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ORIGINAL ARTICLE

Altered white-matter architecture in treatment-naive adolescents with clinical depression

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Background. Depressive disorders are highly prevalent in adolescence and confer a heightened risk of recurrence in adulthood. Insight into the developmental neurocircuitry of depression could advance our understanding of depression and aid the development of effective treatment strategies. Whereas white-matter (WM) abnormalities are strongly implicated in adult depression, we still lack a firm understanding of WM architecture in adolescent depression. Using diffusion tensor imaging (DTI), we set out to investigate WM microstructure in a sample of clinically depressed adolescents relative to matched controls.

Method. We employed tract-based spatial statistics (TBSS) to examine WM microstructure in 25 treatment-naive adolescents with clinical depression relative to 21 matched controls. Using TBSS, we examined fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD). Threshold-free cluster enhancement (TFCE) with family-wise error (FWE) correction was used to control for multiple comparisons.

Results. Our analysis revealed abnormal WM microstructure in clinically depressed adolescents. More specifically, whole-brain analysis revealed that patients had lower FA values in the body of the corpus callosum (CC), coupled with elevated RD and MD, and preserved AD. Conversely, region-of-interest analysis revealed that patients had higher FA values in the uncinate fasciculus (UF), coupled with elevated AD, reduced RD and preserved MD.

Conclusions. In line with neurocircuitry models of depression, our findings suggest that WM abnormalities within pathways facilitating cognitive and emotional functioning are involved in the pathophysiology of depression. Importantly, our findings show that these WM abnormalities are already present early in the course of the disorder.

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Key words: Adolescents, corpus callosum, depression, diffusion tensor imaging, uncinate fasciculus, white matter.

Introduction

Depressive disorders are highly prevalent in childhood and adolescence, with an annual incidence of 6–7% (Costello *et al.* 1996; Merikangas & Avenevoli, 2002). Adolescents with depression form a particular group of concern because suicide, which has a high incidence in depressed youths, is the third leading cause of death between the ages of 15 and 24 years (Murray *et al.* 2000; CDC, 2007). Furthermore, adolescent depression is associated with a two- to fourfold risk of recurrence in adulthood along with ongoing psychosocial problems such as dysfunctional interpersonal relationships, substance abuse and poor occupational functioning (Clark *et al.* 2007; Rao & Chen, 2009). Of note, depression typically co-occurs with anxiety during adolescence, and a double diagnosis accounts for more impairment and more severe internalizing symptoms than either diagnosis alone (Zahn-Waxler *et al.* 2000; Guberman & Manassis, 2011). Remarkably, despite these concerns, the neurobiology of adolescent depression is still poorly understood. The substantial neuronal maturation during adolescence (Casey *et al.* 2008) underscores the need to examine the neurobiology of adolescent depression separately from adults. Yet, neurobiological research in adolescent depression significantly lags behind similar advances in adult depression (Hulvershorn *et al.* 2011). Bearing in mind the increased neuronal plasticity prior to adulthood (Casey *et al.* 2008), studying the neurocircuitry of adolescent depression is crucial in gaining insight

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into the neurodevelopmental trajectories of depression and advancing the development of potential interventions that target these trajectories (Hulvershorn *et al.* 2011). This is of great importance because effective treatment strategies for adolescent depression are relatively scarce.

Neuroimaging studies implicate corticolimbic circuit dysfunction in the pathophysiology of both adult and adolescent depression (Thomas *et al.* 2001; Mayberg, 2003; Rosso *et al.* 2005; Caetano *et al.* 2007; Price & Drevets, 2010; Hulvershorn *et al.* 2011). Key components of this circuitry include the amygdala, hippocampus, anterior cingulate cortex (ACC) and prefrontal cortex (PFC), which regulate the experience, expression and evaluation of emotions (Benes, 2010). A review of neuroimaging findings in pediatric depression (Hulvershorn *et al.* 2011) suggests three possible trajectories for how typical neurodevelopment of this corticolimbic circuitry might be compromised in depression. First, genotype may contribute to early abnormal neurodevelopment that is further worsened by adverse gene–environment interaction; second, typical neurodevelopment early in life may gradually become abnormal with accumulating environmental adversity; and third, typical neurodevelopment through childhood may abruptly become abnormal in adolescence or adulthood, possibly due to a genetic susceptibility. Abnormal development of brain white matter (WM) is thought to constitute one element of the aforementioned corticolimbic circuit dysfunction (Fields, 2008; Herrmann *et al.* 2008). Aberrant structural integrity of corticolimbic WM pathways may impede adaptive emotional functioning, thereby rendering an individual vulnerable to psychopathology.

Diffusion tensor imaging (DTI) has proven a useful magnetic resonance imaging (MRI) technique for examining the orientation and integrity of WM tracts by indexing the diffusion of water molecules in neural tissue (Basser *et al.* 1994). Fractional anisotropy (FA) is the most commonly used DTI parameter, reflecting the tendency of water molecules to diffuse in one direction as opposed to all other directions. As diffusion within WM is strongly restricted by its microstructure, FA values reflect microstructural properties such as myelin thickness and membrane integrity (Kochunov *et al.* 2007). Decreased diffusion along the principal direction of the fiber (axial diffusivity, AD) suggests axonal loss (Budde *et al.* 2009), whereas increased diffusion perpendicular to the principal direction of the fiber (radial diffusivity, RD) suggests demyelination (Song *et al.* 2002). In addition, an increase in the average of water diffusion in all directions (mean diffusivity, MD) suggests diminished myelination (Horsfield & Jones, 2002). In general, decreased FA is coupled with decreased AD and/or increased RD and MD, whereas the opposite accounts for any increase in FA.

DTI studies using a region-of-interest (ROI) approach indicate loss of WM integrity in adult and adolescent depression, as reflected by decreased FA in the frontal and temporal lobes, and the cingulum bundle (Nobuhara *et al.* 2006; Li *et al.* 2007; Yang *et al.* 2007; Shimony *et al.* 2009; Cullen *et al.* 2010). However, by using an ROI approach, important alterations in WM microstructure outside the ROIs may have gone unobserved in these studies. Studies examining whole-brain WM integrity in adult and adolescent depression largely converge on findings of decreased FA in regions such as the corpus callosum (CC), superior longitudinal fasciculus, uncinate fasciculus (UF), sagittal stratum and internal capsule (Ma *et al.* 2007; Cullen *et al.* 2010; Kieseppa *et al.* 2010; Korgaonkar *et al.* 2011; Zhu *et al.* 2011). Of note, some of these WM alterations are also found in healthy adolescents at familial risk for depression (Huang *et al.* 2011), suggesting that specific WM alterations early in life may serve as a vulnerability marker for depression. Finally, FA alterations in depression are also related to greater symptom severity in both adults and adolescents (Zou *et al.* 2008; Zhu *et al.* 2011), and to poor treatment outcomes in adults (Alexopoulos *et al.* 2008).

Despite growing evidence of WM alterations in depression, only a few studies have examined WM microstructural integrity in adolescent depression (Li *et al.* 2007; Ma *et al.* 2007; Cullen *et al.* 2010; Zhu *et al.* 2011). Moreover, methodological issues such as small sample size, non-matched control subjects and medication use may to some extent limit the findings reported by these studies. Importantly, given the singular focus of these studies on FA, microstructural properties underlying the alterations in FA remain unknown. Hence, we still lack a firm understanding of WM architecture in adolescent depression. To mitigate the paucity of data and address the limitations of previous studies, we examined WM integrity in a moderate-sized sample of treatment-naive adolescents with clinical depression relative to matched controls. Additionally, to further characterize WM alterations, we examined AD, RD and MD in regions showing significant group differences in FA. The intention was to shed some new light on the neurocircuitry underlying adolescent depression.

Tract-based spatial statistics (TBSS; Smith *et al.* 2006), a robust and automated technique, was used for the analysis of diffusion-weighted data. We used both whole-brain and ROI TBSS to examine WM microstructure. This is the first study to use ROI-based TBSS to examine WM microstructural integrity in adolescent depression. Unlike traditional ROI analyses, ROI-based TBSS allows voxel-wise analysis

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of FA within an entire WM tract common to all participants (i.e. skeletonized tract), thus minimizing registration errors and partial voluming. Given the hypothesized corticolimbic circuit dysfunction in depression (Mayberg, 2003; Price & Drevets, 2010), the UF was defined as our ROI. The UF is a bidirectional WM tract that connects limbic structures such as the amygdala with the orbitomedial PFC (OMPFC) and subgenual ACC (sACC) (Petrides & Pandya, 2002; Kier *et al.* 2004), thereby subserving emotional processing and memory (Von Der Heide *et al.* 2013). Previous DTI studies largely converge on reduced FA in the UF in depressive disorders (Sexton *et al.* 2009; Cullen *et al.* 2010), while lower as well as higher FA in the UF predicts negative emotionality in healthy individuals (Kim & Whalen, 2009; Westlye *et al.* 2011; Montag *et al.* 2012). Of interest, functional integrity of a corticolimbic circuitry was recently shown to reflect structural integrity of the UF in depressed patients (Steffens *et al.* 2011). We therefore hypothesized the UF a suitable candidate for further clarifying corticolimbic abnormalities in depression.

Based on the putative link between abnormal WM FA and depression (Sexton *et al.* 2009), we hypothesized that, in depressed adolescents, whole-brain analysis of FA would reveal abnormalities within tracts previously implicated in depression. Moreover, we hypothesized that, in depressed adolescents, ROI analysis of FA would reveal abnormalities in the UF. In line with previous TBSS studies (Versace *et al.* 2008; Cole *et al.* 2012), FA was the main dependent variable, with AD, RD and MD providing complementary information to aid interpretation of FA alterations. We therefore hypothesized that reduced FA would be coupled with reduced AD and/or elevated RD and MD, whereas the opposite was expected for any increase in FA. Finally, in line with previous findings (Zou *et al.* 2008; Zhu *et al.* 2011), we hypothesized that abnormal FA values would relate to greater depression symptom severity.

Method

Participants

Forty-six adolescents (25 patients, 21 controls) were selected, as part of the Emotional Pathways Imaging Study in Clinical Adolescents (EPISCA). EPISCA is a longitudinal MRI study in which adolescents with clinical depression and healthy controls were followed over a 6-month period (from January 2010 to August 2012). The clinically depressed group underwent an MRI scanning protocol prior to the start of their regular cognitive behavioral therapy (CBT), and 3 and 6 months after the start of CBT. Healthy control adolescents were recruited through local advertisements. The current study reports on cross-sectional data from both groups.

Inclusion criteria for the patient group were: having clinical depression as assessed by categorical and/or dimensional measures of DSM-IV depressive disorders (for more detail see the section on Clinical Assessment), being referred for CBT at an out-patient care unit, and no current or prior use of antidepressants. Inclusion criteria for the control group were: no current or past DSM-IV diagnoses of Axis I and/or Axis II disorders, no clinical scores on validated mood and behavioral questionnaires, no history of traumatic experiences, and no current psychotherapeutic and/or psychopharmacological intervention of any kind. Exclusion criteria for all participants were: (1) a primary DSM-IV diagnosis of attention deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder, pervasive developmental disorders, post-traumatic stress disorder, Tourette's syndrome, obsessive–compulsive disorder, bipolar disorder, and psychotic disorders, (2) current use of psychotropic medication, (3) current substance abuse, (4) a history of neurological disorders or severe head injury, (5) age <12 or>21 years, (6) pregnancy, (7) left-handedness, (8) IQ score <80, as measured by either the Wechsler Intelligence Scale for Children (WISC; Wechsler, 1991) or the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1997), and (9) general MRI contraindications (e.g. metal implants, claustrophobia).

From the original group of 59 adolescents (29 patients, 30 controls), four (one patient and three controls) were excluded prior to the start of the current DTI study because of image artifacts in T1-weighted anatomical scans. For the current study, an additional nine adolescents were excluded because of: incorrect DTI data collection (one patient and one control), image artifacts in the DTI dataset (one patient and one control), and group-wise matching for age, sex and IQ (one patient and four controls). Eventually, a moderate-sized sample of 46 participants (25 patients, 21 controls) aged 13 to 19 years (mean=15.07, S.D.=1.55) were included in the DTI analysis. Participants were scanned within 2 weeks of initial screening, and all were new to MRI scanning procedures. The medical ethics committee of Leiden University Medical Center approved the study and written informed consent was obtained from all adolescents and their parents.

Clinical assessment

For all participants, several clinical measures were used for categorical and dimensional assessment of DSM-IV depressive disorders. For all patients, after

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the clinical assessment by child and adolescent psychiatrists, categorical DSM-IV diagnoses were further assessed based on the child and parent versions of the Anxiety Disorders Interview Schedule (ADIS; Silverman & Albano, 1996), a diagnostic tool for obtaining DSM-IV-based classifications of anxiety and depressive disorders. Additional scales were then used to assess the severity of depressive and internalizing symptoms, including the Children's Depression Inventory (CDI; Kovacs, 1992), the Revised Child Anxiety and Depression Scale (RCADS; Chorpita *et al.* 2000), the Youth Self-Report (YSR; Achenbach, 1991*b*) and its parent version the Child Behavior Checklist (CBCL; Achenbach, 1991*a*). A detailed description of these questionnaires is provided in the online Supplementary Material. The same measures were applied for the control group, and control participants were excluded when they fulfilled the criteria for a DSM-IV diagnosis or had (sub)clinical scores on clinical questionnaires.

DTI data acquisition and preprocessing

DTI data were collected using a Philips 3.0-T Achieva MRI scanner (Philips Medical Systems, The Netherlands) with an eight-channel sensitivity-encoding (SENSE) head coil. A single-shot echo–planar imaging (EPI) sequence was used with the following scan parameters: repetition time = 11 000 ms, echo time = 56 ms, flip angle = 90°, *b* factor = 1000 s/mm^2, voxel dimensions = 2.3 mm isotropic, number of slices = 73, and no slice gap. DTI data were acquired along 32 directions, together with a baseline image having no diffusion weighting (*b* = 0). The total scanning time was approximately 7 min. Collected DTI data were preprocessed and analyzed using the Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) version 4.1.9. First, DTI data were corrected for distortion and motion artifacts induced by eddy currents or by simple head motions, using affine registration of each diffusion-weighted image to the *b* = 0 reference image. Next, non-brain tissue was removed using the Brain Extraction Tool. Finally, to generate individual FA, AD, RD and MD maps for each participant, the diffusion tensor model was fitted to each voxel using FMRIB's Diffusion Toolbox. AD was defined as the largest eigenvalue (L1), RD was calculated as the average of the two small eigenvalues (L2 and L3), and MD was calculated as the average of the three eigenvalues (L1, L2 and L3).

Whole-brain TBSS

TBSS version 1.2 was used for voxel-wise analysis of the preprocessed FA data. First, individual FA images were aligned to the FMRIB58_FA standard-space image using FMRIB's non-linear registration tool (FNIRT). Next, a mean FA image was generated and thinned to create a mean FA skeleton representing the centers of all tracts common to the entire group. The mean FA skeleton was then thresholded at an FA value of $\geqslant 0.35$ to exclude peripheral tracts and minimize partial voluming. Finally, each participant's aligned FA images were projected onto the mean FA skeleton. In a similar manner, AD, RD and MD data were projected onto the skeleton using the FA registration and skeleton projection parameters. Subsequently, the skeletonized FA, AD, RD and MD data were fed into voxel-wise permutation-based analysis.

ROI TBSS

To test for regional specific FA alterations with ROI-based TBSS, we followed the procedure used by Westlye *et al.* (2009, 2011). A binary mask of the bilateral UF was created as the ROI using the probabilistic Johns Hopkins University (JHU) WM atlas (Mori *et al.* 2005) provided by FSL. The UF was masked by the thresholded mean FA skeleton to include only voxels comprised in both the UF and the skeleton. This confines the statistical analysis to voxels from the center of the tract, thereby minimizing anatomic intersubject variability, registration errors and partial voluming (Westlye *et al.* 2009). The resulting UF mask was used for voxel-wise permutation-based ROI analysis.

Statistical analysis

Given the non-parametric distribution of diffusion-weighted data, non-parametric independent two-sample *t* tests were performed using FSL's permutation-based Randomize tool with threshold-free cluster enhancement (TFCE; Smith & Nichols, 2009). FA was examined throughout the WM skeleton whereas AD, RD and MD were only examined in regions showing significant group differences in FA. Five thousand random permutations were generated to build up the null distribution of the cluster size statistic, while testing the following contrasts: (1) controls > patients, (2) patients > controls, (3) group × age interaction. Age, sex and IQ (demeaned across groups) were included in the analysis as covariates, as these variables could impact the major outcomes under investigation. Given that we tested for higher as well as lower FA in patients relative to controls, the resulting statistical maps were corrected for multiple comparisons (i.e. family-wise error, FWE) at $p < 0.025$ rather than $p < 0.05$. However, to minimize Type II errors, effects that passed the 'gold standard' criterion of $p < 0.05$ FWE corrected are also reported and discussed, albeit with caution.

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As for AD, RD and MD, a statistical threshold of $p<0.05$ FWE corrected was applied, given our explicit hypotheses regarding the direction of effects. The JHU WM and Juelich histological atlases were used to label clusters with significant WM alterations.

To examine the association between FA alterations and symptom severity in patients, CDI depression scores and mean FA values within regions of significant group differences were fed into linear regression analyses in SPSS (SPSS Inc., USA). Age and IQ (demeaned across groups) were included in the analyses as covariates to correct for their confounding effects. As FA values throughout the brain tend to correlate, we aimed to minimize multicollinearity by performing separate regression analyses for every brain region showing significant group differences in FA. As depressive symptoms are known to vary with age during adolescence (Ryan *et al.* 1987), an age×CDI interaction effect on FA was also tested in the same model. Finally, statistical thresholds were adjusted to control for multiple testing (i.e. $p<0.05$ divided by the number of tests).

Results

Sample characteristics

As shown in Table 1, the matched groups did not differ with respect to age ($t_{44}=-1.98$, $p>0.05$), sex (84–86% females; $\chi^2_1=0.26$, $p>0.05$) and IQ ($t_{44}=0.83$, $p>0.05$). The CDI revealed higher depression scores in patients ($t_{29}=-6.56$, $p<0.001$) and the RCADS revealed both higher depression ($t_{32}=-4.97$, $p<0.001$) and anxiety scores ($t_{36}=-4.42$, $p<0.001$) in the patient group. Moreover, the YSR ($t_{39}=-7.1$, $p<0.001$) and CBCL ($t_{29}=-9.54$, $p<0.001$) both revealed more internalizing symptoms in patients. The patient group comprised 25 treatment-naive adolescents with clinical depression, as assessed by categorical and/or dimensional measures of depression. Most patients ($n=18$) fulfilled criteria for one or more co-morbid anxiety disorders on the ADIS, including generalized anxiety disorder, social phobia and panic disorder with agoraphobia (Table 1). Six of these patients also fulfilled criteria for co-morbid externalizing disorders, including attention deficit hyperactivity disorder, oppositional defiant disorder and conduct disorder.

TBSS analysis

As shown in Fig. 1, whole-brain TBSS analysis revealed that patients had lower FA values in the body of the CC ($p<0.025$, TFCE and FWE corrected), coupled with elevated RD and MD, and preserved AD ($p<0.05$, TFCE and FWE corrected). Compared to controls, patients did not show higher FA values in any WM tracts. By contrast, ROI-based TBSS analysis in the UF revealed that patients had higher FA values in the anterior segment of the left UF ($p<0.05$, TFCE and FWE corrected), coupled with elevated AD, reduced RD and preserved MD ($p<0.05$, TFCE and FWE corrected). WM tracts with lower FA values for patients than for controls were not identified in the ROI-based analysis.

Table 1. *Demographic and clinical characteristics of adolescents with clinical depression (patients) and healthy control participants (controls)*

Characteristic	Patients ($n=25$)	Controls ($n=21$)
Age (years)	15.6±1.4	14.7±1.6
Sex (M/F)	4/21	3/18
IQ	104±8.32	106.1±8.4
CDI[a]	18.5±9.7*	4.6±3.3*
RCADS Depression[b]	11.2±5.7*	4.3±3.1*
RCADS Anxiety[b]	31.5±15.2*	14.4±9.7*
YSR Internalizing[b]	24.1±8.2*	8.4±6.3*
CBCL Internalizing[b]	18.3±6.6*	3.6±2.9*
Current co-morbidity		
Anxiety disorder only	12	0
Anxiety+externalizing disorder	6	0

IQ, Intelligence quotient; CDI, Children's Depression Inventory; RCADS, Revised Child Anxiety and Depression Scale; YSR, Youth Self-Report; CBCL, Child Behavior Checklist.

[a] One patient did not complete the questionnaire.

[b] Three patients and their parents/primary caregivers did not complete the questionnaire.

Because less than 20% of the items in the CDI, RCADS, YSR and CBCL were missing, expectation maximization as the regression method was used to calculate the scale scores.

Values are given as mean±standard deviation or number.

* Significant at $p<0.001$.

FA alterations and symptom severity

Two separate regression analyses were performed (one for CC and one for UF) to address the association between observed FA alterations and symptom severity in patients (adjusted for age and IQ). Hence, statistical thresholds were set at $p<0.025$ (i.e. $p<0.05$ divided by the number of tests). As illustrated in Fig. 2, mean FA values in regions of the CC showing significant group differences demonstrated a trend for a negative association with CDI depression scores ($\beta=-0.43$, $p=0.055$). That is, lower FA values were associated with more depressive symptoms. By contrast, mean FA values in regions of the UF showing significant group differences did not correlate with CDI

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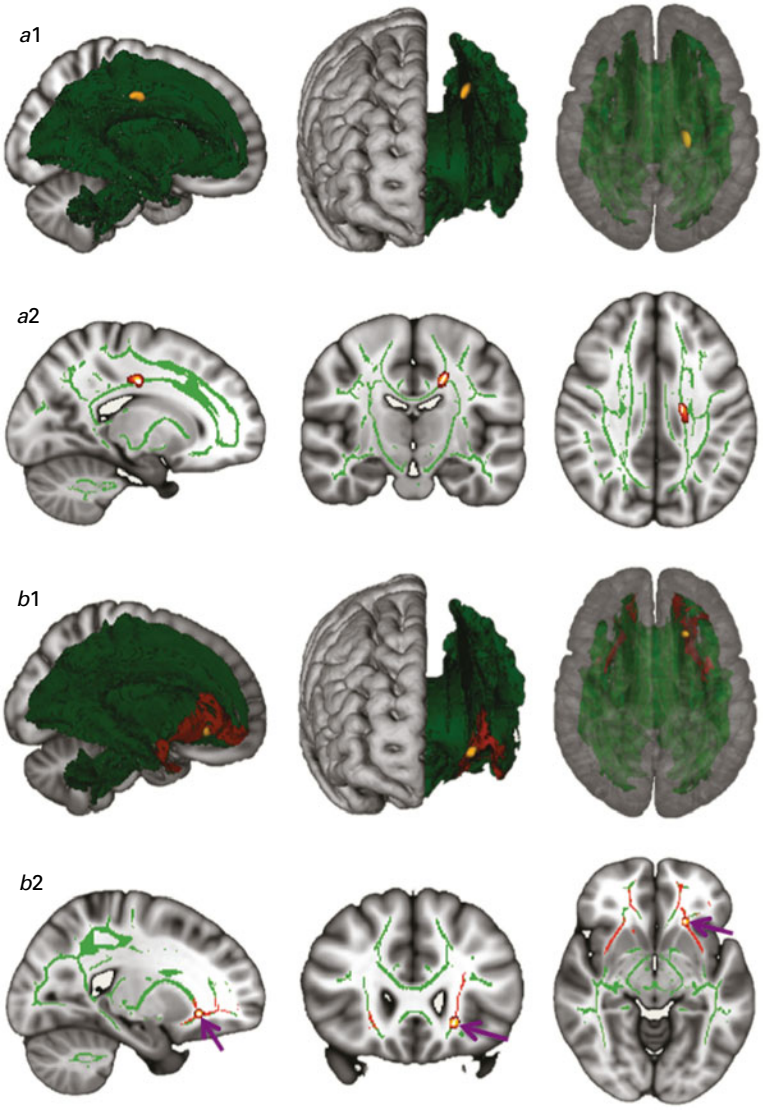

Fig. 1. (*a*) Whole-brain tract-based spatial statistics (TBSS) results. Three-dimensional (3D) renderings (*a*1) and sagittal, coronal and axial sections (*a*2) of the white-matter (WM) skeleton (green), with a subregion of the corpus callosum (CC) showing significantly reduced fractional anisotropy (FA) in patients relative to healthy controls [$p<0.025$, threshold-free cluster enhancement (TFCE) and family-wise error (FWE) corrected] (yellow/orange). Reduced FA in this subregion was coupled with elevated RD and MD, and preserved AD ($p<0.05$, TFCE and FWE corrected). (*b*) Region-of-interest (ROI) TBSS. 3D renderings (*b*1) and sagittal, coronal and axial sections (*b*2) of the WM skeleton (green) and the bilateral uncinate fasciculus (UF) (red), with a subregion of the UF showing significantly elevated FA in patients relative to healthy controls ($p<0.05$, TFCE and FEW corrected) (yellow/orange). Elevated FA in this subregion was coupled with elevated axial diffusivity (AD), reduced radial diffusivity (RD) and preserved mean diffusivity (MD) ($p<0.05$, TFCE and FEW corrected). For better visibility, the results are thickened using the 'tbss-fill' command, and purple arrows mark the effect site. All images are in radiological convention (right is left and *vice versa*).

depression scores ($\beta=-0.30$, $p=0.15$). Finally, no age × symptom severity interaction was found for FA in the CC ($\beta=-0.05$, $p=0.85$) or the UF ($\beta=-0.55$, $p=0.05$).

Discussion

The current study used whole-brain and ROI-based TBSS to examine WM microstructural integrity in a sample of treatment-naive adolescents with clinical depression relative to matched controls. We hypothesized that, in depressed adolescents, whole-brain analysis of FA would reveal abnormalities within tracts previously implicated in depression, whereas ROI analysis of FA would reveal abnormalities in the UF. Moreover, we hypothesized that reduced FA would be coupled with reduced AD and/or elevated RD and

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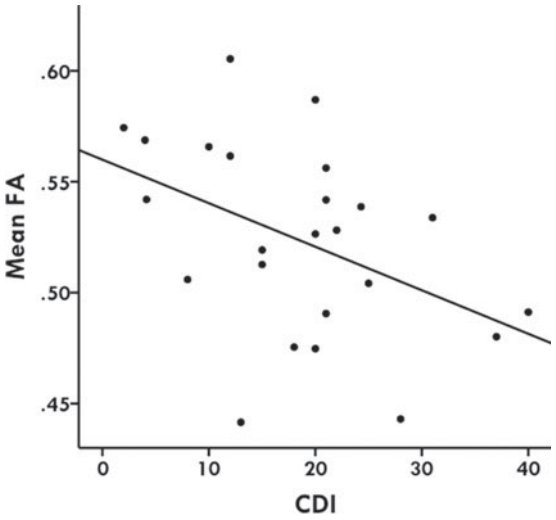

Fig. 2. Scatter plot visualizing a trending negative association between patients' fractional anisotropy (FA) in the effect site of the corpus callosum (CC) and Children's Depression Inventory (CDI) scores ($\beta = -0.43$, $p = 0.055$).

MD, whereas the opposite was expected for any increase in FA. Whole-brain analysis revealed that patients had lower FA values in the body of the CC, coupled with elevated RD and MD, and preserved AD. Conversely, ROI analysis revealed that patients had higher FA values in the UF, coupled with elevated AD, reduced RD and preserved MD. Moreover, a trend for an association was found between reduced FA in the CC and more severe depressive symptoms in patients. These results largely confirm this study's hypotheses and add to converging lines of evidence implicating WM abnormalities in the pathophysiology of depression.

Several DTI studies implicate reduction in CC FA in both adult and adolescent depression (Sexton *et al.* 2009; Cullen *et al.* 2010; Kieseppa *et al.* 2010; Korgaonkar *et al.* 2011). In line with these reports, our whole-brain analysis revealed reduced FA in the body of the CC in adolescents with clinical depression. Of note, this reduction in FA was coupled with elevated RD and MD, and preserved AD, suggesting that demyelination (i.e. elevated RD and MD) without axonal loss (i.e. preserved AD) could underlie lower FA in the CC. Further analysis also revealed a trending association between reduced FA in the body of the CC and more severe depressive symptoms in patients, which in line with previous reports (Lamar *et al.* 2010; Cole *et al.* 2012). The CC is a thick interhemispheric fiber tract that connects most of the neocortex and is composed of neural circuits implicated in cognitive and emotional processing (Gazzaniga, 2000; Paul *et al.* 2006; Tamietto *et al.* 2007). The CC integrates interhemispheric information but also facilitates inhibition of cortical areas by homologous cortical areas (Bloom & Hynd, 2005). Of note, the body of the CC contains fibers that connect to the cingulate, insular and temporal cortices (Seltzer & Pandya, 1986), areas frequently implicated in depression (Thomas *et al.* 2001; Mayberg, 2003; Rosso *et al.* 2005; Caetano *et al.* 2007; Price & Drevets, 2010). Decreased WM integrity of the CC, as indicated by lower FA values, may thus hinder interhemispheric interactions and promote widespread network dysfunction in adolescents with depression. Consistent with this notion, abnormal interhemispheric processing of emotions was previously shown in depression (Davidson & Irwin, 1999), and various studies implicate widespread network dysfunction in the pathophysiology of depression (Drevets *et al.* 2008; Price & Drevets, 2010). Our finding, together with previous reports of altered CC microstructure in depression, raises the possibility that alterations in CC microstructure might reflect a vulnerability marker for affective disorders. This notion is further supported by a recent study demonstrating altered CC microstructure in healthy adolescents at familial risk for depression (Huang *et al.* 2011).

In addition to our whole-brain analysis, our ROI-based analysis revealed elevated FA values in the left UF in adolescents with clinical depression. This increase in FA was coupled with elevated AD and reduced RD, suggesting that abnormally increased fiber bundle coherence (i.e. elevated AD) and myelination (i.e. reduced RD) could underlie higher FA in the UF. Various studies implicate abnormal UF microstructure in the pathophysiology of adult and adolescent depression (Sexton *et al.* 2009; Cullen *et al.* 2010). The UF serves an integral role in corticolimbic interactions by linking limbic structures such as the amygdala with the OMPFC and sACC (Petrides & Pandya, 2002; Kier *et al.* 2004). The amygdala, OMPFC and sACC are part of a ventral corticolimbic circuit that supposedly evaluates the emotional significance of a stimulus and produces an affective response to that stimulus (Phillips *et al.* 2003*a*). We speculate that exaggerated directional coherence within the UF, as reflected by higher FA values, might mediate exaggerated function and functional connectivity in this ventral corticolimbic circuit and impede mood regulation. Indeed, elevated function of the amygdala, OMPFC and sACC on the one hand and augmented bottom-up (amygdala–sACC) and top-down (OMPFC–amygdala) functional interactions on the other are thought to underlie some of the affective symptoms in depression (Phillips *et al.* 2003*b*; Stein *et al.* 2007; Price & Drevets, 2010; Masten *et al.* 2011). Following this perspective, Steffens *et al.* (2011) show that, in depressed patients, higher FA in the left UF relates to increased functional connectivity between the amygdala and the ventrolateral PFC

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(VLPFC), possibly reflecting aberrant top-down emotion regulation. As the VLPFC communicates with the amygdala through the OMPFC (Phillips *et al.* 2003*a*, 2008), this finding suggests a tight relationship between abnormal UF microstructure and suboptimal corticolimbic interactions. Our finding therefore not only complements previous findings that implicate corticolimbic circuit dysfunction in the pathophysiology of depression, but further clarifies changes in the microstructural properties of a corticolimbic WM pathway strongly implicated in depressive disorders.

There is currently a misconception in interpreting elevated FA in pathological conditions (e.g. affective disorders), as higher FA is thought to reflect healthier WM (Thomason & Thompson, 2011). However, some data do suggest that, in specific disease processes or developmental stages, an increase in FA might be a pathologic process caused by neuronal changes (Li *et al.* 2011; Thomason & Thompson, 2011). As such, higher FA values have been reported in affective disorders (Versace *et al.* 2008; Ayling *et al.* 2012) and in other psychiatric conditions (Hubl *et al.* 2004; Nakamae *et al.* 2008; Li *et al.* 2011). Our analysis revealed that, in depressed adolescents, reduced FA in the CC was driven by demyelination without axonal loss whereas elevated FA in the UF was mainly driven by exaggerated fiber bundle coherence and myelination. Our findings therefore suggest that adolescent depression may involve a pathologic process in which exaggerated as well as hampered neuroplasticity may give rise to the experience of depression.

Our finding of elevated FA in the UF, however, contrasts with previous reports of reduced FA in the UF in mainly adults with depression (Sexton *et al.* 2009). We suggest three possible explanations for these discrepancies. First, the typical neuromaturation of the UF follows an inverted U-shaped path, with increasing FA values from early childhood to the early thirties followed by decreasing FA values after the age of 36 (Lebel *et al.* 2012). We speculate that depression could involve accelerated abnormal maturation of the UF, as reflected by an earlier increase in FA during adolescence and an earlier decrease in FA during adulthood. This could partly explain the elevated FA values in our sample of clinically depressed adolescents but may also account for the reduced FA frequently reported in adults with depression. Second, chronic depression in adults and medication use in both adults and adolescents are thought to influence neural microstructure (Sexton *et al.* 2009; Hulvershorn *et al.* 2011). These confounding effects make it difficult to replicate findings, and could explain some of the discrepancies between our and previous findings of altered UF microstructure in depression. Finally, in contrast to previous studies, we used ROI-based TBSS to examine UF microstructure. Whereas traditional ROI analyses search for alterations in overall FA within an entire tract, ROI-based TBSS allows voxel-wise analysis of local FA alterations within an entire tract common to all participants (e.g. skeletonized UF tract). Although this difference in analytical approach may yield discrepant findings, TBSS has proved more robust and sensitive in revealing true alterations in FA by minimizing registration errors and partial voluming (Smith *et al.* 2006).

Our analysis revealed that WM alterations within the CC and UF were located exclusively in the left hemisphere. Depression studies report abnormal CC and UF microstructure in the left as well as the right hemisphere (Sexton *et al.* 2009), so a consensus regarding lateralization is still lacking. Nevertheless, interhemispheric imbalance is often observed in depressive disorders. For instance, abnormal interhemispheric processing of emotions accompanies depressed mood (Davidson & Irwin, 1999) whereas left hemisphere lesions often induce depressed mood (Braun *et al.* 1999; Vataja *et al.* 2001). Our findings thus add to the notion that interhemispheric imbalance may be involved in the pathophysiology of depression.

Study limitations and strengths

The cross-sectional nature of this study does not allow for conclusions regarding causality. Hence, we cannot ascertain whether microstructural alterations reported in this study preceded or followed the onset of depressive symptoms. Moreover, because mainly young adolescents were included in our sample, we were not able to examine age-related changes in FA and its potential contribution to the pathophysiology of adolescent depression. Additionally, the small number of adolescent males in our sample did not allow for an adequate test of an age × gender interaction effect on depressive symptoms. Nevertheless, in larger samples girls demonstrate increasing depressive symptoms during adolescence, whereas in boys depressive symptoms tend to decline slightly during adolescence (Wichstrom, 1999; Angold *et al.* 2002). Longitudinal research in larger samples with a wide age range and a more balanced male-to-female ratio, and DTI studies of individuals at risk for affective disorders, could tackle these limitations. In addition, as socio-economic status and illness duration were not assessed, we cannot rule out the possibility that WM differences may be attributable to these variables. Regarding illness duration, however, it should be noted that the included group did not receive any treatment prior to this study, which might suggest a relatively short illness duration. Finally, in line with other studies examining adolescent depression, depression co-occurred with

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anxiety in most of our patients, and this might affect the specificity of our results. This co-morbidity, however, is deemed a typical element of clinical depression in adolescents, and exclusion of these patients therefore would have resulted in a highly atypical sample (Zahn-Waxler *et al*. 2000; Costello *et al*. 2003; Cullen *et al*. 2009). Despite these limitations, our study has several strengths that increase the reliability of our results. First, to circumvent potential confounding effects of medication or psychotherapy on WM microstructure, only treatment-naive participants were included in our sample. Second, to allow more accurate group comparison of WM integrity, patients and healthy controls were matched for age, sex and IQ, while including these variables in the analyses as covariates to account for their possible confounding effects. Finally, TBSS was used for both whole-brain and ROI analysis to minimize registration errors and partial voluming, thus allowing more robust and sensitive investigation of WM microstructure.

Conclusions

In summary, adolescents with clinical depression showed WM microstructural alterations within pathways facilitating cognitive and emotional functioning. These findings add to converging lines of evidence implicating WM abnormalities in the pathophysiology of depression, and suggest that these abnormalities are already present early in the course of the disorder. For a deeper understanding of WM architecture in depressive disorders, it would be both important and interesting to examine whether WM alterations predict susceptibility, treatment response and risk of relapse in depressive disorders. Our group will address these questions in subsequent studies using longitudinal data from the EPISCA cohort.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291713003000.

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Declaration of Interest

None.

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