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Brain & Development 29 (2007) 649–655

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Asymmetry of prefrontal cortical convolution complexity in males with attention-deficit/hyperactivity disorder using fractal information dimension

Xiaobo Li [a], Jiefeng Jiang [a], Wanlin Zhu [a], Chunshui Yu [b], Manqiu Sui [c], Yufeng Wang [c], Tianzi Jiang [a,*]

[a] *National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100080, PR China*
[b] *Department of Radiology, Xuanwu Hospital, Beijing, PR China*
[c] *Institute of Mental Health, Peking University, Beijing, PR China*

Received 22 January 2007; received in revised form 24 April 2007; accepted 26 April 2007

Abstract

Background and purpose: Prefrontal cortex, known to be a crucial region for the function of attention, is generally thought to be largely associated with the pathogenesis of attention-deficit hyperactivity disorder (ADHD). Most previous structural imaging studies of ADHD reported abnormality of grey matter volume in prefrontal region. However, volume measure is affected by the size of the interrogated brain, which may cause the inconsistence of the volume based findings. The purpose of the current paper is to use a scale-free measure, fractal information dimension (FID), to assess the prefrontal cortical convolution complexity and asymmetry in ADHD patients. *Methods:* MRI scans from 12 boys with ADHD and 11 controls were carefully processed. Prefrontal cortex was outlined manually. FIDs of bilateral prefrontal cortical surface were examined in each case. Group differences of the bilateral prefrontal cortical convolution complexities and the asymmetry pattern were statistically tested. *Results:* We found a left-greater-than-right prefrontal cortical convolution complexity pattern in both groups. However, compared with healthy controls, the left prefrontal cortical convolution complexities of ADHD patients were significantly reduced, resulting in significant reduction of the normal left-greater-than-right cortical convolution complexity asymmetry pattern. *Conclusion:* This study confirms and extends the existing anatomical knowledge about the brains of people with ADHD. The cortical convolution analysis method may also be applied to quantitatively assess changes in other neuropsychiatric syndromes as well.

Keywords: Anatomic MRI; Asymmetry pattern; Attention-deficit hyperactivity disorder; Cortical convolution complexity; Information dimension; Prefrontal cortex

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a frequent neuropsychiatric disorder in childhood and adolescence. It was first reported 100 years ago as a childhood disorder found mainly in boys [1]. The diagnosis of ADHD is currently characterized by the clinical symptoms of inattention, concentration deficits, hyperactivity and impulsivity [2,3]. Prefrontal cortex is known to be a crucial region for the function of attention [4], and is generally thought to be the underlying brain region for the pathogenesis of ADHD [5,6]. Early neuropsychology investigators noted similarities between ADHD patients and prefrontal lobe injured patients, leading them to hypothesize that ADHD was associated largely with frontal, especially prefrontal lobe dysfunction [7,8]. The

* Corresponding author. Tel.: +86 10 8261 4469; fax: +86 10 6255 1993.
E-mail address: jiangtz@nlpr.ia.ac.cn (T. Jiang).

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doi:10.1016/j.braindev.2007.04.008

"prefrontal" model was also supported by the success of stimulant medications and animal models implication dopamine pathway that had a strong predilection for prefrontal cortex [9,10]. Using the refined neurocognitive models based on executive process and inhibition, ADHD was suggested to be largely associated with the abnormalities in right prefrontal cortex [11].

The recent developments of magnetic resonance imaging (MRI) techniques since early 1990s have made it possible to *in vivo* assess the anatomical brain abnormalities of ADHD. Among the series of structural MRI studies, structural brain abnormalities of the prefrontal lobes in children with ADHD were frequently reported. Some studies reported the reduction of the grey matter volume of prefrontal lobe, in the left, right, or both hemispheres [12–18]. All of these studies measured the grey matter volume either by calculating the absolute grey matter volume, or by VBM. Two very recent studies reported reduced cortical thickness in bilateral prefrontal cortices in ADHD patients [19,20].

The previous structural MRI studies have indicated the prefrontal cortical abnormalities in ADHD. However, volume is a gross measure which is significantly affected by the individual brain size in the study sample. Specifically, the volume is determined by cortical area and thickness. With the same cortical thickness, a bigger size brain with larger cortical area would lead to greater cortical volume. This is a possible cause of the inconsistent findings in previous volume based imaging studies. More robust imaging measures are expected to quantify the brain structural differences by avoiding the effect of brain sizes, and detect the prefrontal structure abnormalities aided by common used cortical volume and thickness measures.

The purpose of the current study is to assess the cortical convolution (or gyrification) complexity by using the fractal information dimension (FID). To our knowledge, this work is the first study to assess the cortical convolution complexity in ADHD. FID of a three-dimensional (3D) point data evaluates the level (or complexity by another word) of the geometrical convolution of the 3D surface [21]. A higher cortical convolution complexity results in a greater FID value. It is scale-free by a self-normalization. Hence FID is not affected by the size of the brain region. In view of findings from previous imaging and neuropsychological studies, we predicted that we would detect the abnormality of prefrontal cortical convolution complexity in ADHD patients.

2. Materials

2.1. Subjects

Fourteen boys with ADHD were recruited for this MRI scanning protocol. Two were excluded because of the poor image qualities due to head motions. Thus this study included 12 patients with ADHD and 11 normal healthy children, all were males and right-handed. No significant differences were found between patients and controls in subject characteristics (for patients: age 13.48 ± 1.11 yrs, range 11.0–14.8 yrs; educational level 8.0 ± 1.0 yrs, 15.5 ± 3.0 yrs for father, 13.5 ± 3.0 yrs for mother), (for controls: age 13.35 ± 0.49 yrs, range 12.5–14.1 yrs; educational level 8.0 ± 1.0 yrs, 15.0 ± 3.5 yrs for father, 15.0 ± 2.5 yrs for mother). Sibship was not present in all subjects. We limited this study to boys to eliminate the gender effect based on previous findings of gender-based differences in structural MRI reported in [22,14]. We also limited our study to right-handed subjects so as to avoid the possible hemispherical cortical differences caused by handedness. All subjects were with $80 < \mathrm{IQ} < 130$. Specifically, mean IQ for patients was 103 (SD 18) and for control 112 (SD 12). Although there is a trend, the IQ for the ADHD subjects and the control group did not differ significantly ($P = 0.077$).

The ADHD children were recruited from the Mental Health School of Peking University. All of them met DSM-IV criteria, where six children met the criteria for inattention-type and the others met combined-type. The diagnosis of ADHD was confirmed by a child neurologist (SHM) based a semi-structured diagnostic interview [23,24]. Rating scales and questionnaires were completed by a parent and a teacher of each child. Children who met all criteria were included as participants with ADHD.

The normal controls were recruited from local middle schools with similar education levels to those of the ADHD subjects. All controls were screened for inattentiveness, overactivity and/or impulsiveness by the same tests applied to the ADHD patients. For both ADHD and control subjects, other inclusion criteria included: (i) no history of neurological disease and diagnosis of schizophrenia, affective disorder, pervasive developmental disorder; (ii) Full scale Wechsler Intelligence Scale for Chinese Children-Revised (WISCC-R) [24] score 80–130.

This study was approved by the Research Ethics Review Board of Institute of Mental Health, Peking University. Written informed consent was obtained from a parent of each subject. All children agreed to participate in the study.

2.2. MRI data acquisition

All MRI scans were performed on a 3.0 T whole-body MR scanner with a receive-only whole head coil for signal amplification. A series of T1-weighted three-dimensional structural images (spoiled-gradient recall echo in a steady state, repetition time (TR) = 1770 ms, echo time (TE) = 3.92 ms, inversing time (TI) =

1100 ms, flip angle = 12°, field of view = 256 × 256 mm, matrix = 512 × 512, slice thickness = 1 mm, 192 contiguous slices) were acquired. Thus the size of each voxel was 0.5 × 0.5 × 1.0 mm. Head movement was limited by foam padding within the head coil and a restraining band across the forehead.

3. Methods

3.1. MRI data preprocessing

In the first step of image preprocessing, one of the normal controls, with visually the least deviation from a normal head position, was chosen to be the template and all scans were realigned using SPM2 software (http://www.fil.ion.ucl.ac.uk/spm/). This rigid body registration was used for defining the prefrontal lobes on each scan. Extracerebral tissue was eliminated by using automated skull striping software (http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html). Tissue segmentation was automatically processed using previously reported procedures [25].

3.2. Prefrontal region localization

An image-based definition of prefrontal cortex [26,27] was applied to outline the prefrontal cortex. The prefrontal cortex was defined as the frontal region between the first coronal slice that contained brain tissue and the third coronal slice anterior to the one containing the most anterior temporal stem. The temporal stem was traced in a series of sequential coronal images extending from the level of the amygdala anteriorly to the level of the lateral geniculate body posteriorly [28]. As shown in Fig. 1, the temporal stem was labeled as the red line bar. And in Fig. 1(b), the frontal region in front of the green line was defined as prefrontal. The slices containing the prefrontal region were determined manually by two raters blind to diagnosis. The chosen region using the landmark of temporal stem matched the one using the landmark of corpus callosum very well. Six randomly selected cases from the whole cases were involved to establish inter-rater reliability. Inter-class correlation coefficients for inter-rater reliability were 0.98 for both left and right prefrontal GM volume.

3.3. Prefrontal cortical convolution complexity measuring

For each case, the voxels on the interface of GM–CSF in the prefrontal region was detected. Fig. 2(a) illustrated the acquired voxels from the MR image, and (b) the corresponding points of a left side prefrontal cortex in 3D space. Here we define the whole points in Fig. 2(b) as a point set, F. Due to a partial volume effect, the true cortical surface does not appear to be immediately adjacent to CSF. However, this does not significantly affect the value of the cortical shape complexity because the detected surface should be an isometric surface, which keeps the same surface convolution variations as the true cortical surface. A discrete surface smoothing method was used to remove segmentation variability from the cortical surface [29]. The feasibility of this geometric smoothing method for 3D point data has previously been validated [29].

To assess the complexity and asymmetry patterns of the cortical convolution in two groups of subjects, the information dimensions of the left and right side prefrontal cortical surfaces in each case were calculated. Information dimension is one of the most widely used fractal dimensions for discrete data sets. Let F be any non-empty bounded subset of $\mathbf{R}^n$, $N_\delta(F)$ be the smallest number of sets of diameter at most δ which can cover F, and $N_\delta(F_i)$ be the number of the boxes with i points inside. Here the box can be considered as a cube with edge = δ. The probability of one box containing i points would be $P_i(\delta) = N_\delta(F_i)/N_\delta(F)$. The information capacity is defined by $I(\delta) = -\sum_{i=1}^{N_\delta(F)} P_i(\delta) \lg P_i(\delta)$, and the FID is defined by [30]:

$$\mathrm{FID}(F) = \lim_{\delta \to 0} \frac{I(\delta)}{-\lg \delta}.$$

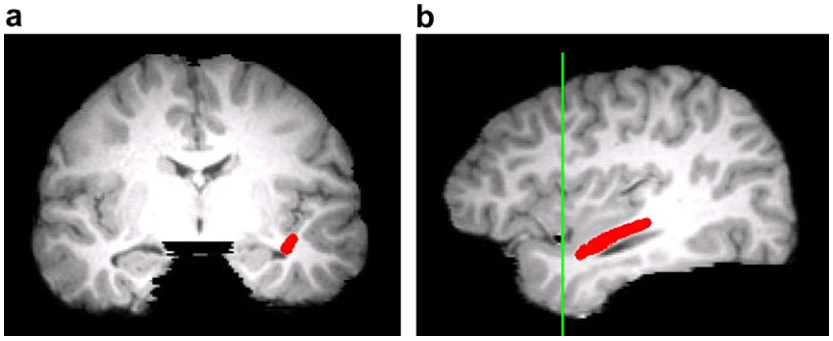

Fig. 1. Locations of the temporal stem (labeled as the red bar in (a) and (b)) and of the prefrontal region (the frontal region on the left side of the green line segment in (b)). (For interpretation of the references in colour in this figure legend, the reader is referred to the web version of this article.)

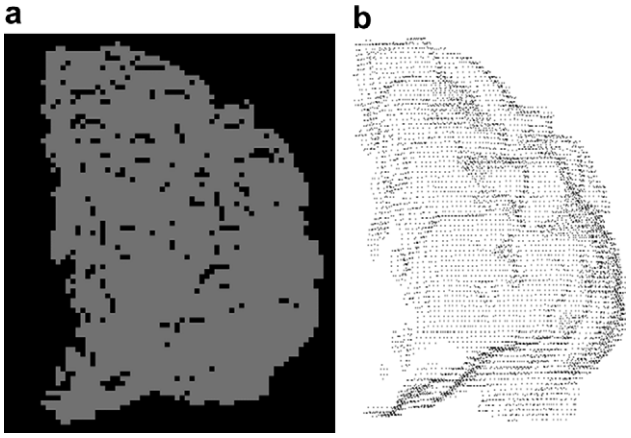

Fig. 2. The detected voxels from the boundary of GM and CSF on the left prefrontal region, (a) the voxels in 3D image and (b) the point data representing the locations of the centers of the voxels in 3D Euclidean space.

In a unified 3D domain containing a point set sampled from a 3D surface, information dimension is a positive scalar from 0 to 3. A greater value of the information dimension represents that the 3D surface has more complicated geometric convolution. Since information dimension is a newly introduced measure in brain imaging study, we would like to give some visual examples rather than only mathematical representations to demonstrate the rationale of the measure. Here we give two simulated examples in 2D and 3D. From Fig. 3(a)–(c), we see three half circles with the same diameter but increased surface convolution level represented by increased FID values. However, any two surfaces with the same shape convolution representation but different scales have the same FID value. For example two half circles with the shape of Fig. 3(a) but different diameters have the same FID value. This demonstrates the scale-free feature of FID. This valuable feature automatically avoids the brain size effect. A further example was demonstrated in Fig. 4, where surfaces were generated within the same 3D domain. A certain number of grid points were sampled from the three surfaces, from which the FIDs were calculated. The results depicted that the data sampled from a surface with more shape convolution complexity had higher value of FID. Hence, FID of a 3D data set reflects the complexity of geometric shape convolution of the sampling surface.

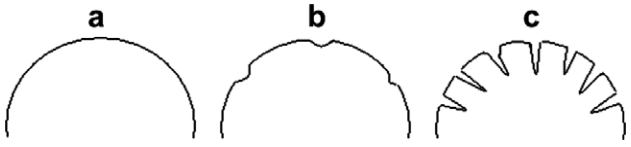

Fig. 3. 2D validation of the cortical convolution complexity measure by three half circles with the same diameter; from (a) to (c) the shapes have intuitively increased convolution complexity and clearly increased area values.

In our work, we first calculated the min–max box which coved the F, and set the size of the box as unit = 1. The input $\delta_i = 0.5$. Hence, the unit box was first segmented into $2^3 = 8$ small boxes. Set the edge of a voxel is a, then we iteratively subdivided the small box by $\delta_{i+1} = 0.5\delta_i$ until $|\mathrm{FID}(F(\delta_i)) - \mathrm{FID}(F(\delta_{i+1}))| \leqslant 10^{-5}$ with $\delta_{i+1} > 2/a$. If the termination criterion of $|\mathrm{FID}(F(\delta_i)) - \mathrm{FID}(F(\delta_{i+1}))| \leqslant 10^{-5}$ can not be reach when $\delta_{i+1} > 2/a$, the iteration stops just before $\delta_{i+1} > 2/a$. The shape convolution complexity measure of this region, $\mathrm{FID}(F(\delta_{i+1}))$, was given as a positive scalar between 0 and 3, where the greater of $\mathrm{FID}(F(\delta_{i+1}))$, the more complex of the cortical surface convolution. For the cortex of human brain, this measure reflects the complexities of the shapes of cerebral sulci and gyri and the relative size of cortical surface area in a normalized region.

3.4. Statistics

The group differences in lateralization were compared by means of analysis of variance (controls vs. patients) with repeated measures (left vs. right hemisphere) on the FID values, investigating main effects for hemi-

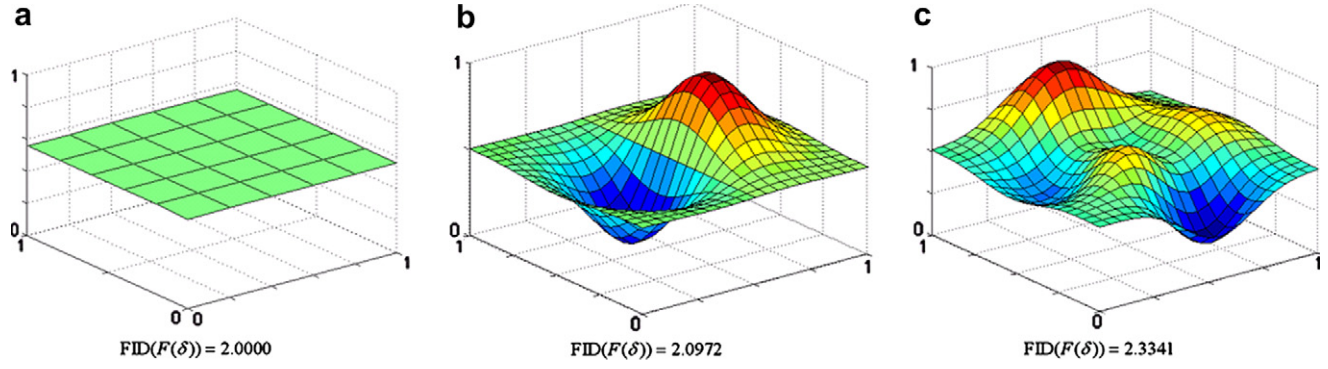

Fig. 4. Validation of the cortical convolution complexity measure by simulated 3D data: (a) sampling point data from a flattening surface domain without shape variation, $\mathrm{FID}(F(\delta)) = 2.0000$; (b) sampling point data from a surface domain with shape variation, $\mathrm{FID}(F(\delta)) = 2.0972$; (c) sampling point data from a surface domain with more shape variation than in (b), $\mathrm{FID}(F(\delta)) = 2.3341$.

sphere, for cortical convolution complexity and a hemisphere-by-complexity interaction. Post hoc between-group comparisons of left and right prefrontal cortical convolution complexities were performed using unpaired Student's t tests. In each subject group, left and right prefrontal cortical convolution complexities were also performed using unpaired Student's t tests.

Asymmetry coefficients (AC) for the convolution complexity measurements were obtained by defining $AC = (R - L)/0.5(R + L)$, where R and L were the complexity measurements in the right and left prefrontal regions, respectively. The more positive the AC, the more right lateralized the cortical convolution complexity.

For the whole subjects, correlation between the asymmetry coefficient (AC) and IQ was assessed. In the patient group, correlation between AC and the two sub-types by diagnosis was also assessed.

4. Results

Group-by hemispherical interaction by the repeated measure showed a trend for significance [$F = 3.31$, $df = 1$, $p = 0.083$]. The post hoc in-group analysis, as in Fig. 5(a), showed that both control and patient groups had left-greater-right complexity pattern in prefrontal cortical convolution. Meanwhile, the between-group analysis, as in Fig. 5(b), depicted that the left side prefrontal cortical convolution complexity was significantly decreased in patients. Fig. 5(c) showed that the normal left-greater-than-right prefrontal cortical convolution asymmetry (AC) in right-handed subjects was significantly reduced in ADHD boys. Table 1 gave all details of the FID values in both groups and the analysis results.

We did not found significant correlation between AC and general IQ scores. The AC was either not significantly correlated with the sub-types in patients.

5. Discussion

In this study, we applied fractal information dimension (FID) to evaluate the prefrontal cortical convolution complexities of males with ADHD. This method can also be applied to the whole brain. In a unified 3D domain containing a point set sampled from a 3D surface, a greater value of FID represents that the 3D surface has higher geometric convolution level and larger surface area, whereas a smaller FID value means the surface is smoother or flatter with smaller surface area. Hence, FID can also represent the surface area in a unified domain. The FID is not affected by the real size of the interrogated domain. In another word, it is scale-free. Hence, for any human brain or a region of human

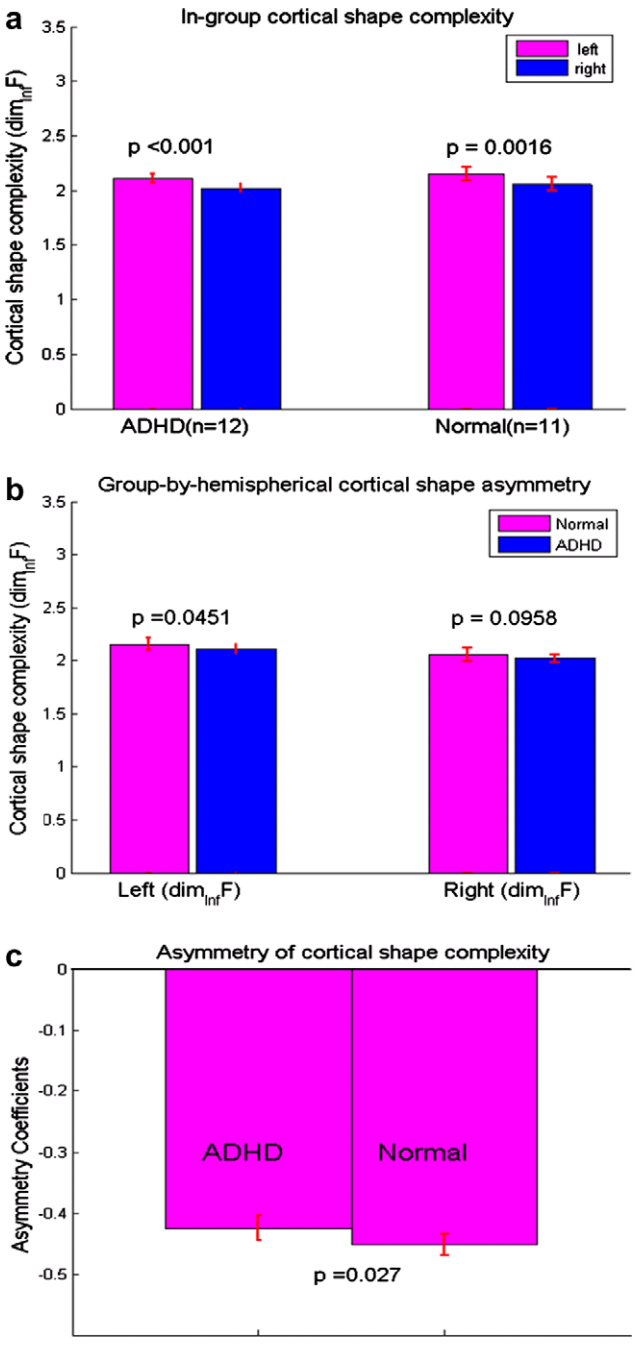

Fig. 5. (a) Illustration of the within-group hemispherical asymmetry patterns of prefrontal cortical convolution complexity; (b and c) the between-group differences of the left and right side prefrontal cortical shape complexity, where the asymmetry coefficient = $(R - L)/0.5(R + L)$.

brain, a greater FID value shows a higher cortical convolution level of the cerebral sulci and gyri. This valuable measure, aided by cortical thickness and volume, can better describe the neuroanatomical underpinnings of the disorder.

An alternative measure was proposed in Ref. [31] that described the convolution complexity of the cortical surface by the fractal dimension of a multi-resolution

Table 1
Comparison of right and left hemispherical prefrontal cortical convolution asymmetry patterns in 12 boys with ADHD and 11 comparison healthy boys

	ADHD ($n = 12$)	Normal ($n = 11$)	P	Findings
L_FID(F)	2.1069 ± 0.0401	2.1514 ± 0.0591	0.0451	ADHD < Normal
R_FID(F)	2.0196 ± 0.0376	2.0564 ± 0.0626	0.0958	NSD
AC	-0.425 ± 0.02	-0.0452 ± 0.0173	0.027	ADHD < Normal

The significance threshold was $p = 0.05$. The symbols L_ and R_ represented the complexity measure in the left and right hemispheres and *NSD* meant that there were no significant differences between two comparison groups. FID(F) is the cortical convolution complexity measure. $AC = (R - L)/0.5(R + L)$, is the asymmetry coefficient used to assess the probability that the mean of the distribution differed significantly from zero.

parametric mesh. It was used to measure the differences of the cortical complexities in normal aging and Alzheimer's disease [32], age-related cortical convolution differences in normal children [33], gender-related cortical asymmetry and complexity patterns in normal young men and women [34], and the abnormal cortical complexity in Williams Syndrome [35]. Compared with this existing cortical convolution complexity measure, the current procedure does not need to fit a parametrical surface to the delineated sulci, but smoothes the data using a discrete spring model which takes the intrinsic geometry of the discrete surface, curvatures, into consideration [29]. This model removes noise from a given discrete shape with causing shrinkage and geometrical singularities. The proposed measure is reliable and can be more easily implemented in practice.

We found significantly reduced cortical convolution complexity in the left side prefrontal region in ADHD boys. Our finding is consistent with many of recent neuroimaging reports. Several studies reported volume reduction in the left side dorsolateral prefrontal cortex (DLPFC) in ADHD children [14,15] and in ADHD adults [36]. Hesslinger et al. found diminished left orbito-frontal brain volume in adult ADHD patients [6]. A longitudinal MRI study reported reduced cortical thickness in left prefrontal cortex in ADHD children [20]. Our finding, gathering with these previous findings, may imply that compared with the control subjects, the left side prefrontal cortical GM of ADHD males are not well developed.

Moreover, the affected prefrontal region reported in our study and previous studies is largely associated with attention, working memory, planning and organization of a task, inhibitory control, social behavior and impulse control. Although the underlying pathophysiological mechanism causing ADHD is still not well understood [37], left side prefrontal cortex has been suggested to play an important role in anatomical network in ADHD pathophysiology [38]. The neuroanatomical abnormalities in this region may contribute to the cause of ADHD. Previous functional imaging studies in patients with ADHD appear to support our observation of the abnormalities in left prefrontal cortical shape complexities. Decreased metabolic activations in left prefrontal regions in ADHD adolescents were reported by performing an continuous auditory task [39]; and decreased cerebral blood flow in the left prefrontal cortices in ADHD boys were shown in Ref. [40]. Both studies indicated the lack of normal development in the left prefrontal lobes of ADHD children.

There are some limitations in our study. First, the study was limited by its small sample size, caused by the stringent recruiting criteria of right-handed males with narrow age and IQ ranges. The findings require replication in a larger sample of subjects. In addition, this study only focused on the prefrontal cerebral convolution complexity. Future work can consider with the assessment of other regions, such as temporal lobes which may also have any structural abnormalities associated with ADHD.

Acknowledgements

The authors gratefully acknowledge Prof. Robert W. McCarley in Harvard Medical School for checking the correctness of the prefrontal cortex region detection result. Sincere gratitude also goes to Dr. Yong He and Dr. Chaozhe Zhu for proof reading the manuscript. The first author sincerely acknowledges the support of K.C. Wong Education Foundation, Hong Kong, Grant No. 20041020090243. This work was partially supported by the Natural Science Foundation of China, Grant Nos. 30425004, 30570509 and 60121302, and the National Key Basic Research and Development Program (973) Grant No. 2003CB716100.

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