Psychological Medicine (2013), **43**, 1093–1107. © Cambridge University Press 2012
doi:10.1017/S0033291712001869

ORIGINAL ARTICLE

Disturbed microstructural integrity of the frontostriatal fiber pathways and executive dysfunction in children with attention deficit hyperactivity disorder

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Background. Attention deficit hyperactivity disorder (ADHD) is recognized as an early-onset neuropsychiatric disorder with executive dysfunctions and neurobiological deficits. The authors compared executive functions and microstructural integrity of the frontostriatal circuit in children with ADHD and typically developing children.

Method. We assessed 25 children with ADHD and 25 age-, sex-, handedness- and intelligence-matched typically developing children by using psychiatric interviews, the Wechsler Intelligence Scale for Children – third edition, and the tasks involving executive functions in the Cambridge Neuropsychological Test Automated Battery. The frontostriatal tracts were reconstructed by diffusion spectrum imaging tractography and were subdivided into four functionally distinct segments, including dorsolateral, medial prefrontal, orbitofrontal and ventrolateral tracts. Tract-specific and matched case-control analyses were used and generalized fractional anisotropy values were computed.

Results. Children with ADHD had lower generalized fractional anisotropy of all the bilateral frontostriatal fiber tracts and poorer performance in verbal and spatial working memory, set-shifting, sustained attention, cognitive inhibition and visuospatial planning. The symptom severity of ADHD and the executive functioning performance significantly correlated with integrity of the frontostriatal tracts, particularly the left orbitofrontal and ventrolateral tracts. Children with ADHD also demonstrated loss of the leftward asymmetry in the dorsolateral and medial prefrontal tracts that was present in typically developing children.

Conclusions. Our findings demonstrate disturbed structural connectivity of the frontostriatal circuitry in children with ADHD and add new evidence of associations between integrity of the frontostriatal tracts and measures of core symptoms of ADHD and a wide range of executive dysfunctions in both groups.

Received 14 March 2012; Revised 22 June 2012; Accepted 12 July 2012; First published online 15 August 2012

Key words: Attention deficit hyperactivity disorder, Cambridge Neuropsychological Test Automated Battery, diffusion spectrum imaging, executive function, frontostriatal tracts.

Introduction

Attention deficit hyperactivity disorder (ADHD) is recognized as an early-onset neuropsychiatric disorder with lifelong executive dysfunctions (Seidman *et al*. 2006). A recent meta-analysis revealed medium to large effect sizes of the impairment in response inhibition, working memory, executive planning, and a small effect size in the deficits in attentional set shifting in ADHD (Chamberlain *et al*. 2011). The prefrontal cortex (Fuster, 1999), including the dorsolateral prefrontal cortex (DLPFC) (Fuster, 2002), medial prefrontal cortex (MPFC) (Konishi *et al*. 2010), orbitofrontal cortex (OFC) (Price, 1999) and ventrolateral prefrontal cortex (VLPFC) (Wolf *et al*. 2009), plays a major role in subserving executive functions (Curtis & D'Esposito, 2003), such as the DLPFC for action planning (Fuster, 2002), the MPFC for shifting under novel situations (Konishi *et al*. 2010), the OFC for reward-guided behavior (Price, 1999), and the VLPFC for holding online of both spatial and non-spatial information (Wolf *et al*. 2009).

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The evidence that ADHD is associated with neurobiological deficits in the frontostriatal network (Spencer *et al*. 2002) has been demonstrated from morphometric studies showing reduced prefrontal (Wang *et al*. 2007), caudate nucleus (Valera *et al*. 2007), putamen (Wang *et al*. 2007) and globus pallidus (Overmeyer *et al*. 2001) volume and cortical thickness (Shaw *et al*. 2006); and functional imaging studies showing frontal (Kim *et al*. 2002) and striatal (Teicher *et al*. 2000) hypoperfusion and hypoactivity (Dickstein *et al*. 2006). Recently, diffusion tensor imaging (DTI) has been used to investigate the microstructure integrity of white matter tracts (Ashtari *et al*. 2005; Casey *et al*. 2007; Hamilton *et al*. 2008; Makris *et al*. 2008; Silk *et al*. 2009*a*, *b*; Konrad *et al*. 2010; Cao *et al*. 2010; Nagel *et al*. 2011). Fractional anisotropy (FA) is usually used as an index to reflect white matter integrity (Johansen-Berg & Behrens, 2009). Abnormal white matter microstructures relevant to ADHD have been found by DTI in various regions including the frontostriatal tract (Ashtari *et al*. 2005; Casey *et al*. 2007; Pavuluri *et al*. 2009; Konrad *et al*. 2010; Liston *et al*. 2011), cerebellum (Ashtari *et al*. 2005), superior longitudinal fasciculus (Konrad *et al*. 2010) and the corticospinal tract (Hamilton *et al*. 2008). Among those regions, disturbed frontostriatal microstructural integrity is recognized as the most consistent finding in ADHD. In addition, FA values in the left striatum were significantly associated with ADHD symptom severity in children with ADHD (Peterson *et al*. 2011) but not in adults with ADHD (Konrad *et al*. 2010).

Several lines of evidence support that the frontostriatal circuitry provides important signals related to cognitive functions (Cubillo *et al*. 2011). For example, maturation of frontostriatal connectivity contributed to an increase in efficiency of go/no-go task performance in neurotypical participants (Liston *et al*. 2006). FA in prefrontal fiber tracts was negatively correlated with cognitive impulsivity assessed by the go/no-go test in parent–child dyads with ADHD (Casey *et al*. 2007). Functional imaging studies showed that abnormal frontostriatal activation was associated with executive control (Konrad *et al*. 2006) and task switching (Dibbets *et al*. 2010) in ADHD.

Despite considerable interest in both ADHD and DTI research, to our best knowledge, there has been no study to correlate the microstructural integrity of frontostriatal tracts and a wide range of executive functions or to use diffusion spectrum imaging (DSI) to reconstruct frontostriatal tracts and to probe microstructural abnormalities along these tracts that may be related to the functional deficits observed in children with ADHD. In contrast to DTI, DSI is able to resolve crossing fibers by performing more comprehensive diffusion measurements than DTI (Wedeen *et al*. 2005). Tractography reconstructed from DSI data has been successfully demonstrated to resolve crossing fiber tracts (Wedeen *et al*. 2008) and has been used to investigate white matter integrity in obsessive–compulsive disorder (Chiu *et al*. 2011), alcoholism (Liu *et al*. 2010) and autism (Lo *et al*. 2011).

Using a matched case-control study design, the present study aimed to compare the executive functions and microstructural integrity and asymmetry patterns of the four frontostriatal tracts, i.e. dorsolateral-caudate, medial prefrontal-caudate, orbitofrontal-caudate, and ventrolateral-caudate tracts, comparing the DSI tractography of children with ADHD and typically developing children, and to investigate whether the white matter tract integrity of frontostriatal circuit was directly correlated with ADHD symptoms and executive functions. We hypothesized that frontostriatal connectivity was involved in ADHD pathophysiology and that disturbed frontostriatal fiber integrity was correlated with ADHD symptoms and executive functions.

Method

Participants and procedure

The Research Ethics Committee at the National Taiwan University Hospital (NTUH) approved this study prior to the study implementation (NTUH Institutional Review Board no. 200612093M; ClinicalTrials.gov no. NCT00529893). The procedures and purpose of the present study were clearly explained to the participants and their parents, who then provided written informed consent, followed by the Chinese Kiddie epidemiologic version of the Schedule for Affective Disorders and Schizophrenia (K-SADS-E) interviews for each child's Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) psychiatric diagnoses. The participants were also assessed using the Wechsler Intelligence Scale for Children – third edition (WISC-III) and the Cambridge Neuropsychological Test Automated Battery (CANTAB).

We recruited 25 Taiwanese children with ADHD consecutively from the child psychiatric clinic of National Taiwan University Hospital, Taipei, Taiwan, and 25 typically developing children matched individually for age, sex, handedness and full-scale intelligence quotient (IQ) from the schools with similar school districts to the ADHD group rather than through advertisement (Supplementary Table S1). All participants were right-handed, as assessed with the Edinburgh Inventory (Oldfield, 1971). Children with ADHD were clinically diagnosed according to the DSM-IV criteria and confirmed by the K-SADS-E

interview (Gau *et al*. 2005; Gau & Shang, 2010*a*) by S.S.G. The patients were excluded if they had a lifetime clinical diagnosis of psychosis, mood disorders, learning disability, substance use or autism spectrum disorders, or current diagnosis of anxiety spectrum disorders. Of them, 18 (72.0%) had been treated with medication before recruitment, and 16 (64.0%) were diagnosed with DSM-IV ADHD combined type, eight (32.0%) with predominantly inattentive type, and one (4.0%) with predominantly hyperactive/impulsive type.

We recruited the typically developing participants in the present study if they did not have any current or lifetime DSM-IV psychiatric disorders based on the K-SADS-E interviews. Participants who had any past or current medical or neurological illness, who currently took psychotropic medication, or whose IQ score assessed by the WISC-III was less than 80 were excluded.

The 18 participants with ADHD, who had taken psychotropic medication before, did not take any medication for treating ADHD for at least 1 week before the assessments. All the participants received the same clinical, neuropsychological and magnetic resonance imaging (MRI) assessments.

Clinical measures

The Chinese version of the Swanson, Nolan, and Pelham, version IV scale (*SNAP-IV*) *– parent form*

The SNAP-IV, a 26-item scale, consists of 'inattention' (items 1–9), 'hyperactivity/impulsivity' (items 10–18) and 'oppositionality' (items 19–26), corresponding to the core symptoms of DSM-IV ADHD and oppositional defiant disorder symptom criteria, respectively (Swanson *et al*. 2001). The 26 items of the SNAP-IV are rated on a four-point Likert scale, with scores of 0–3 representing: 'not at all', 'just a little', 'quite a bit' and 'very much'. The norms and psychometric properties of the Chinese SNAP-IV for parent reports have been established in Taiwan (Gau *et al*. 2008).

Executive function measures

The CANTAB is a computerized test battery targeting multiple neuropsychological functions, with standardized procedures and solid psychometric properties (Luciana & Nelson, 1998). The validity of the CANTAB has been confirmed by the demonstrations of comparable effects following manipulations of homologous neural regions and of common effects of pharmacological agents often used in the treatment of ADHD (Chamberlain *et al*. 2011). Four CANTAB tasks involving executive abilities were used to assess the non-verbal executive function (Gau & Shang, 2010*b*).

Intra–extra dimensional set shift (*IED*)

The IED assessed a subject's ability to selectively maintain attention on the specific attribute of compound stimuli across different examples, or intradimensional shift, and then to shift their attention to a previously irrelevant attribute of stimuli, or extradimensional shift (Downes *et al*. 1989). Two dimensions, namely purple shapes and white lines, were used in this test. Simple stimuli were either shapes or lines, whereas compound stimuli consisted of shapes and lines. The test comprised nine stages with increasing difficulty. Initially, the participant had to attend to different simple and compound stimuli within the shape dimension. For example, two different shapes were presented either without lines (simple stimulus) or with lines (compound stimulus), and the participant had to switch attention only between these two shapes, and the lines were irrelevant; these were the intradimensional shifts. In the last step, the participant was required to shift attention to the previously irrelevant line dimension; these were the extradimensional shifts. Throughout the IED task, the participant was required to discover rules, initially through trial and error. Once the rule was achieved on six consecutive occasions, the computer established a new rule. Despite these changes, the participant had to try to make as many correct choices as possible. Two major indices were included in the present study: (1) adjusted total errors: calculated by adding 25 for each stage not attempted due to failure; and (2) adjusted total trials: adding 50 for each stage not attempted due to failure at an earlier stage.

Rapid visual information processing (*RVP*)

The RVP, a 4-min visual continuous performance test modified from Wesnes & Warburton's task (Wesnes & Warburton, 1984), is designed to assess sustained attention capacity and inhibition control (Sahakian *et al*. 1989). Digits (ranging from 2 to 9) appeared one at a time (100 digits/min) in the center of the screen in a random order. For approximately 3 min, the participant had to detect three target sequences (3–5–7, 2–4–6, 4–6–8) and respond (within 1800 ms after the onset of the last number) using a press pad when the last number was seen (7, 6 and 8, respectively). A total of 16 target sequences occurred every 2 min. The participant was instructed to detect as many target sequences (27 in total) as possible. Four indices were presented in the present study: (1) probability of hits (*h*, the participant responding correctly): total hits divided by the sum of total hits and total misses;

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(2) probability of false alarms (*f*, the participant responding inappropriately): total false alarms divided by the sum of total false alarms and total correct rejections; (3) *B″* calculated as $[(h-h^2)-(f-f^2)]/[(h-h^2)+(f-f^2)]$: a signal detection measure of the strength of trace required to elicit a response; and (4) mean latency: mean time taken to respond in correct responses.

Spatial working memory (*SWM*)

The SWM is a self-ordered search test (Petrides & Milner, 1982). On each trial of this task, a number of colored boxes were displayed on the screen. At the bottom right corner of the screen, there was a black column. The participant had to touch the colored boxes one at a time to open them. If a box contained a token, he/she had to move it to the column. Once a token was found inside of a box, there would never be another token inside of the same square. In order to perform the task most efficiently without searching repeatedly in previously targeted locations, the participant had to remember where he/she had searched and found a token. The order in which the participant searched the colored boxes was self-determined, and the number of boxes started at two. The participant ultimately completed four trials each with two boxes, three boxes, four boxes, six boxes and eight boxes. Two major indices were presented in the current study: (1) strategy utilization: the number of search sequences starting with a novel box in the difficult problems (both six- and eight-box problems); (2) total errors: calculated as between errors + within errors – double errors.

Stockings of Cambridge (*SOC*)

The SOC assesses spatial planning based on the Tower of London test (Shallice, 1982). Two displays consisting of three stockings each were shown on a computer touch screen. Three balls were distributed in both the upper and the lower stocking displays. The placement of the balls in the upper display was the template for the lower display. Thus, the participant was required to move the balls in the lower display until the three balls were located at the same places as indicated in the upper display. Before moving the balls, the participant was asked to plan their moves ahead and to use as few moves as possible in order to copy the upper display. After this initial thinking time, the participant started moving the balls. The starting position of the balls was varied so that the solution could be reached after a minimum of two, three, four or five moves. Initially, two moves were needed to copy the upper display; thereafter, difficulty was increased stepwise up to five moves. In total, 12 planning problems were presented. For each trial, the participant also completed a yoked control condition in order to provide baseline measures of motor initiation and executive times. Four major indices were presented in the current study: (1) problems solved in the specified minimum number of moves; (2) total moves; (3) initial thinking time: the difference in reaction time taken to select the first ball for the same problem under the two conditions; and (4) subsequent thinking time: the difference in time between selecting the first ball and completing the problem for the same problem under the two conditions.

MRI data acquisition

Participants were scanned on 3T MRI system (Trio, Siemens, Germany) with a 32-channel head coil. Both T2-weighted (T2W) structure MRI and DSI were acquired with the same slice orientation and range. The T2W images were acquired using a turbo spin echo sequence [repetition time (TR) = 5920 ms, echo time (TE) = 102 ms, matrix size = 256 × 256, spatial resolution = 0.98 mm × 0.98 mm and slice thickness = 3.9 mm]. DSI was performed using a twice-refocused balanced echo diffusion echo planar imaging sequence (Reese *et al*. 2003) [TR = 9100 ms, TE = 142 ms, image matrix size = 128 × 128, spatial resolution = 2.5 mm × 2.5 mm, slice thickness = 2.5 mm]. A total of 102 diffusion-encoding gradients with the maximum diffusion sensitivity $b_{max} = 4000\ s/mm^2$ were sampled on the grid points in a half sphere of the three-dimensional *q*-space with $|q| \leqslant 3.6$ units.

DSI data analysis

The data in the unsampled half sphere of the three-dimensional *q*-space were filled based on the symmetry property of the *q*-space data, i.e. $S(q) = S(-q)$, followed by filling zeros in the eight corners outside the sphere. Fourier transformation was performed based on the Fourier relation between the echo signal $S(q)$ and the diffusion probability density function $P(r)$ (Callaghan, 1991). The orientation distribution function (ODF) was determined by computing the second moment of $P(r)$ along each radial direction (Wedeen *et al*. 2005). The ODF was reconstructed onto 362 directions corresponding to the vertices of a six-fold regularly tessellated dodecahedron projected onto a sphere. The orientations of individual crossing fibers were determined by decomposing the original ODF into several constituent ODFs (Yeh, 2008). Generalized FA (GFA) was derived from the original ODF as the index of white matter integrity. The formula of deriving the value of GFA is expressed as (the standard deviation of ODF)/(the root mean square of ODF) (Tuch, 2004).

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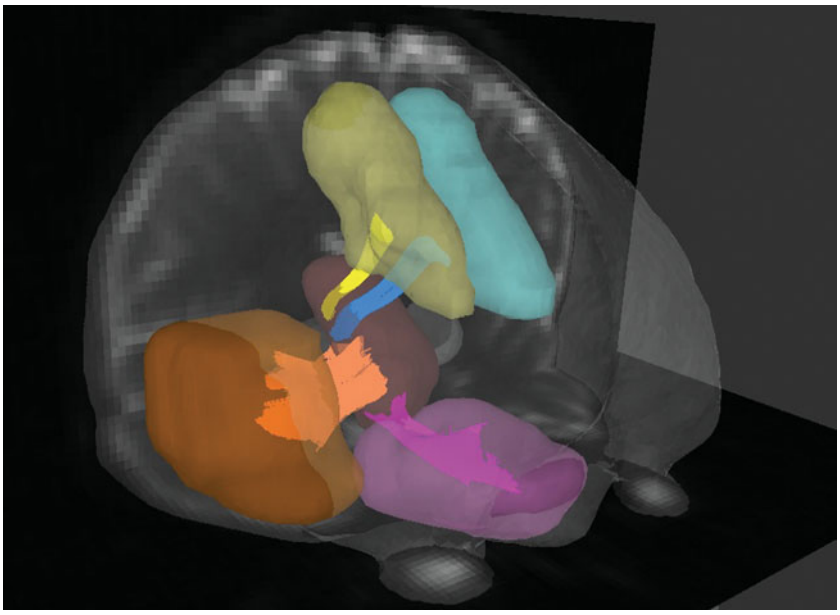

Fig. 1. Regions of interest (ROIs) and reconstructed targeted tracts in the right hemisphere. The ROIs at the dorsolateral prefrontal cortex (light yellow), medial prefrontal cortex (light blue), orbitofrontal cortex (pink), ventrolateral prefrontal cortex (brown) and caudate nucleus (ochre) are shown. The dorsolateral prefrontal–caudate tract (yellow), the medial prefrontal–caudate tract (blue), the orbitofrontal–caudate tract (pink) and the ventrolateral prefrontal–caudate tract (orange) are shown as well. For better orientation, T2-weighted images in coronal and axial views are inserted, and a transparent brain contour is overlaid.

Reconstruction and analysis of frontostriatal fiber tracts

The caudate nucleus curves around the ventricular system and receives projections from associated areas of the cortex. The projections are particularly dense from the prefrontal cortex, which projects to the head of the caudate (Kamali *et al*. 2010). To divide the frontostriatal fiber tracts into four tract bundles corresponding to different cortical regions in bilateral hemispheres, five regions of interest (ROIs) were identified using MARINA software (Bender Institute of Neuroimaging, Germany). These five regions were the caudate nucleus, DLPFC, MPFC, OFC and VLPFC on the Montreal Neurological Institute (MNI) template. Linear transformations between the non-attenuated image (b_0) of the DSI and T2W image, and nonlinear transformation between the T2W image and MNI template were performed so that the image coordinates of DSI data could be transformed to the MNI space. The coordinates of the ROIs defined on the MNI template were then mapped onto individual participants' DSI data through the inverse transformation using the calculated deformation matrix.

A streamline-based fiber-tracking algorithm was performed based on the resolved fiber vector fields provided by DSI. The voxels with GFA values higher than 0.1, compatible with the value of 0.05 based on high angular resolution diffusion imaging (HARDI) data (Berman *et al*. 2008), were selected as the white matter regions and used as seed voxels for tractography (Lo *et al*. 2011). Consistent with previous reports, the GFA value derived from HARDI data was mostly linear with, but lower than, the FA value derived from conventional DTI (Gorczewski *et al*. 2009; Fritzsche *et al*. 2010).

For nearest neighboring voxels with multiple fiber orientations, the orientation closest to the previous propagating direction was selected for interpolation. By moving the seed point with a proceeding length of 0.4 voxels for each step along the most coincident orientation, the new starting point was then obtained. The tracking would stop if all of the angle deviations in the neighboring voxels were higher than a given angular threshold of 60°. Four bundles of frontostriatal fiber tracts, namely, caudate nucleus–DLPFC (dorsolateral), caudate nucleus–MPFC (medial prefrontal), caudate nucleus–OFC (orbitofrontal) and caudate nucleus–VLPFC (ventrolateral), were determined (Fig. 1). GFA values corresponding to different fiber bundles were sampled according to the position coordinates of the tracts, and the mean GFA value for each fiber bundle was calculated.

The tractography was reconstructed by using in-house software (DSI Studio; http://dsi-studio.labsolver.org). Tract-specific sampling of GFA was performed using an in-house mean-path analysis algorithm developed in Matlab (The Mathworks, USA)

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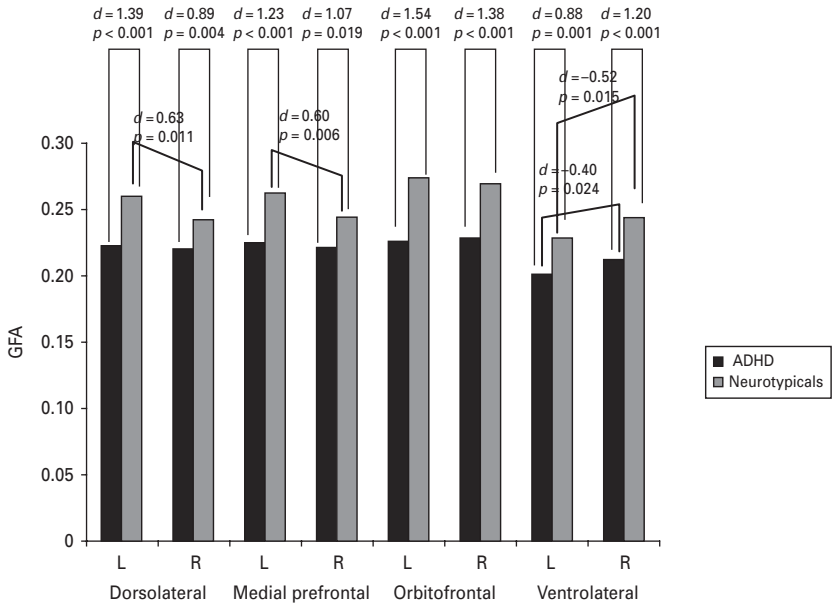

Fig. 2. Comparisons of mean generalized fractional anisotropy (GFA) for frontostriatal tracts between children with attention deficit hyperactivity disorder (ADHD) and typically developing children, and between left (L) and right (R) hemispheres. *d*, Cohen's *d*.

(Lo *et al*. 2011). Asymmetric differences in GFA values were determined for each pair of dorsolateral, medial prefrontal, orbitofrontal and ventrolateral tracts using a lateralization index (LI):

$$\text{LI} = (\text{mean GFA of left fibers} - \text{mean GFA of right fibers})/\text{average GFA of bilateral fibers}.$$

Statistical analyses

We used SAS version 9.1 (SAS Institute Inc., USA) to conduct data analysis. The descriptive results were displayed as frequency and percentage for categorical variables, and mean and standard deviation for continuous variables. To conduct a matched case-control analysis for continuous variables, we used a linear multilevel model to compare the mean scores of IQ, the SNAP-IV, the CANTAB test, the GFA and LI values of the four pairs of frontostriatal tracts between the ADHD and typically developing groups. For the GFA values, a general linear model analysis for repeated measures was used with the sides (left and right hemispheres) and tracts (dorsolateral, medial prefrontal, orbitofrontal and ventrolateral) as the within-subject variables and groups (ADHD and typically developing) as the between-subject variable. Then the *post hoc* analysis was performed using the paired *t* test (two-tailed) to compare the differences in the GFA values of dorsolateral, medial prefrontal, orbitofrontal and ventrolateral tracts within the same subjects. The α value was pre-selected at the level of $p < 0.05$. The effect sizes were further computed using Cohen's *d*, with small, medium and large effect sizes as Cohen's *d* 0.3 to 0.5, 0.5 to 0.8, and $\geqslant 0.8$, respectively.

To control for inflation of type I error in calculating multiple univariate correlations, multiple linear regression models with the backward elimination procedure were conducted to find the relationship between the measures of executive function and the GFA measures of the four pairs of bilateral frontostriatal tracts (dorsolateral, medial prefrontal, orbitofrontal and ventrolateral). The GFA values of the eight frontostriatal tracts were entered as independent variables, and ADHD symptoms based on the SNAP-IV and each of the performance scores on the CANTAB tasks as the dependent variables. We used a backward elimination procedure to identify the fitted model containing the variables from eight frontostriatal tracts which maintained significant effects on each of CANTAB measures. The R^2 value provided a quantitative measure of how well the fitted model with frontostriatal tracts predicted the CANTAB measures.

Results

Group differences

As expected, we found more severe ADHD and oppositional symptoms (all *p* values <0.001) in children with ADHD than in typically developing children. Children with ADHD had significantly lower GFA values than typically developing children in the four pairs of frontostriatal tracts (Cohen's *d*, 0.88–1.54; Fig. 2). Children with ADHD did not demonstrate

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Table 1. *Comparisons of executive functions between children with ADHD and typically developing children*

	ADHD	TD	*F*	*p*	Cohen's *d*
Intra-extra dimensional set shift					
Total errors, adjusted	38.48 (22.12)	23.84 (19.04)	6.29	0.019	0.71
Total trials, adjusted	125.04 (38.72)	94.28 (34.21)	8.86	0.007	0.84
Rapid visual information processing					
Probability of hits	0.38 (0.18)	0.51 (0.17)	9.46	0.005	−0.73
Probability of false alarm	0.03 (0.03)	0.01 (0.02)	5.85	0.024	0.68
B″	0.74 (0.20)	0.89 (0.12)	12.55	0.002	−0.92
Mean latency, ms	626.00 (195.60)	490.94 (144.87)	8.60	0.007	0.78
Spatial working memory					
Strategy utilization	35.44 (5.05)	31.88 (4.93)	6.36	0.019	0.71
Total errors	36.32 (17.69)	24.68 (19.22)	4.97	0.036	0.63
Stockings of Cambridge					
Problems solved in minimum moves	7.08 (1.63)	7.88 (1.86)	4.00	0.057	−0.46
Total moves	19.29 (2.63)	17.50 (1.55)	9.07	0.006	0.83
Mean initial thinking time, ms	3289.11 (1751.51)	4713.62 (2240.03)	7.05	0.014	−0.71
Mean subsequent thinking time, ms	1806.92 (1936.87)	1079.71 (601.43)	3.97	0.058	0.51

ADHD, Attention deficit hyperactivity disorder; TD, typically developing children.
Data are given as mean (standard deviation).

Table 2. *Final model of prediction of inattention and hyperactivity–impulsivity symptoms in children with ADHD by four bilateral frontostriatal tracts*

		SNAP-IV[a]			
		Inattention		Hyperactivity–impulsivity	
		β	*p*	*β*	*p*
Dorsolateral	L	–	–	−394.25	0.001
Medial prefrontal	R	–	–	−279.11	0.006
Orbitofrontal	R	−127.09	<0.001	–	–
Ventrolateral	R	–	–	−131.77	0.068
F values		$F_{1,22} = 16.54$, $p < 0.001$		$F_{3,20} = 6.96$, $p = 0.002$	
R^2		0.43		0.51	

ADHD, Attention deficit hyperactivity disorder; L, left; R, right.
[a] Based on parental report on the Chinese version of the Swanson, Nolan and Pelham, version IV scale.

significant left-to-right asymmetry in the dorsolateral and medial prefrontal pairs as shown in typically developing children (Fig. 2) and had lower LIs of the medial prefrontal ($d = 0.53$; $p = 0.047$) and dorsolateral ($d = 0.57$; $p = 0.051$) tracts than typically developing children.

Compared with the typically developing children, children with ADHD had more IED total errors (adjusted) and IED total trials (adjusted), lower RVP probability of hits, higher RVP probability of false alarm, lower RVP *B″* value, and longer RVP mean latency, poorer SWM strategy utilization and more SWM total errors, and more SOC total moves and shorter SOC mean initial thinking time (Table 1).

Prediction of ADHD symptoms and executive functions by frontostrial GFA

The multiple linear regression with backward elimination analysis revealed that the GFA value of the right orbitofrontal tract was significantly associated with inattention, and GFA of the left dorsolateral and right medial prefrontal fiber tracts was significantly associated with hyperactivity/impulsivity within the ADHD group (Table 2).

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Table 3. *Final model of prediction of executive functions in children with ADHD and typically developing children by four bilateral frontostriatal tracts*

		Intra-extra dimensional set shift				Rapid visual information processing					
		Total errors, adjusted		Total trials, adjusted		Probability of false alarm		*B″*		Mean latency, ms	
		β	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Children with ADHD											
Orbitofrontal	L	456.94	0.007	757.54	0.010	0.68	0.012	−4.22	0.014	–	–
	R	–	–	–	–	–	–	–	–	–	–
Ventrolateral	L	−442.06	0.002	−774.31	0.002	–	–	−2.84	0.082	–	–
	R	–	–	–	–	–	–	5.76	0.015	–	–
F values		$F_{2,22}=8.13$, $p=0.002$		$F_{2,22}=7.63$, $p=0.003$		$F_{1,23}=7.39$, $p=0.012$		$F_{3,21}=3.88$, $p=0.024$			
R^2		0.42		0.41		0.24		0.36			
Typically developing children											
Medial prefrontal	L	–	–	–	–	−0.19	.084	1.24	0.082	–	–
Orbitofrontal	L	262.66	0.022	419.36	0.042	–	–	–	–	3936.40	<0.001
	R	–	–	–	–	–	–	–	–	−2946.83	0.009
Ventrolateral	R	−430.10	0.003	−761.64	0.004	–	–	–	–	–	–
F values		$F_{2,22}=5.96$, $p=0.009$		$F_{2,22}=5.43$, $p=0.012$		$F_{1,23}=3.26$, $p=0.084$		$F_{1,23}=3.32$, $p=0.082$		$F_{2,22}=8.75$, $p=0.002$	
R^2		0.35		0.33		0.12		0.13		0.44	

		Spatial working memory				Stockings of Cambridge							
		Strategy utilization		Total errors		Problems solved in minimum moves		Total moves		Mean initial thinking time		Mean subsequent thinking time	
		β	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Children with ADHD													
Dorsolateral	L	–	–	–	–	–	–	–	–	–	–	61874.84	0.014
Orbitofrontal	L	78.37	0.054	334.50	0.016	–	–	–	–	−34690.97	0.013	–	–
	R	–	–	–	–	−34.30	0.006	40.33	0.063	–	–	–	–
Ventrolateral	L	–	–	–	–	–	–	–	–	–	–	−32675.44	0.061
F values		$F_{1,23}=4.13$, $p=0.054$		$F_{1,23}=6.72$, $p=0.016$		$F_{1,23}=9.12$, $p=0.006$		$F_{1,23}=3.85$, $p=0.063$		$F_{1,23}=7.40$, p = 0.013		$F_{2,21}=3.60$, $p=0.045$	
R^2		0.15		0.23		0.28		0.15		0.25		0.26	

Typically developing children												
Dorsolateral	R	−230.16	0.010	−590.66	0.003	–	–	−29.09	0.016	40362.23	0.022	–
Medial prefrontal	R	184.25	0.048	–	–	–	–	–	–	–	–	–
Orbitofrontal	L	–	–	300.41	0.014	–	–	–	–	–	–	–
Ventrolateral	L	–	–	−285.43	0.025	–	–	–	–	–	–	–
	R	–	–	326.56	0.043	–	–	–	–	–	–	–
F values			$F_{2,22}=3.11$, $p=0.048$		$F_{4,20}=4.39$, $p=0.010$				$F_{1,23}=6.75$, $p=0.016$		$F_{1,23}=6.04$, $p=0.022$	
R^2			0.31		0.47				0.23		0.21	

ADHD, Attention deficit hyperactivity disorder; L, left; R, right.

Table 3 presents significant associations between frontostriatal microstructural integrity and executive functions. In summary, within the ADHD group, results showed (1) that left orbitofrontal and left ventrolateral GFA values were significantly associated with IED total errors (adjusted) and IED total trials (adjusted); (2) that left orbitofrontal GFA was significantly associated with RVP probability of false alarm and RVP *B″* (right ventrolateral GFA, too); (3) that left orbitofrontal GFA was significantly associated with SWM total errors; (4) that right and left dorsolateral GFA values were significantly associated with SOC problems solved in minimum moves and SOC mean initial thinking time; and (5) that left dorsolateral GFA was significantly associated with SOC mean subsequent thinking time (Table 3).

In the typically developing group, we found (1) that the GFA values of the left orbitofrontal and right ventrolateral fiber tracts were significantly associated with IED total errors (adjusted) and IED total trials (adjusted); (2) that the GFA values of the left and right orbitofrontal tracts were significantly associated with RVP mean latency; (3) that right dorsolateral and medial prefrontal GFA values were significantly associated with SWM strategy utilization; (4) that GFA values of the right dorsolateral, left orbitofrontal, left ventrolateral and right ventrolateral tracts were significantly associated with SWM total errors; and (5) that right dorsolateral GFA was significantly associated with SOC total moves and SOC mean initial thinking time (Table 3).

Discussion

With the strengths of using tractography-based analysis, complete assessments of clinical symptoms and executive function, and a matched case-control study design with matching at the individual level, we found that children with ADHD had disturbed microstructural integrity of all four pairs of frontostriatal tracts, and that clinical symptomatology and executive functions correlated with integrity of the frontostriatal tracts, particularly the left orbitofrontal and ventrolateral fiber tracts. Our findings lend evidence to support that disturbed frontostriatal integrity might be responsible for the clinical symptoms of and executive dysfunction in ADHD.

Rationale of using DSI for frontostriatal tract analysis

In this study, we used DSI instead of DTI to reconstruct the frontostriatal tracts and study the microstructural integrity of the tracts. The rationale is as follows. DTI determines the distribution of water

https://doi.org/10.1017/S0033291712001869 Published online by Cambridge University Press

diffusivity by fitting to it an ellipsoid (called diffusion tensor), and the principal orientation of the diffusion tensor is the direction of the maximal diffusivity (Basser *et al*. 1994). The direction of axonal fibers is then defined by the principal orientation of the diffusion tensor within each voxel. DSI determines the distribution of water diffusivity by reconstructing the ODF of water diffusion within each voxel (Wedeen *et al*. 2005). The number and direction of axonal fiber directions are then determined by the number and direction of local maxima of the ODF within each voxel. To reconstruct the ODF, DSI performs a more comprehensive diffusion measurement than DTI, and so DSI has higher angular resolution to resolve intravoxel fiber crossing. The ability of resolving intravoxel crossing fibers has significant impact on tractography. It has been shown that tractography based on DTI tends to produce false fiber pathways especially in regions where there are crossing fibers (Wedeen *et al*. 2008). The frontostriatal tracts project onto the caudate nucleus from the frontal lobe. In the course, they cross frequently with callosal fibers and association fibers. Therefore, fiber tractography of the frontostriatal tracts based on DTI is very challenging and requires extensive manual editing to delete the false tracts. In contrast, DSI tractography of the frontostriatal tracts is more reproducible, and allows more accurate segmentation of the frontostriatal tracts. Using fiber pathways as a guide, we can analyse the microstructural integrity along each individual tract to study the anatomical underpinning of the disease in light of a well-defined tract object. Using this approach, we not only confirmed the impaired microstructural integrity of the frontostriatal tracts in ADHD, but we also demonstrated the association of these fiber tracts with core symptoms and a wide range of executive function in both typically developing and disease groups.

Abnormalities of white matter integrity

Reduced white matter integrity of all the frontostriatal tracts in ADHD is consistent with previous DTI studies (Ashtari *et al*. 2005; Pavuluri *et al*. 2009; Liston *et al*. 2011), suggesting that frontostriatal integrity changes may be the structural correlates for ADHD. Low GFA values may reflect axonal degeneration, or a less well-organized tract (Mori & Zhang, 2006).

Loss of asymmetry

A loss of leftward asymmetry specifically in the dorsolateral and medial prefrontal tracts in ADHD advances our knowledge about reduced left prefrontal cortex (Shaw *et al*. 2009) and white matter (Mostofsky *et al*. 2002) in ADHD. The relative balance of left *versus* right hemispheric activity in the frontostriatal network may be involved in selective attention to details and avoidance of distraction by extraneous stimuli (Weissman & Banich, 1999). Hence, alterations of the asymmetry in the frontostriatal tracts may play an important role in the anatomical network in ADHD (Rubia *et al*. 2000).

Frontostriatal tracts and ADHD symptoms

Disturbed right orbitofrontal tract integrity specifically accounted for inattention symptoms, in line with the cognitive models of impaired attentional control in ADHD (Castellanos *et al*. 2006). Recent studies showed an increased functional connectivity between the right OFC and various brain regions related to attention modulation (Diekhof *et al*. 2009). Right orbitofrontal (McCrea, 2009) and caudate (Campbell *et al*. 2009) abnormalities resulted in significant attentional deficits.

Furthermore, our finding that the GFA value of the left dorsolateral and right medial prefrontal tracts correlated with the hyperactivity/impulsivity symptoms is a new contribution to this topic. Although no previous studies have examined the association between the integrity of the frontostriatal fiber tract and ADHD symptoms, some limited studies using different imaging approaches have provided similar evidence. Previous studies have reported volume reduction in the left DLPFC (Kates *et al*. 2002; Mostofsky *et al*. 2002; Seidman *et al*. 2006) and the association between hypoactivity in the left DLPFC and more severe hyperactivity symptoms (Spalletta *et al*. 2001) in patients with ADHD.

Frontostriatal tracts and executive function

To the best of our knowledge, this is the first study that demonstrates a direct association between frontostriatal microstructural integrity, mainly the orbitofrontal and ventrolateral fiber tracts, and executive functions measured by the CANTAB in children with ADHD and typically developing children as well. Correlations between the left orbitofrontal and ventrolateral tract integrity and set-shifting measured by the IED lend evidence to support the role of frontostriatal circuitry in cognitive flexibility (Kehagia *et al*. 2010). Earlier studies have demonstrated impairment in IED task performance in patients with Parkinson's disease, which involved dysfunction of frontal lobes and basal ganglia (Downes *et al*. 1989). Owen *et al*. (1991) have also found impaired ability to shift response set in patients with frontal lobe excisions. In addition, recent neuroimaging studies have shown that attentional set-shifting was related to activation of

the VLPFC (Shafritz *et al*. 2005; Hampshire & Owen, 2006), anterior cingulate cortex (Shafritz *et al*. 2005), striatum (Shafritz *et al*. 2005) and a ventral–prefrontal–striatal circuit (Monchi *et al*. 2001). Moreover, the OFC was reported to probably mediate attentional set-shifting by reducing interference from salient stimuli (Kehagia *et al*. 2010). Taken together, aberrant connectivity in the orbitofrontal and ventrolateral tracts may be a pathophysiological mechanism underlying attentional set-shifting deficits in ADHD.

Successful performance on the RVP requires sustained attention, inhibition control and performance monitoring. Using positron emission tomography, Coull *et al*. (1996) have found that RVP task performance was associated with activation in the inferior frontal gyrus, parietal cortex, fusiform gyrus and supplementary motor area. Functional MRI studies have demonstrated that the strongest positive correlations between activation magnitude and RVP task performance were found in the frontoparietal regions (Lawrence *et al*. 2003). Our finding of association between left orbitofrontal tract integrity and sustained attention and inhibition control measured by the RVP adds support to abundant evidence from functional neuroimaging studies suggesting that inhibitory control and error detection are associated with such brain regions as the OFC (Elliott & Deakin, 2005; Rubia *et al*. 2010) and basal ganglia (Jahfari *et al*. 2011; Liu *et al*. 2011).

Earlier studies have found impairments in SWM task performance in patients with frontal lobe excisions (Owen *et al*. 1990). In addition, SWM task performance correlated significantly with the frontal lesion load in patients with multiple sclerosis (Foong *et al*. 1997). An association of SWM task performance with left orbitofrontal tract integrity in ADHD is consistent with the finding of reduced activation of the orbitofrontal region during working memory tasks in adults with ADHD (Wolf *et al*. 2009), similar to the finding of deficits in SWM associated with left frontal lesions (du Boisgueheneuc *et al*. 2006), and extend the recent finding of a significant association between FA in the left frontoparietal network and SWM task performance (Vestergaard *et al*. 2011).

Earlier studies have demonstrated impairment in the original version of the SOC task performance in patients with anterior cortical damage, including frontoparietal and frontotemporal lesions (Shallice, 1982). Owen *et al*. (1990) have found that the thinking time subsequent to the first move in the SOC task was significantly prolonged in patients with frontal lobe excisions. Investigations with functional neuroimaging techniques have also demonstrated the critical role of the prefrontal cortex and basal ganglia in the process of spatial planning (Rowe *et al*. 2001; Beauchamp *et al*. 2003; Newman *et al*. 2009). These prior results are supported by the current study demonstrating significant correlations of left orbitofrontal and left dorsolateral microstructure integrity with spatial planning and problem solving assessed by the SOC. Previous research supported that the thinking time of spatial planning is correlated with greater regional blood flow, with a peak of activation in the left frontal region (Rowe *et al*. 2001), that orbitofrontal region is activated during the spatial planning task (Tower of London) (Elliott *et al*. 1997; Rowe *et al*. 2001), that the DLPFC aids in the maintenance of information by directing attention to internal representations of sensory stimuli and planning (Curtis & D'Esposito, 2003), and that lesions in the DLPFC are associated with organizational and planning dysfunctions (Makris *et al*. 2007). Taken together, our findings suggest that disturbed white matter integrity in the left dorsolateral and orbitofrontal tracts may underlie the deficits in spatial planning and problem solving in ADHD.

The present study found that inattentive symptoms and measures of executive function correlated with integrity of the orbitofrontal tracts. Previous studies demonstrated that the orbitofrontal region was innervated by mesolimbic and mesocortical dopamine pathways (Depue & Collins, 1999). Alternations in dopamine neurotransmission were linked to inattentive symptoms (Genro *et al*. 2010; Shang *et al*. 2011) and executive function deficits (Arnsten & Li, 2005). Our findings lend evidence to support the role of dopamine in the pathophysiology of ADHD through neuromodulatory influences over frontostriatal circuits (Del Campo *et al*. 2011).

Limitations

Our findings should be interpreted in the context of some limitations. First, a cross-sectional study design has prevented us from determining whether the white matter abnormalities observed in these frontostriatal tracts reflect the primary pathophysiology of ADHD or are the consequences of a compensatory neurodevelopmental process. Second, the present study only focused on the frontostriatal tracts. Exploration of frontotemporal (Konrad *et al*. 2010) and fronto-striato-parieto-cerebellar (Rubia *et al*. 2009) networks, which may be associated with executive dysfunction in ADHD, is warranted. Third, we cannot completely exclude any potential long-term effects of medication on microstructural integrity of the frontostriatal tracts given that 18 children with ADHD had taken medication for treating ADHD at least 1 week before the scan. Fourth, due to the matched design, we were not able to study the age effect in the whole sample. It

https://doi.org/10.1017/S0033291712001869 Published online by Cambridge University Press

merits further investigation to clarify the developmental trajectory of the microstructural integrity of the frontostriatal and other tracts using a longitudinal study design.

Several features of this study constitute its strengths, including carefully matching each child with ADHD with a typically developing child of the same age, sex, handedness and IQ using the same DSI protocol and analysis. In addition, the study used several measures of clinical symptoms, intelligence, and a wide range of executive functions rather than a single test.

Summary and implications

Combining previous DTI studies and our DSI tractography analysis, there is strong evidence to support disturbed white matter tract integrity of the four frontostriatal circuits (i.e. dorsolateral-caudate, medial prefrontal-caudate, orbitofrontal-caudate and ventrolateral-caudate) in children with ADHD, and associations between integrity of the frontostriatal tracts and measures of ADHD symptoms in children with ADHD and executive functions in children with ADHD and typically developing children as well. Further imaging genetics research on the relationship between frontostriatal circuitry, executive function and candidate genes is warranted.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291712001869.

Acknowledgements

This study was supported by grants from the National Health Research Institute (NHRI-EX98-9407PC, NHRI-EX100-10008PI), and grants from the National Science Council (NSC96-2628-B-002-069-MY3, NSC99-2321-B-002-037), Taiwan.

Declaration of Interest

None.

References

Arnsten AF, Li BM (2005). Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. *Biological Psychiatry* **57**, 1377–1384.

Ashtari M, Kumra S, Bhaskar SL, Clarke T, Thaden E, Cervellione KL, Rhinewine J, Kane JM, Adesman A, Milanaik R, Maytal J, Diamond A, Szeszko P, Ardekani BA (2005). Attention-deficit/hyperactivity disorder: a preliminary diffusion tensor imaging study. *Biological Psychiatry* **57**, 448–455.

Basser PJ, Mattiello J, LeBihan D (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal* **66**, 259–267.

Beauchamp MH, Dagher A, Aston JA, Doyon J (2003). Dynamic functional changes associated with cognitive skill learning of an adapted version of the Tower of London task. *Neuroimage* **20**, 1649–1660.

Berman JI, Chung S, Mukherjee P, Hess CP, Han ET, Henry RG (2008). Probabilistic streamline *q*-ball tractography using the residual bootstrap. *Neuroimage* **39**, 215–222.

Callaghan P (1991). *Principles of Nuclear Magnetic Resonance Microscopy*. Clarendon Press: Oxford.

Campbell LE, Daly E, Toal F, Stevens A, Azuma R, Karmiloff-Smith A, Murphy DG, Murphy KC (2009). Brain structural differences associated with the behavioural phenotype in children with Williams syndrome. *Brain Research* **1258**, 96–107.

Cao Q, Sun L, Gong G, Lv Y, Cao X, Shuai L, Zhu C, Zang Y, Wang Y (2010). The macrostructural and microstructural abnormalities of corpus callosum in children with attention deficit/hyperactivity disorder: a combined morphometric and diffusion tensor MRI study. *Brain Research* **1310**, 172–180.

Casey BJ, Epstein JN, Buhle J, Liston C, Davidson MC, Tonev ST, Spicer J, Niogi S, Millner AJ, Reiss A, Garrett A, Hinshaw SP, Greenhill LL, Shafritz KM, Vitolo A, Kotler LA, Jarrett MA, Glover G (2007). Frontostriatal connectivity and its role in cognitive control in parent–child dyads with ADHD. *American Journal of Psychiatry* **164**, 1729–1736.

Castellanos FX, Sonuga-Barke EJ, Milham MP, Tannock R (2006). Characterizing cognition in ADHD: beyond executive dysfunction. *Trends in Cognitive Sciences* **10**, 117–123.

Chamberlain SR, Robbins TW, Winder-Rhodes S, Muller U, Sahakian BJ, Blackwell AD, Barnett JH (2011). Translational approaches to frontostriatal dysfunction in attention-deficit/hyperactivity disorder using a computerized neuropsychological battery. *Biological Psychiatry* **69**, 1192–1203.

Chiu CH, Lo YC, Tang HS, Liu IC, Chiang WY, Yeh FC, Jaw FS, Tseng WY (2011). White matter abnormalities of fronto-striato-thalamic circuitry in obsessive-compulsive disorder: a study using diffusion spectrum imaging tractography. *Psychiatry Research* **192**, 176–182.

Coull JT, Frith CD, Frackowiak RS, Grasby PM (1996). A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. *Neuropsychologia* **34**, 1085–1095.

Cubillo A, Halari R, Giampietro V, Taylor E, Rubia K (2011). Fronto-striatal underactivation during interference inhibition and attention allocation in grown up children with attention deficit/hyperactivity disorder and persistent symptoms. *Psychiatry Research* **193**, 17–27.

Curtis CE, D'Esposito M (2003). Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences* **7**, 415–423.

Del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW (2011). The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. *Biological Psychiatry* **69**, e145–e157.

Depue RA, Collins PF (1999). Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. *Behavioral and Brain Sciences* **22**, 491–517.

Dibbets P, Evers EA, Hurks PP, Bakker K, Jolles J (2010). Differential brain activation patterns in adult attention-deficit hyperactivity disorder (ADHD) associated with task switching. *Neuropsychology* **24**, 413–423.

Dickstein SG, Bannon K, Castellanos FX, Milham MP (2006). The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. *Journal of Child Psychology and Psychiatry* **47**, 1051–1062.

Diekhof EK, Falkai P, Gruber O (2009). Functional interactions guiding adaptive processing of behavioral significance. *Human Brain Mapping* **30**, 3325–3331.

Downes JJ, Roberts AC, Sahakian BJ, Evenden JL, Morris RG, Robbins TW (1989). Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. *Neuropsychologia* **27**, 1329–1343.

du Boisgueheneuc F, Levy R, Volle E, Seassau M, Duffau H, Kinkingnehun S, Samson Y, Zhang S, Dubois B (2006). Functions of the left superior frontal gyrus in humans: a lesion study. *Brain* **129**, 3315–3328.

Elliott R, Deakin B (2005). Role of the orbitofrontal cortex in reinforcement processing and inhibitory control: evidence from functional magnetic resonance imaging studies in healthy human subjects. *International Review of Neurobiology* **65**, 89–116.

Elliott R, Frith CD, Dolan RJ (1997). Differential neural response to positive and negative feedback in planning and guessing tasks. *Neuropsychologia* **35**, 1395–1404.

Foong J, Rozewicz L, Quaghebeur G, Davie CA, Kartsounis LD, Thompson AJ, Miller DH, Ron MA (1997). Executive function in multiple sclerosis. The role of frontal lobe pathology. *Brain* **120**, 15–26.

Fritzsche KH, Laun FB, Meinzer HP, Stieltjes B (2010). Opportunities and pitfalls in the quantification of fiber integrity: what can we gain from Q-ball imaging? *Neuroimage* **51**, 242–251.

Fuster JM (1999). Synopsis of function and dysfunction of the frontal lobe. *Acta Psychiatrica Scandinavica* (Suppl.) **395**, 51–57.

Fuster JM (2002). Frontal lobe and cognitive development. *Journal of Neurocytology* **31**, 373–385.

Gau SS, Chong MY, Chen TH, Cheng AT (2005). A 3-year panel study of mental disorders among adolescents in Taiwan. *American Journal of Psychiatry* **162**, 1344–1350.

Gau SS, Shang CY (2010*a*). Executive functions as endophenotypes in ADHD: evidence from the Cambridge Neuropsychological Test Battery (CANTAB). *Journal of Child Psychology and Psychiatry* **51**, 838–849.

Gau SS, Shang CY (2010*b*). Improvement of executive functions in boys with attention deficit hyperactivity disorder: an open-label follow-up study with once-daily atomoxetine. *International Journal of Neuropsychopharmacology* **13**, 243–256.

Gau SS, Shang CY, Liu SK, Lin CH, Swanson JM, Liu YC, Tu CL (2008). Psychometric properties of the Chinese version of the Swanson, Nolan, and Pelham, version IV scale – parent form. *International Journal of Methods in Psychiatric Research* **17**, 35–44.

Genro JP, Kieling C, Rohde LA, Hutz MH (2010). Attention-deficit/hyperactivity disorder and the dopaminergic hypotheses. *Expert Review of Neurotherapeutics* **10**, 587–601.

Gorczewski K, Mang S, Klose U (2009). Reproducibility and consistency of evaluation techniques for HARDI data. *Magma* **22**, 63–70.

Hamilton LS, Levitt JG, O'Neill J, Alger JR, Luders E, Phillips OR, Caplan R, Toga AW, McCracken J, Narr KL (2008). Reduced white matter integrity in attention-deficit hyperactivity disorder. *Neuroreport* **19**, 1705–1708.

Hampshire A, Owen AM (2006). Fractionating attentional control using event-related fMRI. *Cerebral Cortex* **16**, 1679–1689.

Jahfari S, Waldorp L, van den Wildenberg WP, Scholte HS, Ridderinkhof KR, Forstmann BU (2011). Effective connectivity reveals important roles for both the hyperdirect (fronto-subthalamic) and the indirect (fronto-striatal-pallidal) fronto-basal ganglia pathways during response inhibition. *Journal of Neuroscience* **31**, 6891–6899.

Johansen-Berg H, Behrens TE (editors) (2009). *Diffusion MRI: From Quantitative Measurement to In-vivo Neuroanatomy*. Academic Press: London.

Kamali A, Kramer LA, Hasan KM (2010). Feasibility of prefronto-caudate pathway tractography using high resolution diffusion tensor tractography data at 3T. *Journal of Neuroscience Methods* **191**, 249–254.

Kates WR, Frederikse M, Mostofsky SH, Folley BS, Cooper K, Mazur-Hopkins P, Kofman O, Singer HS, Denckla MB, Pearlson GD, Kaufmann WE (2002). MRI parcellation of the frontal lobe in boys with attention deficit hyperactivity disorder or Tourette syndrome. *Psychiatry Research* **116**, 63–81.

Kehagia AA, Murray, GK, Robbins TW (2010). Learning and cognitive flexibility: frontostriatal function and monoaminergic modulation. *Current Opinion in Neurobiology* **20**, 199–204.

Kim BN, Lee JS, Shin MS, Cho SC, Lee DS (2002). Regional cerebral perfusion abnormalities in attention deficit/hyperactivity disorder. Statistical parametric mapping analysis. *European Archives of Psychiatry and Clinical Neuroscience* **252**, 219–225.

Konishi S, Hirose S, Jimura K, Chikazoe J, Watanabe T, Kimura HM, Miyashita Y (2010). Medial prefrontal activity during shifting under novel situations. *Neuroscience Letters* **484**, 182–186.

Konrad A, Dielentheis TF, El Masri D, Bayerl M, Fehr C, Gesierich T, Vucurevic G, Stoeter P, Winterer G (2010). Disturbed structural connectivity is related to inattention and impulsivity in adult attention deficit hyperactivity disorder. *European Journal of Neuroscience* **31**, 912–919.

Konrad K, Neufang S, Hanisch C, Fink GR, Herpertz-Dahlmann B (2006). Dysfunctional attentional networks in children with attention deficit/hyperactivity disorder: evidence from an event-related functional magnetic resonance imaging study. *Biological Psychiatry* **59**, 643–651.

Lawrence NS, Ross TJ, Hoffmann R, Garavan H, Stein EA (2003). Multiple neuronal networks mediate sustained attention. *Journal of Cognitive Neuroscience* **15**, 1028–1038.

Liston C, Malter Cohen M, Teslovich T, Levenson D, Casey BJ (2011). Atypical prefrontal connectivity in attention-deficit/hyperactivity disorder: pathway to disease or pathological end point? *Biological Psychiatry* **69**, 1168–1177.

Liston C, Watts R, Tottenham N, Davidson MC, Niogi S, Ulug AM, Casey BJ (2006). Frontostriatal microstructure modulates efficient recruitment of cognitive control. *Cerebral Cortex* **16**, 553–560.

Liu HS, Chou MC, Chung HW, Cho NY, Chiang SW, Wang CY, Kao HW, Huang GS, Chen CY (2011). Potential long-term effects of MDMA on the basal ganglia-thalamocortical circuit: a proton MR spectroscopy and diffusion-tensor imaging study. *Radiology* **260**, 531–540.

Liu IC, Chiu CH, Chen CJ, Kuo LW, Lo YC, Tseng WY (2010). The microstructural integrity of the corpus callosum and associated impulsivity in alcohol dependence: a tractography-based segmentation study using diffusion spectrum imaging. *Psychiatry Research* **184**, 128–134.

Lo YC, Soong WT, Gau SS, Wu YY, Lai MC, Yeh FC, Chiang WY, Kuo LW, Jaw FS, Tseng WY (2011). The loss of asymmetry and reduced interhemispheric connectivity in adolescents with autism: a study using diffusion spectrum imaging tractography. *Psychiatry Research* **192**, 60–66.

Luciana M, Nelson CA (1998). The functional emergence of prefrontally-guided working memory systems in four- to eight-year-old children. *Neuropsychologia* **36**, 273–293.

Makris N, Biederman J, Valera EM, Bush G, Kaiser J, Kennedy DN, Caviness VS, Faraone SV, Seidman LJ (2007). Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. *Cerebral Cortex* **17**, 1364–1375.

Makris N, Buka SL, Biederman J, Papadimitriou GM, Hodge SM, Valera EM, Brown AB, Bush G, Monuteaux MC, Caviness VS, Kennedy DN, Seidman LJ (2008). Attention and executive systems abnormalities in adults with childhood ADHD: a DT-MRI study of connections. *Cerebral Cortex* **18**, 1210–1220.

McCrea SM (2009). A cognitive neuropsychological examination of the Das-Naglieri cognitive assessment system subtests: a report of three stroke cases studied longitudinally during recovery. *International Journal of Neuroscience* **119**, 553–599.

Monchi O, Petrides M, Petre V, Worsley K, Dagher A (2001). Wisconsin Card Sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *Journal of Neuroscience* **21**, 7733–7741.

Mori S, Zhang J (2006). Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron* **51**, 527–539.

Mostofsky SH, Cooper KL, Kates WR, Denckla MB, Kaufmann WE (2002). Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. *Biological Psychiatry* **52**, 785–794.

Nagel BJ, Bathula D, Herting M, Schmitt C, Kroenke CD, Fair D, Nigg JT (2011). Altered white matter microstructure in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* **50**, 283–292.

Newman SD, Greco JA, Lee D (2009). An fMRI study of the Tower of London: a look at problem structure differences. *Brain Research* **1286**, 123–132.

Oldfield RC (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* **9**, 97–113.

Overmeyer S, Bullmore ET, Suckling J, Simmons A, Williams SC, Santosh PJ, Taylor E (2001). Distributed grey and white matter deficits in hyperkinetic disorder: MRI evidence for anatomical abnormality in an attentional network. *Psychological Medicine* **31**, 1425–1435.

Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia* **28**, 1021–1034.

Owen AM, Roberts AC, Polkey CE, Sahakian BJ, Robbins TW (1991). Extra-dimensional *versus* intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia* **29**, 993–1006.

Pavuluri MN, Yang S, Kamineni K, Passarotti AM, Srinivasan G, Harral EM, Sweeney JA, Zhou XJ (2009). Diffusion tensor imaging study of white matter fiber tracts in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. *Biological Psychiatry* **65**, 586–593.

Pennington BF, Ozonoff S (1996). Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry* **37**, 51–87.

Peterson DJ, Ryan M, Rimrodt SL, Cutting LE, Denckla MB, Kaufmann WE, Mahone EM (2011). Increased regional fractional anisotropy in highly screened attention-deficit hyperactivity disorder (ADHD). *Journal of Child Neurology* **26**, 1296–1302.

Petrides M, Milner B (1982). Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia* **20**, 249–262.

Price JL (1999). Prefrontal cortical networks related to visceral function and mood. *Annals of the New York Academy of Sciences* **877**, 383–396.

Reese TG, Heid O, Weisskoff RM, Wedeen VJ (2003). Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo. *Magnetic Resonance in Medicine* **49**, 177–182.

Robbins TW (2007). Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Philosophical Transactions of the Royal Society of London* **362**, 917–932.

Rowe JB, Owen AM, Johnsrude IS, Passingham RE (2001). Imaging the mental components of a planning task. *Neuropsychologia* **39**, 315–327.

Rubia K, Cubillo A, Smith AB, Woolley J, Heyman I, Brammer MJ (2010). Disorder-specific dysfunction in right inferior prefrontal cortex during two inhibition tasks in boys with attention-deficit hyperactivity disorder compared to boys with obsessive-compulsive disorder. *Human Brain Mapping* **31**, 287–299.

Rubia K, Halari R, Cubillo A, Mohammad AM, Brammer M, Taylor E (2009). Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naive children with ADHD during a rewarded continuous performance task. *Neuropharmacology* **57**, 640–652.

Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, Andrew C, Bullmore ET (2000). Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI. *Neuroscience and Biobehavioral Reviews* **24**, 13–19.

Sahakian B, Jones G, Levy R, Gray J, Warburton D (1989). The effects of nicotine on attention, information processing, and short-term memory in patients with dementia of the Alzheimer type. *British Journal of Psychiatry* **154**, 797–800.

Seidman LJ, Valera EM, Makris N, Monuteaux MC, Boriel DL, Kelkar K, Kennedy DN, Caviness VS, Bush G, Aleardi M, Faraone SV, Biederman J (2006). Dorsolateral prefrontal and anterior cingulate cortex volumetric abnormalities in adults with attention-deficit/hyperactivity disorder identified by magnetic resonance imaging. *Biological Psychiatry* **60**, 1071–1080.

Shafritz KM, Kartheiser P, Belger A (2005). Dissociation of neural systems mediating shifts in behavioral response and cognitive set. *Neuroimage* **25**, 600–606.

Shallice T (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society of London* **298**, 199–209.

Shang CY, Gau SS, Liu CM, Hwu HG (2011). Association between the dopamine transporter gene and the inattentive subtype of attention deficit hyperactivity disorder in Taiwan. *Progress in Neuropsychopharmacology and Biological Psychiatry* **35**, 421–428.

Shaw P, Lalonde F, Lepage C, Rabin C, Eckstrand K, Sharp W, Greenstein D, Evans A, Giedd JN, Rapoport J (2009). Development of cortical asymmetry in typically developing children and its disruption in attention-deficit/hyperactivity disorder. *Archives of General Psychiatry* **66**, 888–896.

Shaw P, Lerch J, Greenstein D, Sharp W, Clasen L, Evans A, Giedd J, Castellanos FX, Rapoport J (2006). Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry* **63**, 540–549.

Silk TJ, Vance A, Rinehart N, Bradshaw JL, Cunnington R (2009*a*). Structural development of the basal ganglia in attention deficit hyperactivity disorder: a diffusion tensor imaging study. *Psychiatry Research* **172**, 220–225.

Silk TJ, Vance A, Rinehart N, Bradshaw JL, Cunnington R (2009*b*). White-matter abnormalities in attention deficit hyperactivity disorder: a diffusion tensor imaging study. *Human Brain Mapping* **30**, 2757–2765.

Spalletta G, Pasini A, Pau F, Guido G, Menghini L, Caltagirone C (2001). Prefrontal blood flow dysregulation in drug naive ADHD children without structural abnormalities. *Journal of Neural Transmission* **108**, 1203–1216.

Spencer TJ, Biederman J, Wilens TE, Faraone SV (2002). Overview and neurobiology of attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry* **63** (Suppl. 12), 3–9.

Swanson JM, Kraemer HC, Hinshaw SP, Arnold LE, Conners CK, Abikoff HB, Clevenger W, Davies M, Elliott GR, Greenhill LL, Hechtman L, Hoza B, Jensen PS, March JS, Newcorn JH, Owens EB, Pelham WE, Schiller E, Severe JB, Simpson S, Vitiello B, Wells K, Wigal T, Wu M (2001). Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. *Journal of the American Academy of Child and Adolescent Psychiatry* **40**, 168–179.

Teicher MH, Anderson CM, Polcari A, Glod CA, Maas LC, Renshaw PF (2000). Functional deficits in basal ganglia of children with attention-deficit/hyperactivity disorder shown with functional magnetic resonance imaging relaxometry. *Nature Medicine* **6**, 470–473.

Tuch DS (2004). Q-ball imaging. *Magnetic Resonance in Medicine* **52**, 1358–1372.

Valera EM, Faraone SV, Murray KE, Seidman LJ (2007). Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. *Biological Psychiatry* **61**, 1361–1369.

Vestergaard M, Madsen KS, Baare WF, Skimminge A, Ejersbo LR, Ramsoy TZ, Gerlach C, Akeson P, Paulson OB, Jernigan TL (2011). White matter microstructure in superior longitudinal fasciculus associated with spatial working memory performance in children. *Journal of Cognitive Neuroscience* **23**, 2135–2146.

Wang J, Jiang T, Cao Q, Wang Y (2007). Characterizing anatomic differences in boys with attention-deficit/hyperactivity disorder with the use of deformation-based morphometry. *American Journal of Neuroradiology* **28**, 543–547.

Wedeen VJ, Hagmann P, Tseng WY, Reese TG, Weisskoff RM (2005). Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. *Magnetic Resonance in Medicine* **54**, 1377–1386.

Wedeen VJ, Wang RP, Schmahmann JD, Benner T, Tseng WY, Dai G, Pandya DN, Hagmann P, D'Arceuil H, de Crespigny AJ (2008). Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. *Neuroimage* **41**, 1267–1277.

Weissman DH, Banich MT (1999). Global–local interference modulated by communication between the hemispheres. *Journal of Experimental Psychology. General* **128**, 283–308.

Wesnes K, Warburton DM (1984). Effects of scopolamine and nicotine on human rapid information processing performance. *Psychopharmacology* (*Berlin*) **82**, 147–150.

Wolf RC, Plichta MM, Sambataro F, Fallgatter AJ, Jacob C, Lesch KP, Herrmann MJ, Schonfeldt-Lecuona C, Connemann BJ, Gron G, Vasic N (2009). Regional brain activation changes and abnormal functional connectivity of the ventrolateral prefrontal cortex during working memory processing in adults with attention-deficit/hyperactivity disorder. *Human Brain Mapping* **30**, 2252–2266.

Yeh F, Wedeen V, Tseng WI (2008). A recursive algorithm to decompose orientation distribution function and resolve intra-voxel fiber directions. *Proceedings of International Society for Magnetic Resonance in Medicine* **16**, 40.