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Research article

Neuroanatomical deficits correlate with executive dysfunction in boys with attention deficit hyperactivity disorder

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HIGHLIGHTS

- Neuroanatomical deficits in male drug-naive ADHD children without comorbidity.
- Reduced frontal gray matter volumes in ADHD.
- Structural deficits correlated with executive dysfunction in ADHD.

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ABSTRACT

Previous structural imaging studies have revealed gray matter volume abnormalities to reflect the etiology of attention deficit hyperactivity disorder (ADHD), however, which are confounded by age, medication and comorbidity and also ignore the core feature of brain structure in the executive impairments of ADHD. In the present study, we explored gray matter volume abnormalities in male children and adolescents with ADHD who were drug-naive and without comorbidities, and tried to connect structural data and behavioral executive dysfunction to provide more information regarding the brain–behavior relationships in ADHD. Seventy-two male subjects (37 patients and 35 controls) underwent three-dimensional high-resolution structural magnetic resonance imaging and executive function assessments, including the Stroop Color–Word Test and Wisconsin Card Sorting Test (WCST). Voxel-based morphometry with diffeomorphic anatomical registration through exponentiated Lie algebra was used to identify gray matter volume differences between the ADHD and controls. Correlation analyses were performed to identify neuroanatomical deficits that were associated with executive dysfunctions. Significantly reduced gray matter volumes were identified in the right orbitofrontal cortex, right primary motor/premotor cortex, left anterior cingulate cortex and left posterior midcingulate cortex of ADHD patients compared with controls ($P < 0.05$, corrected for family-wise errors). In patients group, the gray matter volumes of the right orbitofrontal cortex and left posterior midcingulate cortex were positively correlated with the completed categories on the WCST, and the gray matter volume of the left posterior midcingulate cortex was negatively correlated with the total and non-perseverative errors on the WCST ($P < 0.05$). The present findings show gray matter volume reductions in motor regions as well as the orbitofrontal and cingulate cortex; this evidence supports theories that suggest frontal abnormalities in children and adolescents with ADHD at early illness stage. The correlations between structural abnormalities and executive dysfunction suggest that neuroanatomical substrate deficits are implicated in the pathophysiology of ADHD.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed childhood-onset neuropsychiatric disorder; it is reported to have a worldwide prevalence of 5.3% in children and adolescents and is characterized by an age-inappropriate pattern of inattention, hyperactivity–impulsivity or both [1]. ADHD frequently occurs concomitantly with various externalizing and

Abbreviations: BA, brodmann area; MNI, Montreal Neurological Institute.

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internalizing disorders [2] and is associated with impairments in several domains of executive function such as inhibitory control, cognitive flexibility and strategic planning [3]. Given ADHD's burden on society, families and individual patients, a wealth of neuroimaging studies have been performed to clarify the causes and underlying mechanisms of ADHD.

Initially, neuroimaging researchers embraced a prefrontal-striatal-cerebellar model of ADHD pathophysiology. However, subsequent functional magnetic resonance imaging (fMRI) findings have developed models of ADHD that consist of several different large-scale networks, such as attentional, visual, motor and default-mode networks [4]. Structural MRI (sMRI) complements fMRI by assessing brain structures on a morphological level, finding the relevance of the abnormal brain structures to the pathophysiological processes that likely reflect the etiology of ADHD [5]. By surveying whole-brain structures utilizing a fully automated technique, voxel-based morphometry (VBM) allows for an unbiased assessment of both gray and white matter volumes separately [6]. Structural studies that utilized VBM to study children and adolescents with ADHD have revealed various abnormalities in almost all four lobes of the cerebrum as well as the cerebellum; additionally, abnormalities have been detected in several specific structures such as the basal ganglia, cingulate cortex and hippocampus [7,8]. However, several important discrepancies should be noted in the previous literature. For example, Wang et al. observed greater right occipital lobe volumes in ADHD patients [9] whereas volumetric reductions in this region were reported by Sasayama et al. [10]. These inconsistent results may be the result of diversity in the samples, comorbidities and medications of the ADHD patients. In particular, previous research has suggested that ADHD with comorbidities displays core symptoms, clinical outcomes and treatment responses that are distinct from ADHD patients without comorbidities [11]. Therefore, it was unclear if ADHD or another comorbid disorders accounted for the observed structural differences. Likewise, the effect of medications on brain structures has also been demonstrated in the literature, suggesting stimulant medication may normalize such as anterior cingulate cortex volume [12]. Therefore, the existence of comorbidities and medications may confuse our understanding the primary pathophysiology of ADHD.

As previously mentioned, patients with ADHD often exhibit deficits in executive function and these deficits have been reported in the neuropsychological literature [13]. Although, there is evidence supporting the notion that executive function plays a role in the expression of specific behaviors and psychiatric symptoms, it is unclear whether deficits in executive function in ADHD are directly related to structural neural alterations. A meta-analysis of fMRI literature on ADHD identified dysfunction in multiple neuronal systems that are involved in higher-level cognitive and sensorimotor functions [14]. However, it is poorly understood whether the brain regions with altered functional activity related to executive function represent structural abnormalities. Given that brain structure may be the neural substrate of executive function, it is necessary to explore the association between structural abnormalities in the brain and executive dysfunction in children and adolescents with ADHD [15].

The diffeomorphic anatomical registration through exponentiated Lie algebra (DARTEL) is a relatively new VBM method with high regional sensitivity and provides an unbiased analysis to explore voxel-wise brain abnormalities automatically [16]. In the present study, we aimed to identify structural abnormalities in children and adolescents with ADHD who were drug-naive and without comorbidities, comparing them with healthy controls using the VBM approach based on DARTEL, which may help determine what is the nature of brain abnormalities in the pure form of untreated child ADHD, and whether the time of ADHD symptom onset is the critical period for the structure volume change. In addition, we also aimed to determine if these structural alterations correlate with executive function deficits in ADHD, in order to provide important information relevant to models of pathogenesis.

2. Materials and methods

2.1. Participants

This study was approved by the local ethics committee. All subjects were well informed about the goal and procedures of this experiment and were fully willing to participate in, and written informed consent was obtained from the guardians of all subjects. Three experienced child psychiatrists (L.G., Y.L., and N.H.) ascertained a diagnosis of ADHD using the Chinese modified version of Structured Clinical Interview for DSM-IV-TR Axis I disorders, Research Version (SCID-I, Patient Edition) [17]. Children with oppositional defiant disorder, Tourette's disorder, conduct disorder or any other comorbid Axis I psychiatric disorder were excluded from the study. Details of other exclusion criteria are provided in the Supplementary data. The final study included 37 right-handed, drug-naive, male patients with ADHD (mean age, 9.9 years $\pm$ 2.4 [standard deviation]; age range, 7–16 years; 26 with the combined subtype and 11 with the inattentive subtype of ADHD).

The healthy controls were recruited using advertisements in local schools. They were screened using the Chinese modified version of SCID-I (Non-patient Edition) to exclude any Axis I psychiatric diagnosis, and all of their first-degree relatives were free of psychiatric illness. Exclusion criteria for healthy controls were identical to the criteria used for ADHD patients. As a result, the healthy controls consisted of 35 right-handed males (mean age, 10.7 years $\pm$ 2.6; age range, 8–15 years). The mean IQ did not significantly differ between ADHD patients and controls ($P > 0.05$).

2.2. Behavioral measures and executive function tests

Primary behavioral measures for all subjects consisted of the attention problem scores from the Child Behavioral Checklist (CBCL), Parent version [18] and the hyperactivity–impulsivity scores and hyperactivity index from the revised Conners' Parent Rating Scale (CPRS) [19]. Executive function was measured using the modified Wisconsin Card Sorting Test (WCST) [20] and the Stroop Color–Word (Stroop-CW) Test [21] (details are provided in the Supplementary data).

2.3. sMRI data acquisition and preprocessing

A daily quality assurance protocol was utilized to establish the stability of the MRI system using a water phantom. We acquired high-resolution T1-weighted images using a 3T MRI system (Trio; Siemens) with a 3-dimensional spoiled gradient-recalled imaging sequence, and the VBM analyses were performed using SPM8 (details are provided in the Supplementary data).

2.4. Statistical analysis

Our analysis of gray matter volume differences between ADHD patients and healthy controls was performed voxel-by-voxel using a two-sample *t*-test in SPM8, with age and total brain volume as the covariates. The statistical cluster-level threshold was set at $P < 0.05$, with family-wise error correction. Then, Pearson's correlation analyses were performed in SPSS 16.0 to assess the relationship between anatomical abnormalities and executive function controlling for age and total brain volume as confounding variables ($P < 0.05$, uncorrected) (details are provided in the Supplementary data).