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Brain abnormalities in adults with Attention Deficit Hyperactivity Disorder revealed by voxel-based morphometry

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ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) commonly affects children, although the symptoms persist into adulthood in approximately 50% of cases. Structural imaging studies in children have documented both cortical and subcortical changes in the brain. However, there have been only a few studies in adults and the results are inconclusive.

Method: Voxel-based morphometry (VBM) was applied to 44 adults with ADHD, Combined subtype, aged 18–54 years and 44 healthy controls matched for age, sex and IQ.

Results: ADHD patients showed reduced gray matter (GM) volume in the right supplementary motor area (SMA). Using more lenient thresholds we also observed reductions in the subgenual anterior cingulate (ACC) and right dorsolateral prefrontal (DLPFC) cortices and increases in the basal ganglia, specifically in the left caudate nucleus and putamen. There was a positive correlation between the cumulative stimulant dose and volume in the right SMA and DLPFC clusters.

Conclusions: The findings suggest that adults with ADHD show brain structural changes in regions belonging to the so-called cool executive function network. Long-term stimulant medication may act to normalize these GM alterations.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most prevalent neuropsychiatric disorders, affecting about 5% of children (Polanczyk et al., 2007). Although it was originally believed to be a disorder of childhood, there is evidence that the symptoms persist into adulthood in approximately 50% of cases (Pironti et al., 2014). In adults, symptoms of hyperactivity, impulsivity and deficit of attention tend to be expressed in the form of inner restlessness, inability to relax, impatience, difficulty to make decisions, affective instability and stress intolerance (Kooij et al., 2010). These symptoms can significantly disrupt patients' daily life activities, especially in the absence of adequate coping skills (Amico et al., 2011).

Numerous structural neuroimaging studies have examined ADHD in children. A meta-analysis of studies using region of interest (ROI) analyses found reductions in overall brain volume, and in several frontal regions, the posterior inferior cerebellar vermis, the splenium of the corpus callosum and the right caudate nucleus (Valera et al., 2007) ROI analysis however, has the disadvantage that examined areas are selected a priori meaning that changes in non-selected areas or in areas that do not conform to known anatomical divisions may be missed (Rubia et al., 2014). Whole brain techniques like voxel-based morphometry (VBM) avoid this problem, comparing all cortical and subcortical gray matter (GM) between patients and controls at once and automatically generating clusters where changes are maximal (Hoekzema et al., 2012). Studies applying VBM to children with ADHD have broadly confirmed the findings of ROI studies but have documented a

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more detailed pattern of volume reductions in the frontal lobe, including the dorsolateral and orbitofrontal cortices, as well as finding volume reductions in subregions of the temporal, parietal and occipital lobes and the anterior and posterior cingulate cortex (Cubillo et al., 2012; De La Fuente et al., 2013; Hoekzema et al., 2012). Different meta-analysis of these studies found reductions in GM, especially in the basal ganglia, as well as slightly greater GM volumes in the left posterior cingulate cortex (Ellison-Wright et al., 2008; Frodl and Skokauskas, 2012; Nakao et al., 2011). However, the meta-analysis of Nakao et al. (2011) also found evidence for normalization of the basal ganglia changes with age and in association with the use of stimulant medication.

Whereas structural imaging studies of children with ADHD are plentiful, there have been only a few studies in adults with the disorder. These studies have mostly focused on evaluating if patients share GM abnormalities in fronto-striato-cerebellar circuits that sustain attention, inhibition, cognitive control, motivation, and emotion but the results are inconclusive. Studies using a whole-brain analysis did not detect significant differences between patients and controls (Amico et al., 2011; Onnink et al., 2014; Pironti et al., 2014; Seidman et al., 2011, 2006), except for the studies of Ahrendts et al. (2011) and Almeida Montes et al. (2010). The former found that ADHD patients showed a significant reduction in GM volume bilaterally in the occipital lobes (Ahrendts et al., 2011), and the latter showed reductions in the right caudate nucleus (Almeida Montes et al., 2010). However, some of these studies in adult population carried out an exploratory ROI analysis and found that compared to healthy subjects, ADHD patients showed deficits in overall cortical GM (Seidman et al., 2006), various regions within the frontal lobe, including the orbitofrontal and dorsolateral cortices and the inferior frontal gyrus, the anterior cingulate cortex, the parietal and occipital lobes, the cerebellum and the caudate and putamen nuclei (Almeida Montes et al., 2010; Amico et al., 2011; Hesslinger et al., 2002; Onnink et al., 2014; Pironti et al., 2014; Seidman et al., 2011; Seidman et al., 2006). Also, one study reported an increase of GM volume in regions within the occipital and parietal lobes, the dorsolateral prefrontal cortex and the dorsal mid cingulate cortex in ADHD patients relative to controls (Pironti et al., 2014).

The discrepancies between childhood and adult brain structural findings in ADHD could be genuine, perhaps reflecting the above mentioned meta-analytic finding that increasing age and treatment with stimulants may tend to normalize brain structure (Nakao et al., 2011). Alternatively, they could simply be a function of the relative lack of studies in ADHD adult population, their generally smaller sample sizes, or possibly other factors related to the inclusion of comorbid conditions or no discrimination between ADHD subtypes (Cortese and Castellanos, 2012; Spencer et al., 2013).

In the present study, we evaluated changes in a larger sample of adults with ADHD and controls using a VBM analysis. We also investigated the association between changes found and clinical factors and exposure to stimulant medication.

2. Methods

2.1. Participants

Forty-six right-handed adult ADHD combined subtype (ADHD-C) were recruited from the Hospital Universitari Vall d'Hebron and the Benito Menni CASM. Two ADHD patients were excluded from the analyses due to movement in the MRI images, therefore, our final sample consisted of forty-four patients (demographic data for the sample is shown in Table 1).

Clinical diagnosis was made by a team of ADHD expert psychiatrists and psychologists, based on the Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Test Revised (DSM-IV-TR) (APA, 2004) and confirmed with the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Epstein and Johnson, 1999; Ramos-Quiroga et al., 2012), the Wender Utah Rating Scale (WURS) (Ward et al., 1993), the ADHD Rating Scale (DuPaul, 1998) and the Conners Adult ADHD Rating Scale (CAARS) (Conners, 1999). Exclusion criteria were (a) age younger than 18 or older than 65 years, (b) left-handedness, (c) history of brain trauma or neurological disease, and (d) substance use disorder (abuse/dependence) of drugs including cocaine, heroin, synthetic drugs or alcohol. All subjects were evaluated to exclude comorbidity with other major psychiatric or personality disorders using the Structured Clinical Interview for Axis I (SCID-I) (First et al., 2002) and Axis II (SCID-II) (First et al., 1997) respectively to prevent that the findings of our study reflected brain abnormalities not related to ADHD per se but to its comorbid disorders.

Twenty-nine patients were medicated only with methylphenidate (mean ± SD; relative daily doses (mg/day) 42.24 ± 16.17; treatment duration (months) 25.20 ± 24.41) and 15 had never received any pharmacological treatment. The stimulant-treated ADHD patients were discontinued at least 4 days prior to the MRI.

The control sample consisted of forty-four right-handed healthy individuals recruited from non-medical staff working in the hospital Benito Menni CASM, their relatives and acquaintances, plus independent sources in the community. They met the same exclusion criteria as the ADHD group. Although they were not assessed using specific clinical scales of ADHD, they were interviewed by a group of clinical psychologists and were excluded if they had any psychiatric disorder or were taking any type of psychotropic medication other than non-regular use of benzodiazepines or other similar drugs for insomnia. They were also questioned about family history of mental illness and excluded if a first-degree relative had experienced symptoms consistent with major psychiatric disorder and/or if they had received in- or outpatient psychiatric care.

Both the ADHD and control group were matched for age, gender and IQ, as estimated by the Word Accentuation Test (Test de Acentuación de Palabras, TAP) (Del Ser et al., 1997), a test requiring pronunciation of Spanish words whose accents have been removed. The TAP has been standardized against the Wechsler Adult

Table 1
Demographic and clinical characteristics of the sample.

	ADHD N=44 Mean (SD)	Control N=44 Mean (SD)	*p* value	χ^2 value
Age (years)	31.61 (11.38)	32.57 (10.63)	0.68	
Sex (male/female)	29/15	29/15		1.00
Education (years)	17.96 (3.76)	18.38 (4.53)	0.70	
TAP, mean	22.42 (4.49)	23.10 (3.88)	0.47	
TAP_FISQ	101.24 (8.06)	102.38 (7.45)	0.53	
Current IQ (WAIS-III)	105.00 (7.53)	105.97 (11.38)	0.66	
WURS	51.95 (11.09)			
ADHD Rating Scale	32.15 (9.12)			
CAARS				
Inattention	22.29 (7.68)			
Hyperactivity	20.80 (8.45)			
Impulsivity	18.56 (7.84)			
Problems with self-concept	9.51 (4.34)			
DSM-IV inattentive symptoms	17.49 (4.88)			
DSM-IV hyperactivity-impulsivity symptoms	15.80 (6.64)			
DSM-IV total ADHD symptoms	33.29 (9.85)			
ADHD Index	21.61 (6.08)			