Structural development of the basal ganglia in attention deficit hyperactivity disorder: A diffusion tensor imaging study

Timothy J. Silk\textsuperscript{a,⁎,} Alasdair Vance\textsuperscript{b}, Nicole Rinehart\textsuperscript{c}, John L. Bradshaw\textsuperscript{d}, Ross Cunnington\textsuperscript{a}

\textsuperscript{a}School of Psychology and Queensland Brain Institute, University of Queensland, Brisbane, Queensland, Australia
\textsuperscript{b}Academic Child Psychiatry Unit, Department of Paediatrics, University of Melbourne, Royal Children’s Hospital, Murdoch Childrens Research Institute, Melbourne, Victoria, Australia
\textsuperscript{c}School of Psychology, Psychiatry & Psychological Medicine, Monash University, Clayton, Victoria, Australia

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A B S T R A C T

One of the most consistently reported brain regions of structural and functional difference in attention deficit hyperactivity disorder (ADHD) is the basal ganglia, particularly the caudate nucleus. Examining the structural organization of the basal ganglia in ADHD is important because it is the center of wider fronto-striatal networks, reported to be dysfunctional in ADHD. Fifteen right-handed 8- to 18-year-old males with ADHD-combined type and 15 right-handed, age- and performance IQ-matched healthy males underwent diffusion tensor imaging. Caudate, putamen and thalamus were manually identified as regions of interest (ROIs) and tested for differences in fractional anisotropy and mean diffusivity. Measures of fractional anisotropy (FA) showed the expected increase with age within the whole-brain volume and within putamen and thalamus ROIs for both ADHD and control groups. In the caudate nucleus, however, developmental changes in FA with age were significantly different between ADHD and control groups. This study shows that the developmental trajectory of micro-structural organization within the caudate nucleus is different in children with ADHD compared with controls over ages 8–18 years. We suggest that the difference in developmental trajectories arises predominantly during mid-late adolescence and may reflect a developmental delay that begins to normalise over this critical late adolescent age.

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1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed neurodevelopmental disorders, characterized behaviourally with problems of inattention and/or hyperactivity/impulsivity that interfere with aspects of children’s academic, professional, and/or social lives, making it of high clinical importance.

Through various neuroimaging studies it is now emerging that ADHD may be a disorder of abnormal neuronal circuitry fundamentally important for attentional and cognitive control, in particular involving frontal, striatal and parietal areas (Giedd et al., 2001; Booth et al., 2005; Silk et al., 2005; Vaidya et al., 2005; Vance et al., 2007; Silk et al., 2008). At the center of this network, and one of the most consistently reported regions of structural and functional difference in ADHD, is the striatum (caudate and putamen) of the basal ganglia (Castellanos et al., 1994; Filipek et al., 1997; Rubia et al., 1999; Castellanos et al., 2002; Durston et al., 2003; Booth et al., 2005).

The striatum is the entry point of the basal ganglia and has a wide distribution of connections to fronto-parietal cortical systems involved in the cognitive control of attention, response inhibition, and working memory. Functional imaging studies using techniques such as single photon emission computed tomography, positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) have consistently found anomalous activation in the striatum in ADHD, most commonly reduced compared with controls (Lou et al., 1989; Vaidya et al., 1998; Rubia et al., 1999, 2001; Durston et al., 2003; Booth et al., 2005), but also sometimes increased compared with controls (Bush et al., 1999; Schweitzer et al., 2003). Our previous research has consistently shown under-activation in the caudate nucleus in both children and adolescents with ADHD during spatial working memory tasks (Silk et al., 2005; Vance et al., 2007; Silk et al., 2008). Similarly, in studies of structural brain imaging, irregularity of caudate volume and asymmetry is a replicated finding in ADHD, although studies differ as to whether the asymmetry biases the right or the left caudate (Castellanos et al., 1994; Filipek et al., 1997; Castellanos et al., 2002). Structural differences in the caudate nucleus are clinically important since, even within healthy control groups, volumetric differences in the caudate correlate with measures of attention and hyperactivity/impulsivity (Mataro et al., 1997).

While conventional structural MRI can provide valuable information about brain regional macrostructure and volume, the method of diffusion tensor imaging (DTI) allows further examination of microstructure and cellular structural integrity of brain regions. DT images provide a measure of the direction and extent of diffusion of water...
within the brain. These images thereby reflect the cellular or neural organization of the underlying tissue by the way it constrains water diffusion. In an environment with no obstructions, water diffusion is random and approximately equal in all directions (isotropic diffusion). By contrast, in highly regular parallel myelinated axons, water diffusion is constrained along the direction of the axonal fibres (anisotropic diffusion). Such diffusion properties are typically quantified by two measures derived from DT images: Mean diffusivity (MD), representing apparent mobility of water, which is simply the magnitude of diffusion in each measured voxel (in mm²/s); and fractional anisotropy (FA), which is an index of the ‘directionality’ of diffusion in each voxel. Therefore, because the direction and extent of water diffusion depend on the underlying structure of tissue, differences in cellular structure can be inferred from the measures of FA and MD. While DTI is known for its ability to explore white-matter integrity and connectivity, predominately using FA measures, MD measures can also be used to investigate grey-matter pathology. Although the exact relationship of MD measures and the neural environment is not clear, an increase in MD is most likely to indicate an increase in the extra-cellular volume, signifying differences in structural barriers and cytoarchitecture (Sykova, 2004). Studies examining cortical grey-matter (consisting of main cell bodies and little myelinated neurons) generally report little or no anisotropy effect (e.g. Snook et al., 2005). However, deep subcortical grey matter has been shown to have changing diffusion properties (Mukherjee et al., 2001; Snook et al., 2005; Rose et al., 2008), attributed to either a greater fraction of, or maturation of, the internal white-matter tracts that pass through these highly connected structures (Mukherjee et al., 2001).

Previous DTI studies of brain development in children have generally shown that FA increases with maturation throughout the brain, from infancy to childhood (Morriss et al., 1999; Mukherjee et al., 2001) and from childhood to adolescence (Barnea-Goraly et al., 2005; Schnithorst et al., 2005; Snook et al., 2005; Ashtari et al., 2005). This most likely represents the continuing myelination of axonal fibre pathways throughout childhood and adolescence, imposing greater directional constraint on water diffusion (hence increased FA). Additionally, some studies have reported this same increase in FA with age specifically within regions of the basal ganglia during normal development (Morriss et al., 1999; Mukherjee et al., 2001; Snook et al., 2005). DTI methods have been used to examine impairments in neuronal arrangement and integrity of basal ganglia structures in various clinically presented brain pathologies such as schizophrenia (Rose et al., 2006) and HIV encephalitis (Ragin et al., 2005); however, we are not aware of any previous studies that have examined structural integrity of the striatum/basal ganglia with DTI in children and adolescents with ADHD. The only previous DTI study of children with ADHD used a voxel-based morphometry (VBM) approach on white-matter maps that excluded the basal ganglia (Ashtari et al., 2005).

Therefore, despite the large and influential body of research regarding volumetric and functional abnormalities in the striatum associated with ADHD, the development of microstructure and cellular organization within the basal ganglia in children and adolescents with ADHD, as indexed by DTI methods, is still unknown. In this study we specifically aimed to examine micro-structural integrity within the basal ganglia and developmental trajectories in children and adolescents with ADHD compared with controls using DTI.

We manually identified the head of the caudate nucleus, the putamen/globus pallidus (whole lentiform nucleus), and the thalamus as regions of interest, and specifically tested for differences in FA and MD within these regions in ADHD and matched control groups. Given the structural and functional abnormalities in the striatum that have previously been reported in ADHD, we hypothesized that children with ADHD would have different diffusion properties in the striatum, particularly the caudate nucleus, as the center of crucial fronto-striatal networks.

2. Methods

2.1. Participants

Fifteen male children aged 8–18 years (mean 12.6±2.4 years) fulfilling DSM-IV criteria for attention deficit hyperactivity disorder — combined type, were identified in a specialised clinic for ADHD based at the Royal Children’s Hospital, Melbourne, Australia. Diagnosis was defined by the Anxiety Disorders Interview Schedule for Children (A-DISC) (Silverman and Albano, 1996), a semi-structured clinical interview with the child’s parent(s); and by the Abbreviated Conners’ Rating Scale (ACRS) (Conners, 1985), a parent and/or teacher report assessing the core symptom domains of ADHD-CT (teacher and parent, n = 13; parent only, n = 2). Subscale scores greater than 1.5 standard deviations above the mean for a given child’s age and gender were used as inclusion criteria for the ADHD group. Performance IQ (pIQ) was also within the normal range for every child (mean 104.9±11.5). The children were predominantly medication naive (n = 12) or medication free for 24 h before scanning (n = 3), and met the inclusion criteria of living in a family home (not in an institution) and attending normal primary or secondary schools.

Fifteen healthy male control participants were matched in age (mean 12.9±2.6 years) and pIQ (mean 111.6±9.2) to the ADHD group. Normal behavioural functioning was screened in the control participants using the Parent form of the Child Behaviour Checklist in order to exclude psychiatric disorders, and the ACRS to screen for characteristics of ADHD. All participants were right-handed, and all had no known other medical, neurological or psychiatric disorders. All participants and parents/guardians gave informed consent, and all procedures were approved by the Human Research Ethics Committee of the Royal Children’s Hospital, Melbourne.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>FA</th>
<th>MD</th>
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<th>FA</th>
<th>MD</th>
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<tbody>
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<td>ADHD</td>
<td></td>
<td></td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate</td>
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<td>9.18±0.26</td>
<td>Putamen</td>
<td>0.14±0.02</td>
<td>9.29±0.29</td>
</tr>
<tr>
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<td>8.76±0.21</td>
<td>Thalamus</td>
<td>0.26±0.01</td>
<td>9.15±0.20</td>
</tr>
<tr>
<td>R</td>
<td>0.16±0.02</td>
<td>9.27±0.18</td>
<td>R</td>
<td>0.26±0.01</td>
<td>9.07±0.18</td>
</tr>
</tbody>
</table>

Fig. 1. Caudate, putamen/globus pallidus, and thalamus ROIs for a single subject in native space, displayed over the FA map (left) and B0 image (right).
Fig. 2. Scatterplot correlation trends of fractional anisotropy with age, measured in bilateral caudate, putamen/globus pallidus and thalamus ROIs in the ADHD and control groups. Correlation coefficients are shown on the right-hand side of each graph. (* = significant correlation, P<0.01, one-tailed).
2.2. Data acquisition and analysis

Data were acquired on a 3-Tesla GE Sigma MR scanner (GE, Medical Systems, USA), at the Brain Research Institute, Austin Health, Melbourne. Participants lay supine with their head supported in a volume coil. Diffusion weighting echo-planar images (EPI) were acquired along 28 diffusion gradient directions for acquisition of 50 slices through the whole brain (TR = 5800 ms, TE = 16 ms, FOV = 240 mm², 96 x 96 matrix, 2.5 mm in-plane resolution, b value of 1100 s/mm², slice thickness = 2.5 mm).

Analyses of diffusion-weighted images were conducted using FSL’s (FMRIB, Oxford, UK) software: FMRIB’s Diffusion Toolbox (FDT). Initially Eddy Current Correction was run to correct for gradient-coil distortions and small head motions, using affine registration to a reference volume. Maps of fractional anisotropy (FA) and mean diffusivity (MD) were calculated from the diffusion-weighted images using DTIFit which fits a diffusion tensor model to each voxel.

2.3. Region of interest (ROI) analysis

Basal ganglia ROIs were determined separately for each subject in the head of the caudate nucleus, the putamen/globus pallidus (whole lentiform nucleus), and the thalamus in both hemispheres. ROIs were manually drawn on the axial slices of each individual’s DT images in native space. Using MRicro (Rorden, USA), ROIs were determined using both the FA map and a B0 image within the DTI set (i.e. T2-weighted image with no diffusion weighting). The B0 map was used to most accurately determine medial borders of the caudate and thalamus, as the contrast between these nuclei and CSF of the ventricles was optimal. The lateral borders and the putamen/globus pallidus were determined using the FA map, as it clearly displays the internal and external capsules bordering medial and lateral sides. During the manual drawing of the ROIs, the experimenters conservatively selected the boundaries taking care not to include voxels of extremely high FA that lie on the boundary of the subcortical nuclei and the surrounding CSF and internal capsule. To increase validity and decrease researcher bias, two researchers independently determined the ROI borders for each subject; then a conjunction of the two ROIs was used as the final ROI (see Fig. 1 for example).

Median FA and MD values were then calculated from all voxels within each ROI for each participant. In addition to the conservative ROI selection, median values within each ROI were used since they are less affected by outliers than mean values. This is particularly important within the basal ganglia nuclei since they are bordered by voxels with extremely high FA values in the internal capsule which may contribute to ROI means via partial volume effects. Statistical analyses (independent t-tests) were conducted using statistical software (SPSS v12.0.1, USA) in order to compare the median FA and MD values in each ROI between ADHD and control participants. A significance threshold of P < 0.05 was used.

2.4. Correlation analysis

Correlations between age and median FA and MD measures were examined within each of the six ROIs, as well as across the whole brain (mean of whole-brain FA and MD), in order to examine the developmental trajectory of FA and MD changes with age. Linear regression was performed using Spearman’s correlation for both FA and MD versus age within the ADHD and control groups and versus symptom severity (Conners Parent Rating Scale scores) for the ADHD group alone. Fisher’s transformation was then used to test for significant differences in the correlations with age for ADHD compared with control groups.

3. Results

3.1. ROI analysis

The mean FA and MD values for the control and ADHD participants in each of the ROIs are presented in Table 1. As can be seen, mean FA and MD values were very similar between control and ADHD groups in each of the ROIs. Independent t-tests showed no significant differences between groups in any of the ROIs (P > 0.05).

3.2. Correlation analysis

The mean FA calculated across the whole brain for each participant showed the expected increase with age in both ADHD (r₂ = 0.64, N = 15, P < 0.01, one-tailed) and control groups (r₂ = 0.46, N = 15, P < 0.05, one-tailed). There was no significant difference in these correlations with age between the two groups.

Within the basal ganglia and thalamus ROIs, FA values showed the expected increase with age in all regions except for the caudate nucleus in the control group (Fig. 2). ROIs in which FA was significantly correlated with age are marked in Fig. 2; they included the putamen/globus pallidus and thalamus for both ADHD and control groups and the caudate nucleus for the ADHD group only (P < 0.01, one-tailed).

In the caudate nucleus, the control group appeared to show little change in FA values over age (right caudate: r₂ = 0.04; left: r₂ = 0.03).
The difference between these correlations with age in the controls compared with the ADHD group was significant in the right caudate nucleus \( (z = 2.16, N = 30, P < 0.05) \).

Correlations between MD and age showed a small negative trend in all ROIs, but none was significant \( (P > 0.05) \). There were also no significant correlations between FA or MD and symptom severity (CPRS scores) in the ADHD group \( (P > 0.05) \).

Post-hoc analyses were conducted to further examine the relationship between FA and age in the caudate nucleus in the control group. When the results in Fig. 2 are examined, it is apparent that FA values in the few older control adolescents, from 15–18 years, showed relatively low FA values in the caudate nucleus. This would have affected the linear relationship between FA and age when examined over the full age range of all participants. We therefore re-examined FA correlations with age in the control children only within the central early-adolescent age range, 11–14 years inclusive (8 males, mean age 12.9 ± 1.1 years; matching in age to the mean of the whole control and ADHD samples). We also further explored the underlying diffusion properties giving rise to changes in FA by examining the absolute magnitudes of diffusion along the primary, secondary, and tertiary diffusion directions (first, second, and third eigenvalues). This allowed a fuller comparison of diffusion properties within the basal ganglia in our control group compared with previous studies of young and early-adolescent control children.

As can be seen in Fig. 3, FA values within the caudate nucleus showed the expected increase with age in the control children over this early-adolescent age range. Correlations between age and FA were significant in both left and right caudate ROIs \( (P < 0.01, \text{one-tailed}) \). The analysis of eigenvalues showed that the increase in FA with age was due to a reduction in the magnitude of diffusion along perpendicular directions (with significant negative correlation in \( \lambda_2 \)) but with little change in the magnitude along the primary direction of diffusion. This is entirely consistent with the age-related changes in FA and eigenvalues of diffusion within the caudate nucleus reported previously by Snook et al. (2005) in normally developing children up to 13 years of age.

4. Discussion

Although the pathophysiology underlying ADHD is unclear, the striatum of the basal ganglia, particularly the caudate nucleus, has consistently been found to show both functional and structural differences compared with findings in controls (Castellanos et al., 1994; Filipek et al., 1997; Rubia et al., 1999; Castellanos et al., 2002; Durston et al., 2003; Booth et al., 2005). This is the first study to examine the development of micro-structural organization within the basal ganglia in children and adolescents with ADHD, as indexed by DTI. The findings revealed that while there was no overall difference in diffusion properties within the basal ganglia and thalamus in children with ADHD when averaged across the whole age range (8–18 years), the developmental changes in FA measures of micro-structural organization specifically within the caudate nucleus were significantly different in those with ADHD compared with controls.

Overall, the values of FA and MD identified within the basal ganglia and thalamus (FA: 0.15 to 0.3; MD: 8.0 to 10.0 × 10^{-4} \text{mm}^2/\text{s}) were consistent with those reported previously in healthy children and adolescents (Mukherjee et al., 2001; Snook et al., 2005). We also generally found the expected increase in FA with age when averaged across the whole brain, as well as within most of the basal ganglia and thalamus ROIs, also consistent with previous studies of healthy children and adolescents (Barnea-Goraly et al., 2005; Schmithorst et al., 2005; Snook et al., 2005; Ashtari et al., 2007). The only exception was in the caudate nucleus, which showed significantly different developmental trajectories in the ADHD and control groups.

In the caudate nucleus, the younger adolescents in our control group showed exactly the developmental change reported by Snook et al. (2005); that is, an increase in FA with age, caused primarily by a decrease in the magnitude of diffusion perpendicular to the major fibre tracts (second and third eigenvalues) with little change in diffusion along the primary direction. This is suggested to reflect ongoing myelination or dendritic pruning, which may reduce the density of crossing or branching fibres and thereby decrease the extent of water diffusion perpendicular to the major fibre pathways.

Across the whole age range from early to late adolescence, however, only the ADHD group showed this expected increase in FA with age. We therefore tentatively suggest that the differences in developmental trajectories in the caudate nucleus arise predominantly from differences in late adolescence. No previous studies have reported developmental changes in the caudate nucleus in late adolescence. The study of Snook et al. (2005) examined only children up to 13 years, while other developmental studies have not specifically examined the caudate nucleus (Barnea-Goraly et al., 2005; Schmithorst et al., 2005; Snook et al., 2005; Ashtari et al., 2007). Our results suggest that the developmental increase in FA in the caudate nucleus may slow or end in mid to late adolescence; however, further research would be required to confirm this. Nonetheless, our results do clearly show that developmental changes in FA in the caudate nucleus in children with ADHD, from 8 to 18 years of age, are similar to those seen only in the early-adolescent control group (up to 15 years of age), and are significantly different from developmental changes found in controls over the full age range from early to late adolescence.

Castellanos et al. (2002) found that volumetric development for nearly all brain regions in children with ADHD paralleled (at a lower volume) the growth curves for controls, with the exception of the caudate nucleus and the cerebellum. In the caudate, the difference between ADHD and controls appeared to normalise and became negligible by mid-adolescence (approximately 15 years). Similarly, our results would be consistent with a developmental delay in maturation of the caudate nucleus in ADHD that continues throughout late adolescence, possibly to catch up with that of controls, over the same late adolescent age that caudate volumes appear to normalise in those with ADHD (Castellanos et al., 2002).

The caudate nucleus is a central part of fronto-striatal circuits that are crucial for the cognitive control of attention, working memory, and executive functioning, and are consistently shown to be dysfunctional in children and adolescents with ADHD (Lou et al., 1989; Vaidya et al., 1998; Rubia et al., 1999, 2001; Durston et al., 2003; Booth et al., 2005). In this study, we have shown that the development of microstructure within the caudate nucleus over early to late adolescent ages is different in those with ADHD compared with controls. Our results suggest that the differences in developmental trajectories arise predominantly during late adolescence and may reflect a developmental delay in ADHD; however, further research focusing specifically on the late adolescent age group is needed. In particular, it would be crucial for further research to examine whether the changes in FA in the caudate nucleus during late adolescence are associated with better functional or clinical outcomes in those with ADHD and may therefore reflect a developmental delay that begins to normalise, along with caudate volume, in late adolescence. It is also likely that there may be further structural differences in the caudate nucleus in ADHD to which DTI is not sensitive. Other techniques, such as MR spectroscopy or PET receptor binding, together with studies of DTI and previous functional and structural MRI studies, would provide a more complete picture of the cellular micro-level and macro-level development of the caudate nucleus in children and adolescence with ADHD.

In summary, DTI provides a powerful tool for examining structural development within the brain, particularly within subcortical nuclei such as the basal ganglia and thalamus. In the current study, we found that the structural development of the caudate nucleus is different in children with ADHD compared with healthy controls over ages 8–18 years, and that only control children up to around 15 years show
the age-related increase in diffusion properties that has previously been reported (Snook et al., 2005). Further research is now needed to specifically examine developmental differences in structure of the caudate nucleus over this critical age period during late adolescence.

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The full reference list is available in the original document.