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Global and local grey matter reductions in boys with ADHD combined type and ADHD inattentive type

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) has reliably been associated with global grey matter reductions but local alterations are largely inconsistent with perhaps the exception of the caudate nucleus. The aim of this study was to examine local and global brain volume differences between typically developing children (TD) and children with a diagnosis of ADHD. We also addressed whether these parameters would differ between children with the ADHD-combined type (ADHD-C) and those with the ADHD-inattentive type (ADHD-I). Using an ROI approach caudate volume differences were also examined. 79 boys between the ages of 8 and 17 participated in the study. Of those 33 met diagnostic criteria for the ADHD-C and 15 for the ADHD-I subtype. 31 boys were included in the TD group. Structural magnetic resonance imaging data were analysed using voxel-based morphometry. The ADHD group had significantly lower global and local grey matter volumes within clusters in the bilateral frontal, right parietal and right temporal regions compared to TD. A significant group by age interaction was found for right caudate nucleus volume. No differences between the ADHD-C and ADHD-I groups were found. Right caudate nucleus volume and age are more strongly related in ADHD than in TD consistent with previous research.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common childhood developmental disorder defined by age-inappropriate levels of inattention, impulsivity and hyperactivity (American Psychiatric Association (APA), 2013). It is commonly associated with impairments in social, cognitive, educational and emotional domains (e.g., Ek et al., 2011; Martel et al., 2007; Nijmeijer et al., 2008; Shaw et al., 2014; Willcutt et al., 2012).

Neuroimaging studies of children and adolescents with ADHD have reported anomalous brain structure including global and local reductions in brain volume (Frodl and Skokauskas, 2012; Nakao et al., 2011). Meta-analyses of regional volumetric differences have implicated smaller basal ganglia structures including the right globus pallidus, putamen and bilateral caudate in children and the anterior cingulate cortex (ACC) in adults with ADHD (Frodl and Skokauskas, 2012; Nakao et al., 2011). However, the studies included in the meta-analyses were based on small, often underpowered samples. A recent investigation with a relatively large sample (n=131) of adults with ADHD only found subtle differences in global volumetric measures but no differences in local grey matter volumes (Maier et al., in press). Investigations in paediatric ADHD with larger samples (n >20) have reported grey matter reductions in the bilateral caudate and cerebellum (Yang et al., 2008), predominantly right-sided frontal–pallidal–parietal regions (McAlonan et al., 2007), bilateral frontal and cerebellar regions (Carmona et al., 2005), left dorsolateral/precentral prefrontal cortex (PFC) (Stevens and Haney-Caron, 2012) as well as no differences compared to typically developing control participants (Villemonteix et al., 2015). Inconsistencies across studies may be explained by differences in sample characteristics (medication status, age, gender ratios, comorbid conditions) or the structural neuroimaging methodology used. ADHD is heterogeneous in nature with inattentive symptoms accounting for varying levels of disorgor dysexecutive function and hyp/or dysexecutive function and hyperactive/impulsive symptoms relating to varying levels of abnormal reward discounting, social disinhibition and/or emotional dysregulation (Frick and Nigg, 2012). Therefore, most ADHD samples are likely to consist of differing individual neuropsychological and/or neurobiological profiles.

Despite the heterogeneity, several previous studies and subsequent meta-analyses have reported volume reductions of the

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caudate nucleus in children with ADHD (Frodl and Skokauskas, 2012; Nakao et al., 2011), which seem to normalise with increasing age (Carrey et al., 2012; Nakao et al., 2011). Caudate asymmetry may also be different in individuals with ADHD (Castellanos et al., 1994) with abnormalities more often observed on the right (Almeida Montes et al., 2010; Filipek et al., 1997; Tremols et al., 2008; Valera et al., 2007). Relative greater right than left caudate nucleus volume has been associated with higher attentional impulsiveness and higher ADHD symptom ratings in healthy young adults (Dang et al., 2016) as well as parent-rated symptoms of inattention in children without an ADHD diagnosis (Schrimsher et al., 2002).

The caudate nucleus plays a major role in relaying information from the prefrontal cortex to the basal ganglia and thalamus and back to the PFC (Arnsten and Rubia, 2012). Evidence from lesion studies in humans and animals and functional neuroimaging studies suggests that the caudate nucleus is crucial for attentional control (Crofts et al., 2001) and goal-directed action (Grahn et al., 2008). Tasks that probe attentional and executive function processes such as response inhibition and working memory during functional magnetic resonance imaging elicit less activation of the caudate nucleus in individuals with ADHD compared to control participants (e.g., Cubillo et al., 2011; Silk et al., 2005; Vance et al., 2007).

ADHD according to DSM-IV (APA, 1994) has been divided into three subtypes: a combined type (ADHD-C), which shares symptoms of hyperactivity and inattention, an inattentive type (ADHD-I), which exhibits primarily symptoms of inattention with no or few hyperactive/impulsive symptoms and a less common hyperactive type (ADHD-H), which shows hyperactive/impulsive symptoms but no or few difficulties in the domain of attention. These subtypes show limited stability over time, in contrast to the general diagnosis (Willcutt et al., 2012) suggesting subtypes may add little extra information to diagnosis and treatment. In recognition of the lack of evidence for concrete subcategories of ADHD, DSM5 denominates varying levels of hyperactive/impulsive and inattentive symptoms no longer subtypes but presentations (APA, 2013). The ICD10 equivalent of ADHD, hyperkinetic disorder does not distinguish between subtypes and/or presentations.

There is considerable debate as to whether ADHD subtypes have common or distinct underlying neurobiology. Neuroimaging studies have often failed to detect differences between the ADHD-C and ADHD-I subtypes but many of these studies were underpowered (Willcutt et al., 2012). A recent study in adults with ADHD (Maier et al., in press) comprising a relatively large sample of 66 individuals with a diagnosis of ADHD-C and 60 individuals with a diagnosis of ADHD-I only reported a trend for reduced grey matter in the left dorsolateral PFC (dlPFC) in the inattentive compared to the combined type. Few studies to date have examined volume differences between ADHD subtypes in children and adolescents with ADHD. Carmona et al. (2005) found no differences in grey matter volume between the two subtypes albeit in a very small sample and Pineda et al. (2002) also failed to detect significant volumetric differences of the caudate nucleus between children with ADHD-C and ADHD-I.

In this study we aimed to compare local and global grey matter volumetric differences between children with ADHD and typically developing children (TD). We expected to find reductions in both global and regional grey matter volumes in the ADHD group compared to TD. Due to inconsistent results of previous studies we did not make predictions as to the specific regions showing volume loss in ADHD. However, given meta-analytic findings of reduced caudate volume in ADHD we decided to test caudate volume differences hypothesising that the ADHD group would exhibit reductions in the volume of right caudate nucleus compared to TD. As it has previously been suggested that caudate volume shows a differential developmental trajectory in children with ADHD we were interested in the relationship between caudate volume and age and whether these would differ for each group. Given uncertainties with regard to structural differences between ADHD subtypes we further aimed to address the question of whether there are global and local volumetric differences in grey matter in boys with ADHD-C and ADHD-I compared to each other.

2. Methods

2.1. Participants

A total of 79 male participants took part in the study (age range 8.0–17.5 years). 48 boys meeting DSM-IV criteria for ADHD were recruited through an outpatient child psychiatry unit. Of these 33 met diagnostic criteria for ADHD-C and 15 met diagnostic criteria for ADHD-I. The Anxiety Disorders Child and Parent Interview Schedule (ADIS) (Silverman and Nelles, 1988) was used to ascertain diagnosis including comorbid conditions of oppositional defiant disorder and/or conduct disorder. In addition the Conners Parents Rating Scale (long version) (Conners et al., 1998) and the Child Behavior Checklist (CBCL) (Achenbach, 1978) were administered to obtain dimensional measures of inattentive and hyperactive/impulsive symptoms. The ADHD group were greater than 1.5 standard deviations from the mean score for young people of their age and gender on these symptom measures – ADHD-C (inattentive and hyperactive/impulsive symptoms) and ADHD-I (inattentive symptoms). The majority of children (75%) were medication-naïve at the time of testing. Those that were on stimulant medication (30% of the ADHD-C and 13% of the ADHD-I group) were required to withhold medication for 48 h prior to scanning. Mean treatment duration for children exposed to stimulant medication was 9.4 months (SD 4.1). Table 1 summarises comorbid conditions and medication information for the clinical group. All participants had a full-scale IQ of above 70 as measured by the Wechsler Intelligence Scale for Children (4th Edition). A proportion of ADHD participants also met diagnostic criteria for oppositional defiant disorder (37.5%), persistent depressive disorder (16.7%) and anxiety disorders (29.2%). 31 healthy typically developing boys were recruited through local schools and matched to the patients on age. The control participants and their caregiver also completed the semi-structural clinical interview (ADIS) for both the parent and the child and no diagnoses were apparent. None of the children had known other medical, neurological or psychiatric disorders and all were right-handed. Informed consent was obtained from both a parent and the child, and all procedures were approved by the Human Research Ethics Committee of the Royal Children's Hospital, Melbourne, Australia.

Table 1
Comorbidities and medication information for total ADHD group and each subtype.

	ADHD-C (n=33)	ADHD-I (n=15)	Total ADHD (n=48)
Anxiety disorders	8	6	14 (29.2%)
Generalized anxiety	6	4	
Separation anxiety	2	2	
Social phobia	3	3	
Persistent Depressive Disorder	3	5	8 (16.7%)
ODD	16	2	18 (37.5%)
CD	1	0	1 (2.1%)
Medication naïve	23	13	36 (75.0%)
Stimulant ADHD medication	10	2	12 (25.0%)
Other medication	2	1	3 (6.3%)
Fluoxetine	1	1	
Atomoxetine	1	0	