 2017;155:370-82.
38. Kramer JH, Quitania L, Dean D, et al. Magnetic resonance imaging correlates of set shifting. *J Int Neuropsychol Soc* 2007;13:386-92.
39. Mahone EM, Ranta ME, Crocetti D, et al. Comprehensive examination of frontal regions in boys and girls with attention-deficit/hyperactivity disorder. *J Int Neuropsychol Soc* 2011;17:1047-57.
40. Sgouros S, Goldin JH, Hockley AD, et al. Intracranial volume change in childhood. *J Neurosurg* 1999;91:610-6.
41. Benjamini Y, Hochberg Y. Controlling the false discovery rate — a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol* 1995;57:289-300.

42. Grizenko N, Lachance M, Collard V, et al. Sensitivity of tests to assess improvement in ADHD symptomatology. *Can Child Adolesc Psychiatr Rev* 2004;13:36-9.
43. Kim BN, Cummins TD, Kim JW, et al. Val/Val genotype of brain-derived neurotrophic factor (BDNF) Val(6)(6)Met polymorphism is associated with a better response to OROS-MPH in Korean ADHD children. *Int J Neuropsychopharmacol* 2011;14:1399-410.
44. Steele M, Jensen PS, Quinn DMP. Remission versus response as the goal of therapy in ADHD: a new standard for the field? *Clin Ther* 2006;28:1892-908.
45. Levy F. Synaptic gating and ADHD: a biological theory of comorbidity of ADHD and anxiety. *Neuropsychopharmacology* 2004;29:1589-96.
46. Sonuga-Barke EJ. Causal models of attention-deficit/hyperactivity disorder: from common simple deficits to multiple developmental pathways. *Biol Psychiatry* 2005;57:1231-8.
47. Gage FH, Bjorklund A, Stenevi U. Local regulation of compensatory noradrenergic hyperactivity in the partially denervated hippocampus. *Nature* 1983;303:819-21.
48. Kerns KA, McInerney RJ, Wilde NJ. Time reproduction, working memory, and behavioral inhibition in children with ADHD. *Child Neuropsychol* 2001;7:21-31.
49. Smith A, Taylor E, Rogers JW, et al. Evidence for a pure time perception deficit in children with ADHD. *J Child Psychol Psychiatry* 2002;43:529-42.
50. Miller AM, Bansal R, Hao X, et al. Enlargement of thalamic nuclei in Tourette syndrome. *Arch Gen Psychiatry* 2010;67:955-64.
51. Plichta MM, Vasic N, Wolf RC, et al. Neural hyporesponsiveness and hyperresponsiveness during immediate and delayed reward processing in adult attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2009;65:7-14.
52. Posner J, Nagel BJ, Maia TV, et al. Abnormal amygdalar activation and connectivity in adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2011;50:828-37.e3.
53. Evans GW, Swain JE, King AP, et al. Childhood cumulative risk exposure and adult amygdala volume and function. *J Neurosci Res* 2016;94:535-43.
54. Chang JC, Lin HY, Lv J, et al. Regional brain volume predicts response to methylphenidate treatment in individuals with ADHD. *BMC Psychiatry* 2021;21:26.
55. Strauss M, Reif A, Ulke C, et al. Is brain arousal regulation a predictor of response to psychostimulant therapy in adult ADHD patients? *Eur Arch Psychiatry Clin Neurosci* 2020;270:1073-6.
56. Arns M, Vollebregt MA, Palmer D, et al. Electroencephalographic biomarkers as predictors of methylphenidate response in attention-deficit/hyperactivity disorder. *Eur Neuropsychopharmacol* 2018;28:881-91.
57. Stein T, Moritz C, Quigley M, et al. Functional connectivity in the thalamus and hippocampus studied with functional MR imaging. *AJNR Am J Neuroradiol* 2000;21:1397-401.
58. Bush G. Attention-deficit/hyperactivity disorder and attention networks. *Neuropsychopharmacology* 2010;35:278-300.
59. Wolf RC, Plichta MM, Sambataro F, et al. Regional brain activation changes and abnormal functional connectivity of the ventrolateral prefrontal cortex during working memory processing in adults with attention-deficit/hyperactivity disorder. *Hum Brain Mapp* 2009;30:2252-66.
60. Janssen RJ, Mourao-Miranda J, Schnack HG. Making individual prognoses in psychiatry using neuroimaging and machine learning. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2018;3:798-808.