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ORIGINAL ARTICLE

Association between microstructural integrity of frontostriatal tracts and school functioning: ADHD symptoms and executive function as mediators

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Background. Deficits in executive function (EF), impaired school functioning and altered white matter integrity in frontostriatal networks have been associated with attention-deficit/hyperactivity disorder (ADHD). However, relationships between impairments in these areas are unclear. Using a sample of youths with and without ADHD, this study examined the association between microstructural integrity of frontostriatal tracts and school dysfunction and the mediating roles of EF and ADHD symptoms in this association.

Method. The sample included 32 Taiwanese youths with ADHD and 32 age-, sex-, handedness- and IQ-matched typically-developing (TD) youths. Participants were assessed using psychiatric interviews, parent reports on ADHD symptoms and school functioning, and EF measures from the Cambridge Neuropsychological Test Automated Battery (CANTAB). The frontostriatal tracts were reconstructed by diffusion spectrum imaging (DSI) tractography and were subdivided into four functionally distinct segments: caudate–dorsolateral, caudate–medial prefrontal, caudate–orbitofrontal and caudate–ventrolateral tracts.

Results. Youths with ADHD, relative to TD youths, showed altered white matter integrity in all four bilateral pairs of frontostriatal tracts (decreased general fractional anisotropy, GFA), had poor attention, vigilance and response inhibition, and showed impaired school functioning. Altered microstructural integrity in frontostriatal tracts was significantly associated with school dysfunction, which was mediated by EF measures of attention/vigilance and response inhibition in addition to inattention and hyperactivity symptoms.

Conclusions. Our findings demonstrate an association between white matter integrity in the frontostriatal networks and school functioning and suggest that EF deficits and ADHD symptoms may be the mediating mechanisms for this association. Future research is needed to test the directionality and specificity of this finding.

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Key words: Attention-deficit/hyperactivity disorder, diffusion spectrum imaging tractography, executive function, frontostriatal tracts, mediators, school function.

Introduction

Executive function (EF) refers to complex, top-down cognitive processes such as planning, attention, working memory, cognitive flexibility and response inhibition (Pennington & Ozonoff, 1996; Zelazo & Carlson, 2012) that are required for efficient and effective goal-oriented behaviors. Impaired EF, subserved by the prefrontal lobes, is one of the central deficits in attention-deficit/hyperactivity disorder (ADHD) (Barkley, 1997; Gau & Shang, 2010), including deficits in response inhibition, attention or vigilance, working memory and planning (Kain & Perner, 2003; Willcutt *et al*. 2005; Chamberlain *et al*. 2011). ADHD symptoms (i.e. inattention and hyperactivity/impulsivity) and impaired EF are both reported to contribute to the poor school, academic and social functioning often observed in youths with ADHD (Barkley, 1997; Sonuga-Barke, 2003; Loe & Feldman, 2007). Given

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that individuals with ADHD, relative to healthy controls, tend to show medium to large decrements in response inhibition, vigilance and working memory (for meta-analytical reviews, see Willcutt *et al.* 2005; Chamberlain *et al.* 2011) and that these processes are key components of EF, this study used two neuropsychological tasks, the Rapid Visual Information Processing (RVP) task and the Spatial Working Memory (SWM) task, from the Cambridge Neuropsychological Test Automated Battery (CANTAB) to tap deficits in these domains of EF.

Neuroimaging research in ADHD has led to investigations of the neurobiological underpinning of this disorder, suggesting abnormalities in the frontostriatal networks as the underlying pathophysiology of ADHD (Silk *et al.* 2009; Tamm *et al.* 2012). Most neuroimaging studies, however, focus on cortical gray matter or specific subcortical structures (Tamm *et al.* 2012; van Ewijk *et al.* 2012). The meta-analytic review by van Ewijk *et al.* (2012) suggested that white matter abnormalities underlying the connectivity in the frontostriatal–cerebellar circuitry might, in part, be implicated in the pathophysiology of ADHD.

Diffusion tensor imaging (DTI) allows for the examination of water diffusion in different tissues and the organization of white matter tracts *in vivo* (Conturo *et al.* 1999) and thus plays an important role in the study of structural connectivity in the brain. Using DTI, abnormal white matter microstructures in children with ADHD have been found, with disturbed frontostriatal microstructural integrity representing the best-replicated finding, either with lower fractional anisotropy (FA) (Ashtari *et al.* 2005; Kobel *et al.* 2010; de Zeeuw *et al.* 2012) or higher FA (Silk *et al.* 2009; Davenport *et al.* 2010; Li *et al.* 2010; Peterson *et al.* 2011; Tamm *et al.* 2012). Greater FAs are typically thought to reflect coherent white matter organization and greater myelination of fibers (Mori & Zhang, 2006); however, some argue that greater FAs observed in ADHD may present an abnormal reduction in neuronal branching (Silk *et al.* 2009). van Ewijk *et al.* (2014) recently suggested that sample characteristics such as age, gender or IQ may be unlikely to explain why FA values have been found to be both lower and higher in ADHD, relative to controls, across different studies. Instead, the authors suggest that there may be two different types of white matter pathology and mechanisms underlying FA alterations in ADHD: one mechanism characterized by decreased FA in ADHD and linked to familial vulnerability to the disorder, and the other characterized by increased FA in ADHD and linked to the clinical state of ADHD (i.e. the behavioral symptoms). Additionally, increased FA may potentially reflect a compensatory mechanism for brain dysfunction (Holzapfel *et al.* 2006) or poor cognitive functioning (Tuch *et al.* 2005).

Diffusion spectrum imaging (DSI), an advanced technique of diffusion-weighted imaging, is more capable of resolving fiber crossings than DTI (Wedeen *et al.* 2008) and yields a more accurate and detailed presentation of complex neural pathways by acquisition of a large number of diffusion-weighted images with different diffusion-encoding gradients (Tournier *et al.* 2004; Tuch, 2004; Hess *et al.* 2006; Wedeen *et al.* 2008). DSI thus provides flexibility that permits delineation of fiber pathways in areas where fiber crossings are substantial or the fiber architecture is complex and multidirectional. Therefore, in this study, we used DSI to examine the integrity of white matter fiber tracts in frontostriatal regions in youths with and without ADHD. Thus far, only two studies have used DSI tractography to examine microstructural integrity of white matter tracts in ADHD and they reported that youths with ADHD, relative to typically-developing (TD) youths, had lower generalized fractional anisotropy (GFA), an index of microstructural integrity in the DSI, in the frontostriatal networks (Shang *et al.* 2013; Wu *et al.* 2014).

Past DTI research correlating white matter abnormalities with ADHD symptoms (i.e. inattention and hyperactivity/impulsivity) have been mixed. Ashtari *et al.* (2005) reported lower cerebellar FA associated with parent-reported inattention in ADHD; Nagel *et al.* (2011) found lower FA values in a broad range of brain regions related to ADHD symptoms, especially inattention, in ADHD; and de Zeeuw *et al.* (2012) found decreased frontostriatal FA related to teacher-reported, but not parent-reported, attention problems only in TD youth. By contrast, Peterson *et al.* (2011) reported higher left striatum FA values associated with parent- and teacher-reported ADHD symptoms in ADHD. Still others found no significant associations between FA values in any of their regions of interest (ROIs) and hyperactivity in ADHD (Hamilton *et al.* 2008). The only two available DSI studies reported lower FA values in the frontostriatal networks significantly associated with inattention and hyperactivity (Shang *et al.* 2013; Wu *et al.* 2014).

Regarding significant associations between disturbed white matter integrity and cognitive dysfunctions in ADHD, in a DTI study by Casey *et al.* (2007), for example, lower FA in frontostriatal tracts was associated with less cognitive control assessed by go/no-go task in parent–child dyads with ADHD. Lower FAs in the right orbitofrontal and superior longitudinal fasciculus were related to more commission errors and poorer attention performance respectively in adults with ADHD in a DTI study by Konrad *et al.* (2010). Recent DSI research studies have shown that integrity

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of the frontostriatal tracts, particularly the left orbitofrontal and ventrolateral tracts, was correlated significantly with poor EF performance (Shang *et al.* 2013) and with attention measures in the continuous performance test, but only in TD youths (Wu *et al.* 2014).

No research has investigated the link between disturbed white matter integrity and impaired school functioning (e.g. poor academic performance, impaired social interactions and behavioral problems at school), which is often observed in youths with ADHD. Given that youths with ADHD tend to show EF deficits (Gau & Shang, 2010; Chamberlain *et al.* 2011), school adjustment problems (Sonuga-Barke, 2003; Biederman *et al.* 2004; Loe & Feldman, 2007; Wu & Gau, 2013) and disturbed white matter integrity (Liston *et al.* 2011; van Ewijk *et al.* 2012), we conducted this study not only to examine the degree of impairment in these aspects in youths with ADHD, as compared to TD youths, but also to investigate the linkage between frontostriatal tract integrity, EF, ADHD symptoms and school functioning. We focused on frontostriatal tracts because review studies have suggested that abnormalities in the structural and functional connectivity in the frontostriatal–cerebellar circuitry may be implicated in the pathophysiology of ADHD (Bush *et al.* 2005; Konrad & Eickhoff, 2010; Cubillo *et al.* 2012; van Ewijk *et al.* 2012) and that disturbed microstructural integrity in the frontostriatal network in ADHD represents one of the best-replicated findings (Ashtari *et al.* 2005; Silk *et al.* 2009; Davenport *et al.* 2010; Kobel *et al.* 2010; Li *et al.* 2010; Peterson *et al.* 2011; de Zeeuw *et al.* 2012; Tamm *et al.* 2012). Specifically, we hypothesized that ADHD symptoms and EF deficits may be the mechanisms linking disturbed frontostriatal tracts integrity and school dysfunctioning. In other words, connectivity deficits in frontostriatal networks may contribute directly to ADHD symptoms (inattention and hyperactivity) in addition to executive dysfunction, which is highly associated with ADHD (Liston *et al.* 2011). ADHD symptoms or EF deficits may then give rise to impaired school functioning.

Method

Participants and procedures

The sample included 32 Taiwanese youths with DSM-IV diagnosis of ADHD (29 boys; mean age±S.D.=11.4±2.3 years, range 8–17) from the child psychiatric clinic of National Taiwan University Hospital (NTUH), Taiwan, and 32 age-, sex-, handedness- and full-scale IQ-matched TD youths from schools in similar geographical districts through teachers' referral. All participants were right-handed as assessed with the Edinburgh Inventory (Oldfield, 1971), and the two groups did not differ in full-scale IQ (mean±S.D.=109±12.2 for ADHD, 112.4±10.0 for TD, $p=0.082$). All the participants and their parents were interviewed using the Chinese Kiddie epidemiologic version of the Schedule for Affective Disorders and Schizophrenia (K-SADS-E) for the diagnosis of ADHD and other psychiatric disorders (Gau *et al.* 2005) by S.S.-F.G. Participants with a lifetime clinical diagnosis of psychosis, mood disorders, learning disability, substance use, or autism spectrum disorders, current diagnosis of anxiety disorders, or IQ <80 were excluded. The TD participants were enrolled in this study only if they did not have a lifetime diagnosis of ADHD and if they met the same exclusion criteria as the ADHD group.

Participants received the same clinical, magnetic resonance imaging (MRI), diagnostic and neuropsychological assessments within 2 days. Parents returned their reports on their child's ADHD symptoms and school functioning around 1–3 months after the MRI and neuropsychological assessments. The Research Ethics Committee at the NTUH approved this study prior to the study implementation (IRB ID: 200903062R; ClinicalTrials.gov no. NCT00916851). Written informed consent was collected from the participants and their parents after an explanation of the study aims and procedures.

Of the 32 youths with ADHD, 18 were included in a previous investigation (Shang *et al.* 2013), 19 were diagnosed with the combined type (59.38%) and 13 with the predominantly inattentive type (40.62%). Seventeen youths with ADHD (53%) had ever taken methylphenidate but had not taken any medication (including dopaminergic and noradrenergic drugs) for at least 1 week before the MRI and neuropsychological assessments.

Clinical and neuropsychological assessments

The outcome measure was school functioning assessed with parent reports of the Chinese version of the Social Adjustment Inventory for Children and Adolescents (SAICA; John *et al.* 1987; Biederman *et al.* 1993). The mediators included in the study were (1) the participants' inattention and hyperactivity/impulsivity symptoms assessed with parent reports of the Chinese version of the Swanson, Nolan, and Pelham, version IV (SNAP-IV) scale (Swanson *et al.* 2001; Gau *et al.* 2008; see online Supplementary material); and (2) EF assessed with the CANTAB. The RVP task (Sahakian *et al.* 1989) and the SWM task (Petrides & Milner, 1982) from the CANTAB were used to tap deficits in sustained attention, response inhibition, vigilance and working memory (see online Supplementary material).

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The SAICA

The SAICA was designed to assess the adaptive functioning of children and adolescents aged 6–18 years in four social domains: school, spare time activities, peer relationships, and home life (John *et al.* 1987; Biederman *et al.* 1993). Parents completed the SAICA to assess their child's functioning in the past month. This study focused on the school domain of the SAICA. The school functioning scale consisted of assessment on academic performance (in Chinese, English, mathematics, science and social studies), school and social attitude (i.e. attitudes toward homework and toward interactions with teachers and classmates), and school behavioral problems (e.g. disruptive behaviors, getting into fights, withdrawal, vandalism). A mean score, averaging responses on all items on the school domain of the SAICA, was used as a global index of children's school functioning. Items were rated on a four-point scale from 1 (positive or not a problem) to 4 (negative or severe problem) (John *et al.* 1987). A higher score indicates either poorer functioning or more severe problems. The Chinese SAICA was reported to have satisfactory psychometric properties (Gau *et al.* 2006*a*, *b*) and has been widely used in clinical (Gau, 2007), treatment (Griswold *et al.* 2002; Gau *et al.* 2006*a*,*b*) and community (Humphrey & Symes, 2010; Tseng *et al.* 2011; Kawabata *et al.* 2012) studies in child and adolescent populations. In the current sample, Cronbach's α for the school functioning scale was 0.73.

MRI assessments

MRI data acquisition

Participants were scanned on a 3-T MRI system (Trio, Siemens, Germany) with a 32-channel head coil. Both T2-weighted (T2W) structural MR and DS images were acquired in the same transaxial view covering the entire brain. The T2W images were acquired using a fast spin echo sequence, repetition time (TR)/echo time (TE) = 5920 ms/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/TE = 9100 ms/142 ms, image matrix size = 128 × 128, spatial resolution = 2.5 mm × 2.5 mm, and slice thickness = 2.5 mm. A total of 102 diffusion-encoding gradients with a maximum diffusion sensitivity b_{max} = 4000 s mm^{-2} were sampled on the grid points in a half sphere of the three-dimensional (3D) **q**-space.

DSI data analysis

The data in the unsampled half sphere of the 3D **q**-space were filled based on the symmetry property, that is $S(\mathbf{q}) = S(-\mathbf{q})$, followed by filling zeros in the eight corners outside the sphere. Fourier transform was performed based on the Fourier relationship between the diffusion signal $S(\mathbf{q})$ and the diffusion probability density function $P(\mathbf{r})$ (Callaghan, 1991). The orientation distribution function (ODF) was determined by computing the second moment of $P(\mathbf{r})$ along each radial direction (Wedeen *et al.* 2005). The ODF values were calculated in 362 directions corresponding to the vertices of a sixfold regularly tessellated dodecahedron projected onto a sphere. Within each voxel, local fiber orientations were determined by the local maxima of the ODF, and GFA, an index reflecting white matter integrity, was calculated by (standard deviation of the ODF)/(root mean square of the ODF) (Tuch, 2004).

Construction and analysis of frontostriatal fiber tracts

We focused on the frontostriatal tracts, particularly those between the prefrontal cortex (PFC) and the caudate head because the projections are particularly dense between these areas (Afifi & Bergman, 1998). The frontostriatal tracts were constructed using deterministic tractography. The constructed tracts were further divided into four tract bundles connecting to four different prefrontal regions in each hemisphere based on an anatomical study of rhesus monkeys (Yeterian & Pandya, 1991) showing a topological correspondence of the projection from different prefrontal regions, that is the dorsolateral PFC (DLPFC), ventrolateral PFC (VLPFC), orbitofrontal cortex (OFC) and medial PFC (MPFC), to different parts of the caudate nucleus. The tractography was achieved by identifying ROI in the caudate head and four ROIs in the DLPFC, VLPFC, OFC and MPFC on the Montreal Neurological Institute (MNI) template using MARINA software (Bender Institute of Neuroimaging, University of Giessen, Germany). Linear transformations between the non-attenuated image (b_0) of DSI and the T2W image and non-linear transformations between the T2W image and the MNI template were performed so that the coordinates of the ROIs defined on the MNI space were mapped onto an individual's native DSI space through the inverse transformation of the calculated deformation matrix.

A streamline-based fiber tracking algorithm was performed based on the resolved local fiber orientations derived from the ODF. The voxels with GFA >0.1 were selected as the white matter regions in which local fiber orientations were used as seed vectors for fiber tracking (Lo *et al.* 2011). For nearest-neighboring voxels with multiple local fiber orientations, the orientation closest to the previous propagating direction was selected for interpolation. By moving the seed

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point with a proceeding length of 0.4 voxel for each step along the most coincident orientation, a new starting point was obtained. The tracking would stop if all of the angle deviations in the neighboring voxels were greater than a given angular threshold of 60°. In this way, four pairs of frontostriatal tracts (i.e. caudate–DLPFC, caudate–MPFC, caudate–OFC and caudate–VLPFC) were obtained (online Supplementary Fig. S1). GFA values corresponding to different fiber bundles were sampled according to the position coordinates of the tracts, and the mean GFA for each fiber bundle was calculated. The tractography was constructed 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 (The Mathworks, USA; Lo *et al.* 2011).

Statistical analyses

Analyses in this study were performed using SAS version 9.2 (SAS Institute Inc., USA). Analyses of comparisons between ADHD and TD groups in EF, school functioning and the GFA values of the four pairs of frontostriatal tracts are described in the online Supplementary material. To test EF and ADHD symptoms (i.e. inattention and hyperactivity/impulsivity) as mediators in the link between frontostriatal tract integrity and school functioning, we conducted mediation analyses and calculated mediation effects (i.e. indirect effects), following suggestions by Preacher & Hayes (2008). A depiction of the mediation model is presented in Fig. 1. We used the overall sample (n=64) to increase the range of variances in the study variables and to maximize the statistical power to detect significant mediation/indirect effects. A bootstrapping procedure, with bias-corrected confidence intervals (CIs), was used to test the significance of the mediation effects with 1000 bootstrap samples to yield more valid estimates of the indirect effects (Preacher & Hayes, 2008). Because no study has examined the association between frontostriatal tract integrity and school functioning and the mediators underlying this association, to avoid letting clinically relevant associations go unrecognized due to stringent thresholding, we did not apply Bonferroni correction to adjust the significance level, as it is too conservative and prone to Type II error (Perneger, 1998). The use of the bootstrapping procedure and the reporting of magnitudes and CIs of indirect effects should allow readers to evaluate the importance and significance of the results (Nakagawa, 2004). In addition, no proper guidelines in terms of methods of correction for multiple comparisons for such data have been established. The best method to validate the findings in this study would be a replication in an independent sample with a larger sample size, and such efforts are underway. Participants' age and gender were included in the analyses as covariates.

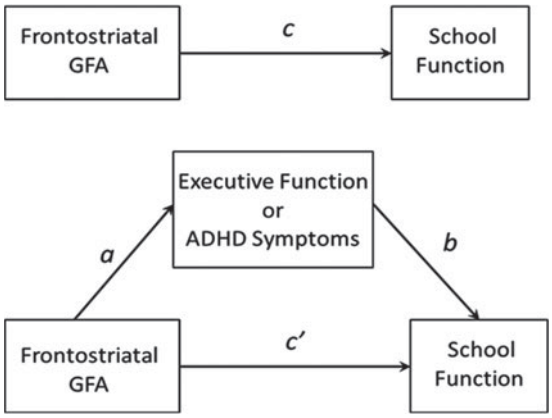

Fig. 1. Mediation model of frontostriatal tracts and school function. General fractional anisotropy (GFA) measures of the four pairs of bilateral frontostriatal tracts (caudate–dorsolateral prefrontal, caudate–medial prefrontal, caudate–orbitofrontal and caudate–ventrolateral prefrontal) were entered individually in separate regression models as the independent variable. Each index of executive function (EF) and core symptoms of attention-deficit/hyperactivity disorder (ADHD) (i.e. inattention *versus* hyperactivity/impulsivity) was tested individually as the mediator in the regression analyses. The product of paths *a* and *b* represented the indirect effects of frontostriatal tract integrity on school functioning through EF or ADHD symptoms.

Results

In summary, compared to TD youths, youths with ADHD had significantly lower GFA values in all four pairs of bilateral frontostriatal tracts (Supplementary Table S1), poorer sustained attention/vigilance and inhibition control assessed by the RVP, and more impairment in all the domains of school functioning (Supplementary Table S2). In general, the frontostriatal tract integrity, particularly in the bilateral caudate–OFC, right caudate–DLPFC and right caudate–VLPFC tracts, was correlated significantly with all the domains of school functions (Supplementary Table S3).

EF and ADHD symptoms as the mediator in the link between frontostriatal tracts and school functioning

To simplify our analysis, we did not use an individual domain of school functioning as the dependent variable; instead, overall school functioning was used as the outcome variable. After controlling for

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participants' age and sex, the white matter integrity of six out of the eight frontostriatal tracts was significantly associated with school functioning (Tables 1–4); the integrity of the left caudate–VLPFC (Table 2) and left caudate–MPFC tracts (Table 3) were associated with school functioning only at a trend level ($p<0.10$).

Tables 1–4 also present the indirect effects of white matter integrity of the frontostriatal tracts on overall school functioning through EF and ADHD symptoms. Following the recommendation by MacKinnon *et al.* (2007), we only interpreted the findings where paths *a* and *b* were significant (Fig. 1) because significant *a* and *b*, coupled with significant *ab*, suggested stronger evidence of a mediation effect than significant *ab* alone.

Response bias (B'') in the RVP task significantly mediated the associations between GFA values of three pairs of the bilateral frontostriatal tracts (i.e. not the left caudate–VLPFC tract) and school functioning, independent of age and gender. That is, the negative association between frontostriatal tract integrity and overall school dysfunctioning can be partially explained by response inhibition. Target sensitivity (A') in the RVP task also significantly mediated the associations of the left caudate–OFC (Table 2) and right caudate–MPFC (Table 4) tracts with school functioning. That is, the negative association between the integrity of these two tracts and overall school dysfunctioning can be partially explained by attention/vigilance ability. Additionally, the probability of a false alarm in the RVP significantly mediated the negative associations between the left caudate–MPFC tract and school dysfunctioning (Table 4). Measures in working memory did not mediate the relationships between frontostriatal tracts and school functioning; that is they were not associated with either frontostriatal tracts or school functioning (Tables 1–4). Moreover, inattention and hyperactivity/impulsivity symptoms each significantly mediated the relationships between the integrity all four pairs of bilateral frontostriatal tracts and school functioning (Tables 1–4).

To examine whether diagnostic group moderated the mediation effects, we conducted additional analyses with moderated mediation models in which diagnostic group functioned as a moderator. None of the mediation effects were moderated by the group status ($p>0.05$). This suggested that the significant mediating mechanisms (i.e. attention/vigilance and response inhibition) underlying the link between white matter integrity in the frontostriatal tracts and school functioning may be similar in the TD group and the ADHD group.

As an exploratory aim, we performed additional mediation analyses, restricting the analyses to the ADHD group or the TD group. Within the ADHD group, only one significant mediation was found; that is, inattention mediated the association between white matter integrity in the right caudate–OFC tract and school functioning (bootstrap $ab=-3.53$, 95% CI −10.26 to −0.81). Within the TD group, only hyperactivity significantly mediated the association between white matter integrity in the left caudate–DLPFC tract and school functioning (bootstrap $ab=1.64$, 95% CI 0.21–5.11).

Discussion

This is the first study to link white matter integrity in frontostriatal regions to children's school functioning and to examine the mediating roles of inattention, hyperactivity and EF deficits in this link. As hypothesized, we found that youths with ADHD, relative to normal controls, showed impairment in the microstructure integrity of white matter pathways in the frontostriatal networks, had poorer performance in EF tasks measuring attention, vigilance and response inhibition, and showed impaired school functioning. Moreover, disturbed microstructural integrity in the frontostriatal tracts was significantly associated with impaired school functioning; thus, EF measures of attention/vigilance and response inhibition, along with symptoms of inattention and hyperactivity, may be the mediating processes involved in this association.

Decreased GFA of frontostriatal tracts in children with ADHD

Consistent with previous DTI (Ashtari *et al.* 2005; Kobel *et al.* 2010; de Zeeuw *et al.* 2012) and DSI studies (Shang *et al.* 2013; Wu *et al.* 2014) reporting decreased FA and GFA values respectively in the frontostriatal networks in ADHD, this study demonstrated that youths with ADHD had lower GFA values in all four bilateral pairs of frontostriatal tracts. Taken together, these findings provide strong evidence to support the notion that disturbed frontostriatal integrity may be one of the core structural underpinnings of ADHD pathophysiology.

Integrity of frontostriatal tracts and school functioning: EF and ADHD symptoms as mediators

Evidence for a significant link between the integrity of frontostriatal tracts and poor school functioning is a new contribution to the literature. Altered white matter integrity of the frontostriatal tracts was associated with school dysfunction including lower academic achievement, more negative attitudes toward homework and toward interactions with teachers and classmates, and more behavioral problems at school (e.g. getting into fights, withdrawal, vandalism). Our data further indicate that certain aspects of EF can explain some

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Table 1. *Mediation effects for the link between caudate–orbitofrontal tracts and overall school functioning*

	Unstandardized estimates (S.E.)				Indirect effects			
Mediators	*a*	*b*	*c*	*c′*	*ab*	Bootstrap *ab*	S.E.	95% CI
Left caudate–orbitofrontal								
SWM								
Strategy utilization	−28.10 (15.45)†	0.00 (0.01)	−6.48 (1.44)***	−6.47 (1.49)***	−0.01	−0.01	0.31	−0.58 to 0.67
Total errors	−25.75 (54.44)	0.00 (0.00)	−6.48 (1.44)***	−6.37 (1.44)***	−0.11	−0.11	0.29	−1.05 to 0.25
RVP								
Probability of hits	0.84 (0.51)	−0.66 (0.36)7†	−6.48 (1.44)***	−5.93 (1.45)***	−0.55	−0.63	0.50	−1.76 to 0.10
Probability of false alarm	−0.12 (0.08)	4.45 (2.21)*	−6.48 (1.44)***	−5.95 (1.43)***	−0.53	−0.67	0.63	−2.85 to −0.02*
A′ (target sensitivity)	0.36 (0.18)*	−2.31 (0.99)*	−6.48 (1.44)***	−5.64 (1.44)***	−0.84	−0.88	0.49	−2.00 to −0.11*
B″ (response bias)	1.23 (0.49)*	−0.93 (0.37)*	−6.48 (1.44)***	−5.33 (1.45)***	−1.15	−1.19	0.59	−2.90 to −0.40*
Mean latency (ms)	−20.38 (511.42)	0.00 (0.00)	−6.48 (1.44)***	−6.47 (1.40)***	−0.01	−0.04	0.41	−0.88 to 0.89
ADHD symptoms								
Inattention	−102.36 (18.58)***	0.05 (0.01)***	−6.48 (1.44)***	−1.12 (1.32)	−5.36	−5.32	1.13	−7.98 to −3.34*
Hyperactivity	−85.87 (17.68)***	0.03 (0.01)**	−6.48 (1.44)***	−4.17 (1.62)*	−2.31	−2.23	1.08	−4.34 to −0.11*
Right caudate–orbitofrontal								
SWM								
Strategy utilization	−25.75 (17.64)	0.00 (0.01)	−7.32 (1.63)***	−7.24 (1.67)***	−0.08	−0.08	0.28	−0.95 to 0.32
Total errors	−51.90 (61.29)	0.00 (0.00)	−7.32 (1.63)***	−7.13 (1.64)***	−0.19	−0.18	0.32	−1.33 to 0.17
RVP								
Probability of hits	0.62 (0.58)	−0.76 (0.35)*	−7.32 (1.63)***	−6.85 (1.60)***	−0.47	−0.60	0.64	−2.01 to 0.49
Probability of false alarm	−0.13 (0.09)	4.58 (2.20)*	−7.32 (1.63)***	−6.75 (1.61)***	−0.57	−0.64	0.59	−2.74 to 0.00
A′ (target sensitivity)	0.28 (0.21)	−2.60 (0.96)**	−7.32 (1.63)***	−6.60 (1.57)***	−0.72	−0.81	0.58	−2.12 to 0.13
B″ (response bias)	1.21 (0.56)*	−0.98 (0.36)**	−7.32 (1.63)***	−6.14 (1.60)***	−1.18	−1.22	0.62	−3.06 to −0.37*
Mean latency (ms)	−416.36 (575.59)	0.00 (0.00)	−7.32 (1.63)***	−7.07 (1.61)***	−0.25	−0.24	0.39	−1.40 to 0.31
ADHD symptoms								
Inattention	−118.12 (20.78)***	0.05 (0.01)***	−7.32 (1.63)***	−1.08 (1.51)	−6.24	−6.17	1.24	−9.38 to −4.21*
Hyperactivity	−86.53 (20.79)***	0.03 (0.01)**	−7.32 (1.63)***	−4.91 (1.75)**	−2.41	−2.55	1.16	−5.07 to −0.55*

SWM, Spatial working memory; RVP, rapid visual information processing; ADHD, attention-deficit/hyperactivity disorder; S.E., standard error; CI, confidence interval; *A′*, a signal detection measure of sensitivity to the target, regardless of response tendency; *B″*, a signal detection measure of the strength of trace required to elicit a response.

a represents the effect of frontostriatal general fractional anisotropy (GFA) on executive function (EF) or ADHD symptoms. *b* represents the effect of EF or ADHD symptoms on school functioning. *c* represents the total (direct and indirect) effect of frontostriatal GFA on school functioning. *c′* represents the direct effect of frontostriatal GFA on school functioning. The product of paths *a* and *b* represents the indirect effect of frontostriatal GFA on school functioning through EF or ADHD symptoms.

† $p<0.10$, * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Table 2. *Mediation effects for the link between caudate–ventrolateral prefrontal tracts and overall school functioning*

	Unstandardized estimates (S.E.)				Indirect effects			
Mediators	*a*	*b*	*c*	*c′*	*ab*	Bootstrap *ab*	S.E.	95% CI
Left caudate–ventrolateral								
SWM								
Strategy utilization	−20.80 (20.15)	0.01 (0.01)	−3.97 (2.07)†	−3.77 (2.10)†	−0.20	−0.18	0.31	−1.29 to 0.16
Total errors	−83.70 (68.97)	0.00 (0.00)	−3.97 (2.07)†	−3.61 (2.10)†	−0.36	−0.34	0.50	−2.42 to 0.17
RVP								
Probability of hits	0.53 (0.66)	−0.90 (0.39)*	−3.97 (2.07)†	−3.49 (2.01)†	−0.48	−0.52	0.65	−2.50 to 0.49
Probability of false alarm	−0.07 (0.11)	5.79 (2.42)*	−3.97 (2.07)†	−3.57 (2.00)†	−0.40	−0.54	0.86	−2.87 to 0.66
A′ (target sensitivity)	0.19 (0.24)	−3.10 (1.06)**	−3.97 (2.07)†	−3.37 (1.96)†	−0.60	−0.63	0.69	−2.70 to 0.57
B″ (response bias)	0.76 (0.65)	−1.26 (0.38)**	−3.97 (2.07)†	−3.01 (1.94)	−0.96	−1.01	0.82	−3.01 to 0.34
Mean latency (ms)	−365.10 (652.98)	0.00 (0.00)	−3.97 (2.07)†	−3.72 (2.05)†	−0.25	−0.32	0.73	−2.38 to 0.86
ADHD symptoms								
Inattention	−71.98 (27.73)*	0.06 (0.01)***	−3.97 (2.07)†	0.08 (1.46)	−4.05	−4.10	1.33	−6.64 to −1.55*
Hyperactivity	−85.19 (24.37)***	0.04 (0.01)***	−3.97 (2.07)†	−0.60 (2.03)	−3.37	−3.30	1.03	−5.65 to −1.54*
Right caudate–ventrolateral								
SWM								
Strategy utilization	−16.70 (21.58)	0.01 (0.01)	−5.75 (2.15)**	−5.59 (2.17)*	−0.16	−0.14	0.33	−1.61 to 0.14
Total errors	−23.55 (74.44)	0.00 (0.00)	−5.75 (2.15)**	−5.63 (2.14)*	−0.12	−0.16	0.43	−1.52 to 0.49
RVP								
Probability of hits	0.66 (0.71)	−0.86 (0.38)*	−5.75 (2.15)**	−5.18 (2.10)*	−0.57	−0.63	0.79	−2.78 to 0.45
Probability of false alarm	−0.18 (0.11)	5.04 (2.42)*	−5.75 (2.15)**	−4.85 (2.14)*	−0.90	−1.03	0.66	−2.89 to −0.13*
A′ (target sensitivity)	0.41 (0.25)	−2.80 (1.06)**	−5.75 (2.15)**	−4.59 (2.10)*	−1.16	−1.24	0.80	−3.07 to 0.02
B″ (response bias)	1.66 (0.67)*	−1.13 (0.39)**	−5.75 (2.15)**	−3.87 (2.14)†	−1.87	−1.89	0.84	−4.38 to −0.68*
Mean latency (ms)	−828.97 (690.19)	0.00 (0.00)	−5.75 (2.15)**	−5.26 (2.16)*	−0.49	−0.54	0.66	−2.29 to 0.37
ADHD symptoms								
Inattention	−98.51 (28.48)***	0.06 (0.01)***	−5.75 (2.15)**	−0.27 (1.61)	−5.48	−5.41	1.51	−9.08 to −2.90*
Hyperactivity	−104.29 (25.14)***	0.04 (0.01)***	−5.75 (2.15)**	−1.93 (2.23)	−3.82	−3.85	1.60	−7.46 to −1.24*

SWM, Spatial working memory; RVP, rapid visual information processing; ADHD, attention-deficit/hyperactivity disorder; S.E., standard error; CI, confidence interval; *A′*, a signal detection measure of sensitivity to the target, regardless of response tendency; *B″*, a signal detection measure of the strength of trace required to elicit a response.

a represents the effect of frontostriatal general fractional anisotropy (GFA) on executive function (EF) or ADHD symptoms. *b* represents the effect of EF or ADHD symptoms on school functioning. *c* represents the total (direct and indirect) effect of frontostriatal GFA on school functioning. *c′* represents the direct effect of frontostriatal GFA on school functioning. The product of paths *a* and *b* represents the indirect effect of frontostriatal GFA on school functioning through EF or ADHD symptoms.

† $p<0.10$, * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Table 3. *Mediation effects for the link between caudate–medial prefrontal tracts and overall school functioning*

	Unstandardized estimates (S.E.)				Indirect effects			
Mediators	*a*	*b*	*c*	*c′*	*ab*	Bootstrap *ab*	S.E.	95% CI
Left caudate–medial prefrontal								
SWM								
Strategy utilization	−31.00 (18.45)	0.01 (0.01)	−3.68 (1.93)†	−3.44 (1.98)†	−0.24	−0.22	0.41	−1.60 to 0.29
Total errors	−91.65 (63.77)	0.00 (0.00)	−3.68 (1.93)†	−3.30 (1.96)†	−0.37	−0.39	0.44	−1.86 to 0.13
RVP								
Probability of hits	0.27 (0.62)	−0.93 (0.39)*	−3.68 (1.93)†	−3.43 (1.86)†	−0.25	−0.32	0.57	−1.82 to 0.59
Probability of false alarm	−0.23 (0.10)*	5.19 (2.55)*	−3.68 (1.93)†	−2.49 (1.97)	−1.19	−1.29	0.66	−2.78 to −0.23*
A′ (target sensitivity)	0.25 (0.22)	−3.04 (1.06)**	−3.68 (1.93)†	−2.93 (1.84)	−0.75	−0.82	0.59	−2.06 to 0.29
B″ (response bias)	1.45 (0.58)*	−1.22 (0.40)**	−3.68 (1.93)†	−1.90 (1.90)	−1.78	−1.78	0.66	−3.51 to −0.80*
Mean latency (ms)	−514.52 (604.58)	0.00 (0.00)	−3.68 (1.93)†	−3.34 (1.91)†	−0.34	−0.35	0.43	−1.49 to 0.26
ADHD symptoms								
Inattention	−78.09 (25.23)**	0.06 (0.01)***	−3.68 (1.93)†	0.82 (1.38)	−4.49	−4.41	1.44	−7.91 to −2.17*
Hyperactivity	−73.90 (22.94)**	0.04 (0.01)***	−3.68 (1.93)†	−0.78 (1.86)	−2.90	−2.86	1.09	−5.69 to −1.30*
Right caudate–medial prefrontal								
SWM								
Strategy utilization	−30.83 (25.65)	0.01 (0.01)	−5.95 (2.62)*	−5.69 (2.66)*	−0.26	−0.23	0.49	−2.04 to 0.26
Total errors	−83.16 (88.52)	0.00 (0.00)	−5.95 (2.62)*	−5.59 (2.63)*	−0.36	−0.34	0.56	−2.79 to 0.20
RVP								
Probability of hits	1.20 (0.84)	−0.83 (0.40)*	−5.95 (2.62)*	−4.95 (2.59)†	−1.00	−1.20	1.05	−3.38 to 0.61
Probability of false alarm	−0.21 (0.14)	5.24 (2.45)*	−5.95 (2.62)*	−4.84 (2.59)†	−1.11	−1.12	0.70	−3.20 to −0.23*
A′ (target sensitivity)	0.63 (0.30)*	−2.82 (1.09)*	−5.95 (2.62)*	−4.18 (2.59)	−1.76	−1.81	1.07	−4.50 to −0.09*
B″ (response bias)	2.14 (0.80)**	−1.17 (0.40)**	−5.95 (2.62)*	−3.44 (2.61)	−2.51	−2.45	1.05	−5.09 to −0.84*
Mean latency (ms)	−837.30 (829.03)	0.00 (0.00)	−5.95 (2.62)*	−5.42 (2.61)*	−0.53	−0.54	0.78	−2.95 to 0.43
ADHD symptoms								
Inattention	−123.66 (33.75)***	0.06 (0.01)***	−5.95 (2.62)*	1.21 (1.95)	−7.16	−7.10	1.98	−12.08 to −3.84*
Hyperactivity	−120.17 (30.41)***	0.04 (0.01)***	−5.95 (2.62)*	−1.33 (2.66)	−4.62	−4.59	1.69	−8.64 to −1.83*

SWM, Spatial working memory; RVP, rapid visual information processing; ADHD, attention-deficit/hyperactivity disorder; S.E., standard error; CI, confidence interval; *A′*, a signal detection measure of sensitivity to the target, regardless of response tendency; *B″*, a signal detection measure of the strength of trace required to elicit a response.

a represents the effect of frontostriatal general fractional anisotropy (GFA) on executive function (EF) or ADHD symptoms. *b* represents the effect of EF or ADHD symptoms on school functioning. *c* represents the total (direct and indirect) effect of frontostriatal GFA on school functioning. *c′* represents the direct effect of frontostriatal GFA on school functioning. The product of paths *a* and *b* represents the indirect effect of frontostriatal GFA on school functioning through EF or ADHD symptoms.

† $p<0.10$, * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Table 4. *Mediation effects for the link between caudate–dorsolateral prefrontal tracts and overall school functioning*

	Unstandardized estimates (S.E.)				Indirect effects			
Mediators	*a*	*b*	*c*	*c′*	*ab*	Bootstrap *ab*	S.E.	95% CI
Left caudate–dorsolateral								
SWM								
Strategy utilization	−31.72 (20.28)	0.01 (0.01)	−4.43 (2.10)*	−4.19 (2.15)†	−0.24	−0.21	0.42	−1.68 to 0.30
Total errors	−100.30 (69.88)	0.00 (0.00)	−4.43 (2.10)*	−4.04 (2.13)†	−0.40	−0.43	0.48	−1.88 to 0.19
RVP								
Probability of hits	0.46 (0.68)	−0.90 (0.39)*	−4.43 (2.10)*	−4.02 (2.03)†	−0.41	−0.54	0.74	−2.42 to 0.56
Probability of false alarm	−0.18 (0.11)	5.29 (2.47)*	−4.43 (2.10)*	−3.50 (2.08)†	−0.93	−1.08	0.69	−2.89 to −0.17*
A′ (target sensitivity)	0.25 (0.24)	−3.03 (1.05)**	−4.43 (2.10)*	−3.69 (2.00)†	−0.74	−0.79	0.73	−2.51 to 0.44
B″ (response bias)	1.31 (0.65)*	−1.21 (0.39)**	−4.43 (2.10)*	−2.85 (2.03)	−1.58	−1.58	0.64	−3.25 to −0.61*
Mean latency (ms)	−442.01 (664.08)	0.00 (0.00)	−4.43 (2.10)*	−4.14 (2.08)†	−0.30	−0.32	0.52	−1.80 to 0.50
ADHD symptoms								
Inattention	−91.59 (27.32)**	0.06 (0.01)***	−4.43 (2.10)*	0.84 (1.53)	−5.27	−5.23	1.61	−8.88 to −2.45*
Hyperactivity	−95.14 (24.29)***	0.04 (0.01)***	−4.43 (2.10)*	−0.70 (2.12)	−3.74	−3.67	1.25	−6.77 to −1.67*
Right caudate–dorsolateral								
SWM								
Strategy utilization	−26.35 (24.39)	0.01 (0.01)	−7.22 (2.41)**	−7.02 (2.45)**	−0.20	−0.17	0.36	−1.58 to 0.19
Total errors	−72.90 (84.08)	0.00 (0.00)	−7.22 (2.41)**	−6.92 (2.42)**	−0.30	−0.25	0.48	−2.19 to 0.23
RVP								
Probability of hits	1.16 (0.79)	−0.78 (0.39)*	−7.22 (2.41)**	−6.31 (2.39)*	−0.91	−1.03	0.99	−3.60 to 0.32
Probability of false alarm	−0.14 (0.13)	5.23 (2.35)*	−7.22 (2.41)**	−6.47 (2.36)**	−0.75	−0.86	0.69	−2.95 to 0.00
A′ (target sensitivity)	0.54 (0.28)†	−2.67 (1.06)*	−7.22 (2.41)**	−5.77 (2.38)*	−1.44	−1.46	0.88	−3.46 to 0.04
B″ (response bias)	1.74 (0.77)*	−1.10 (0.39)**	−7.22 (2.41)**	−5.30 (2.38)*	−1.92	−1.94	0.93	−4.43 to −0.55*
Mean latency (ms)	−618.85 (789.10)	0.00 (0.00)	−7.22 (2.41)**	−6.83 (2.39)**	−0.39	−0.41	0.66	−2.62 to 0.46
ADHD symptoms								
Inattention	−112.43 (32.31)***	0.05 (0.01)***	−7.22 (2.41)**	−1.10 (1.83)	−6.12	−5.92	1.82	−10.53 to −2.99*
Hyperactivity	−106.02 (29.36)***	0.03 (0.01)***	−7.22 (2.41)**	−3.53 (2.44)	−3.68	−3.86	1.71	−7.85 to −1.05*

SWM, Spatial working memory; RVP, rapid visual information processing; ADHD, attention-deficit/hyperactivity disorder; S.E., standard error; CI, confidence interval; *A′*, a signal detection measure of sensitivity to the target, regardless of response tendency; *B″*, a signal detection measure of the strength of trace required to elicit a response.

a represents the effect of frontostriatal general fractional anisotropy (GFA) on executive function (EF) or ADHD symptoms. *b* represents the effect of EF or ADHD symptoms on school functioning. *c* represents the total (direct and indirect) effect of frontostriatal GFA on school functioning. *c′* represents the direct effect of frontostriatal GFA on school functioning. The product of paths *a* and *b* represents the indirect effect of frontostriatal GFA on school functioning through EF or ADHD symptoms.

† $p<0.10$, * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

of the relationships between frontostriatal tract integrity and school functioning. Specifically, altered white matter integrity in the frontostriatal tracts was related to poor response inhibition (*B*″ in RVP), which then led to more school adjustment problems. Moreover, a measure of target sensitivity or vigilance (*A*′ in RVP) significantly mediated the associations of the right caudate–MPFC tract and the left caudate–OFC tract with school functioning. The probability of false alarms in RVP also significantly mediated the associations between the left caudate–MPFC tract and school functioning. Given that successful performance on the RVP requires sustained attention, vigilance and inhibition control (Shang *et al.* 2013), these findings collectively suggest that altered frontostriatal integrity may compromise cognitive functions in these areas. This is not surprising given that myelination of axons and increased fiber density and packing help to facilitate axonal signaling and transmission, thereby giving rise to greater efficiency in cognitive performance (Mabbott *et al.* 2006). Additionally, these findings are consistent with previous research showing that deficits in neural circuits linking regions of the PFC and the striatum are associated with impairment in EF or cognitive function such as cognitive control (Casey *et al.* 1997; Koechlin *et al.* 2003; Liston *et al.* 2006; Cubillo *et al.* 2012; Shang *et al.* 2013), sustained attention (Cubillo *et al.* 2012; Shang *et al.* 2013) and response inhibition (Rubia *et al.* 2010).

Deficits in cognitive functions, in turn, further predicted poor school functioning. Youths with impairment in sustained attention or response inhibition often experience difficulties staying on task for a prolonged period of time (Klarborg *et al.* 2013) or are unable to inhibit impulsive acts or inappropriate, irrelevant responses, all of which are crucial for effective learning and positive social interactions (Barkley, 1997; Uekermann *et al.* 2010). Together, our findings complement and extend the existing research and suggest a possibility that impaired school functioning, a common correlate of ADHD, may be accounted for by deficits in EF (sustained attention, vigilance and response inhibition in particular) that arise from compromised white matter integrity, at least in the frontostriatal regions. Nonetheless, it is important to note that, in half of the cases where mediation effects were significant, measures in the RVP task only partially mediated the associations between frontostriatal tract integrity and school functioning, implying that other mediating processes or mechanisms may be involved. This would be an interesting avenue for future research.

Surprisingly, unlike previous studies linking working memory to the bilateral ventrolateral PFC in adults with ADHD (Wolf *et al.* 2009), to the left frontoparietal networks in TD children (Vestergaard *et al.* 2011) and to the left caudate–OFC tract integrity in children with ADHD (Shang *et al.* 2013), we did not find a significant association between white matter integrity of the frontostriatal tracts and spatial working memory. In addition, measures for working memory were not associated with children's school functioning, which is unexpected given that deficits in working memory have been shown to contribute to inefficient learning, behavioral problems and underachievement in not only children with ADHD (Rapport *et al.* 1999) but also TD children (Jarvis & Gathercole, 2003). These null findings may be attributable to Type II errors because of the small sample used in the mediation analyses. Future studies with a larger sample are needed.

Importantly, we also found evidence to support the hypothesis that both inattention and hyperactivity symptoms may be the mechanisms linking the frontostriatal integrity to children's school functioning. Specifically, altered white matter integrity of all four pairs of bilateral frontostriatal tracts was significantly associated with behavior ratings of both inattention and hyperactivity/impulsivity. This is consistent with a few studies showing that decreased frontostriatal FA was related to teacher-reported attention problems (in normal controls) (de Zeeuw *et al.* 2012) and that frontostriatal GFA values were correlated with symptoms of inattention (Shang *et al.* 2013; Wu *et al.* 2014) and hyperactivity/impulsivity (Shang *et al.* 2013) in children with ADHD. Both inattention and hyperactivity, in turn, were related to impaired school functioning, which has been well documented in previous research (Hinshaw, 1992; Biederman *et al.* 1993; Barkley, 1997; Loe & Feldman, 2007). Our findings extend beyond the current literature by showing that impaired white matter integrity of the frontostriatal tracts may represent an important neurobiological underpinning of ADHD symptoms that are often associated with greater risks for maladaptive functioning in a wide range of life domains in children and adolescents including school, academic and social areas.

Limitations

Our findings should be interpreted in light of the following limitations. First, the reported mediations in this study imply that disturbed microstructural integrity of the frontostriatal fiber pathways results in executive dysfunction and ADHD symptoms, which then lead to impaired school functioning assessed 1–3 months later. However, data from this cross-sectional study are correlational in nature; thus, causality among the study variables remains to be determined. Relatedly, some of the mediators were highly correlated with each other (e.g. r=0.71 between

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inattention and hyperactivity/impulsivity); thus, we were not able to test all the mediators simultaneously in a single model and contrast their specific mediation effects because of the collinearity problem. Second, although our sample size was moderate, relative to other DTI and DSI studies, the total sample of 64 children may still be underpowered to detect some significant mediation effects. In this connection, most of the significant mediation effects were only observed in the overall sample and not within subsamples of youths with ADHD or TD youths, presumably because of restricted ranges of variances in the study variables within groups. Thus, the present findings require validation from future research with larger samples. Third, we did not correct for multiple comparisons in our analyses given the scarce literature on this topic. However, we did use bootstrapping and reported the magnitudes and CIs of the estimates, which should aid in the evaluation of the importance and significance of the findings. Research in an independent sample is necessary to replicate and validate the present findings. Fourth, the majority of the sample were male, and the numbers of participants by ADHD subtypes were relatively small, which precluded us from testing whether our results may have varied by gender or ADHD subtype. Future research with a focus on gender or subtype differences would be informative. Fifth, some children with ADHD in this study had been treated with methylphenidate at some point in their life, although they were not exposed to any medication at least 1 week before assessment. This may have influenced the results. Sixth, we did not specifically investigate the extent to which developmental age influenced the results of the study; instead, we controlled for the effect of age by using a matched design and inclusion of age as a covariate in the analyses. Longitudinal studies with a larger sample size that examine the organization and structure of white matter in the frontostriatal tracts over developmental course and the impact on children's EF, ADHD symptoms and school functioning would greatly advance this field. Finally, the present study only focused on the frontostriatal tracts. It has been documented that the abnormalities in white matter microstructure observed in ADHD are likely to be widespread and not restricted to the frontostriatal networks (Liston *et al.* 2011; van Ewijk *et al.* 2014). Future work that includes control tract(s) with no hypothesized link to EF, ADHD symptoms and school function may help to rule out the possibility of global alterations in the white matter microstructure in contributing to the present findings. Additionally, future research on the frontotemporal (Konrad *et al.* 2010) and fronto-striato-parieto-cerebellar (Rubia *et al.* 2009) networks that may be associated with executive dysfunction in ADHD is warranted. This study also only included tasks that tapped 'cool' EF (Zelazo & Carlson, 2012). Research on the 'hot' affective aspects of EF associated with orbitofrontal and medial PFC (Zelazo & Carlson, 2012) will enhance our understanding of emotional dysregulation, impulsivity and the processing of reward and salience, which are highly relevant for the study of ADHD.

Conclusions

The present study, using DSI, provides the first data to demonstrate the importance of white matter integrity in the frontostriatal networks to children's school functioning. Our findings further suggest that altered white matter integrity of the frontostriatal tracts is linked to poor school functioning through deficits in sustained attention and inhibitory control, along with symptoms of inattention and hyperactivity.

Supplementary material

For supplementary material accompanying this paper, please visit http://dx.doi.org/10.1017/S0033291714001664.

Declaration of Interest

None.

Acknowledgments

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