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Morphological abnormalities in prefrontal surface area and thalamic volume in attention deficit/hyperactivity disorder

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ABSTRACT

Although previous morphological studies have demonstrated abnormalities in prefrontal cortical thickness in children with attention deficit/hyperactivity disorder (ADHD), studies investigating cortical surface area are lacking. As the development of cortical surface is closely linked to the establishment of thalam-ocortical connections, any abnormalities in the structure of the thalamus are likely to relate to altered cortical surface area. Using a clinically well-defined sample of children with ADHD (n=25, 1 female) and typically developing controls (n=24, 1 female), we studied surface area across the cortex to determine whether children with ADHD had reduced thalamic volume that related to prefrontal cortical surface area. Relative to controls, children with ADHD had a significant reduction in thalamic volume and dorsolateral prefrontal cortical area in both hemispheres. Furthermore, children with ADHD with smaller thalamic volumes were found to have greater reductions in surface area, a pattern not evident in the control children. Our results are further evidence of reduced lateral prefrontal cortical area in ADHD. Moreover, for the first time, we have also shown a direct association between thalamic anatomy and frontal anatomy in ADHD, suggesting the pathophysiological process that alters surface area maturation is likely to be linked to the development of the thalamus.

1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting around 5% of children and young people (Polanczyk et al., 2007). It is characterised by pervasive and developmentally inappropriate levels of inattention, impulsivity and hyperactivity, and is a risk factor for the development of other disorders. ADHD was originally considered as a disorder of childhood, but it is increasingly recognised that the symptoms and pathophysiology of ADHD can persist into adulthood (Cubillo et al., 2012).

ADHD is associated with subtle abnormalities in brain structure and function. One of the earliest brain areas considered in the pathophysiology of the disorder was the thalamus (Denhoff et al., 1957) due to its key role in filtering information and stimulus processing (Gaudreau and Gagnon, 2005). Morphological abnormalities of the thalamus (Ivanov et al., 2010) and thalamic volume reduction (Xia et al., 2012) have been demonstrated previously in children with ADHD. Using diffusion tensor imaging, Silk et al. (2009) observed white matter abnormalities within the thalamus in ADHD. Various methods, including functional connectivity analysis, have uncovered thalamic abnormalities in ADHD (Cao et al., 2009; Qiu et al., 2011). Other studies have focused on striatal subcortical circuits thought to subserve attention and executive functioning (Seidman et al., 2005). Morphological abnormalities have also been found across a number of cortical regions in children and adolescents with ADHD (Seidman et al., 2005) supporting the view that cortico–striato–thalamo-cortical (CSTC) loops (Castellanos et al., 2006) play a key role in the pathogenesis of ADHD.

Morphological studies that use surface based morphometric (SBM) approaches suggest that cortical surface area and thickness have developmentally distinct trajectories, with divergent genetic influences (Panizzon et al., 2009). SBM approaches that separate these properties are potentially informative in neurodevelopmental disorders with a putative genetic basis (Palaniyappan and Liddle, 2012). In ADHD, abnormalities in prefrontal cortical thickness have already been shown by several groups (Shaw et al., 2007; Batty et al., 2010), although only two studies have

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investigated cortical surface area (Wolosin et al., 2009; Shaw et al., 2012). Sowell et al. (2003) compared the distance from centre (anterior commissure) across the cortical surface and reported right ventral frontal and temporal reductions in ADHD. This approach reflected a reduction in radial expansion that is more related to white matter volume and thickness than tangential expansion that is reflected by surface area measurements. With an automated technique applied at a lobar level of measurement, bilateral decreases in surface area and cortical folding have been found in children with ADHD (Wolosin et al., 2009). However, this technique precludes the ability to identify the brain region that shows the most prominent surface area reduction. Longitudinal mapping across numerous points covering the entire cortical surface (vertexwise SBM), the maturational trajectory of cortical surface area and gyrification (the degree of cortical folding measured as the ratio of the surface area of'buried' inner cortex within sulcal folds to the 'visible' outer cortex) has been applied in children with ADHD and typically developing controls (Shaw et al., 2012). Intriguingly, while there were no between-group differences in the trajectory of gyrification, children with ADHD showed a significant delay in attaining their peak surface area, particularly in the right prefrontal cortex, partially mirroring an earlier finding showing delayed maturation of cortical thickness (Shaw et al., 2007). Taken together, these findings suggest that a significant maturational lag affecting multiple aspects of cortical morphology might characterise the pathophysiology of ADHD, though the origins of such a deviation in the developmental trajectory are still unclear.

Early development of cortical surface is tightly linked to the establishment of thalamocortical connections (Rakic, 2009). Animal studies suggest that allocation of specific functional areas across the cortical surface depends on both the information contained in the neural plate (protomap) and the cues received from the incoming thalamic axons (protocortex) (Clowry et al., 2010). Experimental cortical lesions that affect surface area in young male animals result in thalamic volumetric reduction (Herman et al., 1997). Thus, bidirectional organising influences between the thalamus and cortical surface are crucial in the development and specialisation of the brain in fetal and early postnatal life. In this context, abnormalities in the structure of the thalamus in putative neurodevelopmental disorders are likely to be related to cortical surface changes, the location of which will help to identify the corticothalamic circuits that are dysfunctional from a very early developmental period.

Using a clinically well-defined sample of children with ADHD and typically developing controls in whom we have previously shown reduced cortical thickness (Batty et al., 2010), we studied the cortical surface area across the entire cortex in a vertexwise fashion. Further, we sought to identify thalamic volumetric abnormality and its relationship with the surface area of the entire cortex. Given the prominence of changes in the prefrontal cortex, we hypothesised that the thalamic volume change in ADHD would be related to the surface area of the prefrontal cortex.

2. Methods

2.1. Participants

2.1.1. ADHD group

Participants were recruited as part of the MIDAS (Motivation Inhibition and Development in ADHD) multi-modal neuroimaging study of ADHD, reported elsewhere (Groom et al., 2010) and using similar participants to the sample described in detail in Batty et al. (2010). Briefly, right-handed children and adolescents aged 9–15 years with a DSM-IV clinical diagnosis of ADHD combined subtype (corresponding to ICD-10 hyperkinetic disorder) and with an established positive response to methylphenidate (MPH) were recruited from child psychiatry and paediatric clinics in Nottinghamshire and Lincolnshire, UK. Parents/carers completed a battery of questionnaires, including the Development and Well-Being Assessment (DAWBA; Goodman et al., 2000), Social Communications Questionnaire (SCQ; Rutter et al., 2003), Strengths and Difficulties Questionnaire (SDQ; Goodman, 2001) and Conners long form (Connors, 1997). Permission was sought to access the child's medical records and to contact their school, and teacher versions of the DAWBA, Conners scale and SDQ were also completed. ADHD diagnosis was confirmed or overturned following a clinical consensus diagnosis meeting, which included a full review of the child's medical history and DAWBA interview transcripts, including computer generated predictions. Neurological abnormalities (e.g,. epilepsy, closed head injury), diagnosis of Tourette syndrome, autism spectrum disorder, bipolar disorder, major depressive disorder, learning disability (operationalised as a full scale IQ < 70), history of psychosis, or current use of psychotropic medication other than melatonin were exclusion criteria. Co-morbid conduct disorder and oppositional defiant disorder (ODD) were not exclusions.

2.1.2. Control group

Letters detailing the study were sent to approximately 600 families of children and adolescents attending primary and secondary schools in Nottinghamshire. From the sample who volunteered to take part, a group of right-handed controls was selected, pair-wise matched for age ($\pm$ 6 months), sex and socio-economic status (SES) to a member of the ADHD group. Parents completed a shortened version of the DAWBA and the same battery of questionnaires as the ADHD group. Exclusion criteria were as detailed for the ADHD group. In addition, any participants with attention scores > 4 on the SDQ (Goodman, 2001) (borderline or probable attention problem) or > 1SD above the mean on the Conners' parent or teacher long form ($n=6$) were excluded.

Ethical approval was granted by the local Research Ethics Committee and Research and Development Departments of the Nottinghamshire Healthcare and LincoInshire Partnership NHS Trusts. After a complete description of the study, written informed consent (parents) and verbal assent (children/adolescents) was obtained. Neuroimaging data were available from 54 children. A quality control inspection assessed images for gross structural abnormalities, motion and other artefacts. Data from five subjects (all controls) were not included because of motion artefacts or poor registration of their scans. In the final sample, we report data from 49 participants; 25 ADHD (age [mean $\pm$ SD], 12.66 $\pm$ 1.78 years) and 24 typically developing controls (12.93 $\pm$ 1.62 years).

2.2. MRI protocol

T1-weighted (T1W) brain images in the sagittal plane were obtained with a Philips Achieva 1.5-T MRI scanner with an eight-channel SENSE head coil using a 3D Turbo Field Echo (TFE) sequence with the following parameters: 160 contiguous slices; repetition time/echo time (TR/TE)=9.9/3.7 ms; matrix size=256 × 256; voxel size, 1 × 1 × 1 mm. Head movement was minimised by the use of foam pads placed within the head coil.

2.3. Surface extraction

Cortical surfaces were reconstructed using FreeSurfer version 5.0 (Fischl et al., 1999) in accordance with the description available on-line (http://surfer.nmr.mgh.harvard.edu/). After completion of skull-stripping and intensity correction, the grey–white matter boundary for each cortical hemisphere was determined using tissue intensity and neighbourhood constraints. With the use of a deformable surface algorithm guided by the grey-cerebrospinal fluid (CSF) intensity gradient, the resulting grey-white interface was expanded to create the pial surface, followed by a spherical morphing procedure and registration based on sulcogyral alignment. The surface boundary was tessellated to generate multiple vertices (and triangles) across the whole brain. All surfaces were visually inspected following an automated topology fixation procedure, and remaining minor defects were manually corrected as recommended by the software guidelines. Automated subcortical segmentation using probabilistic information regarding the location of subcortical structures was carried out using Freesurfer v5.0, with the investigator being blind to the diagnostic group (Fischl et al., 2002). Following this procedure, the right and left thalamic volumes were extracted. Thalamic volume estimation using Freesurfer has been shown to have an impressive consistency with stereological measurement (Keller et al., 2012), while ensuring observer blindness during measurement. We chose whole thalamic volume instead of parcellating the subdivisions of thalamus, as anatomical segmentation of thalamus using structural (T1) MRI scans alone often differs from connectivity-based identification of thalamic subdivisions obtained using white matter tractography or functional connectivity (Traynor et al., 2010).

We used methods described elsewhere (Joyner et al., 2009; Palaniyappan et al., 2011) to obtain maps of vertexwise surface area for the grey matter (pial surface) of the right and left hemisphere. Each of the several thousand vertices on the pial surface generated during the tessellation procedure was assigned the average value of the surface area of the six triangles in their immediate vicinity that define a vertex. These relative areal contraction/expansion maps were smoothed with a full-width at half-maximum Gaussian kernel of 10 mm.

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