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ORIGINAL ARTICLE

Adverse childhood experiences influence white matter microstructure in patients with bipolar disorder

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Background. Bipolar disorder (BD) is associated with adverse childhood experiences (ACE), which worsen the lifetime course of illness, and with signs of widespread disruption of white matter (WM) integrity in adult life. ACE are associated with changes in WM microstructure in healthy humans.

Method. We tested the effects of ACE on diffusion-tensor imaging (DTI) measures of WM integrity in 80 in-patients affected by a major depressive episode in the course of BD. We used whole-brain tract-based spatial statistics in the WM skeleton with threshold-free cluster enhancement of DTI measures of WM microstructure: axial, radial and mean diffusivity, and fractional anisotropy.

Results. ACE hastened the onset of illness. We observed an inverse correlation between the severity of ACE and DTI measures of axial diffusivity in several WM fibre tracts contributing to the functional integrity of the brain and including the corona radiata, thalamic radiations, corpus callosum, cingulum bundle, superior longitudinal fasciculus, inferior fronto-occipital fasciculus and uncinate fasciculus.

Conclusions. Axial diffusivity reflects the integrity of axons and myelin sheaths, and correlates with functional connectivity and with higher-order abilities such as reasoning and experience of emotions. In patients with BD axial diffusivity is increased by lithium treatment. ACE might contribute to BD pathophysiology by hampering structural connectivity in critical cortico-limbic networks.

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Key words: Bipolar disorder, childhood, stress, trauma, white matter.

Introduction

Early psychosocial adversities have been associated with poorer emotional and physical functioning, with higher vulnerability to further trauma exposure, and with higher rates of adult psychopathology (Felitti *et al.* 1998; Rutter, 2002; Edwards *et al.* 2003; Moffitt *et al.* 2005; Anda *et al.* 2006; Teicher *et al.* 2010; Wermter *et al.* 2010). Bipolar disorder (BD) is a progressive and accelerating condition with a cyclical alternating pattern of manic and depressive episodes, and has been associated with neurostructural changes, cognitive deterioration and accumulated medical comorbidity. A history of childhood maltreatment is highly prevalent in patients with BD, and has been associated with an earlier onset of the disorder, worse clinical course, and higher lifetime suicidal ideation and suicide attempts (McIntyre *et al.* 2008; Daruy-Filho *et al.* 2011; Brietzke *et al.* 2012).

An impressive series of studies in healthy subjects associated adverse childhood experiences (ACE) with *in vivo* measures of adult white matter (WM) microstructure. Given the microscopic structure of WM, in normal conditions the integrity of myelinated axons limits the diffusion of water in directions other than along the main axis of the fibre. This tendency to diffuse in one direction as opposed to all others, termed anisotropy, reflects the integrity of axons and myelin sheaths and the bundle coherence of WM tracts, and can be estimated *in vivo* through the application of diffusion-tensor imaging (DTI) techniques (Basser *et al.* 1994; Le Bihan, 2003; Taylor *et al.* 2004*b*). These allow estimation of the tendency to diffuse along the principal direction of the fibre (axial diffusivity; AD) or perpendicular to axonal walls

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(radial diffusivity; RD) (Song *et al.* 2002), and to calculate the variance of the direct measures of the diffusion magnitude in these directions (fractional anisotropy; FA).

Early severe socio-emotional deprivation in Eastern European orphanages has been found to be associated with reduced FA in the left uncinate fasciculus (Eluvathingal *et al.* 2006), paralleling glucose hypometabolism in limbic and paralimbic structures (Chugani *et al.* 2001). A pivotal study in healthy adults associated parental verbal abuse during childhood with a significantly reduced FA in the arcuate fasciculus in the left superior temporal gyrus, in the cingulum bundle by the posterior tail of the left hippocampus, and in the left body of the fornix (Choi *et al.* 2009). The same group then documented an increased mean diffusivity (MD) and RD with decreased FA in the corpus callosum and corona radiata of adults exposed to peer verbal abuse (Teicher *et al.* 2010), and a reduction of FA values in the inferior longitudinal fasciculus of the left lateral occipital lobe in adults who had witnessed domestic violence during childhood (Choi *et al.* 2012). These data suggested an association between childhood maltreatment and the development of fibre pathways that convey the adverse experience to frontal, temporal or limbic regions (Teicher *et al.* 2006). A recent study confirmed that adolescents exposed to childhood maltreatment had lower FA in the superior longitudinal fasciculi, right cingulum bundle projecting to the hippocampus, left inferior fronto-occipital fasciculus, and splenium of the corpus callosum, with lower values being associated with emerging depression during follow-up (Huang *et al.* 2012), thus supporting the hypothesis that WM disruption in circuitries critical for emotional and cognitive processing could be linked with mood disorder psychopathology (Benedetti *et al.* 2011*c*). However, the effects of stress on WM are not limited to ACE, because post-exposure combined reduction in hippocampal volume and connectivity with the prefrontal cortex have been found to mark a maladaptive response to stressful military service (Admon *et al.* 2013).

Changes in WM microstructure have indeed been proposed as structural biomarkers of BD, independent of the effects of ongoing drug treatments. Widespread changes in DTI measures of WM integrity have been reported in untreated BD depressed patients (Benedetti *et al.* 2011*c*), in drug-naive BD patients with mania (Adler *et al.* 2006), in untreated BD patients with first-episode psychosis (Lu *et al.* 2011) and in high-risk unaffected relatives of patients with BD (Sprooten *et al.* 2011). These studies consistently documented an increased diffusivity with reduced FA during illness phases of both manic and depressive polarity, while the few observations in stable euthymic patients showed increased FA in patients with BD compared with controls (Houenou *et al.* 2007; Wessa *et al.* 2009). Long-term administration of lithium, the mainstay for the treatment of BD, has been associated with higher diffusivity along the principal fibre axis (AD, λ_1), thus possibly counteracting the detrimental changes in WM microstructure associated with BD (Benedetti *et al.* 2013). These findings suggest that WM diffusivity changes might be of clinical relevance in BD, and that DTI could provide new biomarkers to estimate susceptibility to the disorder, to track its lifetime progression, to identify new targets for treatment, and to predict and monitor treatment efficacy (Benedetti *et al.* 2011*c*, 2013).

The documented associations between ACE and WM microstructure in healthy subjects, between BD and WM microstructure, and between ACE and outcome of BD, led us to hypothesize that ACE could be associated with altered DTI measures of WM integrity in patients with BD. In the present study, using tract-based spatial statistics (TBSS), we tested this hypothesis in a homogeneous sample of patients affected by a major depressive episode in the course of BD.

Method

Participants and clinical assessment

We studied 80 consecutively admitted in-patients affected by a major depressive episode without psychotic features, with a diagnosis of BP type I (Structured Clinical Interview for DSM Disorders). Patients were either drug-free (n=54) or treated with lithium (n=26). Exclusion criteria were: additional diagnoses on Axis I, mental retardation on Axis II, pregnancy, major medical and neurological disorders, history of drug or alcohol abuse or dependency. Physical examination, laboratory tests and electrocardiograms were performed at admission. No patient had received electroconvulsive therapy within 6 months prior to study enrolment. After complete description of the study to the participants, written informed consent was obtained. The study was approved by the local ethical committee.

Severity of ACE was rated on the Risky Families Questionnaire (RFQ) (Taylor *et al.* 2006) after functional magnetic resonance imaging (fMRI) scanning. The RFQ has been adapted from an instrument originally developed to assess the relationship of family stress to mental and physical health outcomes in adulthood (Felitti *et al.* 1998). The instrument is aimed at rating the degree of harsh parenting with overt family conflict and deficient nurturing experienced by the children in their familial environment. Previous research has validated this questionnaire against clinical interviews

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conducted and coded by trained clinical interviewers; the dual assessments (questionnaire and interview) demonstrated high agreement and reliability (Taylor *et al.* 2004*a*). This approach has been proven successful in detecting the grey matter structural and functional brain correlates of ACE in adult life (Taylor *et al.* 2006; Benedetti *et al.* 2011*b*).

Image acquisition

DTI was performed on a 3.0 Tesla scanner (Gyroscan Intera; Philips, The Netherlands) using spin-echo echo-planar imaging and the following parameters: repetition time (TR)=8753.89 ms; echo time (TE)=58 ms; field of view 231.43 mm (AP), 126.50 mm (FH), 240.00 mm (RL); acquisition matrix 2.14×2.71×2.31; 55 contiguous, 2.3-mm thick axial slices reconstructed with in-plane pixel size 1.88×1.87 mm; sensitivity encoding acceleration factor=2; one b0 and 35 non-collinear directions of the diffusion gradients; b value=900 s/mm^2. Fat saturation was performed to avoid chemical shift artifacts. On the same occasion and using the same magnet, 22 turbo spin echo, T2 axial slices (TR=3000 ms; TE=85 ms; flip angle=90°; turbo factor 15; 5-mm-thick, axial slices with a 512×512 matrix and a 230×230 mm^2 field of view) were acquired to rule out brain lesions.

Data processing and analyses

Image analyses and tensor calculations were carried out using the 'Oxford Center for Functional Magnetic Resonance Imaging of the Brain Statistical Library' (FSL 4.1.4; www.fmrib.ox.ac.uk/fsl/index.html) (Smith *et al.* 2004; Woolrich *et al.* 2009). First, each of the 35 DTI volumes was affine registered to the T2-weighted b=0 volume using FLIRT (FMRIB's Linear Image Registration Tool) (Jenkinson & Smith, 2001). This corrected for motion between scans and residual eddy-current distortions present in the diffusion-weighted images. In addition, trained researchers blind to diagnosis manually inspected each volume of each image to check for head motion artifacts: scans rated as 0 (none) had little or no detectable motion artifact, those rated as 1 (mild) had enough detectable motion to result in subtle concentric bands, 2 (moderate) had significant banding while those rated as 3 (severe) were so extreme that the data were deemed unreliable for analyses (Blumenthal *et al.* 2002). Anisotropy can be estimated through the application of diffusion-sensitizing gradients and the calculation of elements of the diffusion tensor matrix, i.e. the three eigenvalues λ_1, λ_2 and λ_3 (Basser *et al.* 1994; Le Bihan, 2003; Taylor *et al.* 2004*b*). The tendency to diffuse along the principal direction of the fibre (AD, λ_1) reflects the integrity of axons and myelin sheaths, and the bundle coherence of WM tracts (Boretius *et al.* 2012). An increase in RD (the average of λ_2 and λ_3), perpendicular to axonal walls, suggests disrupted myelination (Song *et al.* 2002). MD (average of λ_1, λ_2 and λ_3) is a measure of the average molecular motion, independent of tissue directionality. FA is the square root of the sum of squares (SRSS) of the diffusivity differences, divided by the SRSS of the three diffusivities. After removal of non-brain tissue (Smith, 2002), least-square fits were performed to estimate the FA, eigenvector, and eigenvalue maps. MD was defined as the mean of all three eigenvalues $[(\lambda_1+\lambda_2+\lambda_3)/3]$, AD as the principal diffusion eigenvalue (λ_1), and RD as the mean of the second and third eigenvalues $[(\lambda_2+\lambda_3)/2]$.

Next, all individuals' volumes were skeletonized and transformed into a common space as used in TBSS (Smith *et al.* 2006, 2007). TBSS focuses on the centres of all fibre bundles that are common to the participants (the most compact WM skeleton), thus improving the probability that the given spatial voxels contain data from the same part of the same WM tract of each participant. Briefly, all volumes were non-linearly warped to the FMRIB58_FA template supplied with FSL (http://www.fmrib.ox.ac.uk/fsl/tbss/FMRIB58_FA.html) and normalized to the Montreal Neurological Institute (MNI) space, by use of local deformation procedures performed by FMRIB's Non-Linear Image Registration Tool (FNIRT) (www.fmrib.ox.ac.uk/fsl/fnirt/index.html), a non-linear registration toolkit using a b-spline representation of the registration warp field (Rueckert *et al.* 1999). The common template used in the present study is a high-resolution average of 58 FA volumes from healthy male and female subjects aged 20–50 years. All warped FA volumes were visually inspected for accuracy, which is especially pertinent when analysing datasets with broad age ranges with relatively large interindividual variability in brain size and architecture. FNIRT has been shown to perform native-to-standard warping adequately across several age groups, including children and adolescents (Westlye *et al.* 2010). Next, a mean FA volume of all subjects was generated and thinned to create a mean FA skeleton representing the centres of all common tracts. We thresholded and binarized the mean skeleton at FA>0.20 to reduce the likelihood of partial voluming in the borders between tissue classes, yielding a mask of 137 833 WM voxels. Individual FA values were warped onto this mean skeleton mask by searching perpendicular from the skeleton for maximum FA values. Using maximum FA values from the centres of the tracts further minimizes confounding effects attributable to partial voluming (Smith *et al.* 2006). The resulting tract invariant skeletons for each participant were

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fed into voxelwise permutation-based cross-subject statistics. Similar warping and analyses were used on MD, AD and RD data sampled from voxels with FA>0.20.

Voxelwise DTI analyses were performed using non-parametric permutation-based testing (Nichols & Holmes, 2002) as implemented in RANDOMISE in FSL. We tested for linear effects of ACE on FA, MD, AD and RD across the WM skeleton with general linear models. We accounted for the effects of nuisance covariates that could influence WM structure: age (Kochunov *et al.* 2007), sex (Herting *et al.* 2011), education (Foubert-Samier *et al.* 2012), and duration of lithium treatment in months (Benedetti *et al.* 2013). Threshold-free cluster enhancement (TFCE) (Smith & Nichols, 2009) was used to avoid defining arbitrary cluster-forming thresholds and smoothing levels. TFCE is particularly useful when the spatial correlation length of the signal exceeds that of noise, as it is expected when studying WM tracts. It can be seen as a generalization of the cluster mass statistics (Bullmore *et al.* 1999), using spatial neighbourhood information in non-linear image processing to increase sensitivity and boosting the height of spatially distributed signals, without changing the location of their maxima. Voxelwise levels of significance, corrected for multiple comparisons, were then calculated with a standard permutation testing by building up the null distribution (across permutation of the input data) of the maximum (across voxels) TFCE scores, and then using the 95th percentile of the null distribution to threshold signals at corrected $p<0.05$. The data were tested against an empirical null distribution generated by 5000 permutations for each contrast, thus providing statistical maps fully corrected for multiple comparisons across space. Corrected $p<0.05$ in a minimum cluster size of k=100 was considered significant.

In addition to FA and MD, we analysed the significance of the effects of ACE on the single eigenvalue λ_1 and RD. The eigenvalue λ_1 directly measures diffusion along the principal axis of the WM tracts (AD), thus accounting for those components of the diffusion anisotropy that are related to axonal structure, directionality and branching. RD measures diffusion perpendicular to the fibre, thus being directly influenced by the integrity of myelin sheaths. Previous work has shown that these measures are more able to capture the subtle WM abnormalities associated with bipolar illness and its treatment (Benedetti *et al.* 2011*a*, *c*, 2013).

Results

Clinical and demographic characteristics of the sample are shown in Table 1.

Table 1. *Clinical and demographic characteristics of the sample*

Characteristics	
Sex, *n*	
Female	57
Male	23
Age, years	45.91 (11.46)
Age at onset, years	29.94 (9.84)
Duration of illness, years	15.95 (10.49)
Education, years	10.81 (3.88)
Previous manic episodes, *n*	3.25 (4.51)
Previous depressive episodes, *n*	5.56 (5.56)

Data are given as mean (standard deviation).

In agreement with earlier observations (Daruy-Filho *et al.* 2011), and confirming the clinical relevance of ACE in the present sample, higher ACE as rated on the RFQ were associated with a significantly earlier age of onset of illness (Pearson's $r=0.342$, $p=0.002$; see Fig. 1). The other measures were not associated with RFQ scores.

ACE influenced DTI measures of WM microstructure. Patients with higher RFQ scores showed lower values of AD in several brain WM tracts (Fig. 2).

Differences in AD were observed in two main clusters, which included the corpus callosum and forceps minor, bilateral anterior and posterior cingulum bundle, bilateral corona radiata with anterior and posterior thalamic radiation, bilateral superior longitudinal fasciculus, left inferior fronto-occipital fasciculus and left uncinate fasciculus (see Table 2).

No other effect was significant. In particular, no positive correlation was observed between ACE and AD in any region, and no effect of sex or clinical variables (severity of depression), or any effect of ACE on FA, RD and MD, survived the statistical threshold of $p<0.05$ corrected for multiple comparisons across space.

Discussion

This is the first study to report an effect of ACE on WM integrity in bipolar patients. We observed that the severity of exposure to ACE was associated with decreased DTI measures of AD in many WM tracts connecting cortical and subcortical brain structures.

AD represents the water diffusivity parallel to the axonal fibres, reflecting the greater freedom of water to diffuse along the principal fibre axis rather than to travel across the surrounding myelin sheaths. Both myelin and axonal microstructure, including microtubules and neurofilaments (Kinoshita *et al.* 1999),

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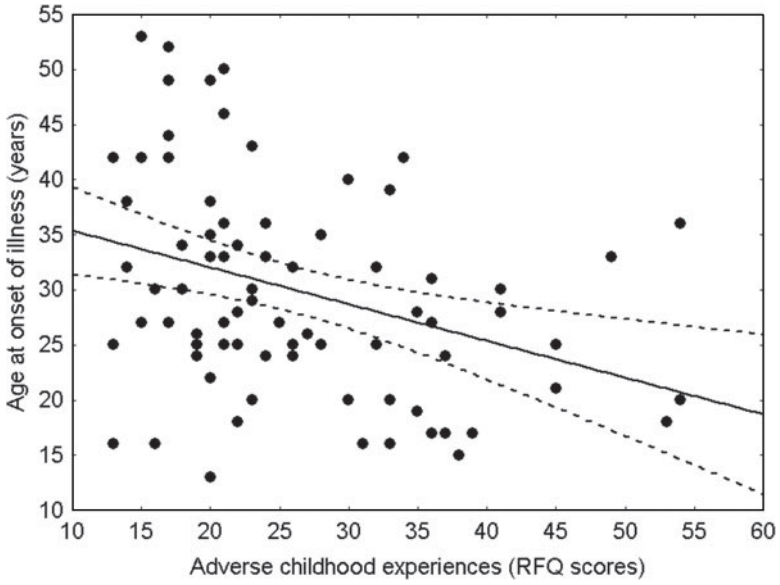

Fig. 1. Inverse correlation (—) between the severity of adverse childhood experiences measured using the Risky Families Questionnaire (RFQ) and onset of illness (Pearson's $r=0.342$, $p=0.002$). The worse the adverse childhood experiences, the earlier the onset of bipolar disorder. The dashed lines represent 95% confidence intervals.

contribute to this diffusion anisotropy. Studies on neurodevelopment have associated AD with fibre diameter and organization (Takahashi *et al.* 2000). Over the human lifespan AD and MD decrease initially, and then increase later in life (Qiu *et al.* 2008; Lebel *et al.* 2012), also reflecting changes in fibre coherence and tortuosity (Dubois *et al.* 2008). AD positively correlates with functional connectivity among brain regions, and with network-related aspects of human brain function also including, as behavioural correlates, the experience of emotions in response to stimuli (Baur *et al.* 2013) and higher-order abilities such as reasoning and cognitive flexibility (Borghesani *et al.* 2013).

Here we observed that ACE were associated with a lower AD in key WM tracts contributing to the functional integrity of the brain. These included interhemispheric connections, limbic, and large frontal, parietal and fronto-occipital connections that have been proposed as key components of the brain network dysfunctions, putatively leading to the cognitive and emotional deficits typical of BD (Brambilla *et al.* 2009; Benedetti *et al.* 2011*a*, *c*). ACE-associated alterations in WM structure could then contribute to the abnormal effective cortico-limbic connectivity observed with fMRI (Arnone *et al.* 2008; Rich *et al.* 2008), and to the affective and cognitive instability observed during the waxing and waning of illness episodes in BD. Examination of the available literature regarding the WM tracts where ACE are associated with decreased AD supports this hypothesis.

The corona radiata contains both descending and ascending axons that carry nearly all of the neural traffic from and to the cerebral cortex. The DTI measures of the corona radiata correlate with performance in executive function and information processing speed (Sasson *et al.* 2012). Prefrontal cortical areas ensure the cognitive control of emotion experience and mood (Beauregard *et al.* 2001; Barrett *et al.* 2007). Their reactivity to stimuli parallels the mood-congruent biases in the processing of emotional stimuli during depression (Elliott *et al.* 2002), and normalize after successful antidepressant treatment in BD (Benedetti *et al.* 2007). The corona radiata showed a reduced integrity in patients with BD (Benedetti *et al.* 2011*c*), soon at the beginning of illness (Barnea-Goraly *et al.* 2009; Pavuluri *et al.* 2009), and with lithium increasing AD proportionally to treatment duration (Benedetti *et al.* 2013). The corona radiata is sensitive to early stress in healthy humans, as documented by measures of reduced integrity in adults exposed to peer verbal abuse (Teicher *et al.* 2010).

The cingulum bundle is located within the WM of the cingulate gyrus and originates from the frontal lobe, rounds the corpus callosum from the genu extending to the splenium, travels along the ventral surface of the hippocampus, and terminates in the amygdala (Schmahmann *et al.* 2007). These connections are crucial for both motivational and emotional aspects of behaviour, integrating disparate modular brain systems involved in attention, memory and emotion regulation that have been considered at the core of mood dysregulation in BD (Davidson *et al.* 2002). In mood disorders a higher directionality of water diffusion in the cingulum bundle is associated

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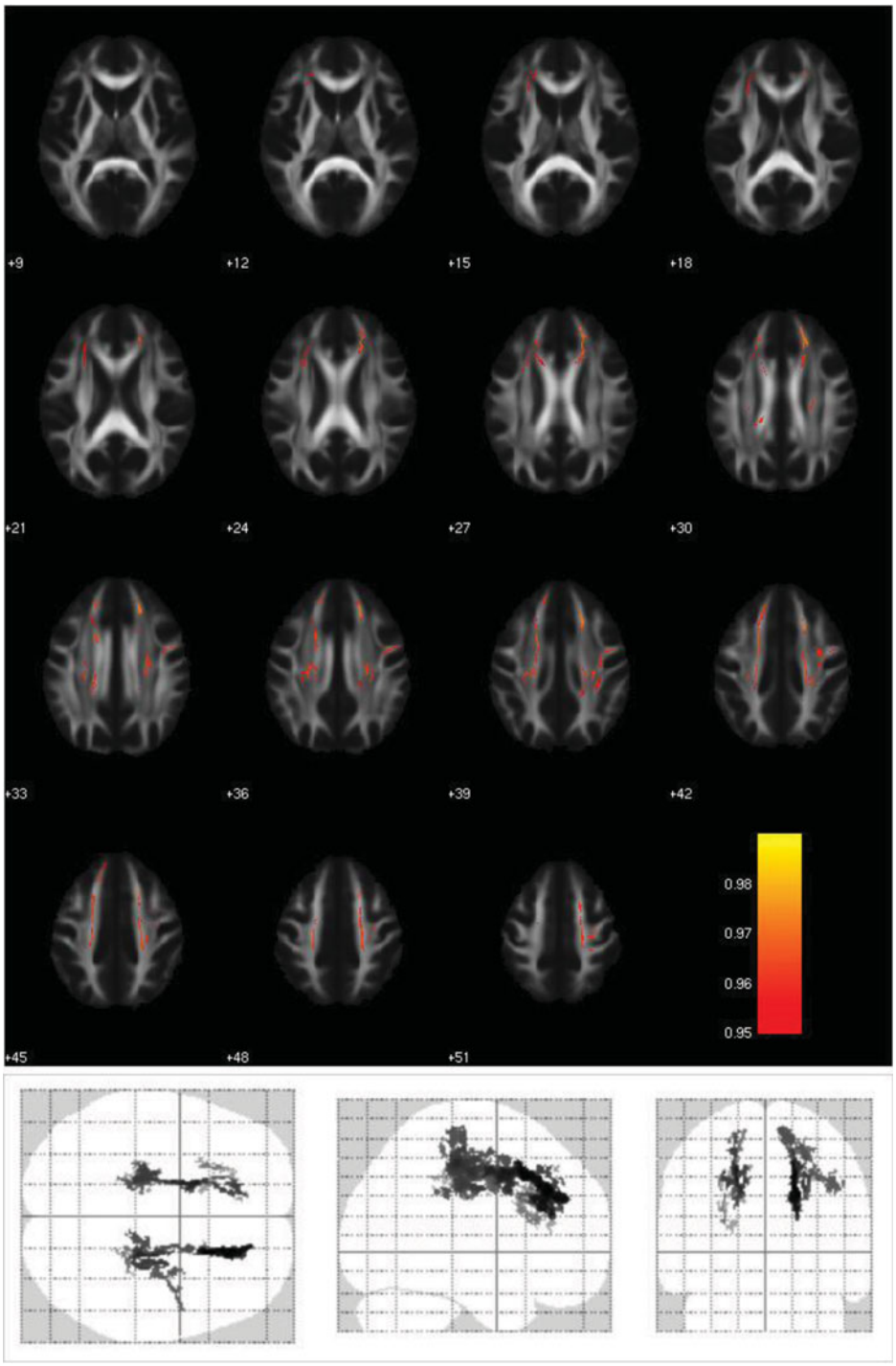

Fig. 2. White matter areas where axial diffusivity showed a significant inverse relationship with adverse childhood experiences (Risky Families Questionnaire scores). Voxels of significant difference are shown on the mean fractional anisotropy (FA) template of the studied sample. The colour bar refers to $1-p$ values for the observed differences. Group differences are mapped onto the mean FA brain template. Numbers are z coordinates in the standard Montreal Neurological Institute (MNI) space. Images are in neurological convention (left side of the brain is represented on the right side of the pictures).

with better hedonic tone (Keedwell *et al.* 2012), better cognitive performance (Schermuly *et al.* 2010) and less psychomotor slowing (Walther *et al.* 2012), memory scores and hippocampal volume (Sexton *et al.* 2010). The cingulum is highly sensitive to early stress, with FA in this area being reduced in healthy

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Table 2. *Effect of ACE on axial diffusivity*[a]

Cluster dimensions and signal peaks: x, y, z	White matter tracts
Voxels: 2752 MNI: 18, 18, 40 R Superior longitudinal fasciculus	Corticospinal tract R Forceps minor Anterior corona radiata R Anterior thalamic radiation R Anterior cingulate gyrus R Body of corpus callosum Splenium of corpus callosum Superior longitudinal fasciculus R Superior corona radiata R
Voxels: 1772 MNI: −18, 7, 41 L Superior longitudinal fasciculus (temporal part)	Uncinate fasciculus L Forceps minor Anterior cingulate gyrus L Posterior cingulate gyrus L Body of corpus callosum Splenium of corpus callosum Anterior thalamic radiation L Anterior corona radiata L Superior corona radiata L Posterior corona radiata L Inferior fronto-occipital fasciculus L Corticospinal tract L Superior longitudinal fasciculus L
Voxels: 345 MNI: −27, 23, 17 L Anterior thalamic radiation	Inferior fronto-occipital fasciculus L Anterior thalamic radiation L Anterior corona radiata L Forceps minor Uncinate fasciculus L Superior longitudinal fasciculus L

ACE, Adverse childhood experiences; MNI, Montreal Neurological Institute; R, right; L, left.

[a] In the first column, dimensions of clusters (number of voxels, mm^3) and localization of signal peaks (MNI coordinates) are given for regions showing maximal differences of tract-based spatial statistics values (signal peak). The second column lists the white matter tracts significantly affected by ACE in the clusters.

humans exposed to parental verbal abuse and being inversely associated with ratings of depression, dissociation and limbic irritability (Choi *et al.* 2009). Again, we had reported a breakdown in the architecture of these WM tracts in BD (Benedetti *et al.* 2011*a*), and that lithium, contrary to stress, promotes a higher directionality of water diffusion in these tracts (Benedetti *et al.* 2013).

The thalamic radiations are two-way fibre connections between the thalamus and cerebral cortex, forming a major part of the internal capsule and corona radiata (Liao *et al.* 2013). The anterior thalamic radiation (ATR) connects the anterior thalamic and dorsomedial nuclei with the prefrontal cortex and medial temporal cortex, and is part of the thalamo-fronto-striatal loops that have been implicated in the pathophysiology of both BD and schizophrenia (Buchsbaum *et al.* 1999; McIntosh *et al.* 2008). Early life stress has been associated with significant reductions in FA in the anterior limb of the internal capsule in non-human primates (Coplan *et al.* 2010). A reduced FA in the ATR has been consistently detected in patients with BD (McIntosh *et al.* 2008; Sussmann *et al.* 2009) soon after the beginning of illness (Pavuluri *et al.* 2009; Lu *et al.* 2012), and in their unaffected relatives (McIntosh *et al.* 2005), among whom FA in the internal capsule was inversely related to cyclothymic temperament (Sprooten *et al.* 2011), thus also suggesting a link with genetic vulnerability for the disorder. Converging ascending and descending medial forebrain bundle and ATR fibre tracts could mediate reward seeking and regulation of affective states in

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healthy and depressed humans (Schoene-Bake *et al.* 2010; Coenen *et al.* 2012). Executive function and processing speed were correlated with anisotropy of the ATR and uncinate fasciculus in late-life depression (Sexton *et al.* 2012). The posterior thalamic radiation (PTR) connects the pulvinar and lateral geniculate nuclei to the posterior parietal and occipital cortex, and its integrity correlates with behavioural reaction time in visuospatial attention tasks (Tuch *et al.* 2005). Impaired orientational coherence or reduced WM integrity has been consistently described in patients with major depressive disorder (MDD) (Liao *et al.* 2013) and with BD (Chan *et al.* 2010; Benedetti *et al.* 2011*c*). Again, lithium counteracted these effects in the ATR and PTR by increasing AD (Benedetti *et al.* 2013).

The corpus callosum provides the major commissural fibre bundles allowing interhemispheric communication. Corpus callosum integrity is crucial for the integration of sensory–motor functions, attention, language and memory, which are frequently impaired in bipolar patients (Brambilla *et al.* 2009). Its structure is sensitive to early stress, because degree of exposure to peer verbal abuse correlates with increased RD and MD and decreased FA (Teicher *et al.* 2010). Abnormal myelination and morphometry have been consistently associated with BD (Bearden *et al.* 2011, Benedetti *et al.* 2011*c*), and with dimensions of BD psychopathology such as aggression (Saxena *et al.* 2012) and suicide (Matsuo *et al.* 2010). These abnormalities persist in euthymic conditions (Emsell *et al.* 2013), when patients show signs of reduced fibre density (Torgerson *et al.* 2012), and again we found lithium to increase AD in the corpus callosum (Benedetti *et al.* 2013). Reduced FA correlates with the genetic liability risk for BD in unaffected relatives (Chaddock *et al.* 2009), and a progressive FA reduction during adolescence, contrary to the expected increase, has been observed in unaffected youth at high risk for BD and proposed as a vulnerability marker for future BD (Versace *et al.* 2010*b*).

The superior longitudinal fasciculus is a huge association fibre tract connecting cortical areas of the frontal, parietal, temporal and occipital lobes, thus being involved in a wide range of functions including executive functioning and emotional regulation, in addition to language processing thanks to its connections to Broca and Wernicke areas (Wakana *et al.* 2004; Makris *et al.* 2005). Adolescents exposed to childhood maltreatment had significantly lower FA values in the bilateral superior longitudinal fasciculus, and those who developed a MDD at follow-up had the lowest values (Huang *et al.* 2012). WM integrity in the superior longitudinal fasciculus was consistently reported to be reduced in BD (Chaddock *et al.* 2009; Versace *et al.* 2010*a*; Benedetti *et al.* 2011*c*), with lithium increasing AD (Benedetti *et al.* 2013). Children with BD or with a first-degree relative with BD showed both a reduced FA in the superior longitudinal fasciculus compared with controls (Frazier *et al.* 2007), and in unaffected individuals at familial risk of mood disorder lower FA in the superior longitudinal fasciculus was associated with increasing genetic liability for BD (Chaddock *et al.* 2009) and with a higher polygenic risk allele load for MDD (Whalley *et al.* 2013). Here we found our most significant peak effects of ACE on AD.

The inferior fronto-occipital fasciculus is a long association bundle that connects the inferior–lateral and dorsolateral prefrontal frontal cortex with posterior temporal and occipital cortices (Schmahmann *et al.* 2007), being thus involved in many brain functions. In healthy humans a reduced FA has been found to be associated with reduced inhibitory cognitive control during response selection (Forstmann *et al.* 2008). FA in the inferior fronto-occipital fasciculus is reduced during BD illness episodes (Zanetti *et al.* 2009; Lu *et al.* 2011), and here lithium increases AD (Benedetti *et al.* 2013). Unaffected siblings had FA values in the inferior fronto-occipital fasciculus that were intermediate to and significantly different from those of healthy volunteers and patients with BD (Mahon *et al.* 2013), and, again, in unaffected relatives FA correlated with genetic risk (Chaddock *et al.* 2009).

Finally, the uncinate fasciculus connects the hippocampus, amygdala and anterior temporal lobe to the medial prefrontal cortex, thus allowing mood regulation and emotional processing, and playing a critical role in memory networks and in the comprehension and regulation of emotional responses to auditory stimuli (Schmahmann *et al.* 2007). Integrity of the uncinate fasciculus may facilitate language- and emotion-based evaluative processes as well as behavioural control functions that delay gratification (Olson *et al.* 2009), is reduced in BD (McIntosh *et al.* 2008; Sussmann *et al.* 2009; Benedetti *et al.* 2011*a*), and lithium treatment positively correlates with AD (Benedetti *et al.* 2013). Moreover, in patients with BD, FA in the uncinate fasciculus positively correlates with the functional coupling between the amygdala and anterior cingulate cortex (Wang *et al.* 2009), which is a critical component of the circuits ensuring adequate emotional processing (Pezawas *et al.* 2005).

These networks are crucial for cognitive functions known to be impaired in bipolar patients (Rubinsztein *et al.* 2000; Sole *et al.* 2012). Early life stress has been found to reduce neurocognitive functioning (executive functioning, visual memory, spatial working memory) and emotional processing in healthy humans (Majer *et al.* 2010; Gould *et al.* 2012).

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We then surmise that ACE could contribute to the impairment of cognitive and emotional processing in BD through the alteration of WM structure in specific networks. These effects of ACE are likely to be associated with other detrimental influences on WM integrity observed in BD. Increased genetic liability to familial BD has been associated with reduced FA across distributed regions of WM in patients and their unaffected relatives (Chaddock *et al.* 2009). Genetic factors affecting the severity of BD also influence WM integrity in BD (Benedetti *et al.* 2013), which is found to be reduced in the main tracts of the WM skeleton (Benedetti *et al.* 2011*c*). Neuroinflammation has been associated with BD, with environmental stress, and with a disrupted integrity of myelin sheaths (Bartzokis, 2012). Gene× environment interactions, including ACE, could then play a major role in the observed relationship between BD and altered DTI measures of WM integrity.

However, the mechanisms by which this might happen remain elusive. The main limitation in interpreting *in vivo* DTI findings is that animal models of DTI measures have been mainly developed to test toxic effects of drugs or to model severe demyelinating diseases (Harsan *et al.* 2006), and not normal human neurodevelopment. The recently described trajectories of change in DTI measures over the human lifespan suggest non-linear relationships with age (Qiu *et al.* 2008; Bartzokis *et al.* 2012; Lebel *et al.* 2012), and current models propose specific effects on brain structures depending on specific sensitive periods in which brain regions and WM tracts could be maximally susceptible to early stress (Andersen & Teicher, 2008). However, prospective studies are still lacking and the available data do not include patients who developed neuropsychiatric diseases.

Given that proliferation and differentiation of oligodendrocytes, and the myelination of axons, are partly controlled by neurotransmitters (Karadottir & Attwell, 2007), factors affecting brain neurotransmitter function in response to stress could contribute to the association between early stress and reduced AD. One example can be found in a polymorphism in the promoter in the serotonin transporter (5-HTTLPR) (Canli & Lesch, 2007), which can independently influence both the behavioural effects of early stressors and WM structure in the general population: carriers of the low-activity alleles showed: (1) a higher association between stress and its worse consequences, including depression and suicide (Caspi *et al.* 2010); and (2) a reduced FA in the uncinate fasciculus (Pacheco *et al.* 2009). Other mechanisms possibly involved include inflammation, which is abnormally elevated in BD (Drexhage *et al.* 2010), also prompted by environmental factors (Padmos *et al.* 2009), and can be increased by psychological distress (Raison *et al.* 2006). Many other genetic and epigenetic mechanisms can mediate the effects of stress (Dudley *et al.* 2011), but their effects on WM have not yet been investigated.

Strengths of the present study include a focused research question and state-of-the-art imaging methods. However, our results must be viewed in the light of several methodological limitations. The lack of a control group limits generalizability of the results, which, however, confirm previous literature in healthy subjects (see Introduction). The sample size allowed us to define the effects of ACE, but did not allow us to test their interaction with clinical variables, or their possible interactions with genetic or pharmacological factors. We measured no biological markers to test for possible mechanisms of the observed effects. Patients were non-drug-naive, and the drug treatments administered during the course of the illness could have influenced DTI measures, alone or interacting with the effects of early stress. Recruitment was in a single centre and in a single ethnic group, thus raising the possibility of population stratifications limiting the generalizability of the findings.

In conclusion, these limitations do not bias the main finding of an effect of ACE on WM microstructure in patients with BD, thus: (1) suggesting shared influences of stress on brain development of healthy and psychiatric populations, to be further confirmed and explored in enlarged and independent samples; and (2) confirming the usefulness of DTI for the study of the structural changes in the brain associated with BD.

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Declaration of Interest

None.

References

Adler CM, Adams J, DelBello MP, Holland SK, Schmithorst V, Levine A, Jarvis K, Strakowski SM (2006). Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: a diffusion tensor imaging study. *American Journal of Psychiatry* **163**, 322–324.

Admon R, Leykin D, Lubin G, Engert V, Andrews J, Pruessner J, Hendler T (2013). Stress-induced reduction

https://doi.org/10.1017/S0033291714000506 Published online by Cambridge University Press

in hippocampal volume and connectivity with the ventromedial prefrontal cortex are related to maladaptive responses to stressful military service. *Human Brain Mapping* **34**, 2808–2816.

Anda RF, Felitti VJ, Bremner JD, Walker JD, Whitfield C, Perry BD, Dube SR, Giles WH (2006). The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *European Archives of Psychiatry and Clinical Neuroscience* **256**, 174–186.

Andersen SL, Teicher MH (2008). Stress, sensitive periods and maturational events in adolescent depression. *Trends in Neurosciences* **31**, 183–191.

Arnone D, McIntosh AM, Chandra P, Ebmeier KP (2008). Meta-analysis of magnetic resonance imaging studies of the corpus callosum in bipolar disorder. *Acta Psychiatrica Scandinavica* **118**, 357–362.

Barnea-Goraly N, Chang KD, Karchemskiy A, Howe ME, Reiss AL (2009). Limbic and corpus callosum aberrations in adolescents with bipolar disorder: a tract-based spatial statistics analysis. *Biological Psychiatry* **66**, 238–244.

Barrett LF, Mesquita B, Ochsner KN, Gross JJ (2007). The experience of emotion. *Annual Review of Psychology* **58**, 373–403.

Bartzokis G (2012). Neuroglialpharmacology: myelination as a shared mechanism of action of psychotropic treatments. *Neuropharmacology* **62**, 2137–2153.

Bartzokis G, Lu PH, Heydari P, Couvrette A, Lee GJ, Kalashyan G, Freeman F, Grinstead JW, Villablanca P, Finn JP, Mintz J, Alger JR, Altshuler LL (2012). Multimodal magnetic resonance imaging assessment of white matter aging trajectories over the lifespan of healthy individuals. *Biological Psychiatry* **72**, 1026–1034.

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

Baur V, Hanggi J, Langer N, Jancke L (2013). Resting-state functional and structural connectivity within an insula–amygdala route specifically index state and trait anxiety. *Biological Psychiatry* **73**, 85–92.

Bearden CE, van Erp TG, Dutton RA, Boyle C, Madsen S, Luders E, Kieseppa T, Tuulio-Henriksson A, Huttunen M, Partonen T, Kaprio J, Lonnqvist J, Thompson PM, Cannon TD (2011). Mapping corpus callosum morphology in twin pairs discordant for bipolar disorder. *Cerebral Cortex* **21**, 2415–2424.

Beauregard M, Lévesque J, Bourgouin P (2001). Neural correlates of conscious self-regulation of emotion. *Journal of Neuroscience* **21**, RC165.

Benedetti F, Absinta M, Rocca MA, Radaelli D, Poletti S, Bernasconi A, Dallaspezia S, Pagani E, Falini A, Copetti M, Colombo C, Comi G, Smeraldi E, Filippi M (2011*a*). Tract-specific white matter structural disruption in patients with bipolar disorder. *Bipolar Disorders* **13**, 414–424.

Benedetti F, Bernasconi A, Blasi V, Cadioli M, Colombo C, Falini A, Lorenzi C, Radaelli D, Scotti G, Smeraldi E (2007). Neural and genetic correlates of antidepressant response to sleep deprivation – a functional magnetic resonance imaging study of moral valence decision, in bipolar depression. *Archives of General Psychiatry* **64**, 179–187.

Benedetti F, Bollettini I, Barberi I, Radaelli D, Poletti S, Locatelli C, Pirovano A, Lorenzi C, Falini A, Colombo C, Smeraldi E (2013). Lithium and GSK3-β promoter gene variants influence white matter microstructure in bipolar disorder. *Neuropsychopharmacology* **38**, 313–327.

Benedetti F, Radaelli D, Poletti S, Falini A, Cavallaro R, Dallaspezia S, Riccaboni R, Scotti G, Smeraldi E (2011*b*). Emotional reactivity in chronic schizophrenia: structural and functional brain correlates and the influence of adverse childhood experiences. *Psychological Medicine* **41**, 509–519.

Benedetti F, Yeh PH, Bellani M, Radaelli D, Nicoletti MA, Poletti S, Falini A, Dallaspezia S, Colombo C, Scotti G, Smeraldi E, Soares JC, Brambilla P (2011*c*). Disruption of white matter integrity in bipolar depression as a possible structural marker of illness. *Biological Psychiatry* **69**, 309–317.

Blumenthal JD, Zijdenbos A, Molloy E, Giedd JN (2002). Motion artifact in magnetic resonance imaging: implications for automated analysis. *NeuroImage* **16**, 89–92.

Boretius S, Escher A, Dallenga T, Wrzos C, Tammer R, Bruck W, Nessler S, Frahm J, Stadelmann C (2012). Assessment of lesion pathology in a new animal model of MS by multiparametric MRI and DTI. *Neuroimage* **59**, 2678–2688.

Borghesani PR, Madhyastha TM, Aylward EH, Reiter MA, Swarny BR, Warner Schaie K, Willis SL (2013). The association between higher order abilities, processing speed, and age are variably mediated by white matter integrity during typical aging. *Neuropsychologia* **51**, 1435–1444.

Brambilla P, Bellani M, Yeh PH, Soares JC (2009). Myelination in bipolar patients and the effects of mood stabilizers on brain anatomy. *Current Pharmacological Design* **15**, 2632–2636.

Brietzke E, Mansur RB, Soczynska JK, Kapczinski F, Bressan RA, McIntyre RS (2012). Towards a multifactorial approach for prediction of bipolar disorder in at risk populations. *Journal of Affective Disorders* **140**, 82–91.

Buchsbaum MS, Hazlett EA, Haznedar MM, Spiegel-Cohen J, Wei TC (1999). Visualizing fronto-striatal circuitry and neuroleptic effects in schizophrenia. *Acta Psychiatrica Scandinavica Supplementum* **395**, 129–137.

Bullmore ET, Suckling J, Overmeyer S, Rabe-Hesketh S, Taylor E, Brammer MJ (1999). Global, voxel, and cluster tests, by theory and permutation, for a difference between two groups of structural MR images of the brain. *IEEE Transactions on Medical Imaging* **18**, 32–42.

Canli T, Lesch KP (2007). Long story short: the serotonin transporter in emotion regulation and social cognition. *Nature Neuroscience* **10**, 1103–1109.

Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE (2010). Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *American Journal of Psychiatry* **167**, 509–527.

Chaddock CA, Barker GJ, Marshall N, Schulze K, Hall MH, Fern A, Walshe M, Bramon E, Chitnis XA, Murray R, McDonald C (2009). White matter microstructural

impairments and genetic liability to familial bipolar I disorder. *British Journal of Psychiatry* **194**, 527–534.

Chan WY, Yang GL, Chia MY, Woon PS, Lee J, Keefe R, Sitoh YY, Nowinski WL, Sim K (2010). Cortical and subcortical white matter abnormalities in adults with remitted first-episode mania revealed by Tract-Based Spatial Statistics. *Bipolar Disorders* **12**, 383–389.

Choi J, Jeong B, Polcari A, Rohan ML, Teicher MH (2012). Reduced fractional anisotropy in the visual limbic pathway of young adults witnessing domestic violence in childhood. *Neuroimage* **59**, 1071–1079.

Choi J, Jeong B, Rohan ML, Polcari AM, Teicher MH (2009). Preliminary evidence for white matter tract abnormalities in young adults exposed to parental verbal abuse. *Biological Psychiatry* **65**, 227–234.

Chugani HT, Behen ME, Muzik O, Juhasz C, Nagy F, Chugani DC (2001). Local brain functional activity following early deprivation: a study of postinstitutionalized Romanian orphans. *NeuroImage* **14**, 1290–1301.

Coenen VA, Panksepp J, Hurwitz TA, Urbach H, Madler B (2012). Human medial forebrain bundle (MFB) and anterior thalamic radiation (ATR): imaging of two major subcortical pathways and the dynamic balance of opposite affects in understanding depression. *Journal of Neuropsychiatry and Clinical Neurosciences* **24**, 223–236.

Coplan JD, Abdallah CG, Tang CY, Mathew SJ, Martinez J, Hof PR, Smith EL, Dwork AJ, Perera TD, Pantol G, Carpenter D, Rosenblum LA, Shungu DC, Gelernter J, Kaffman A, Jackowski A, Kaufman J, Gorman JM (2010). The role of early life stress in development of the anterior limb of the internal capsule in nonhuman primates. *Neuroscience Letters* **480**, 93–96.

Daruy-Filho L, Brietzke E, Lafer B, Grassi-Oliveira R (2011). Childhood maltreatment and clinical outcomes of bipolar disorder. *Acta Psychiatrica Scandinavica* **124**, 427–434.

Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K (2002). Depression: perspectives from affective neuroscience. *Annual Review of Psychology* **53**, 545–574.

Drexhage RC, Knijff EM, Padmos RC, Heul-Nieuwenhuijzen L, Beumer W, Versnel MA, Drexhage HA (2010). The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. *Expert Review of Neurotherapeutics* **10**, 59–76.

Dubois J, Dehaene-Lambertz G, Perrin M, Mangin JF, Cointepas Y, Duchesnay E, Le Bihan D, Hertz-Pannier L (2008). Asynchrony of the early maturation of white matter bundles in healthy infants: quantitative landmarks revealed noninvasively by diffusion tensor imaging. *Human Brain Mapping* **29**, 14–27.

Dudley KJ, Li X, Kobor MS, Kippin TE, Bredy TW (2011). Epigenetic mechanisms mediating vulnerability and resilience to psychiatric disorders. *Neuroscience and Biobehavioral Reviews* **35**, 1544–1551.

Edwards VJ, Holden GW, Felitti VJ, Anda RF (2003). Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: results from the Adverse Childhood Experiences Study. *American Journal of Psychiatry* **160**, 1453–1460.

Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ (2002). The neural basis of mood-congruent processing biases in depression. *Archives of General Psychiatry* **59**, 597–604.

Eluvathingal TJ, Chugani HT, Behen ME, Juhasz C, Muzik O, Maqbool M, Chugani DC, Makki M (2006). Abnormal brain connectivity in children after early severe socioemotional deprivation: a diffusion tensor imaging study. *Pediatrics* **117**, 2093–2100.

Emsell L, Leemans A, Langan C, Van Hecke W, Barker GJ, McCarthy P, Jeurissen B, Sijbers J, Sunaert S, Cannon DM, McDonald C (2013). Limbic and callosal white matter changes in euthymic bipolar I disorder: an advanced diffusion magnetic resonance imaging tractography study. *Biological Psychiatry* **73**, 194–201.

Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *American Journal of Preventive Medicine* **14**, 245–258.

Forstmann BU, Jahfari S, Scholte HS, Wolfensteller U, van den Wildenberg WP, Ridderinkhof KR (2008). Function and structure of the right inferior frontal cortex predict individual differences in response inhibition: a model-based approach. *Journal of Neuroscience* **28**, 9790–9796.

Foubert-Samier A, Catheline G, Amieva H, Dilharreguy B, Helmer C, Allard M, Dartigues JF (2012). Education, occupation, leisure activities, and brain reserve: a population-based study. *Neurobiology of Aging* **33**, 423.e15–423.e25.

Frazier JA, Breeze JL, Papadimitriou G, Kennedy DN, Hodge SM, Moore CM, Howard JD, Rohan MP, Caviness VS, Makris N (2007). White matter abnormalities in children with and at risk for bipolar disorder. *Bipolar Disorders* **9**, 799–809.

Gould F, Clarke J, Heim C, Harvey PD, Majer M, Nemeroff CB (2012). The effects of child abuse and neglect on cognitive functioning in adulthood. *Journal of Psychiatric Research* **46**, 500–506.

Harsan LA, Poulet P, Guignard B, Steibel J, Parizel N, de Sousa PL, Boehm N, Grucker D, Ghandour MS (2006). Brain dysmyelination and recovery assessment by noninvasive *in vivo* diffusion tensor magnetic resonance imaging. *Journal of Neuroscience Research* **83**, 392–402.

Herting MM, Maxwell EC, Irvine C, Nagel BJ (2011). The impact of sex, puberty, and hormones on white matter microstructure in adolescents. *Cerebral Cortex* **22**, 1979–1992.

Houenou J, Wessa M, Douaud G, Leboyer M, Chanraud S, Perrin M, Poupon C, Martinot JL, Paillere-Martinot ML (2007). Increased white matter connectivity in euthymic bipolar patients: diffusion tensor tractography between the subgenual cingulate and the amygdalo-hippocampal complex. *Molecular Psychiatry* **12**, 1001–1010.

Huang H, Gundapuneedi T, Rao U (2012). White matter disruptions in adolescents exposed to childhood

maltreatment and vulnerability to psychopathology. *Neuropsychopharmacology* **37**, 2693–2701.

Jenkinson M, Smith S (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis* **5**, 143–156.

Karadottir R, Attwell D (2007). Neurotransmitter receptors in the life and death of oligodendrocytes. *Neuroscience* **145**, 1426–1438.

Keedwell PA, Chapman R, Christiansen K, Richardson H, Evans J, Jones DK (2012). Cingulum white matter in young women at risk of depression: the effect of family history and anhedonia. *Biological Psychiatry* **72**, 296–302.

Kinoshita Y, Ohnishi A, Kohshi K, Yokota A (1999). Apparent diffusion coefficient on rat brain and nerves intoxicated with methylmercury. *Environmental Research* **80**, 348–354.

Kochunov P, Thompson PM, Lancaster JL, Bartzokis G, Smith S, Coyle T, Royall DR, Laird A, Fox PT (2007). Relationship between white matter fractional anisotropy and other indices of cerebral health in normal aging: tract-based spatial statistics study of aging. *NeuroImage* **35**, 478–487.

Le Bihan D (2003). Looking into the functional architecture of the brain with diffusion MRI. *Nature Reviews Neuroscience* **4**, 469–480.

Lebel C, Gee M, Camicioli R, Wieler M, Martin W, Beaulieu C (2012). Diffusion tensor imaging of white matter tract evolution over the lifespan. *Neuroimage* **60**, 340–352.

Liao Y, Huang X, Wu Q, Yang C, Kuang W, Du M, Lui S, Yue Q, Chan RC, Kemp GJ, Gong Q (2013). Is depression a disconnection syndrome? Meta-analysis of diffusion tensor imaging studies in patients with MDD. *Journal of Psychiatry and Neuroscience* **38**, 49–56.

Lu LH, Zhou XJ, Fitzgerald J, Keedy SK, Reilly JL, Passarotti AM, Sweeney JA, Pavuluri M (2012). Microstructural abnormalities of white matter differentiate pediatric and adult-onset bipolar disorder. *Bipolar Disorders* **14**, 597–606.

Lu LH, Zhou XJ, Keedy SK, Reilly JL, Sweeney JA (2011). White matter microstructure in untreated first episode bipolar disorder with psychosis: comparison with schizophrenia. *Bipolar Disorders* **13**, 604–613.

Mahon K, Burdick KE, Ikuta T, Braga RJ, Gruner P, Malhotra AK, Szeszko PR (2013). Abnormal temporal lobe white matter as a biomarker for genetic risk of bipolar disorder. *Biological Psychiatry* **73**, 177–182.

Majer M, Nater UM, Lin JM, Capuron L, Reeves WC (2010). Association of childhood trauma with cognitive function in healthy adults: a pilot study. *BMC Neurology* **10**, 61.

Makris N, Kennedy DN, McInerney S, Sorensen AG, Wang R, Caviness VS Jr, Pandya DN (2005). Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, *in vivo*, DT-MRI study. *Cerebral Cortex* **15**, 854–869.

Matsuo K, Nielsen N, Nicoletti MA, Hatch JP, Monkul ES, Watanabe Y, Zunta-Soares GB, Nery FG, Soares JC (2010). Anterior genu corpus callosum and impulsivity in suicidal patients with bipolar disorder. *Neuroscience Letters* **469**, 75–80.

McIntosh AM, Job DE, Moorhead TW, Harrison LK, Lawrie SM, Johnstone EC (2005). White matter density in patients with schizophrenia, bipolar disorder and their unaffected relatives. *Biological Psychiatry* **58**, 254–257.

McIntosh AM, Munoz Maniega S, Lymer GK, McKirdy J, Hall J, Sussmann JE, Bastin ME, Clayden JD, Johnstone EC, Lawrie SM (2008). White matter tractography in bipolar disorder and schizophrenia. *Biological Psychiatry* **64**, 1088–1092.

McIntyre RS, Soczynska JK, Mancini D, Lam C, Woldeyohannes HO, Moon S, Konarski JZ, Kennedy SH (2008). The relationship between childhood abuse and suicidality in adult bipolar disorder. *Violence and Victims* **23**, 361–372.

Moffitt TE, Caspi A, Rutter M (2005). Strategy for investigating interactions between measured genes and measured environments. *Archives of General Psychiatry* **62**, 473–481.

Nichols TE, Holmes AP (2002). Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Human Brain Mapping* **15**, 1–25.

Olson EA, Collins PF, Hooper CJ, Muetzel R, Lim KO, Luciana M (2009). White matter integrity predicts delay discounting behavior in 9- to 23-year-olds: a diffusion tensor imaging study. *Journal of Cognitive Neuroscience* **21**, 1406–1421.

Pacheco J, Beevers CG, Benavides C, McGeary J, Stice E, Schnyer DM (2009). Frontal–limbic white matter pathway associations with the serotonin transporter gene promoter region (5-HTTLPR) polymorphism. *Journal of Neuroscience* **29**, 6229–6233.

Padmos RC, Van Baal GC, Vonk R, Wijkhuijs AJ, Kahn RS, Nolen WA, Drexhage HA (2009). Genetic and environmental influences on pro-inflammatory monocytes in bipolar disorder: a twin study. *Archives of General Psychiatry* **66**, 957–965.

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

Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR (2005). 5-HTTLPR polymorphism impacts human cingulate–amygdala interactions: a genetic susceptibility mechanism for depression. *Nature Neuroscience* **8**, 828–834.

Qiu D, Tan LH, Zhou K, Khong PL (2008). Diffusion tensor imaging of normal white matter maturation from late childhood to young adulthood: voxel-wise evaluation of mean diffusivity, fractional anisotropy, radial and axial diffusivities, and correlation with reading development. *NeuroImage* **41**, 223–232.

Raison CL, Capuron L, Miller AH (2006). Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in Immunology* **27**, 24–31.

Rich BA, Fromm SJ, Berghorst LH, Dickstein DP, Brotman MA, Pine DS, Leibenluft E (2008). Neural connectivity in children with bipolar disorder: impairment in the face emotion processing circuit. *Journal of Child Psychology and Psychiatry* **49**, 88–96.

Rubinsztein JS, Michael A, Paykel ES, Sahakian BJ (2000). Cognitive impairment in remission in bipolar affective disorder. *Psychological Medicine* **30**, 1025–1036.

Rueckert D, Sonoda LI, Hayes C, Hill DL, Leach MO, Hawkes DJ (1999). Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Transactions on Medical Imaging* **18**, 712–721.

Rutter M (2002). The interplay of nature, nurture, and developmental influences: the challenge ahead for mental health. *Archives of General Psychiatry* **59**, 996–1000.

Sasson E, Doniger GM, Pasternak O, Tarrasch R, Assaf Y (2012). Structural correlates of cognitive domains in normal aging with diffusion tensor imaging. *Brain Structure and Function* **217**, 503–515.

Saxena K, Tamm L, Walley A, Simmons A, Rollins N, Chia J, Soares JC, Emslie GJ, Fan X, Huang H (2012). A preliminary investigation of corpus callosum and anterior commissure aberrations in aggressive youth with bipolar disorders. *Journal of Child and Adolescent Psychopharmacology* **22**, 112–119.

Schermuly I, Fellgiebel A, Wagner S, Yakushev I, Stoeter P, Schmitt R, Knickenberg RJ, Bleichner F, Beutel ME (2010). Association between cingulum bundle structure and cognitive performance: an observational study in major depression. *European Psychiatry* **25**, 355–360.

Schmahmann JD, Pandya DN, Wang R, Dai G, D'Arceuil HE, de Crespigny AJ, Wedeen VJ (2007). Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. *Brain* **130**, 630–653.

Schoene-Bake JC, Parpaley Y, Weber B, Panksepp J, Hurwitz TA, Coenen VA (2010). Tractographic analysis of historical lesion surgery for depression. *Neuropsychopharmacology* **35**, 2553–2563.

Sexton CE, Mackay CE, Lonie JA, Bastin ME, Terriere E, O'Carroll RE, Ebmeier KP (2010). MRI correlates of episodic memory in Alzheimer's disease, mild cognitive impairment, and healthy aging. *Psychiatry Research* **184**, 57–62.

Sexton CE, McDermott L, Kalu UG, Herrmann LL, Bradley KM, Allan CL, Le Masurier M, Mackay CE, Ebmeier KP (2012). Exploring the pattern and neural correlates of neuropsychological impairment in late-life depression. *Psychological Medicine* **42**, 1195–1202.

Smith SM (2002). Fast robust automated brain extraction. *Human Brain Mapping* **17**, 143–155.

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage* **31**, 1487–1505.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage* **23** (Suppl. 1), S208–S219.

Smith SM, Johansen-Berg H, Jenkinson M, Rueckert D, Nichols TE, Miller KL, Robson MD, Jones DK, Klein JC, Bartsch AJ, Behrens TE (2007). Acquisition and voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics. *Nature Protocols* **2**, 499–503.

Smith SM, Nichols TE (2009). Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage* **44**, 83–98.

Sole B, Bonnin CM, Torrent C, Martinez-Aran A, Popovic D, Tabares-Seisdedos R, Vieta E (2012). Neurocognitive impairment across the bipolar spectrum. *CNS Neuroscience and Therapeutics* **18**, 194–200.

Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* **17**, 1429–1436.

Sprooten E, Sussmann JE, Clugston A, Peel A, McKirdy J, Moorhead TW, Anderson S, Shand AJ, Giles S, Bastin ME, Hall J, Johnstone EC, Lawrie SM, McIntosh AM (2011). White matter integrity in individuals at high genetic risk of bipolar disorder. *Biological Psychiatry* **70**, 350–356.

Sussmann JE, Lymer GK, McKirdy J, Moorhead TW, Munoz Maniega S, Job D, Hall J, Bastin ME, Johnstone EC, Lawrie SM, McIntosh AM (2009). White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging. *Bipolar Disorders* **11**, 11–18.

Takahashi M, Ono J, Harada K, Maeda M, Hackney DB (2000). Diffusional anisotropy in cranial nerves with maturation: quantitative evaluation with diffusion MR imaging in rats. *Radiology* **216**, 881–885.

Taylor SE, Eisenberger NI, Saxbe D, Lehman BJ, Lieberman MD (2006). Neural responses to emotional stimuli are associated with childhood family stress. *Biological Psychiatry* **60**, 296–301.

Taylor SE, Lerner JS, Sage RM, Lehman BJ, Seeman TE (2004*a*). Early environment, emotions, responses to stress, and health. *Journal of Personality* **72**, 1365–1393.

Taylor WD, Hsu E, Krishnan KR, MacFall JR (2004*b*). Diffusion tensor imaging: background, potential, and utility in psychiatric research. *Biological Psychiatry* **55**, 201–207.

Teicher MH, Samson JA, Sheu YS, Polcari A, McGreenery CE (2010). Hurtful words: association of exposure to peer verbal abuse with elevated psychiatric symptom scores and corpus callosum abnormalities. *American Journal of Psychiatry* **167**, 1464–1471.

Teicher MH, Tomoda A, Andersen SL (2006). Neurobiological consequences of early stress and childhood maltreatment: are results from human and animal studies comparable? *Annals of the New York Academy of Sciences* **1071**, 313–323.

Torgerson CM, Irimia A, Leow AD, Bartzokis G, Moody TD, Jennings RG, Alger JR, Van Horn JD,

Altshuler LL (2012). DTI tractography and white matter fiber tract characteristics in euthymic bipolar I patients and healthy control subjects. *Brain Imaging and Behavior* **7**, 129–139.

Tuch DS, Salat DH, Wisco JJ, Zaleta AK, Hevelone ND, Rosas HD (2005). Choice reaction time performance correlates with diffusion anisotropy in white matter pathways supporting visuospatial attention. *Proceedings of the National Academy of Sciences USA* **102**, 12212–12217.

Versace A, Almeida JR, Quevedo K, Thompson WK, Terwilliger RA, Hassel S, Kupfer DJ, Phillips ML (2010*a*). Right orbitofrontal corticolimbic and left corticocortical white matter connectivity differentiate bipolar and unipolar depression. *Biological Psychiatry* **68**, 560–567.

Versace A, Ladouceur CD, Romero S, Birmaher B, Axelson DA, Kupfer DJ, Phillips ML (2010*b*). Altered development of white matter in youth at high familial risk for bipolar disorder: a diffusion tensor imaging study. *Journal of the American Academy of Child and Adolescent Psychiatry* **49**, 1249–1259.e1.

Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S (2004). Fiber tract-based atlas of human white matter anatomy. *Radiology* **230**, 77–87.

Walther S, Hugli S, Hofle O, Federspiel A, Horn H, Bracht T, Wiest R, Strik W, Muller TJ (2012). Frontal white matter integrity is related to psychomotor retardation in major depression. *Neurobiology of Disease* **47**, 13–19.

Wang F, Kalmar JH, He Y, Jackowski M, Chepenik LG, Edmiston EE, Tie K, Gong G, Shah MP, Jones M, Uderman J, Constable RT, Blumberg HP (2009). Functional and structural connectivity between the perigenual anterior cingulate and amygdala in bipolar disorder. *Biological Psychiatry* **66**, 516–521.

Wermter AK, Laucht M, Schimmelmann BG, Banaschweski T, Sonuga-Barke EJ, Rietschel M, Becker K (2010). From nature *versus* nurture, via nature and nurture, to gene × environment interaction in mental disorders. *European Child and Adolescent Psychiatry* **19**, 199–210.

Wessa M, Houenou J, Leboyer M, Chanraud S, Poupon C, Martinot JL, Paillere-Martinot ML (2009). Microstructural white matter changes in euthymic bipolar patients: a whole-brain diffusion tensor imaging study. *Bipolar Disorders* **11**, 504–514.

Westlye LT, Walhovd KB, Dale AM, Bjornerud A, Due-Tonnessen P, Engvig A, Grydeland H, Tamnes CK, Ostby Y, Fjell AM (2010). Life-span changes of the human brain white matter: diffusion tensor imaging (DTI) and volumetry. *Cerebral Cortex* **20**, 2055–2068.

Whalley HC, Sprooten E, Hackett S, Hall L, Blackwood DH, Glahn DC, Bastin M, Hall J, Lawrie SM, Sussmann JE, McIntosh AM (2013). Polygenic risk and white matter integrity in individuals at high risk of mood disorder. *Biological Psychiatry* **74**, 280–286.

Woolrich MW, Jbabdi S, Patenaude B, Chappell M, Makni S, Behrens T, Beckmann C, Jenkinson M, Smith SM (2009). Bayesian analysis of neuroimaging data in FSL. *NeuroImage* **45**, S173–S186.

Zanetti MV, Jackowski MP, Versace A, Almeida JR, Hassel S, Duran FL, Busatto GF, Kupfer DJ, Phillips ML (2009). State-dependent microstructural white matter changes in bipolar I depression. *European Archives of Psychiatry and Clinical Neuroscience* **259**, 316–328.