Neuroanatomical correlates of attention deficit hyperactivity disorder accounting for comorbid oppositional defiant disorder and conduct disorder

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Abstract

Aim: An increasing number of neuroimaging studies have been conducted to uncover the pathophysiology of attention deficit hyperactivity disorder (ADHD). The findings are inconsistent, however, at least partially due to methodological differences. We used voxel-based morphometry (VBM) to evaluate the brain morphology in ADHD after taking into account the confounding effect of oppositional defiant disorder (ODD) and conduct disorder (CD) comorbidity.

Methods: Eighteen children with ADHD and 17 age- and gender-matched typically developing subjects underwent high-spacial resolutional MRI. The regional gray matter volume differences between the children with ADHD and controls were examined with and without accounting for comorbid ODD and CD in a voxel-by-voxel manner throughout the entire brain.

Results: The VBM revealed significantly smaller regional gray matter volume in regions including the bilateral temporal polar and occipital cortices in the subjects with ADHD compared with the controls. Significantly smaller regional gray matter volumes were demonstrated in more extensive regions including the bilateral temporal polar cortices, bilateral amygdala, bilateral occipital cortices, right superior temporal sulcus, and left middle frontal gyrus after controlling for the confounding effect of comorbid ODD and CD.

Conclusion: Morphological abnormalities in ADHD were seen not only in the regions associated with executive functioning but also in the regions associated with social cognition. When the effect of comorbid CD and ODD was taken into account, there

were more extensive regions with significantly smaller volume in ADHD compared to controls.

Key words

Attention deficit hyperactivity disorder, brain, magnetic resonance imaging, voxel-based morphometry

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by pervasive inattention and/or hyperactivity-impulsivity resulting in significant functional impairment. The pathophysiology is presumed to be linked to dysfunction of frontal-striatal-cerebellar circuits, although the exact mechanism has not yet been elucidated. Recently, an increasing number of neuroimaging studies using magnetic resonance images (MRI) or functional MRI have been conducted to uncover the pathophysiology of ADHD. Such studies have demonstrated functional as well as structural abnormalities associated with ADHD in the corpus callosum, prefrontal cortex, caudate nucleus, putamen, globus pallidus, anterior temporal lobe, and cerebellum.[1, 2] The findings are inconsistent, however, at least partially due to different methodologies and subject selection among studies.

Although majority of previous structural MRI studies of ADHD have used regions of interest (ROI) method,[3-10] which could only be applied to a selected set of brain structures, several recent studies have employed relatively newer neuroimaging analysis techniques such as voxel-based morphometry (VBM)[11-14] and surface-based computational image analysis.[15, 16] While most previous morphological analyses with MRI using ROI method have focused on the frontal lobe,[4, 9, 10] basal ganglia,[3, 4, 7, 10] and cerebellum,[3, 6] VBM allows identification of regional differences even with no a priori region of interest, enabling an objective analysis of the whole brain. Accordingly, studies using newer neuroimaging analysis techniques have identified other abnormal regions such as the temporal or parietal lobes in patients with ADHD.[11, 13]

Disruptive behavioral disorders (DBDs), which include oppositional defiant disorder (ODD) and conduct disorder (CD), are common comorbidities of ADHD reported across cultures. Epidemiological studies indicate that the diagnoses of DBDs are present in 40-70% of children with ADHD, and the prevalence of comorbid DBDs in clinical population is probably even higher than in community samples.[17, 18] A substantial proportion of ADHD children with comorbid DBD are known to develop antisocial personality disorder in adulthood.[19] Harpold et al.[20] reported that adults with ADHD with a childhood history of ODD have also increased risk for multiple anxiety disorders, bipolar disorder, and substance use disorders. Despite the high prevalence and the serious consequences of ODD and CD in ADHD patients, only a few previous neuroimaging studies have considered the presence of ODD and CD. Three VBM studies examining ADHD subjects with ODD or CD have showed smaller gray matter volume in several regions, such as in the limbic structures,[21, 22] the basal ganglia,[13] and the cerebellum.[13]

We employed VBM to identify the morphological abnormalities in a voxel-by-voxel manner throughout the entire brain in ADHD subjects compared with the typically developing subjects. Subjects were grouped into those with and without comorbid ODD or CD to account for the effects of comorbidity on brain morphology.

Materials and method

Subjects

Eighteen right-handed (determined using the Edinburgh Inventory[23]) in- and

outpatients with ADHD were recruited from the Mental Health Clinic for Children, Shinshu University Hospital, Japan. Of these, 8 were diagnosed with ADHD alone (Boys/Girls: 6/2), while 10 were diagnosed with comorbid ODD or CD (Boys/Girls: 7/3; 6 with ODD and 4 with CD). ADHD subjects were diagnosed with ADHD-combined type (n=10), inattentive type (n=6), or hyperactive type (n=2) according to Diagnostic and Statistical Manual of Mental Disorders, 4th-edition, text revision (DSM-IV-TR) criteria.[24] Subjects did not meet criteria for any other disorder, including pervasive developmental disorder (PDD), tic, or other affective illness. The Japanese edition of ADHD Rating Scale-IV[25] was used to evaluate the severity of ADHD symptoms. As the original version, the Japanese version has been shown to have adequate reliability and validity.[26] The severity of oppositional defiant behaviors was measured by the Oppositional Defiant Behavior Inventory (ODBI).[27] ODBI is composed of 18 items describing oppositional behaviors. Each item is rated on a 4-point scale ranging from 0 to 3, with a higher score indicating more oppositional behaviors. IQ scores were measured by the Wechsler Intelligence Scale for Children, Third Edition.[28] Seventeen right-handed, age- and gender-matched typically developing subjects were recruited for comparison. The typically developing control group had no history of treatment for psychiatric illness, and they were interviewed by experienced child psychiatrists to rule out any psychiatric disorder.

The exclusion criteria for both groups were mental retardation, learning disability, neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 minutes, a history of

electroconvulsive therapy, and substance abuse or addiction. The ethical committee of the Shinshu University Hospital approved this study. All the subjects gave their written informed consent after a complete explanation of the study.

Insert Table 1 about here

Table 1 shows the demographic characteristics of the subjects. No significant difference was found in age, gender rate, parental socioeconomic status, and handedness index among the three diagnostic groups (Controls / ADHD alone / ADHD with comorbid ODD or CD). No significant difference in IQ and ADHD-RS between subjects with ADHD alone and those with ADHD comorbid with ODD or CD was found. In contrast, ADHD subjects with comorbid ODD or CD showed significantly more severe ODBI than subjects with ADHD alone (P=0.004). Compared to the control group, ADHD-RS and ODBI were significantly higher in subjects with ADHD alone (ADHD-RS: P<0.001, ODBI: P=0.001) and in those with ADHD comorbid with ODD or CD (ADHD-RS: P<0.001, ODBI: P<0.001).

MRI acquisition and Image Processing for VBM

All MRI examinations were performed with a 1.5-T clinical imager (Magnetom Symphony; Siemens), using Magnetization Prepared Rapid Gradient Echo (MP-RAGE); TR/TE= 3000/ 3.48 msec, flip angle 15 degrees, 1.0 mm slice thickness, a field of view 25.6 cm, and a matrix 512 x 512. Image processing for VBM, a fully automatic technique for computational analysis of differences in regional brain volume throughout the entire brain, was conducted using SPM2 (Institute of Neurology, London,

UK). The method for image processing was the same as the previous literature.[29, 30] Briefly, this method involves the following steps: (1) spatial normalization of all images to a standardized anatomical space; (2) extraction of gray and white matter from the normalized images; and (3) analysis of differences in regional gray and white matter volume across the whole brain. The spatial normalization to standard anatomical space was performed in a two-stage process. In the first step, each image was registered to the International Consortium for Brain Mapping template (Montreal Neurological Institute, Montreal, Canada). The normalized images of all participants were averaged and smoothed with 8 mm Gaussian kernel and then used as a new scanner- and population-specific template. In the second normalization step, each image of the entire group was deformed to the study-specific template using a nonlinear spatial transformation. Finally, using a modified mixture model cluster analysis, normalized images were corrected for non-uniformities in signal intensity and partitioned using a study-specific customized prior probability map into gray and white matter, cerebrospinal fluid, and background. In an intensity-modulation step, voxel values of the segmented images were multiplied by the measure of warped and unwarped structures derived from the nonlinear step of the spatial normalization. This step converts relative regional gray matter density to absolute gray matter density expressed as the amount of gray matter per unit volume of brain tissue prior to spatial normalization. The resulting modulated gray and white matter images were smoothed with 12 mm Gaussian kernel.

Statistical Analysis

The demographic characteristics of the subjects were compared among the three diagnostic groups using one-way analysis of variance and chi-square test. The IQ scores were compared using unpaired t test between subjects with ADHD alone and those with ADHD comorbid with ODD or CD. P values less than 0.05 were considered as statistically significant.

Statistical analyses of VBM were performed using an analysis of covariance model.[31] To account for global anatomical variations, the statistical analysis treated the intracranial volume (ICV) and age as confounding covariates and the ADHD diagnosis as condition. To detect the neuroanatomical correlates of ADHD diagnosis accounting for comorbid ODD or CD, a diagnostic variable (1=no comorbidities, 2=ODD or CD) was employed together with ICV and age as confounding covariates in the additional statistical analysis. We also conducted the analysis using the ODBI score instead of the diagnostic variable as a confounding covariate to take into account the sub-threshold conduct problems. To test the hypotheses with respect to regionally specific association with the ADHD diagnosis, the estimates were compared using two linear contrasts. The resulting set of voxel values for each contrast constituted a statistical parametric map of the t-statistic (SPM(t)). The SPM(t)s were displayed at an uncorrected threshold of $P<0.001$ for graphical reporting. The statistics in the tables are transformed to a Z-score to make them more intuitive. The significance of each region was corrected for multiple comparisons using the False Discovery Rate (FDR).[32] The statistical significance level

was set at the FDR-corrected $P < 0.05$.

Results

Group differences in regional brain volume

Insert Table 2 & Figure 1 about here

Table 2 lists the regions that showed smaller gray matter volumes in subjects with ADHD. No significant white matter volume difference between the groups was found. The VBM revealed significantly smaller regional gray matter volumes of regions including the bilateral temporal polar and occipital cortices in the subjects with ADHD compared with the controls. In contrast, after controlling for the confounding effect of comorbid ODD and CD, significantly smaller regional gray matter volumes were demonstrated in the extensive brain regions including the bilateral temporal polar cortices, bilateral amygdala, bilateral occipital cortices, right superior temporal sulcus, and left middle frontal gyrus in the subjects with ADHD (FDR-corrected $P < 0.05$), as shown in figure 1. To account for the sub-threshold conduct problems, we next treated the ODBI score instead of the diagnostic variable as the confounding covariate. The statistical significance level was also set at FDR-corrected $P < 0.05$ employing small volume correction with significant clusters, which were derived from the analysis using diagnostic variable as the covariate, as searched volume. Accounting for the sub-threshold conduct problems did not substantially change the statistical conclusion, as the statistical significance was preserved after adopting the ODBI score as a covariate (FDR-corrected $P<0.05$; right temporal pole: [46 12 -34], $Z=4.2$, [34 16 -32], $Z=4.02$;

right anterior ventral temporal cortex: [44 -8 -46], Z=3.78; right orbitofrontal cortices; [22 18 -20], Z=3.53; left amygdala: [-18 0 -32], Z=3.23; left anterior ventral temporal, and left orbitofrontal cortices: [-22 16 -22], Z=3.11; right superior temporal sulcus: [52 -36 -4], Z=3.36; right occipital cortex: [34 -80 10], Z=3.24; left parietal cortex: [-48 -70 44], Z=3.32). The direct comparison between ADHD subjects with and without ODD or CD showed no significant gray matter volume difference between these diagnostic sub-groups throughout the entire brain (FDR-corrected P>0.08).

Discussion

Our VBM study investigating structural brain differences between ADHD subjects and the control subjects showed that controlling for the confounding effect of comorbid ODD and CD resulted in more extensive regions with significantly smaller volume in ADHD compared to controls. Treating ODD or CD diagnosis as the confounding covariate, significantly smaller volumes were found in the bilateral temporal polar cortices, bilateral amygdala, bilateral occipital cortices, right superior temporal sulcus, and left middle frontal gyrus in the subjects with ADHD compared with the controls.

Children with ADHD have poor performance in executive function tasks.[33, 34] This may be partly due to abnormalities in the dorsolateral prefrontal cortex (DLPFC),[35] which lies in the middle frontal gyrus and is responsible for executive functioning.[36] In the present study, the volume of the left middle frontal gyrus was significantly smaller in subjects with ADHD when the confounding effect of comorbid ODD and CD was

accounted for. A number of previous studies of ADHD using ROI method,[3, 6-8, 10, 37] VBM,[12-14, 38] or surface-based computational morphometry[16] have similarly reported smaller volumes of the DLPFC regions. Functional imaging studies using positron emission tomography or functional MRI have also reported association of DLPFC with ADHD symptoms.[39, 40]

Consistent with previous studies, our study revealed smaller volumes in the anterior temporal region, which plays an important role in social and emotional processing.[41] A VBM study in twins[38] and a study using surface-based computational morphometry[16] have similarly reported abnormalities of anterior temporal regions in ADHD subjects. A study using functional MRI reported decreased metabolism in the similar region.[39] Amygdala is one of the most critical structures in the anterior temporal region playing a crucial role in emotional and social behavior.[42] A few studies including one meta-analysis have reported significantly smaller volumes of the amygdala in subjects with ADHD.[2, 3, 7] These finding may be associated with social-cognitive impairment observed in ADHD children.[43-45] Although social dysfunctioning was not assessed in this study, examining the relationship between social cognition and amgydala volume in ADHD subjects may be required in future studies. The literature suggest that a region of the right superior temporal sulcus, which showed significantly smaller volume in our study, is also involved in social perception, specifically in analyzing the intentions of other people's actions.[46]

Previous reports have been inconsistent regarding the volume of the occipital lobes in subjects with ADHD. Some report smaller volumes in ADHD subjects, [4, 6, 11, 13, 15]

while others report no significant volume differences.[5, 37] Cerebellar and basal ganglia volume deficits have also been reported in number of studies; [12-14] however our results showed no significant volume changes in these regions.

The high rate of coexisting conditions with ADHD is often conceived as the result of ADHD being not a single entity.[47] Of the many different comorbid configurations of ADHD, comorbidity of ADHD and CD has the most data substantiating its consideration as a distinct subtype. They differ from other children with ADHD in several associated features such as family history, longitudinal course, and neurochemical function.[48-50] Although it remains unresolved whether children with ADHD and comorbid conduct problems represent a distinct subtype or a more virulent presentation of ADHD, it seems imprudent to neglect the confounding effects of such comorbidities when studying ADHD.

Only a few neuroimaging studies of ADHD subjects have considered the presence of ODD and CD. A VBM study[13] which accounted for ODD and CD comorbidities reported that volume deficits of the cerebellum and the right globus pallidus were significantly greater compared to controls in children with ADHD plus comorbid ODD or CD, but not in those with ADHD alone. Another VBM study[22] has reported that CD symptoms correlated with smaller gray matter volumes in limbic brain structures while hyperactive/impulsive symptoms were associated with smaller volumes in the frontoparietal and temporal cortices. A VBM study by Sterzer et al.[21] examined 12 male adolescents with CD, 7 of whom fulfilled the diagnostic criteria for ADHD. They reported smallergray matter volumes in the bilateral anterior insula and the left

amygdala in the clinical sample compared to healthy controls. Contrary to these findings, a recent study by De Brito et al.[51] has reported greater gray matter volumes of various regions including frontal, parietal, and temporal lobes in boys with conduct problems. They had selected only boys with callous-unemotional conduct problems and used hyperactivity inattention symptoms as a covariate. Their study shows that the gray matter is larger in a certain type of conduct disorders. These previous studies suggest that considering the confounding effects of the comorbid conduct problems may alter the results of the analyses in neuroimaging studies of ADHD, and the inconsistent results among the other previous neuroimaging studies of ADHD may be partly due to the inadequate consideration of comorbid conditions.

In our study, controlling for the effect of CD/ODD resulted in more extensive regions with significantly smaller volume in ADHD compared to controls, suggesting that the diagnosis of comorbid CD/ODD tends to be associated with increase in the gray matter volume. Given that a positive correlation has been observed in a recent study between callous-unemotional traits and hyperactivity symptoms,[52] our results resemble those reported by De Brito et al.[51] Although, in our study the direct comparison between ADHD subjects with and without ODD or CD showed no significant gray matter volume difference, further studies with an increased number of subjects may allow statistically significant results to be obtained.

There are several limitations to the present study. First, our sample size did not allow us to examine further the potential differential effects of ADHD subtype and sex. A more detailed analysis in homogeneous groups of patients should be performed

in future studies. Second, the average age was greater, although not statistically significant, in the group of ADHD with comorbid ODD or CD compared with the group of ADHD alone, which may have contributed to the difference in focal volume changes. Third, the effect of medication was not considered, although a recent study by Shaw et al.[53] showed no evidence of association between psychostimulant medication and differences in the development of the cerebral cortex. Fourth, our study did not examine subjects with ODD or CD without comorbid ADHD. Including subjects with pure ODD or CD in the study should yield better understanding of the effects of comorbidities.

In conclusion, the morphological analyses of ADHD subjects using VBM revealed smaller volumes of the regions associated with social cognition (i.e. anterior temporal region and superior temporal sulcus) as well as in the regions responsible for executive functioning (i.e. DLPFC). When the effect of comorbid CD and ODD was taken into account, there were more extensive regions with significantly smaller volume in ADHD compared to controls. The inconsistency among previous neuroimaging studies of ADHD may reflect inadequate consideration of ADHD subtypes or comorbidities and differences in methods of image analysis and sample selection. Consideration of the clinical heterogeneity of the ADHD diagnosis and the development of better neuroimaging analysis methods in future studies should result in more precise findings.

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Figure legends

Figure 1. Regions with smaller gray matter volumes in subjects with ADHD

The gray matter regions with significantly smaller volumes in subjects with ADHD compared with controls are rendered onto the averaged image of the whole study sample (N=35) (Voxel threshold: uncorrected $P < 0.001$). L: left, R: right

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Table 1. Subject characteristics and test scores

	ADHD Patients (n=18)							
	ADHD alone (n=8)		Comorbid with ODD or CD(n=10)		Control Subjects (n=17)		F-tests	
Variable	Mean	SD	Mean	SD	Mean	SD	F	P value
Age (range)	8.9 (6-12)	2.4	11.9 (6-16)	3.4	10.0 (6-14)	2.4	2.9	0.07
Gender (Boys / Girls)	6/2		7/3		12/5		$\chi 2$=0.1	0.9
Parental SES†	3.0	0.5	3	0.8	2.5	0.6	2.8	0.08
Handedness (range)‡	93.8 (50-100)	17.7	91.2 (58-100)	16.3	100 (100-100)	0	1.9	0.17
IQ (range)	90.9 (78-104)	10.7	89.2 (73-112)	13.9	……	…	T=0.26	0.8
ADHD-RS (Family, total)	21.1	7.7	22.7	15.4	0.06	0.2	26.5 [a)]	<0.001
ODBI (Family)	16.1	8.2	36.9	16.0	1.1	2.7	30.4 [a)]	<0.001
Hyperactive subtype	2		0		……	…	…	
Inattentive subtype	2		4		……	…	…	
Combined subtype	4		6		……	…	…	

† SES: Socioeconomic status, assessed using the Hollingshead scale. Higher scores indicate lower status.

‡ Determined using Edinburgh Inventory (Oldfield, 1971): Scores greater than 0 indicate right-handedness. A score of 100 indicates strong right-handedness.

[a)] Because the homogeneity of variance was violated according to the Levine's test, Welch F-ratio is reported.

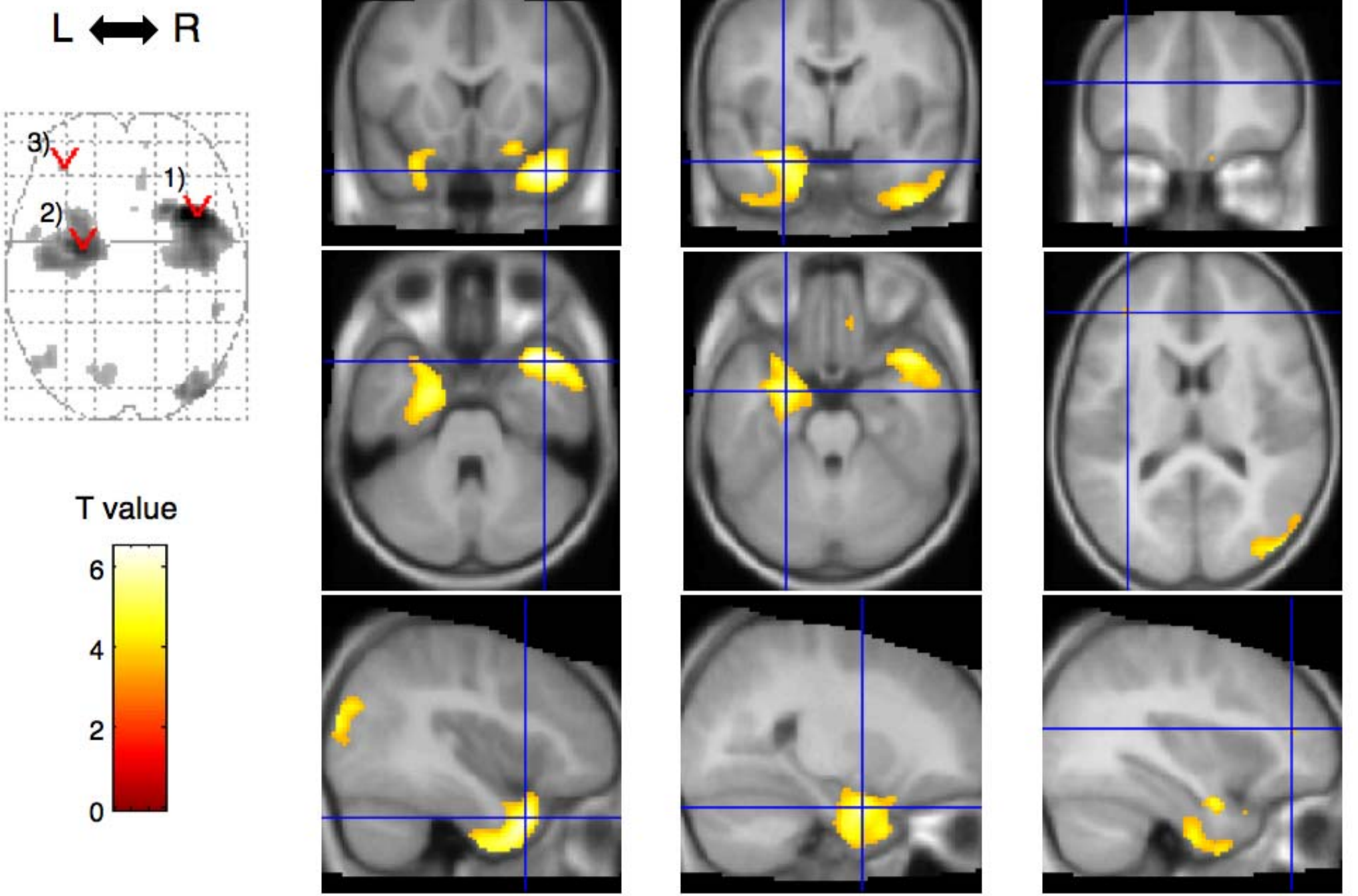
ADHD: Attention-Deficit Hyperactivity Disorder; ODD: Oppositional Defiant Disorder;
CD: Conduct Disorder; ADHD-RS: ADHD rating scale;
ODBI: Oppositional Defiant Behavior Inventory

Table 2. Regional gray matter volume reductions in subjects with ADHD

Brain regions included within significant cluster	Peak coordinate			Z score	FDR-corrected P	Cluster Size (k) (Voxel threshold:
	x	y	z			
No control for the comorbid ODD or CD						
Right temporal pole and anterior ventral temporal cortex	44	12	-34	5.21	0.001	1932
Bilateral occipital cortices	0	-74	6	3.72	0.015	671
Left Amygdala	-26	-4	-30	3.31	0.037	47
Left occipital cortex	-2	-92	-10	3.27	0.041	26
Left anterior ventral temporal cortex	-42	-10	-46	3.23	0.043	11
Left temporal pole	-30	6	-46	3.21	0.045	6
Cosidering the comorbid ODD or CD						
ight amygdala, temporal pole, anterior ventral temporal and orbitofrontal cortic	34	16	-32	5.09	0.003	2027
eft amygdala, temporal pole, anterior ventral temporal and orbitofrontal cortice	-24	-2	-26	4.69	0.003	1743
Right occipital cortex	44	-84	20	4.11	0.005	404
Right superior temporal sulcus	50	-40	-2	3.62	0.012	18
Left paietal cortex	-50	-68	44	3.44	0.018	84
Left middle frontal gyrus	-34	40	16	3.42	0.018	5
Left temporal pole	-52	4	-38	3.36	0.02	25
Left occipital cortex	-12	-78	10	3.31	0.023	51
Left occipital cortex	-18	-72	-8	3.21	0.027	6
Right rectal gyrus	10	34	-26	3.21	0.028	15
Right rectal gyrus	6	18	-16	3.13	0.031	3
Left parahippocampal gyrus	22	-28	-20	3.13	0.032	3
Left parahippocampal gyrus	24	-26	-22	3.1	0.033	1
Right rectal gyrus	12	54	-22	3.1	0.034	1

ADHD: Attention-Deficit Hyperactivity Disorder; ODD: Oppositional Defiant Disorder;
CD: Conduct Disorder; FDR: False Discovery Rate

Figure 1


1) R Temporal Pole
2) L Amygdala
3) L Middle Frontal Gyrus
L ⟷ R
3)
1)
2)
T value
6
4
2
0