

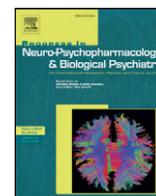
PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/154999>

Please be advised that this information was generated on 2019-11-20 and may be subject to change.



Deviant white matter structure in adults with attention-deficit/hyperactivity disorder points to aberrant myelination and affects neuropsychological performance



A. Marten H. Onnink^{a,c}, Marcel P. Zwiers^b, Martine Hoogman^c, Jeanette C. Mostert^{b,c}, Janneke Dammers^{a,c}, Cornelis C. Kan^a, Alejandro Arias Vasquez^{a,c,d}, Aart H. Schene^a, Jan Buitelaar^{d,e}, Barbara Franke^{a,c,*}

^a Department of Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

^b Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging, Radboud University Nijmegen, Nijmegen, The Netherlands

^c Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

^d Department of Cognitive Neurosciences, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

^e Karakter Child and Adolescent Psychiatric University Centre, Nijmegen, The Netherlands

ARTICLE INFO

Article history:

Received 9 February 2015

Received in revised form 27 April 2015

Accepted 27 April 2015

Available online 5 May 2015

Keywords:

Adult ADHD

Cognitive performance

Corpus callosum

DTI

Radial diffusivity

Symptom severity

ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) in childhood is characterized by gray and white matter abnormalities in several brain areas. Considerably less is known about white matter microstructure in adults with ADHD and its relation with clinical symptoms and cognitive performance. In 107 adult ADHD patients and 109 gender-, age- and IQ-matched controls, we used diffusion tensor imaging (DTI) with tract-based spatial statistics (TBSS) to investigate whole-skeleton changes of fractional anisotropy (FA) and mean, axial, and radial diffusivity (MD, AD, RD). Additionally, we studied the relation of FA and MD values with symptom severity and cognitive performance on tasks measuring working memory, attention, inhibition, and delay discounting. In comparison to controls, participants with ADHD showed reduced FA in corpus callosum, bilateral corona radiata, and thalamic radiation. Higher MD and RD were found in overlapping and even more widespread areas in both hemispheres, also encompassing internal and external capsule, sagittal stratum, fornix, and superior lateral fasciculus. Values of FA and MD were not associated with symptom severity. However, within some white matter clusters that distinguished patients from controls, worse inhibition performance was associated with reduced FA and more impulsive decision making was associated with increased MD. This study shows widespread differences in white matter integrity between adults with persistent ADHD and healthy individuals. Changes in RD suggest aberrant myelination as a pathophysiological factor in persistent ADHD. The microstructural differences in adult ADHD may contribute to poor inhibition and greater impulsivity but appear to be independent of disease severity.

© 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood psychiatric disorder with an estimated prevalence around 5.3% in childhood that persists through adolescence reaching a prevalence of up to 4.9% in adults (Simon et al., 2009). ADHD is associated with global and regional brain volume reductions. Meta-analytic findings show reductions in total cerebral volume, in frontal lobes, cingulate cortex,

and corpus callosum; in addition, robust evidence exists for decreased gray matter volume in subcortical areas (Ellison-Wright et al., 2008; Frodl and Skokauskas, 2012; Nakao et al., 2011; Valera et al., 2007). Differences in subcortical structures such as the putamen and caudate seem to disappear with increasing age (Castellanos et al., 2002; Nakao et al., 2011). Moreover, longitudinal studies show a delay in the age by which peak cortical thickness is reached in ADHD patients (Shaw et al., 2007), which has led to the suggesting that ADHD may be the outcome of a maturational lag that eventually normalizes (Rubia, 2007). More recent results of longitudinal studies indicate, however, that reductions in basal ganglia, which were detected in childhood, persisted into adolescence (Shaw et al., 2014). Cross-sectional studies in adults with ADHD also point to persistent gray matter reductions in subcortical volumes (Frodl et al., 2010; Onnink et al., 2014; Proal et al., 2011; Seidman et al., 2011) as well as in cortical areas (Ahrendts et al., 2011;

Abbreviations: ADHD, Attention-deficit/hyperactivity disorder; DTI, Diffusion tensor imaging; TBSS, Tract-based spatial statistics; FA, Fractional anisotropy; MD, Mean diffusivity; AD, Axial diffusivity; RD, Radial diffusivity; ROI, Region of interest; SAD, Sustained attention dots; SART, Sustained attention to response task.

* Corresponding author at: Radboud University Medical Center, Department of Human Genetics (855), PO Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 24 3614017.

E-mail address: barbara.franke@radboudumc.nl (B. Franke).

Amico et al., 2011; Biederman et al., 2008; Makris et al., 2007; Seidman et al., 2006, 2011), and in cerebellar regions (Proal et al., 2011; Seidman et al., 2011).

Over the last decade, the focus of neuroimaging research has widened from studies of regional volume alterations to studies of altered white matter connections within and among several neural networks (Konrad and Eickhoff, 2010). Advances in diffusion tensor imaging (DTI) allowed non-invasive investigation of white matter tracts connecting cortical and subcortical regions (Thomason and Thompson, 2011). DTI probes both the microstructural organization and the myelination of white matter through measuring the diffusion of water molecules in the tissue (Beaulieu, 2002; Le Bihan et al., 2001). Commonly used parameters are fractional anisotropy (FA) and mean diffusivity (MD), which reflect the preferential directionality of water diffusion along white matter tracts and the magnitude of diffusion, respectively (Le Bihan et al., 2001). Although decreased FA is a characteristic of impaired white matter integrity, its exact neurobiological meaning is not fully understood (Beaulieu, 2002).

Impaired white matter integrity has been found in numerous psychiatric disorders including major depressive disorder (Korgaonkar et al., 2011), bipolar disorder (Barysheva et al., 2013), schizophrenia (Mandl et al., 2013) and ADHD. A meta-analysis in children, adolescents, and adults with ADHD provided evidence of microstructural abnormalities in areas such as the anterior corona radiata (ACR), forceps minor, bilateral internal capsule, and cerebellum (van Ewijk et al., 2012). This meta-analysis only included hypothesis-free whole-brain voxelwise (VBA) approaches and could not provide directionality of findings (e.g., higher or lower FA in ADHD). Hypothesis-driven region of interest (ROI) studies reported that ADHD is in general associated with lower FA in the corpus callosum (Cao et al., 2010), cerebellum (Bechtel et al., 2009), and in several fronto-striatal tracts (Hamilton et al., 2008; Pavuluri et al., 2009; Shang et al., 2013; Wu et al., 2014). Some studies revealed that ADHD patients had higher FA (de Zeeuw et al., 2012; Silk et al., 2009; Tamm et al., 2012) in fronto-striatal regions when compared with healthy controls. A recent study found clusters of decreased FA and MD in most of the major white matter tracts and concluded that white matter alterations are a wide-ranging rather than localized feature in children and adolescents with ADHD (van Ewijk et al., 2014). Analyses using graph theory in combination with whole-brain DTI (e.g., brain connectomics) revealed similarly that, in children and adolescents with ADHD, decreased white matter connectivity in fronto-striatal circuits extended to a larger brain network which encompassed additional cortico-cortical, subcortical, and cerebellar circuits (Hong et al., 2014). The few available DTI studies of adult ADHD patients to date showed decreased FA in tracts such as the cingulum bundle (Makris et al., 2008), the inferior longitudinal fasciculus (ILF) (Konrad et al., 2012), the superior longitudinal fasciculus (SLF) (Cortese et al., 2013; Makris et al., 2008), and the corpus callosum (Dramsahl et al., 2012). Although the current ADHD literature lacks longitudinal DTI studies, decreased FA has been reported in persistent and remitted adult patients with ADHD in comparison with healthy controls. These persistent findings were observed in areas including the corona radiata, sagittal stratum, the retrolenticular internal capsule, and the SLF (Cortese et al., 2013). Conversely, another study found that remitted adult patients did not differ significantly from controls, while patients with persistent ADHD had decreased FA in the uncinate and inferior fronto-occipital fasciculi (Shaw et al., 2015).

Decreased FA is typically accompanied by increased MD values in studies of ADHD. Increased MD is related with decreased cellular density (Alexander et al., 2007) and may reflect abnormalities in ADHD more sensitively than FA (de Luis-Garcia et al., 2015; Lawrence et al., 2013). Moreover, decreased FA might result from increased radial diffusivity (RD) and/or reduced axial diffusivity (AD) (Alexander et al., 2007). While the biological correlates of those measures are not yet entirely clarified, decreases in AD are currently thought to indicate axonal damage or degeneration, and increases in RD with minimal changes

in AD are thought to indicate increased freedom of cross-fibre diffusion and possibly decreased myelination (Alexander et al., 2007; Song et al., 2002). Reporting changes in RD and AD could potentially help elucidate the FA findings in studies of ADHD. In the ADHD childhood literature, reports on RD have shown the entire range from increased RD (Helpern et al., 2011; Nagel et al., 2011) to decreased RD (Silk et al., 2009), and one study reported no change in RD (Tamm et al., 2012). Increased AD (together with an increased FA) has been reported in two childhood studies (Silk et al., 2009; Tamm et al., 2012). A recent study in adult ADHD patients suggested that reductions of FA were driven by changes in RD rather than AD (Shaw et al., 2015).

In addition to case-control comparisons, some studies investigated the behavioural implications of changed white matter variation in patients with ADHD by looking at its association with clinical symptoms or cognitive measures. Although findings in the ADHD literature are heterogeneous and complex, most studies have found that increasing symptom severity was associated with decreased FA (Ashtari et al., 2005; Nagel et al., 2011; Shang et al., 2013), but also with higher FA (Peterson et al., 2011; van Ewijk et al., 2014). In an adult ADHD study, attentional performance correlated with FA and MD in the right SLF, and measures of impulsivity correlated with FA in right orbitofrontal fibre tracts (Konrad et al., 2010).

Taken together, there is strong evidence for wide-spread white matter differences in ADHD patients compared to controls, and these may be related to ADHD symptomatology and cognitive functioning. Findings in the ADHD literature differ in precise location and directionality, which makes comparison of studies difficult. This is likely due to differences in sample characteristics (e.g., gender, age ranges), small sample sizes, and methodological differences (e.g., use of VBA versus ROI approaches). Relative to childhood and adolescent ADHD studies, there are few DTI studies in adult patients, and those are hampered by small sample sizes and by the use of ROIs instead of whole-brain approaches (except for the study by Cortese et al. (2013)). In adult ADHD, only few studies investigated AD and RD (Shaw et al., 2015), associations with ADHD symptomatology (Dramsahl et al., 2012; Shaw et al., 2015), and cognitive performance (Konrad et al., 2012). Therefore, an overall picture of white matter pathology in adult ADHD is currently lacking.

In this study, we used DTI to comprehensively compare white matter variation in adults with ADHD and healthy controls. We investigated values of FA, MD, AD, and RD using tract-based spatial statistics (TBSS), which is a whole-skeleton voxel-by-voxel analysis (Smith et al., 2006). Within the ADHD group, we investigated associations of FA and MD with clinical symptom scores and cognitive measures. These cognitive measures were selected to cover prominent cognitive domains commonly affected in adults with ADHD (e.g., working memory, attention, inhibition, and delay discounting/impulsivity). Based on the current literature, we expected to find (a) widespread decreases of FA and increases of MD and RD in ADHD, and (b) associations of FA with symptom severity and cognitive performance.

2. Materials and methods

2.1. Subjects and procedure

In total, 216 individuals (107 patients with persistent ADHD, 109 healthy controls) from the Dutch cohort of the International Multicentre persistent ADHD Collaboration (IMpACT) (Franke et al., 2010) participated in this study. The patients and an age-, gender-, and IQ-matched group of healthy controls were recruited through the Department of Psychiatry of the Radboud University Medical Center and through advertisements.

Patients were included if they met DSM-IV-TR criteria for ADHD in childhood as well as adulthood, as assessed by a psychiatrist. At the time of inclusion into the study, participants were assessed using the Diagnostic Interview for Adult ADHD (DIVA) (Kooij, 2010). This

Table 1
Demographic, clinical, and cognitive characteristics of ADHD patients and healthy controls (HC).

	ADHD (N = 107)	HC (N = 109)	Test of significance
Gender (males/females)	41/66	47/62	$\chi^2 = 0.51, p = .47$
Age (years)	35.00 ± 10.30	36.08 ± 10.97	$t(1,214) = 0.74, p = .46$
IQ ^a	108.13 ± 14.43	110.97 ± 15.36	$t(1,214) = 1.40, p = .16$
Inattention symptoms ^b	7.27 ± 1.56	0.59 ± 1.29	$t(1,214) = -34.48, p < .0001$
Hyperactivity/impulsivity symptoms ^b	5.65 ± 2.36	0.59 ± 1.12	$t(1,214) = -19.96, p < .0001$
Digit span ^c	6.77 ± 2.2	7.53 ± 2.38	$F(1,208) = 6.56, p < .01$
SAD ^d	3.53 ± 0.26	3.42 ± 0.19	$F(1,202) = 11.94, p < .001$
SART ^e	11.02 ± 4.76	9.29 ± 5.04	$F(1,187) = 5.31, p = .02$
Delay discounting ^f	0.038 ± 0.064	0.010 ± 0.015	$F(1,187) = 16.31, p < .0001$
DTI acquisition protocol ^g	35 (33%)	23 (21%)	$\chi^2 = 3.71, p = .05$
One or more depressive episode(s) (remitted) ^h	52 (57%)	12 (11%)	
Anxiety disorder (remitted) ^h	22 (23%)	6 (6%)	
Substance use disorder (remitted) ^h	21 (20%)	6 (6%)	
Borderline Personality D ^h	10 (9%)	–	
Medication-naive	20 (19%)	–	
On stimulant medication	64 (60%)	–	
Medication in the past	14 (13%)	–	
On atomoxetine	9 (8%)	–	

Demographic information representing means ± standard deviations or percentage per group.

^a Prorated from Block Design and Vocabulary of WAIS-III-R.

^b As measured with the ADHD-DSM-IV Self Rating scale (Kooij et al., 2005).

^c Digit Span raw backwards score (working memory).

^d Errors Sustained Attention Dots (SAD) task (attention).

^e Commission errors Sustained Attention to Response Task (SART) (inhibition).

^f Score on Delay Discounting task (impulsivity).

^g First version of DTI acquisition protocol.

^h As measured by the Structured Clinical Interview for DSM-IV for axis I (Groenestijn et al., 1999) and axis II (Weertman et al., 2000) disorders.

interview focuses on the 18 DSM symptoms of ADHD and uses concrete and realistic examples to thoroughly investigate, whether a symptom is currently present or was present in childhood. In order to obtain information about ADHD symptoms and impairment in childhood, additional information was acquired from parent and school reports, whenever possible. The Structured Clinical Interview for DSM-IV (SCID-I & SCID-II) was used for comorbidity assessment (see Table 1). Assessments were carried out by trained professionals (psychiatrists or psychologists). In addition, a quantitative measure of clinical symptoms was obtained using the ADHD-DSM-IV Self Rating scale (Kooij et al., 2005).

Exclusion criteria for participants were psychosis, alcohol or substance use disorder in the last 6 months, current major depression, full-scale IQ estimate <70 (assessed using the Wechsler Adult Intelligence Scale-III), neurological disorders, sensorimotor disabilities, non-Caucasian ethnicity, and medication use other than psychostimulants, atomoxetine, or bupropion. An additional exclusion criterion for the healthy control subjects was a current neurological or psychiatric disorder according to SCID-I and SCID-II. This study was approved by the regional ethics committee (Centrale Commissie Mensgebonden Onderzoek: CMO Regio Arnhem–Nijmegen; Protocol number III.04.0403). Written informed consent was obtained from all participants.

2.2. Acquisition of diffusion-weighted images

Whole-brain imaging was performed with a 1.5 Tesla MR scanner (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) and a standard 8 channel head coil. A 3D T1-weighted MPRAGE anatomical scan was obtained from each subject (Repetition Time (TR) = 2730 ms, Echo Time (TE) = 2.95 ms, Inversion Time (TI) = 1000 ms, flip angle = 7°, field of view = 256 × 256 × 176 mm³, voxel size = 1.0 × 1.0 × 1.0 mm³). The T1 images served as high resolution anatomical reference image for diffusion imaging data. Transversely oriented diffusion-weighted images were acquired using a twice-refocused spin-echo-planar-imaging sequence that minimized imaging distortions from eddy currents (Reese et al., 2003). The diffusion imaging data were acquired using two different protocols. Fifty-eight subjects

were scanned with the following protocol: TR = 10200 ms, TE = 95 ms, field of view = 320 × 320 × 160 mm³, voxel size = 2.5 × 2.5 × 2.5 mm³, 6/8 partial Fourier. Four images without diffusion-weighting (b = 0 s/mm²) and 30 images with diffusion-weighting (b = 900 s/mm², diffusion directions = 34) applied along non-collinear directions were acquired. The remaining 158 subjects were scanned with an improved second protocol, which was implemented to reduce motion artifacts during scanning. Parameters that differed from the first protocol were TR (6700 ms), TE (85 ms), field of view (220 × 220 × 140 mm³), and scans were acquired with full Fourier acquisition, other parameters were unchanged. For each slice, the diffusion-weighting for the 30 images changed to b = 900 s/mm². Acquisition protocol was included as covariate in all analyses.

2.3. Preprocessing and skeletonization of diffusion-weighted images

The diffusion-weighted data was preprocessed using an in-house developed algorithm. In short, the diffusion-weighted images of each subject were realigned on the unweighted image using mutual information routines from SPM8 (Wellcome Trust Center for Neuroimaging). Next, an iteratively reweighted-least-squares algorithm (PATCH) was used to robustly correct for head and cardiac motion artifacts in the diffusion-weighted data (Zwiers, 2010). Using DTIFIT from the FMRIB's Diffusion Toolbox (part of FMRIB's Software Library (FSL)), FA images were created and subsequently fed into the TBSS pipeline (Smith et al., 2006). Here, all individual FA maps were nonlinearly registered to the FMRIB58_FA template using FSL's nonlinear registration tool FNIRT. Then, the nonlinear transforms found in the previous stage were applied to all subjects to bring them into standard Montreal Neurological Institute (MNI) space. A mean FA image was created and thinned to create a mean FA skeleton which represents the centres of all tracts common to the group. A threshold of 0.2 was used to avoid partial voluming effects. Individual FA images were then mapped onto this skeleton resulting in a skeletonized FA image for each individual. Finally, each participant's FA, MD, AD, and RD image was projected onto this skeleton, and resulting data were used for voxel-wise statistics.

2.4. Neuropsychological assessment

Cognitive functioning of participants was assessed by a neuropsychological test battery that was composed to cover multiple cognitive domains earlier found affected in ADHD (Mostert et al., submitted for publication): (i) working memory, assessed via the WAIS-III Digit Span task (Wechsler, 1997); (ii) attention, measured with the response bias variable of the Sustained Attention Dots task (De Sonneville, 1999); (iii) inhibition, tested via the Sustained Attention to Response Task (SART) (Smit et al., 2004); and (iv) delay discounting/impulsivity assessed via the Delay Discounting task (Dom et al., 2006). Assumptions with respect to the residuals were checked and neuropsychological measures were log-transformed if necessary to achieve a normal distribution. Outliers were defined as having a score more extreme than 4-times the standard deviation above or below the mean per group. Details of task and outcome measures are described in Supplementary Table S1.

2.5. Statistical analysis

First, we performed a between-subject whole-skeleton voxel-wise analysis using TBSS, in which we compared patients to control subjects on values of FA, MD, AD, and RD. In all analyses, gender, age, and scan acquisition protocol were included in the model as nuisance regressors. Threshold-free cluster enhancement (TFCE) was applied to obtain cluster-wise statistics corrected for multiple comparisons. Briefly, this method transforms local T-statistics into TFCE statistics that reflect both the size of the local effect (or “height”) and the cluster extent (Smith and Nichols, 2009). With the obtained TFCE maps, “randomize” then calculates a p-value (p-corrected) for each voxel, corrected for whole-skeleton family-wise error (FWE) rate via permutation testing (5000 permutations). The TFCE-corrected p-value maps were thresholded at $P_{FWE} = 0.05$, and we report regions that contained clusters of at least ten contiguous suprathreshold voxels. Significant results were localized to anatomical locations using the Johns Hopkins University (JHU)—ICBM-DTI-81 white matter labels atlas (Mori et al., 2008) and the white matter tractography atlas (Hua et al., 2008). To estimate the effect size of significant clusters, spatially averaged scores were calculated from significant clusters for each subject, and subsequently partial eta-squared was calculated using SPSS version 21 (IBM, Chicago, IL).

Secondly, within the ADHD group we performed two whole-skeleton regression analyses in TBSS similar to van Ewijk et al. (2014). This analysis was performed using self-reported symptom counts on both dimensions (inattention and hyperactivity/impulsivity) as two separate predictors. Gender, age, and scan acquisition protocol were included in the model as nuisance regressors. The TFCE-corrected p-value maps were thresholded at $P_{FWE} = 0.05$. In addition, two analyses were performed in the ADHD group to further investigate significant between-group findings from the first TBSS analysis in an ROI approach for their link with symptom severity. From each significant FA and MD cluster, an ROI mask was created and was then back-projected to the original images of each individual; subsequently, spatially averaged FA and MD values were obtained. Partial correlation analyses were performed (in SPSS) to identify correlations between the extracted average of FA and MD for each cluster and self-reported symptom count on both dimensions, adjusting for gender, age, and scan acquisition protocol.

Third, similar partial correlation analyses as listed above were performed (in SPSS) for the extracted average of FA and MD (for each cluster) and cognitive measures (working memory, attention, inhibition, delay discounting/impulsivity), adjusting for gender, age, and scan acquisition protocol. These partial correlation analyses were performed in the whole group. Post-hoc analyses were carried out for significant findings, in which the ADHD and control group were tested separately to explore potential group-specific effects. For the two latter analyses, Bonferroni correction was used and the p-value of 0.05 was

divided by the number of significant FA and MD clusters and multiplied by two for the analysis with symptom dimensions and multiplied by four for the analysis with the four cognitive measures.

Lastly, to explore whether stimulant medication or a history of comorbid major depressive disorder, the most frequent comorbidity of ADHD in our cohort, confounded our between-group results, general linear models (GLM) were used (in SPSS). The extracted mean values from the significant between-group FA, MD, RD, and AD clusters were included as dependent factors. For the GLM of medication, healthy controls ($N = 109$), medication-naïve patients ($N = 20$), and patients using stimulant treatment ($N = 64$) were added as between subject factors. For the GLM of depression history, healthy controls with no history of depressive episodes ($N = 95$), ADHD patients with no history of depressive episodes ($N = 43$), and ADHD patients with one or more episodes in the past ($N = 52$) were added as between subject factors. Post-hoc analyses were performed using Fisher's least significant difference (LSD).

3. Results

3.1. Demographic, clinical and cognitive measures

Across the two groups, there were no significant differences in age of participants or in gender distribution. As expected, patients with ADHD scored significantly higher on ADHD symptom counts and significantly worse on cognitive measures, compared to the control group. The details are summarized in Table 1.

3.2. Between-group TBSS analysis of white matter microstructure

The whole-skeleton voxel-based between-group analysis with TBSS identified several clusters of decreased FA and increased MD and RD in the ADHD group when compared to the control group (Table 2, Fig. 1). No regions of increased FA or reduced MD or RD were observed, and no differences were observed for AD. For FA, differences between patients and controls were located in the body and splenium of the corpus callosum, anterior and superior corona radiata, posterior thalamic radiation, and tapetum. For MD and RD, overlapping regions were found, although case-control differences were even more widespread in both right en left hemisphere, also encompassing internal and external capsule, sagittal stratum, fornix, and SLF. The same pattern of results was observed when the analysis for FA was limited to the single scan acquisition protocol on which most scans were performed ($N = 158$; Supplementary Table 4).

AD and RD are derived from three quantitative indices (i.e. eigenvalues— λ_1 , λ_2 , λ_3) that index tissue structure based on water molecule displacement. The first eigenvalue (λ_1) measures AD, while RD is the average of the second (λ_2) and third (λ_3) eigenvalue. As a consequence, the signal-to-noise ratio of RD is $\sqrt{2}$ (the square root of 2) times higher than that of AD, which results in less power (through higher standard errors) to detect AD differences than RD differences. The absence of significant AD clusters in conjunction with positive RD clusters in our sample might thus have been due to power differences. In order to clarify this, we extracted mean AD and RD with standard errors from the significant between-group FA clusters. As expected, we found that the standard error for AD ($3.14E-06$) was 1.27 times higher than the one for RD ($2.46E-06$). The mean RD values significantly higher in the ADHD group compared to controls, ($F(1, 211) = 18.880$, $p = .00002$), while mean AD values were not ($F(1, 211) = .739$, $p = .391$). Furthermore, when we decomposed RD by extracting mean λ_2 and λ_3 from the significant between-group FA clusters and compared them between patients and controls, we found significant differences between patients and controls for both λ_2 ($F(1, 211) = 18.901$, $p = .00002$) and λ_3 ($F(1, 211) = 16.719$, $p = .00006$).

Table 2
Clusters showing significant differences in Fractional Anisotropy (FA), Mean Diffusivity (MD), and Radial Diffusivity (RD) between ADHD patients (N = 107) and healthy controls (N = 109).

Cluster	White matter tracts overlapping with the clusters (size of overlap in >10 voxels) ^a	Size (voxels) ^b	MNI coordinates (x;y;z)	Partial eta ^{2c}	p ^d
<i>Clusters with significantly lower FA in ADHD patients</i>					
1	Body and splenium of CC	453	−1;−26;23	.080	.042
2	Splenium of CC, SCR (R), PCR (R)	141	24;−35;28	.062	.046
3	Body of CC, SCR (R)	140	17;−24;33	.068	.040
4	Splenium of CC	56	16;−36;29	.055	.049
5	PCR (R)	32	18;7;34	.048	.049
6	PTR (R), Tapetum (R)	16	30;−51;15	.037	.049
<i>Clusters with significantly higher MD in ADHD patients</i>					
1	Body, splenium and genu of CC, EC (L + R), ACR (L + R), PCR (L + R), SCR (L), posterior limb of IC (L + R), retrolenticular part of IC (L + R), anterior limb of IC (L), sagittal stratum (R), cingulum, fornix (cres)/stria terminalis (L), CP (L), PTR (L + R), SFOF (L), fornix (cres)/Stria terminalis (R)	6763	37;−31;5	.153	.037
2	SLF (L)	407	−49;−38;12	.126	.042
3	EC (L)	40	−35;−9;−11	.086	.047
4	Sagittal stratum (L)	36	−42;−13;−15	.076	.048
5	Sagittal stratum (L)	16	−40;−23;−7	.059	.049
<i>Clusters with significantly higher RD in ADHD patients</i>					
1	Body, splenium and genu of CC, ACR (L + R), SCR (L + R), PCR (L + R), PTR (L + R), EC (L), retrolenticular part of IC (L + R), anterior limb of IC (L), posterior limb of IC (L + R), fornix (cres)/stria terminalis (L), sagittal stratum (L), SFOF (L), UF (L), SLF (L + R)	8411	2;−27;23	.133	.027
2	Sagittal stratum (R), EC (R), Fornix (cres)/Stria terminalis (R)	454	35;−13;−12	.099	.045
3	SLF (L)	386	−56;−24;5	.122	.044
4	SLF (L)	119	−18;28;30	.049	.048

CC corpus callosum, ACR anterior corona radiata, FA fractional anisotropy, MD mean diffusivity, PCR posterior corona radiata, RD radial anisotropy, SCR superior corona radiata, RPIC retrolenticular part of IC, PTR posterior thalamic radiation (include optic radiation), PLIC posterior limb of IC, SLF superior longitudinal fasciculus, IC internal capsule, EC external capsule, SFOF superior fronto-occipital fasciculus, and UF uncinata fasciculus.

^a White matter tracts as defined with the Johns Hopkins University White Matter Label Atlas.

^b Cluster size > 10 voxels.

^c Partial eta squared based on mean FA, MD and RD of the cluster.

^d P < .05, FWE-corrected, controlling for gender, age and scan acquisition protocol.

3.3. Association test of FA and MD with symptom scores in patients with ADHD

The whole-skeleton voxel-based regressions with TBSS in the patients showed that both ADHD symptom domains (inattention and hyperactivity/impulsivity) were not associated with FA or with MD. Furthermore, the partial correlation analyses of mean values of the significant between-group FA and MD clusters with either symptom domain did not show any significant correlations ($p_{adj} > .05$).

3.4. Association of FA and MD with cognitive measures in patients and controls

In the whole group, the partial correlation analyses showed that inhibition performance was negatively correlated with FA in cluster 4 ($r = -.265$; $p = .0001$), such that worse inhibition (i.e., more commission errors on the SART) was linked to lower FA. The delay discounting score was positively correlated with MD in cluster 1 ($r = .242$; $p = .0008$), such that steeper discounting on the Delay Discounting task (i.e., higher impulsivity) was linked to higher MD. To further explore which group contributed to the effects reported above, post-hoc analyses in the patients and in the control group separately revealed that the correlation with inhibition performance was predominantly present in the control group ($r = -.288$; $p = .004$) and did not reach significance in the ADHD patient group ($r = -.179$; $p = .099$). Steeper delay discounting was correlated with MD only in the ADHD patient group ($r = .283$; $p = .009$) and not among controls ($r = .032$; $p = .750$) (Fig. 2). There were no significant results for working memory or attentional performance (Table 3).

3.5. Effect of medication use and depression history on significant between-subject clusters of FA, MD, and RD

Sensitivity analyses were conducted to examine possible effects of stimulant medication use or depression history on significant clusters from the between-group analysis for FA, MD, and RD. Extracted mean values from the significant between-group clusters for FA, MD, and RD did not differ between medication-naïve and stimulant-treated patients ($p > .05$) (Supplementary Table S2). There were no differences on the extracted mean values between ADHD patients with no history of depressive episodes and ADHD patients with one or more episodes in the past ($p > .05$) (Supplementary Table S3).

4. Discussion

In this study we examined white matter microstructure in adult patients with ADHD and healthy controls. Compared to the healthy individuals, patients with ADHD showed significantly reduced FA and increased MD and RD in several brain regions, but no differences in AD. While FA and MD differences were not related with symptom severity, lower FA in the splenium of the corpus callosum was associated with worse inhibition performance, and higher MD in several ROIs was associated with higher impulsivity.

Strongest effects were found in the body and splenium of the corpus callosum. This supports earlier reports that white matter anomalies in the corpus callosum are one of the most consistently found features in childhood ADHD (Cao et al., 2010; Pavuluri et al., 2009; Qiu et al., 2011; van Ewijk et al., 2014) and adult ADHD (Dramsahl et al., 2012; Konrad et al., 2010), although some studies did not find corpus callosum abnormalities (de Zeeuw et al., 2012; Hamilton et al., 2008; Hong et al., 2014; Nagel et al., 2011; van Ewijk et al., 2012). Importantly, reduced FA

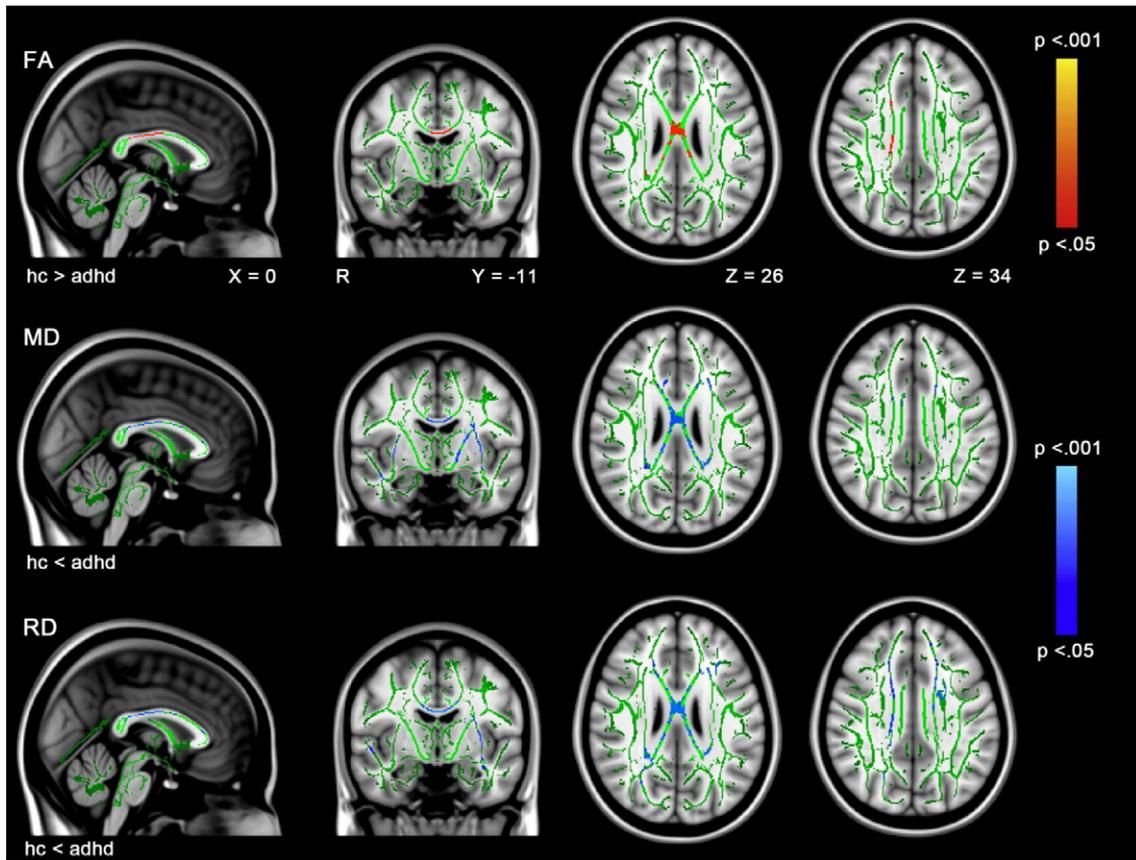


Fig. 1. Results from the tract-based spatial statistics (TBSS) analyses displayed on the MNI152 brain. Hot colors represent increased values, and cool colors represent decreased values. Decreased fractional anisotropy (FA), increased mean diffusivity (MD) and radial diffusivity (RD) are shown in individuals with ADHD compared to controls (threshold-free cluster enhancement, $p < .05$, corrected).

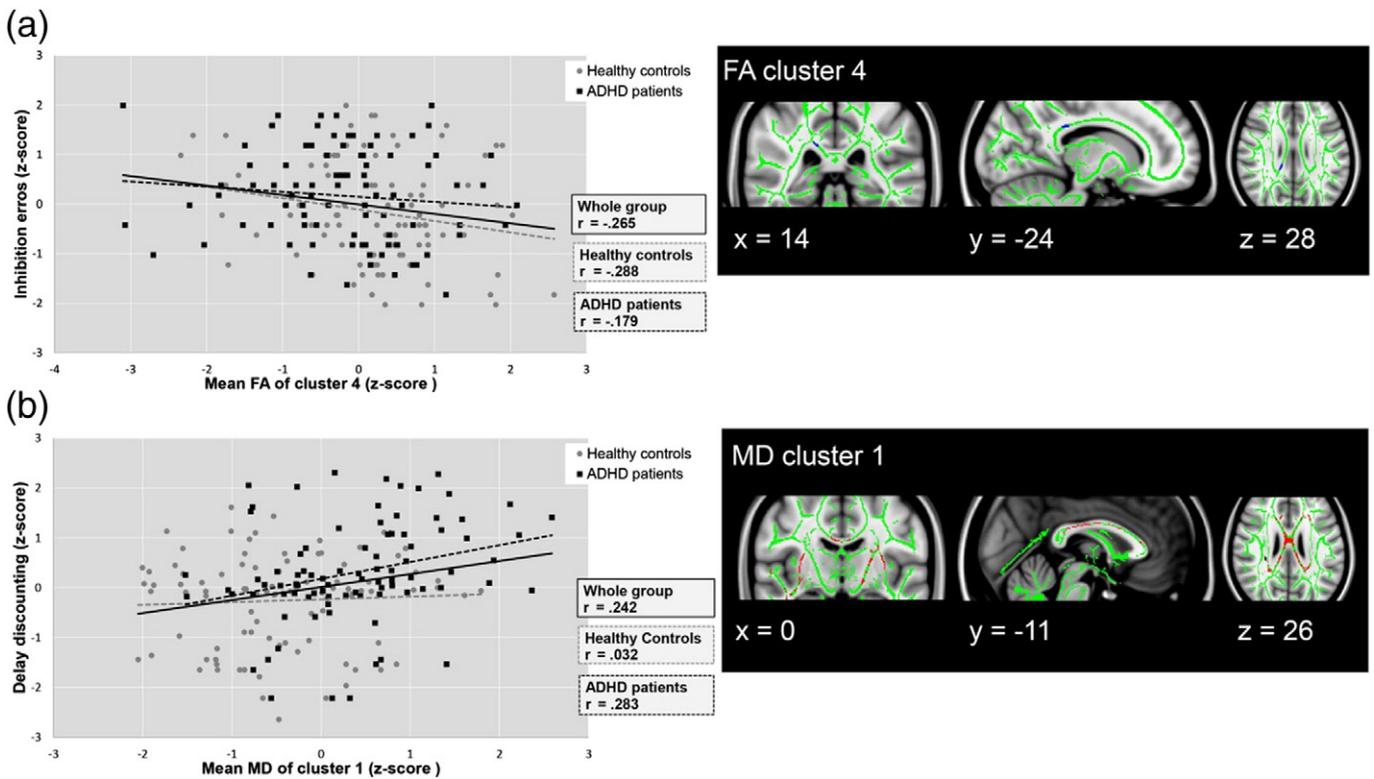


Fig. 2. Correlations between inhibition performance and mean FA in cluster 4 (a) and delay discounting score and mean MD in cluster 1 (b) for ADHD patients and controls separately; $*p < .05$. Worse inhibition was reflected by a higher number of commission errors as measured with the Sustained Attention to Response Task (SART) task, and higher impulsivity was reflected by steeper discounting in the Delay Discounting task.

Table 3
Partial correlations between mean Fractional Anisotropy (FA) and Mean Diffusivity (MD) of between-subject clusters and cognitive measures controlling for age, gender, and scan protocol.

	Digit span ^a	SAD ^b	SART ^c	Delay discounting ^d
	109 HC/103 ADHD (N)	106 HC/100 ADHD (N)	100 HC/90 ADHD (N)	102 HC/88 ADHD (N)
FA cluster 1	.136*	-.105	-.223*	-.140
FA cluster 2	.039	-.127	-.068	-.051
FA cluster 3	-.066	-.090	-.036	-.133
FA cluster 4	.063	-.088	-.265**	-.213*
FA cluster 5	.1	-.054	-.101	-.043
FA cluster 6	.163*	-.018	-.054	-.175
MD cluster 1	-.054	.201*	.160*	.242**
MD cluster 2	-.063	.214*	.072	.121
MD cluster 3	-.108	.135	.094	.182*
MD cluster 4	-.099	.144*	.071	.142
MD cluster 5	-.033	.118	.033	.185*

* Indicates an uncorrected significance of $p < .05$.

** Indicates a corrected significance of $p < .001$.

^a Digit Span raw backwards score (working memory).

^b Errors Sustained Attention Dots (SAD) task (attention).

^c Commission errors Sustained Attention to Response Task (SART) (inhibition).

^d Score on Delay Discounting task (impulsivity).

values in the splenium were associated with worse inhibition performance. Poorer response inhibition in healthy children has been correlated previously with decreased FA (and increased MD) in the splenium (Paolozza et al., 2014). It has been linked to decreased splenium volume in children prenatally exposed to polychlorinated biphenyls (Stewart et al., 2003) and in adults with bipolar disorder (Bearden et al., 2011), populations also characterized by insufficient inhibitory control. The splenium of the corpus callosum connects interhemispheric somatosensory, auditory, occipital, and motor areas, which are important for visual object recognition and discrimination. Possibly, commission errors arise due to insufficient transmission of visual information to the brain areas executing inhibitory control. Our results show that the association between splenium FA and inhibition performance was weaker in patients than in healthy individuals, suggesting that this structure is less functional in ADHD patients.

Besides the corpus callosum, the observed differences in posterior and superior regions of the corona radiata are consistent with ADHD studies in childhood (Nagel et al., 2011; Qiu et al., 2011) and adulthood (Cortese et al., 2013). These regions are continuations of the posterior limb of the internal capsule to the sensorimotor cortex and contain axons primarily involved in low-level motor function. Alterations in these tracts might contribute to sensorimotor deficits in adult ADHD (Valera et al., 2010). Compared to controls, ADHD patients showed reduced FA in the posterior thalamic radiation consistent with an earlier finding in adult ADHD (Cortese et al., 2013), although a childhood study showed increased rather than decreased FA in this area (Peterson et al., 2011). The thalamic radiation contains fibres that run towards the occipital cortex carrying visual information and might be related to structural visual cortex abnormalities (Ahrendts et al., 2011) and functional visual deficits (Kim et al., 2014) in adult ADHD.

Our findings of increased MD suggest that white matter cellular density is lower in ADHD patients (Alexander et al., 2007). In agreement with earlier studies (de Luis-Garcia et al., 2015; Lawrence et al., 2013), these findings for MD were observed in more widespread areas of the brain than those for FA and our finds support a recent study that increased MD was correlated with worse performance indicators of ADHD (Conners Continuous Performance Test) (de Luis-Garcia et al., 2015).

Moreover, increased MD within a large cluster encompassing widespread regions was associated with steeper delay discounting. Steeper delay discounting occurs when smaller immediate rewards are preferred over larger delayed rewards, and is linked to impulsivity. Earlier studies found similarly that steeper delay discounting was associated with higher MD (and lower FA) in bilateral frontal/temporal lobes and in fronto-striatal tracts (Olson et al., 2009; Peper et al., 2013). A recent

resting-state functional connectivity study in childhood ADHD showed that steeper delay discounting was related to differences in reward circuit connectivity (Costa Dias et al., 2013). In conclusion, aberrant structural and functional connectivity possibly influences the balanced interaction between the reward network and other cognitive control regions. This may unveil vulnerability to impulsive decision making in ADHD. Future research could benefit from using a connectomics approach, combined with multimodal imaging that includes diffusion measures as well as functional MRI (Hong et al., 2014; Shenton et al., 2014).

Decreased FA found in ADHD patients was driven by increases in RD rather than changes in AD. Although the biological correlates of those measures are not yet entirely clarified, it is believed that increases in RD (with minimal changes in AD) reflect decreased myelination, while decreases in AD reflect axonal damage or degeneration (Alexander et al., 2007; Song et al., 2002). Whereas studies in young children and adolescents with ADHD suggest delayed myelination (Nagel et al., 2011; Tamm et al., 2012), our results support the only other adult ADHD study that has investigated AD/RD and point to atypical myelination not only being delayed but rather representing a persistent anomaly in ADHD (Shaw et al., 2015). This implicates myelination as a novel target for genomic studies and for more tailored pharmacological treatment interventions.

We used two approaches to investigate effects of FA and MD on symptom severity. The first approach was a voxel-based regression with TBSS adapted from van Ewijk et al. (2014). The second approach was a conventional ROI analysis using the mean FA and MD of significant between-group clusters as predictors for symptoms. Both approaches yielded non-significant results, consistent with another adult ADHD study showing no association between corpus callosum differences and symptom severity (Dramsahl et al., 2012). While this suggests that white matter differences in adult ADHD are independent of disease severity, a vast amount of literature does show relations with severity (Ashtari et al., 2005; Nagel et al., 2011; Shang et al., 2013; Shaw et al., 2015; van Ewijk et al., 2014). A firm conclusion on whether this can be explained by differences based on e.g. the age of the sample will have to await future analyses in larger samples. International collaboration in consortia like the Enabling Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium (www.ENIGMA.ini.usc.edu), which runs a ADHD working group, might provide increased power to clarify this point.

Our findings did not differ between drug-naïve ADHD patients and stimulant medicated patients which supports prior studies that found no confounding effects of (stimulant) medication (de Zeeuw et al.,

2012; Hamilton et al., 2008; van Ewijk et al., 2014). Additionally, our findings did not differ between ADHD patients with a history of major depression and ADHD patients without this comorbidity. Since deviant white matter integrity has also been found in numerous psychiatric disorders, it would be of particular interest to go across diagnostic boundaries in future studies and investigate whether certain white matter abnormalities are specific for ADHD or are shared between disorders.

While our DTI study sample is the largest one published to date for adult ADHD, it also has a limitation. We used two different diffusion scan acquisition protocols. However, this could not have biased our results, as group representation did not differ across protocols, and all analyses were performed with protocol as a covariate. Moreover, the same pattern of results held up when the main between-subject TBSS analysis for FA was limited to the single protocol on which most scans were performed, albeit with lower significance ($P_{FWE} = .10$) (see Supplementary Table S4). Additionally, we could not extensively study the role of comorbid substance abuse, which is an important concern considering the increased risk of substance use disorders in patients with ADHD (Gorzowska et al., 2014; Wilens, 2004). Adolescent substance use has harmful effects on the development of white matter characteristics (Bava et al., 2013) and prefrontal cortex volume (Lejuez et al., 2010). Importantly, microstructural damage in corpus callosum has been suggested as a risk factor for alcohol use disorders (De Bellis et al., 2008).

In conclusion, this study demonstrates white matter microstructure alterations in adult ADHD and point to abnormal myelination. These white matter changes might represent a core trait of persistent ADHD that is independent of disease severity. The white matter microstructure alterations may have specific functional relevance given that lower FA in the corpus callosum was related to inhibition problems and increased MD in wide-spread tracts was related to impulsive decision making.

Conflict of interests

Cornelis C. Kan was a paid member of the European Adult ADHD Advisory Board of Eli Lilly in 2011 and 2012. Jan Buitelaar has served as a consultant, advisory board member, or speaker for Bristol-Myers Squibb, Janssen Cilag BV, Eli Lilly, Novartis, Schering-Plough, Shire, Servier, and UCB. He is not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties. Barbara Franke has received a speaker fee from Merz. The other authors report no financial relationships with commercial interests.

Acknowledgements

The authors thank Paul Gaalman for technical assistance with MRI scanning. The authors also thank all of the participants of this study. We would also like to thank the anonymous reviewers for their valuable comments. This study was supported by a grant from the Brain & Cognition Excellence Program and a Vici grant (to BF) of the Netherlands Organization for Scientific Research (NWO, grant numbers 433-09-229 and 016-130-669) and in part by the Netherlands Brain Foundation (grant number, 15F07[2]27). The research leading to these results also received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement no. 602805 (Aggressotype) and no. 602450 (IMAGEMEND). In addition, the research received funding from the National Institutes of Health (NIH) Consortium grant U54 EB020403, supported by a cross-NIH alliance that funds Big Data to Knowledge Centers of Excellence (BD2K).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.pnpbp.2015.04.008>.

References

- Ahrendts J, Rusch N, Wilke M, Philipsen A, Eickhoff SB, Glauche V, et al. Visual cortex abnormalities in adults with ADHD: a structural MRI study. *World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry* 2011;12:260–70.
- Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. *Neurother J Am Soc Exp Neurother* 2007;4:316–29.
- Amico F, Stauber J, Koutsouleris N, Frodl T. Anterior cingulate cortex gray matter abnormalities in adults with attention deficit hyperactivity disorder: a voxel-based morphometry study. *Psychiatry Res* 2011;191:31–5.
- Ashtari M, Kumra S, Bhaskar SL, Clarke T, Thaden E, Cervellione KL, et al. Attention-deficit/hyperactivity disorder: a preliminary diffusion tensor imaging study. *Biol Psychiatry* 2005;57:448–55.
- Barysheva M, Jahanshad N, Foland-Ross L, Altschuler LL, Thompson PM. White matter microstructural abnormalities in bipolar disorder: a whole brain diffusion tensor imaging study. *NeuroImage Clin* 2013;2:558–68.
- Bava S, Jacobus J, Thayer RE, Tapert SF. Longitudinal changes in white matter integrity among adolescent substance users. *Alcohol Clin Exp Res* 2013;37(Suppl. 1):E181–9.
- Bearden CE, van Erp TG, Dutton RA, Boyle C, Madsen S, Luders E, et al. Mapping corpus callosum morphology in twin pairs discordant for bipolar disorder. *Cereb Cortex* 2011;21:2415–24.
- Beaulieu C. The basis of anisotropic water diffusion in the nervous system—a technical review. *NMR Biomed* 2002;15:435–55.
- Bechtel N, Kobel M, Penner I-K, Klarhöfer M, Scheffler K, Opwis K, et al. Decreased fractional anisotropy in the middle cerebellar peduncle in children with epilepsy and/or attention deficit/hyperactivity disorder: a preliminary study. *Epilepsy Behav* 2009;15:294–8.
- Biederman J, Makris N, Valera EM, Monuteaux MC, Goldstein JM, Buka S, et al. Towards further understanding of the co-morbidity between attention deficit hyperactivity disorder and bipolar disorder: a MRI study of brain volumes. *Psychol Med* 2008;38:1045–56.
- Cao Q, Sun L, Gong G, Lv Y, Cao X, Shuai L, et al. The macrostructural and microstructural abnormalities of corpus callosum in children with attention deficit/hyperactivity disorder: a combined morphometric and diffusion tensor MRI study. *Brain Res* 2010;1310:172–80.
- Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA* 2002;288:1740–8.
- Cortese S, Imperati D, Zhou J, Proal E, Klein RG, Mannuzza S, et al. White matter alterations at 33-year follow-up in adults with childhood attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2013;74:591–8.
- Costa Dias TG, Wilson VB, Bathula DR, Iyer SP, Mills KL, Thurlow BL, et al. Reward circuit connectivity relates to delay discounting in children with attention-deficit/hyperactivity disorder. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol* 2013;23:33–45.
- De Bellis MD, Van Voorhees E, Hooper SR, Gibler N, Nelson L, Hege SG, et al. Diffusion tensor measures of the corpus callosum in adolescents with adolescent onset alcohol use disorders. *Alcohol Clin Exp Res* 2008;32:395–404.
- de Luis-García R, Cabus-Pinol G, Imaz-Roncero C, Argibay-Quinones D, Barrio-Arranz G, Aja-Fernandez S, et al. Attention deficit/hyperactivity disorder and medication with stimulants in young children: a DTI study. *Prog Neuropsychopharmacol Biol Psychiatry* 2015;57:176–84.
- De Sonneville L. Amsterdam Neuropsychological Tasks: a computer-aided assessment program. *Comput Psychol* 1999;6:187–203.
- de Zeeuw P, Mandl RC, Pol H, Hilleke E, van Engeland H, Durston S. Decreased frontostriatal microstructural organization in attention deficit/hyperactivity disorder. *Hum Brain Mapp* 2012;33:1941–51.
- Dom G, D'haene P, Hulstijn W, Sabbe B. Impulsivity in abstinent early- and late-onset alcoholics: differences in self-report measures and a discounting task. *Addiction* 2006;101:50–9.
- Dramsahl M, Westerhausen R, Haavik J, Hugdahl K, Plessen KJ. Adults with attention-deficit/hyperactivity disorder—a diffusion-tensor imaging study of the corpus callosum. *Psychiatry Res* 2012;201:168–73.
- Ellison-Wright I, Ellison-Wright Z, Bullmore E. Structural brain change in attention deficit hyperactivity disorder identified by meta-analysis. *BMC Psychiatry* 2008;8:51.
- Franke B, Vasquez AA, Johansson S, Hoogman M, Romanos J, Boreatti-Hummer A, et al. Multicenter analysis of the SLC6A3/DAT1 VNTR haplotype in persistent ADHD suggests differential involvement of the gene in childhood and persistent ADHD. *ENeuropsychopharmacol Off Publ Am Coll ENeuropsychopharmacol* 2010;35:656–64.
- Frodl T, Skokauskas N. Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. *Acta Psychiatr Scand* 2012;125:114–26.
- Frodl T, Stauber J, Schaaff N, Koutsouleris N, Scheuerecker J, Ewers M, et al. Amygdala reduction in patients with ADHD compared with major depression and healthy volunteers. *Acta Psychiatr Scand* 2010;121:111–8.
- Gorzowska I, Gorzkowski G, Samochowiec A, Suchancka A, Samochowiec J. An interaction between a polymorphism of the serotonin transporter (5HTT) gene and the clinical picture of adolescents with combined type of ADHD (hyperkinetic disorder) and youth drinking. *Psychiatr Pol* 2014;48:541–51.
- Groenestijn MAC, Akkerhuis G, Kupka R, Schneider N, Nolen W. Gestructureerd klinisch interview voor de vaststelling van DSM-IV as I stoornissen (SCID-I) [Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I)]. Lisse, The Netherlands: Swets & Zeitlinger; 1999.
- Hamilton LS, Levitt JG, O'Neill J, Alger JR, Luders E, Phillips OR, et al. Reduced white matter integrity in attention-deficit hyperactivity disorder. *Neuroreport* 2008;19:1705–8.

- Helpem JA, Adisetiyo V, Falangola MF, Hu C, Di Martino A, Williams K, et al. Preliminary evidence of altered gray and white matter microstructural development in the frontal lobe of adolescents with attention-deficit hyperactivity disorder: a diffusional kurtosis imaging study. *J Magn Reson Imaging* 2011;33:17–23.
- Hong SB, Zalesky A, Fornito A, Park S, Yang YH, Park MH, et al. Connectomic disturbances in attention-deficit/hyperactivity disorder: a whole-brain tractography analysis. *Biol Psychiatry* 2014;76:656–63.
- Hua K, Zhang J, Wakana S, Jiang H, Li X, Reich DS, et al. Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. *Neuroimage* 2008;39:336–47.
- Kim S, Chen S, Tannock R. Visual function and color vision in adults with attention-deficit/hyperactivity disorder. *J Optom* 2014;7:22–36.
- Konrad K, Eickhoff SB. Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. *Hum Brain Mapp* 2010;31:904–16.
- Konrad A, Dielentheis TF, El Masri D, Bayerl M, Fehr C, Gesierich T, et al. Disturbed structural connectivity is related to inattention and impulsivity in adult attention deficit hyperactivity disorder. *Eur J Neurosci* 2010;31:912–9.
- Konrad A, Dielentheis TF, El Masri D, Dellani PR, Stoeter P, Vucurevic G, et al. White matter abnormalities and their impact on attentional performance in adult attention-deficit/hyperactivity disorder. *Eur Arch Psychiatry Clin Neurosci* 2012;262:351–60.
- Kooij JJ. Adult ADHD. Diagnostic assessment and treatment. 1st ed. Amsterdam: Pearson Assessment and Information BV; 2010.
- Kooij JJ, Buitelaar JK, van den Oord EJ, Furer JW, Rijnders CA, Hodiomont PP. Internal and external validity of attention-deficit hyperactivity disorder in a population-based sample of adults. *Psychol Med* 2005;35:817–27.
- Korgaonkar MS, Grieve SM, Koslow SH, Gabrieli JD, Gordon E, Williams LM. Loss of white matter integrity in major depressive disorder: evidence using tract-based statistical analysis of diffusion tensor imaging. *Hum Brain Mapp* 2011;32:2161–71.
- Lawrence KE, Levitt JG, Loo SK, Ly R, Yee V, O'Neill J, et al. White matter microstructure in attention-deficit/hyperactivity disorder subjects and their siblings. *J Am Acad Child Adolesc Psychiatry* 2013;52:431–40.
- Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, et al. Diffusion tensor imaging: concepts and applications. *J Magn Reson Imaging* 2001;13:534–46.
- Lejuez CW, Magidson JF, Mitchell SH, Sinha R, Stevens MC, de Wit H. Behavioral and biological indicators of impulsivity in the development of alcohol use, problems, and disorders. *Alcohol Clin Exp Res* 2010;34:1334–45.
- Makris N, Biederman J, Valera EM, Bush G, Kaiser J, Kennedy DN, et al. Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. *Cereb Cortex* 2007;17:1364–75.
- Makris N, Buka SL, Biederman J, Papadimitriou GM, Hodge SM, Valera EM, et al. Attention and executive systems abnormalities in adults with childhood ADHD: a DT-MRI study of connections. *Cereb Cortex* 2008;18:1210–20.
- Mandl RC, Rais M, van Baal GC, van Haren NE, Cahn W, Kahn RS, et al. Altered white matter connectivity in never-medicated patients with schizophrenia. *Hum Brain Mapp* 2013;34:2353–65.
- Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, et al. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage* 2008;40:570–82.
- Mostert J, Onnink AMH, Klein M, Dammers J, Hameit A, Schulten T, et al. Cognitive heterogeneity in adult Attention Deficit / Hyperactivity Disorder: a systematic analysis of neuropsychological measurements, submitted for publication.
- Nagel BJ, Bathula D, Herting M, Schmitt C, Kroenke CD, Fair D, et al. Altered white matter microstructure in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2011;50:283–92.
- Nakao T, Radua J, Rubia K, Mataix-Cols D. Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. *Am J Psychiatry* 2011;168:1154–63.
- Olson EA, Collins PF, Hooper CJ, Muetzel R, Lim KO, Luciana M. White matter integrity predicts delay discounting behavior in 9- to 23-year-olds: a diffusion tensor imaging study. *J Cogn Neurosci* 2009;21:1406–21.
- Onnink AM, Zwiers MP, Hoogman M, Mostert JC, Kan CC, Buitelaar J, et al. Brain alterations in adult ADHD: effects of gender, treatment and comorbid depression. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol* 2014;24:397–409.
- Paolozza A, Treit S, Beaulieu C, Reynolds JN. Response inhibition deficits in children with fetal alcohol spectrum disorder: relationship between diffusion tensor imaging of the corpus callosum and eye movement control. *NeuroImage Clin* 2014;5:53–61.
- Pavuluri MN, Yang S, Kamineni K, Passarotti AM, Srinivasan G, Harral EM, et al. Diffusion tensor imaging study of white matter fiber tracts in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2009;65:586–93.
- Peper JS, Mandl RC, Braams BR, de Water E, Heijboer AC, Koolschijn PC, et al. Delay discounting and frontostriatal fiber tracts: a combined DTI and MTR study on impulsive choices in healthy young adults. *Cereb Cortex* 2013;23:1695–702.
- Peterson DJ, Ryan M, Rimrodt SL, Cutting LE, Denckla MB, Kaufmann WE, et al. Increased regional fractional anisotropy in highly screened attention-deficit hyperactivity disorder (ADHD). *J Child Neurol* 2011;26:1296–302.
- Proal E, Reiss PT, Klein RG, Mannuzza S, Gotimer K, Ramos-Olazagasti MA, et al. Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood. *Arch Gen Psychiatry* 2011;68:1122–34.
- Qiu M-g, Ye Z, Li Q-y, Liu G-j, Xie B, Wang J. Changes of brain structure and function in ADHD children. *Brain Topogr* 2011;24:243–52.
- Reese TG, Heid O, Weisskoff RM, Wedeen VJ. Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo. *Magn Reson Med* 2003;49:177–82.
- Rubia K. Neuro-anatomic evidence for the maturational delay hypothesis of ADHD. *Proc Natl Acad Sci U S A* 2007;104:19663–4.
- Seidman LJ, Valera EM, Makris N, Monuteaux MC, Boriell DL, Kelkar K, et al. Dorsolateral prefrontal and anterior cingulate cortex volumetric abnormalities in adults with attention-deficit/hyperactivity disorder identified by magnetic resonance imaging. *Biol Psychiatry* 2006;60:1071–80.
- Seidman LJ, Biederman J, Liang L, Valera EM, Monuteaux MC, Brown A, et al. Gray matter alterations in adults with attention-deficit/hyperactivity disorder identified by voxel based morphometry. *Biol Psychiatry* 2011;69:857–66.
- Shang CY, Wu YH, Gau SS, Tseng WY. Disturbed microstructural integrity of the frontostriatal fiber pathways and executive dysfunction in children with attention deficit hyperactivity disorder. *Psychol Med* 2013;43:1093–107.
- Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci U S A* 2007;104:19649–54.
- Shaw P, De Rossi P, Watson B, Wharton A, Greenstein D, Raznahan A, et al. Mapping the development of the basal ganglia in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2014;53(780–789). (e711).
- Shaw P, Sudre G, Wharton A, Weingart D, Sharp W, Sarlls J. White matter microstructure and the variable adult outcome of childhood attention deficit hyperactivity disorder. *ENeuropsychopharmacol Off Publ Am Coll* 2015;40(3):746–54.
- Shenton ME, Kubicki M, Makris N. Understanding alterations in brain connectivity in attention-deficit/hyperactivity disorder using imaging connectomics. *Biol Psychiatry* 2014;76:601–2.
- Silk TJ, Vance A, Rinehart N, Bradshaw JL, Cunnington R. White-matter abnormalities in attention deficit hyperactivity disorder: a diffusion tensor imaging study. *Hum Brain Mapp* 2009;30:2757–65.
- Simon V, Czobor P, Balint S, Meszaros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry J Ment Sci* 2009;194:204–11.
- Smit AS, Eling PA, Coenen AM. Mental effort causes vigilance decrease due to resource depletion. *Acta Psychol (Amst)* 2004;115:35–42.
- Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage* 2009;44:83–98.
- Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 2006;31:1487–505.
- Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 2002;17:1429–36.
- Stewart P, Fitzgerald S, Reihman J, Gump B, Lonky E, Darvill T, et al. Prenatal PCB exposure, the corpus callosum, and response inhibition. *Environ Health Perspect* 2003; 111:1670.
- Tamm L, Barnea-Goraly N, Reiss AL. Diffusion tensor imaging reveals white matter abnormalities in attention-deficit/hyperactivity disorder. *Psychiatry Res Neuroimaging* 2012;202:150–4.
- Thomason ME, Thompson PM. Diffusion imaging, white matter, and psychopathology. *Annu Rev Clin Psychol* 2011;7:63–85.
- Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2007;61:1361–9.
- Valera EM, Spencer R, Zeffiro TA, Makris N, Spencer TJ, Faraone SV, et al. Neural substrates of impaired sensorimotor timing in adult attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2010;68:359–67.
- van Ewijk H, Heslenfeld DJ, Zwiers MP, Buitelaar JK, Oosterlaan J. Diffusion tensor imaging in attention deficit/hyperactivity disorder: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2012;36:1093–106.
- van Ewijk H, Heslenfeld DJ, Zwiers MP, Faraone SV, Luman M, Hartman CA, et al. Different mechanisms of white matter abnormalities in attention-deficit/hyperactivity disorder: a diffusion tensor imaging study. *J Am Acad Child Adolesc Psychiatry* 2014; 53:790–9.
- Wechsler D. Wechsler Memory Scale-Third Edition. San Antonio, TX: The Psychological Corporation; 1997.
- Weertman A, Arntz A, Kerkhofs M. Gestructureerd diagnostisch interview voor DSM-IV persoonlijkheidsstoornissen (SCID II) [Structural clinical interview for DSM-IV personality disorders (SCID II)]. Lisse, The Netherlands: Swets & Zeitlinger; 2000.
- Wilens TE. Attention-deficit/hyperactivity disorder and the substance use disorders: the nature of the relationship, subtypes at risk, and treatment issues. *Psychiatr Clin North Am* 2004;27:283–301.
- Wu YH, Gau SS, Lo YC, Tseng WY. White matter tract integrity of frontostriatal circuit in attention deficit hyperactivity disorder: association with attention performance and symptoms. *Hum Brain Mapp* 2014;35:199–212.
- Zwiers MP. Patching cardiac and head motion artefacts in diffusion-weighted images. *Neuroimage* 2010;53:565–75.