Effects of early-life adversity on white matter diffusivity changes in patients at risk for major depression

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Background: Relatives of patients with major depressive disorder (MDD) and people who experienced early-life adversity are at risk for MDD. The aim of our study was to investigate whether unaffected first-degree healthy relatives (UHRs) of patients with MDD show changes in white matter fibre connections compared with healthy controls and whether there are interactions between early-life adversity and these microstructural changes. **Methods:** Unaffected, healthy first-degree relatives of patients with MDD and healthy controls without any family history for a psychiatric disease underwent high angular resolution diffusion imaging with 61 diffusion directions. Data were analyzed with tract-based spatial statistics, and findings were confirmed with tractography. **Results:** Twenty-one UHRs and 24 controls participated in our study. The UHRs showed greater fractional anisotropy than controls in the body and splenium of the corpus callosum, inferior fronto-occipital fasciculus (IFO), left superior longitudinal fasciculus (SLF) and right fornix. The UHRs who experienced more early-life adversity had greater fractional anisotropy than those with less early-life adversity in the splenium of the corpus callosum, fornix, IFO and SLF; in controls, early-life adversity was found to be associated with decreased fractional anisotropy in these fibre tracts. **Limitations:** Studying participants' strategies for coping with early-life adversity would have been helpful. Crossing fibres in tracts are a general limitation of the method used. **Conclusion:** Altogether, our findings provide evidence for greater fractional anisotropy in UHRs and for interaction between early-life adversity and family risk on white matter tracts involved in cognitive–emotional processes. Whether stronger neural fibre connections are associated with more resilience against depression needs to be addressed in future studies.

Introduction

Mental disorders are a major cause of long-term disability and are a direct cause of mortality, with about 800 000 individuals dying from suicide every year worldwide and a high proportion of these deaths being related to major depressive disorder (MDD).[1] Potent risk factors for MDD are neuroticism, sex and psychosocial adversity, whereby psychosocial adversity interacts with both neuroticism and with sex.[2] Another strong risk factor is a family history of depression,[3] and a review of twin studies found concordance rates of 0.23–0.67 for monozygotic twins and 0.14–0.43 for dizygotic twins,[4] indicating the importance of genetic factors. A recent meta-analysis provided evidence that the serotonin transporter polymorphism 5-HTTLPR moderates the relation between stress, particularly early-life adversity, and depression.[5] Because of the genetic background, assessment of first-degree relatives of patients with MDD may provide a powerful model in which to investigate biologic vulnerability.[6]

Detecting that neuroplasticity may play a core role in the pathophysiology of MDD has expanded our knowledge of the disease in recent years.[7] This concept was supported by experimental studies that have shown that excessive cortisol secretion and excessive production of inflammatory cytokines,

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which can be triggered by inflammation or psychological stress, impair neuronal plasticity and neurogenesis in the hippocampus, a temporal lobe brain region involved in learning, memory and affect regulation.[7] Family risk studies on the biologic background of vulnerability for MDD have determined that alterations in the stress–hormone axis, cognitive function, and structural changes like those in the hippocampus are present even before the onset of the disease. Healthy first-degree relatives of patients with depression have been shown to have higher cortisol levels in the morning than healthy participants who reported no affective episodes in a first-degree relative;[8–10] however, this finding could not be replicated in a study comparing high-risk twins with low-risk twins.[11] In the latter study, monozygotic high-risk twins had significantly higher evening cortisol levels than monozygotic low-risk twins.[11] In line with the above-mentioned experimental research about the effect of cortisol on the hippocampus[7] is the finding that small hippocampal and dorsolateral prefrontal cortex volumes were apparent before the manifestation of clinical symptoms of MDD in patients at family risk for MDD[12] and that smaller hippocampal volumes were found in adolescents whose parents had MDD.[13] Moreover, it has been reported that healthy twins who had a co-twin with a history of unipolar disorder performed worse than healthy low-risk twins on cognitive functions like declarative memory, executive function and language processing, suggesting that cognitive dysfunctions are present before the onset of the disease.[14]

Diffusion tensor imaging (DTI) is an important step forward for characterizing microstructural changes or differences. Previously, studies of white matter bundles were restricted to postmortem evaluation of fibre systems. Diffusion tensor imaging is sensitive to the properties of diffusion of water molecules, and, as such, this technique can be used to map and characterize the 3-dimensional diffusion of water as a function of spatial location.[15] Since water molecules interact with tissue structure, DTI can help reveal the characteristics of the architectural organization of the brain. In a meta-analysis[16] of whole-brain DTI studies of patients with MDD, we detected significantly decreased fractional anisotropy values in the superior longitudinal fasciculus (SLF) in patients with MDD compared with healthy controls. This effect was significantly more pronounced in studies that included only untreated patients than in those that included treated patients. Fractional anisotropy values in the SLF were also smaller in studies that included patients with a longer illness duration and more severe depression.[16] Region of interest (ROI)–based DTI studies in patients with late-life depression have consistently reported reduced fractional anisotropy values in prefrontal brain regions.[17–22] Reduced fractional anisotropy in the cingulate cortex has also been detected.[19,23,24] In addition, Yang and colleagues[22] and Murphy and colleagues[19] reported a reduction in fractional anisotropy values in the parahippocampal gyrus. On the other hand, Lu and colleagues[25] detected an increase in fractional anisotropy values in areas of the brain associated with mood regulation, such as the right superior frontal gyrus to right pallidum and left superior parietal gyrus to right superior occipital gyrus, by performing tractography analysis in patients with MDD.

A recent study using tract-based spatial statistics (TBSS) identified a reduction of fractional anisotropy in the SLF in 18 healthy adolescents at familial risk for unipolar depression compared with 13 healthy controls.[26] Investigating unaffected first-degree relatives (UHRs) of adults with MDD, who are at a higher risk for MDD,[27] with DTI is novel and might shed more light into underlying biologic substrates of vulnerability. The aim of the present study was to investigate microstructural changes in white matter tracts in UHRs compared with healthy controls without any family risk for psychiatric diseases by means of TBSS and tractography. It can be difficult to draw conclusions on the basis of whole-brain methods on specific tracts because of the high amount of fibre crossings in the brain. Here, tractography is a complementary method that allows the investigation of predefined fibre bundles. We expected that fractional anisotropy in frontotemporal regions would be reduced in UHRs compared with controls. We also investigated whether there are interactions between early-life adversity as a risk factor for MDD and the microstructural changes in white matter tracts.

Methods

Participants

The UHRs recruited for participation in this study were siblings or children of adult patients undergoing treatment for recurrent MDD in the mental health services department of the Adelaide and Meath Hospital, incorporating the National Children's Hospital and St. James's Hospital, which are teaching hospitals of Trinity College Dublin, Ireland. The diagnosis of the patients' MDD was confirmed by psychiatric consultants based on DSM-IV criteria. We also recruited healthy controls without any family history of psychiatric disease from the local community via announcements. Groups were age- and sex-matched. Each participant was carefully screened and examined for medical conditions so that neither the controls nor the UHRs had a personal history of neurologic or psychiatric disorders (Axis I or Axis II), or a history of severe medical illness, head injury or substance abuse. No UHR was a relative of another UHR. We excluded UHRs when their first-degree family members had a comorbid diagnosis in addition to MDD. The UHRs and controls were evaluated by a psychiatrist (A.C.) for any psychiatric conditions; this evaluation included the Structured Clinical Interview for DSM-IV Axis I (SCID-I)[32] and Axis II (SCID-II)[33] disorders. Demographic variables, inclusion and exclusion criteria were documented using a standardized questionnaire and through a structured interview with the psychiatrist. We used the Student t test to assess differences in demographic and clinical variables and the χ^2 test for sex distribution.

We obtained written informed consent from all participants after providing a detailed description of the study, which was designed and performed in accordance with the ethical standards laid out by the Declaration of Helsinki and was approved by the ethics committee of the Adelaide and Meath Hospital.

Rating instruments

All study participants completed self- and observer-rated scales. The rating scales used were the Hamilton Rating Scale for Depression (HAM-D),[28] Beck Depression Inventory (BDI),[29] Childhood Trauma Questionnaire (CTQ),[31] Beck Anxiety Inventory,[30] Eysenck Personality Questionnaire[34] and SCID-II. The CTQ was used to assess childhood stress. This questionnaire is a self-report instrument that assesses 5 types of childhood mistreatment: emotional, physical and sexual abuse, and emotional and physical neglect. Reliability and validity of the CTQ, including measures of convergent and discriminative validity from structured interviews, stability over time and corroboration, have been established.[35] Owing to the small number of participants in each group who reported childhood trauma, we used median split as well as linear correlations for statistical analyses.

Diffusion tensor imaging

Magnetic resonance images were obtained using a 3-T Philips Achieva scanner. We also obtained high angular resolution diffusion images with 61 diffusion directions (field of view $200 \times 257 \times 126$ mm, 60 slices, no gap, spatial resolution $1.8 \times 1.8 \times 2.1$ mm, repetition time 12561 ms, echo time 59 ms, flip angle 90°, half k-space acquisition [half scan factor = 0.68], sensitivity encoding parallel imaging factor 2.5, β-values 0, 1200 s/mm^2, with spectral presaturation inversion recovery fat suppression and dynamic stabilization in an image acquisition time of 15 min, 42 s).

Diffusion tensor imaging data preprocessing

Data were converted from a Philips PAR/REC format to NIfTI and B-matrix text-file formats using ExploreDTI. Thereafter, data were transferred to an ExploreDTI file and transferred to a voxel size of $2 \times 2 \times 2$ mm. With our acquisition voxel size, there is no significant partial volume effect associated with this technique. Diffusion tensor estimation was linear. We applied motion correction to all data to adjust for movement during scanning using a cubic interpolation and restore function with the lowest speed but highest accuracy. Eddy currency correction was also used.[36] To check the quality of the data, we first reviewed the DTI data by looping them. ExploreDTI also allowed us to look at the residuals and the outlier profiles, which were in order. Finally we checked the motion correction parameters. Movement during scanning was less than 2 mm in any direction and less than 3° rotation in sagittal, coronal or axial planes for all participants.

Tract-based spatial statistics

For TBSS implemented in FSL (www.fmrib.ox.ac.uk/fsl/), we extracted the fractional anisotropy and the mean, axial (λ1) and radial diffusivity (λ2 + λ3)/2) and fed them into the same FSL tools used in the subsequent steps described hereafter. The TBSS technique projects all participants' fractional anisotropy data onto a mean fractional anisotropy tract skeleton before applying voxelwise cross-subject statistics. In brief, all participants' fractional anisotropy data were aligned into a common space with the nonlinear registration tool FNIRT, which uses a B-spline representation of the registration warp field. The target template was the FMRIB58_FA standard space image. Next, we performed nonlinear and affine transformations to MNI152 space and then merged all images into a 4-dimensional image containing all participants. The mean of all images was created and fed into a script creating the mean skeletonized image. Each participant's aligned fractional anisotropy data were then projected onto this skeleton, and the resulting data were fed into voxelwise cross-subject statistics. We performed a voxelwise statistical analysis of the individual skeleton images of all participants derived in TBSS by means of threshold-free cluster enhancement using 5000 permutations for each test.[37] Threshold-free cluster enhancement takes a raw statistic image and produces an output image in which the voxelwise values represent the amount of cluster-like local spatial support. Each new value of a voxel is given by the sum of the scores of all supporting sections. The output value is therefore a weighted sum of the local clustered signal, without the need for a hard cluster-forming thresholding. Threshold-free cluster enhancement has the advantage over cluster-based thresholding because it does not need arbitrary thresholds defined a priori that introduce instability in the overall processing chain. Furthermore, the amount of spatial smoothing is itself arbitrary, given that the expected signal extent is very rarely known in advance of the analysis.[38]

We also used a median split for childhood stress to test for interactions between childhood stress and diagnosis of MDD. We opted to use this procedure because both groups were healthy without significant differences in early-life adversity and because there were only a few participants who met the cut-off thresholds for traumatization. The statistical threshold was set at $p < 0.05$, fully corrected for multiple comparisons using threshold-free cluster enhancement across all white matter fibre bundles in the whole brain to find differences between UHRs and controls for fractional anisotropy and mean, radial and axial diffusivity (eigenvalue λ1). We extracted fractional anisotropy values from significant clusters for further graphic representation, and we identified areas of significant differences using the following FSL tools: the Harvard-Oxford Structural Atlas and the JHU ICBM-DTI and tractography atlases[39] (www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html#wm).

Tractography

All data were transformed into Montreal Neurological Institute (MNI) space. Seed point resolution was $2 \times 2 \times 2$ mm with a seed fractional anisotropy threshold of 0.2. Deterministic tractography was applied with ExploreDTI.[40] First, we conducted whole-brain tractography in each participant using a linear interpolation. Then, individual tracts that showed significant alterations in previous DTI studies of patients with MDD were isolated using protocols similar to the knowledge-based multiple region approach previously described for the association tracts.[41] The protocols are described in detail below. The ExploreDTI software allows isolation of tracts

passing through 2 ROIs (using the "AND" operator) or not passing through an ROI (using the "NOT" operator).

We used 2 ROIs per tract to extract the white matter fibre tracts uncinate fasciculus (UF), crus of the fornix, inferior fronto-occipital fasciculus (IFO) and SLF showing significance in the whole-brain TBSS analysis.

For the UF, which connects the anterior temporal lobe with the orbitofrontal and frontopolar cortices, we placed the ROIs on the most posterior coronal slice in which the temporal lobe is separated from the frontal lobe. The first ROI included the entire temporal lobe, and the second ROI was placed at the same coronal level and included the entire projections toward the frontal lobe. Moreover, we used an ROI with the "NOT" operator to avoid fibres from the IFO and the cingulum.

The crus of the fornix contain fibres from the hippocampus and the parahippocampal cortex. We placed the first ROI in the coronal section at the level of the middle hippocampal body, and the second ROI was placed where the body and crus of the fornix are clearly visible.

The SLF connects parts of the parietal lobule and posterior temporal lobe with the prefrontal lobe in a bidirectional way. For the SLF, we placed the first ROI at the level of the middle of the posterior limb of the internal capsule, and the second ROI was placed at the middle of the splenium. At these levels, the SLF is seen as a green triangular region lateral to the superior-to-inferior corticospinal blue fibres. We used ROIs with the "NOT" operator to avoid fibres crossing from the IFO and pyramidal tracts.[42]

The IFO connects the dorsolateral and premotor prefrontal cortices with the posterior part of the parietal, temporal and occipital lobes as well as the caudal cingulate cortex. We used 2 ROIs to isolate the IFO. For tractography of the IFO, we placed 2 ROIs along the course of the IFO in the coronal plane of the DTI images at the level of the anterior commissure and pontine crossing fibres, respectively.[43]

All ROIs were drawn on the coloured fractional anisotropy–weighted maps, and the investigator (T.F.) was blind to diagnosis. For all participants, we used the same numbers and locations of ROIs. We calculated interrater reliability after 2 raters independently performed tractography in 20 participants. Intraclass correlations were between 0.90 and 0.95 for mean fractional anisotropy values in the tracts. After performing the tractography for all tracts for all individuals, the mean fractional anisotropy and the axial and radial diffusivity were extracted and entered into SPSS software for further analysis. These parameters were subjected to an analysis of covariance with group (UHR, control) and early-life adversity (median split on CTQ total score) as fixed factors and with age and sex as covariates.

Results

Participants

We included 21 UHRs and 24 age- and sex-matched controls in our study. The demographic and clinical characteristics of participants are summarized in Table 1. The UHRs did not differ from controls in age, sex, education and weight. Subthreshold depression scores derived from the HAM-D[28] were significantly higher, and scores from the self-rating BDI[29] tended to be significantly greater among UHRs than controls, but all values were still within the normal range (Table 1). Neuroticism and childhood trauma scores did not differ between the groups, and early-life adversity was not associated with higher depression scores. Based on the cut-off for traumatization only 6 of our participants with family history and 4 without family history reported childhood trauma.

Table 1: Demographic and clinical characteristics of unaffected relatives of patients with major depressive disorder and healthy controls

Characteristic	Group; mean (SD)*		$t_{1,43}$	*p* value
	Control, *n* = 24	UHR, *n* = 21		
Age, yr	34.7 (11.0)	38.1 (14.5)	0.92	0.37
Sex,† female/male	14/10	13/8	0.06	0.81
Education, yr	16.6 (2.4)	15.9 (2.8)	0.94	0.35
Weight, kg	71.5 (17.1)	67.3 (13.4)	0.90	0.37
21-item Hamilton Depression Scale[28] score	1.5 (1.7)	4.0 (3.9)	2.7	0.012
Beck Depression Inventory[29] score	1.5 (2.1)	3.7 (5.7)	1.7	0.09
Beck Anxiety Inventory[30] score	6.0 (5.2)	5.9 (4.3)	0.07	0.95
Neuroticism score	2.8 (3.0)	3.4 (2.9)	0.68	0.50
Childhood Trauma Questionnaire[31] score	31.3 (6.8)	31.3 (5.4)	0.02	0.98
Emotional neglect	7.2 (2.9)	7.4 (2.9)	0.30	0.77
Physical neglect	6.2 (1.6)	6.3 (1.8)	0.15	0.88
Sexual abuse	5.6 (1.4)	5.5 (1.2)	–0.15	0.88
Emotional abuse	6.5 (2.0)	6.3 (1.9)	–0.29	0.77
Physical abuse	5.8 (1.7)	5.7 (1.4)	–0.17	0.87

SD = standard deviation; UHR = unaffected relatives of patients with major depressive disorder.
*Unless otherwise indicated.
†χ^2 test for sex differences between groups.

Tract-based spatial statistics

We detected significantly greater fractional anisotropy values in UHRs than controls in the posterior body and splenium of the corpus callosum, left SLF, left IFO, left external capsule and left anterior thalamic radiation (Fig. 1, Table 2). Mean radial or longitudinal diffusivity (λ1) did not differ significantly between the groups.

There were no significant main effects of early-life adversity (participants without childhood stress versus those with at least minor childhood stress). However, we detected a significant 2-way interaction between group (UHR, control) and early-life adversity for fractional anisotropy in 3 clusters ($p < 0.05$, corrected for multiple comparisons across the whole brain). The first large cluster was mainly in the right temporoparietal white matter and involved the splenium and the body of the corpus callosum, right IFO and right SLF (k = 3612 voxels, MNI coordinates *x*, *y*, *z* = 32,–35, 4 for the most significant voxel; see Fig. 2 for individual coordinates). The second cluster was located in the right orbitofrontal cortex (right IFO; k = 41 voxels, MNI coordinates *x*, *y*, *z* = 25, 19, –16). The third cluster was in the right frontal cortex (right IFO, UF; k = 13 voxels, MNI coordinates *x*, *y*, *z* = 22, 22, –9). Analysis of the UHR and control groups separately showed that UHRs who reported at least minor childhood stress had greater fractional anisotropy than UHRs who reported no childhood stress. On the other hand, controls who reported having childhood stress showed lower fractional anisotropy than controls who reported no childhood stress. Extracting the fractional anisotropy values from the seed voxel in each region allowed us to graphically depict these associations. Childhood stress correlated positively with fractional anisotropy in UHRs and negatively in controls, as shown in Figure 2.

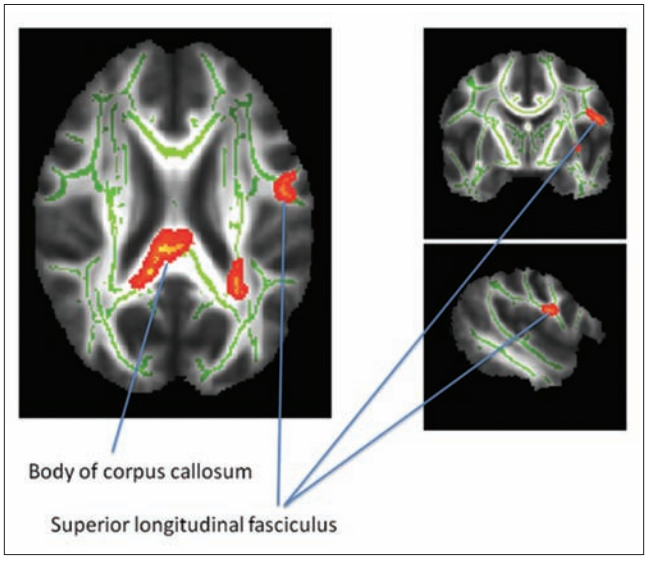

Fig. 1: Comparison of fractional anisotropy in fibre tracts between UHRs and healthy controls. We found increased fractional anisotropy values in the posterior body of the corpus callosum (MNI coordinates *x*, *y*, *z* = 9, –30, 24) with extensions of the cluster into the splenium and the superior longitudinal fasciculus (MNI coordinates *x*, *y*, *z* = –48, –6, 21) in UHRs compared with controls (see also Table 2). Significant areas are highlighted in red–yellow (corrected for multiple comparisons) and displayed in radiologic convention: left is right and right is left. Tract names are derived from ICBM-DTI-81 white-matter labels and tractography atlas.[39] MNI = Montreal Neurological Institute; UHR = unaffected first-degree relatives of patients with confirmed major depressive disorder.

Tractography

To further explore the differences between groups, we performed deterministic tractography (Table 3). We detected greater mean fractional anisotropy values in the right fornix ($F_{1,39} = 5.8$, $p = 0.020$), right IFO ($F_{1,39} = 4.0$, $p = 0.048$) and left SLF ($F_{1,39} = 5.7$, $p = 0.022$) in UHRs compared with controls. No significant differences were found for the UF. No main effect of early-life adversity was detected; however, we found significant interactions between group and early-life adversity for fractional anisotropy in the right SLF ($F_{1,39} = 5.2$, $p = 0.028$). Here, UHRs tended to have greater fractional anisotropy in the right SLF when they had reported at least mild early-life adversity events ($F_{1,17} = 3.2$, $p = 0.09$). We observed a trend toward significant interactions for fractional anisotropy in the left fornix ($F_{1,39} = 3.8$, $p = 0.06$). In controls, fractional anisotropy in the left fornix was greater when they reported more early-life adversity ($F_{1,20} = 3.7$, $p = 0.07$). No significant effects were detected for radial, axial or mean diffusivity.

Discussion

Our study revealed that UHRs had greater fractional anisotropy than controls in the body and splenium of the corpus callosum. Moreover, greater fractional anisotropy was detected in the left external capsule and the pre– and postcentral lobes, changes that might be related to the IFO and SLF, respectively. The tractography analysis showed greater fractional anisotropy in the right IFO, left SLF and right fornix in UHRs compared with controls. A recent study by Huang and

Table 2: Fractional anisotropy differences between unaffected relatives of patients with major depressive disorder and controls*

			MNI coordinates		
Region†	Voxels	*p* value‡	*x*	*y*	*z*
Body–splenium of corpus callosum	261	0.039	9	–30	24
Body of corpus callosum	62	0.046	–11	–28	26
Body of corpus callosum (left IFO, anterior thalamic radiation)	158	0.041	–27	–45	21
Left posterior corona radiate (left corticospinal tract)	95	0.045	–26	–24	25
Left post- and precentral gyrus (left SLF)	71	0.045	–48	–6	21
Left external capsule (left IFO)	20	0.049	–33	–10	6

IFO = inferior fronto-occipital fasciculus; MNI = Montreal Neurological Institute; SLF = superior longitudinal fasciculus; UHR = unaffected relatives of patients with major depressive disorder.
*The table shows regions with increased fractional anisotropy values for the UHR compared with the control group.
†The Harvard-Oxford Structural Atlas and ICBM-DTI-81 white-matter labels atlas were used for region identification.[39]
‡The *p* values, family-wise error–corrected for multiple testing across the whole brain fibre tracts, are < 0.05 in all participants.

colleagues[44] involving adolescents at familial risk for MDD reported lower fractional anisotropy in the left SLF, IFO, cingulum, UF and splenium of the corpus callosum. The mean age of participants in our study was more than 20 years older than that in the study by Huang and colleagues.[44] Since adolescence is the peak risk period for the development of unipolar depressive disorder,[45] it may be that the participants recruited in our study were those who did not experience a depressive episode, had a lower overall risk or were resilient. In fact, other risk factors like neuroticism or greater early-life adversity did not differ between UHRs and controls, suggesting that these other risk factors might not have been present in this population.

Lower fractional anisotropy in adolescents might reflect a greater vulnerability to depression, and greater fractional anisotropy in adults who did not become depressed might be related to resilience. Interestingly, increased fractional anisotropy in the affected fibre systems of the corpus callosum, IFO and SLF have been shown to be associated with better cognitive functions like executive functioning, working memory and attention processing.[46] A recent magnetic resonance imaging study involving combat veterans with a self-reported history of blast-related concussion showed that 11 veterans without depression had greater fractional anisotropy values in the SLF than 11 veterans who had depression, a finding

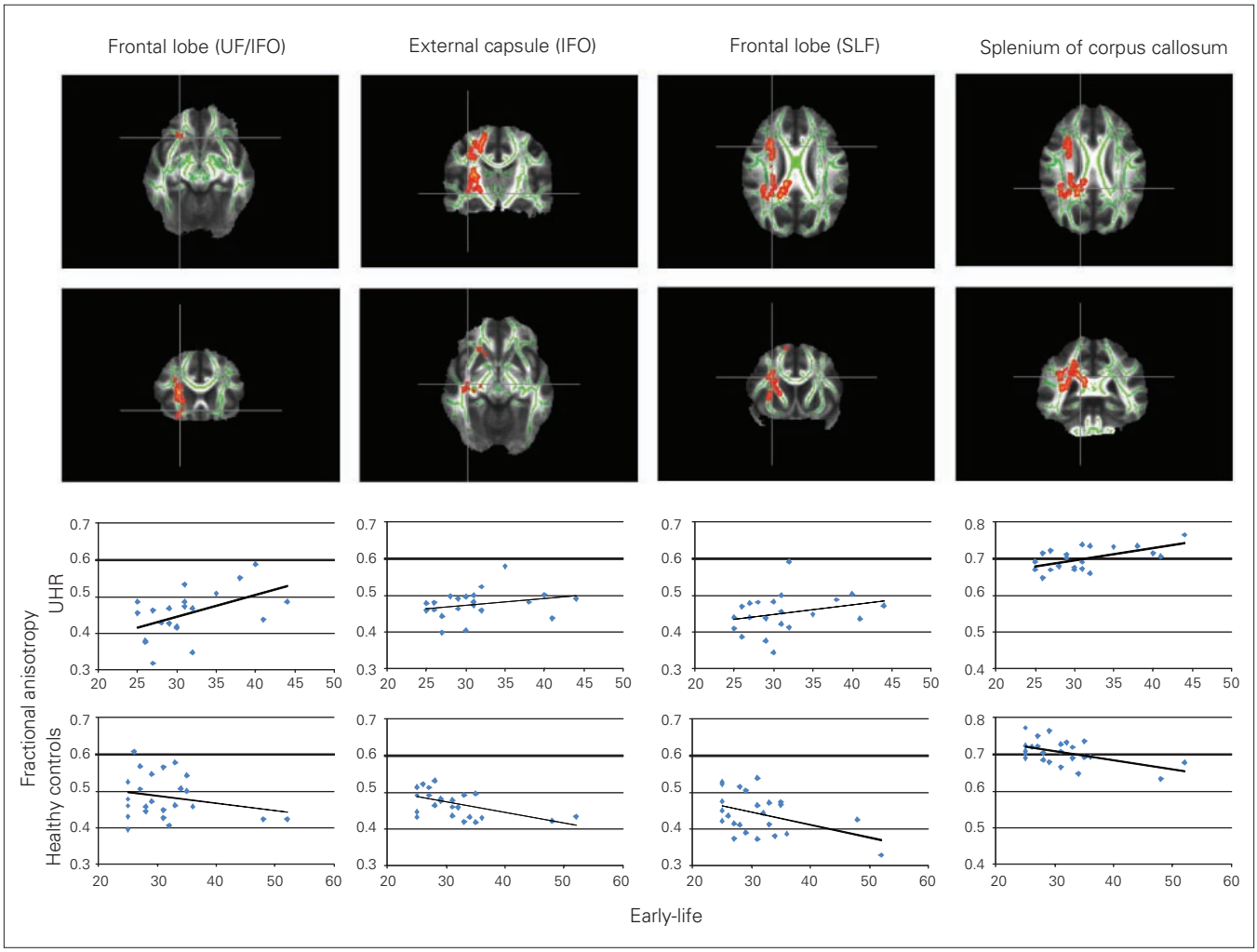

Fig. 2: Interaction between group (UHRs, control) and childhood stress. Depicted are significant areas in the frontal lobe (UF, IFO; most significant MNI coordinates *x*, *y*, *z* = 22, 22, –9), external capsule (IFO; MNI coordinates *x*, *y*, *z* = 32, –18, 4), frontal lobe (SLF; MNI coordinates *x*, *y*, *z* = 27, 9, 25) and the splenium of the corpus callosum (MNI coordinates *x*, *y*, *z* = 18, –43, 27) and are highlighted red–yellow (corrected for multiple comparisons) in axial (row 1) and coronal (row 2) slices. Images are displayed in the radiologic convention: left is right and right is left. The UHRs had greater fractional anisotropy with more early-life adversity, whereas controls had lower fractional anisotropy with more early-life adversity. Correlations between fractional anisotropy in the voxel of the peak coordinate and early-life adversity (Childhood Trauma Questionnaire[31]) are shown in row 3 for UHRs (UF/IFO: $r = 0.47$, $p = 0.03$, IFO: $r = 0.37$, $p = 0.09$, SLF: $r = 0.34$, $p = 0.12$, corpus callosum: $r = 0.50$, $p = 0.02$) and in row 4 for controls (UF: $r = –0.11$, $p = 0.6$, IFO: $r = –0.57$, $p = 0.004$, SLF: $r = –0.33$, $p = 0.11$, corpus callosum: $r = –0.39$, $p = 0.06$). Names of tracts that might be involved are derived from the JHU White-Matter Tractography Atlas.[39] IFO = inferior fronto-occipital fasciculus; MNI = Montreal Neurological Institute; SLF = superior longitudinal fasciculus; UF = uncinate fasciculus; UHR = unaffected first-degree relatives of patients with confirmed major depressive disorder.

that might also support the idea that greater fractional anisotropy is associated with resilience against depression.[47] In experimental studies, resilience to stress has been associated with the capacity to constrain stress-induced increases in corticotrophin-releasing hormone and corticosterone through an elaborated negative feedback system[48,49] and via expression of brain-derived neurotrophic factor (BDNF).[50,51] In turn, BDNF function has been found to be associated with structural brain changes.[52] Hippocampal BDNF might be involved in the development of neural circuits that control adequate stress adaptations,[51] and these circuits would involve the fornix. Our cross-sectional study allows us to only speculate about resilience. It would be highly important to investigate risk and protective factors longitudinally in future studies.

Executive and working memory functions served by the fornix, IFO, SLF and corpus callosum have been found to be altered in patients with MDD. The fornix connects the hippocampus to the septal region and mamillary bodies[53] and is involved in functions for learning and memory.[54] The IFO is involved in awareness and executive functions[55] by connecting the dorsolateral and premotor prefrontal cortices to posterior parts of the parietal, temporal and occipital lobes as well as the caudal cingulate gyrus.[56] In patients with MDD, alterations in emotional visual perception and reduced fractional anisotropy in the IFO have been reported.[57–59] The SLF connects lateral parts of the inferior parietal lobule with the lateral inferior prefrontal lobe in a bidirectional way[60] and plays a role in the frontoparietal circuit involved in working memory.[60,61]

With respect to our second study objective, we found interactions between early-life adversity and differences between UHRs and controls mainly for fractional anisotropy in the right frontal and orbitofrontal lobes, likely involving the IFO, SLF and UF, as well as the splenium and genu of the corpus callosum in the TBSS analysis. Tractography also allowed us to observe such an interaction for the right SLF and the left fornix. In these tracts, greater fractional anisotropy was associated with more early-life adversity in UHRs, whereas in controls more early-life adversity was associated with lower fractional anisotropy. This interaction was seen in the correlation analysis and in the analysis of covariance, in which we used early-life adversity as a dichotomic factor (no early-life adversity, at least minor early-life adversity), indicating that even minor childhood events seem to have effects on brain fibre connections. In agreement with our finding of greater fractional anisotropy in participants with more early-life adversity is a study that reported greater fractional anisotropy in the left superior temporal gyrus in healthy participants with histories of exposure to parental verbal abuse compared with healthy controls.[62] However, the findings of other previous DTI studies assessing effects of early-life adversity were inconsistent with this finding and showed that decreases of fractional anisotropy in the corpus callosum;[63] left UF;[64] and left cingulum, fornix and arcuate fasciculus[65] were associated with childhood abuse. Individual differences in response to stress seem to implicate the BDNF system and a negative stress hormone feedback control.[48] Thus, our finding of opposite effects of stress on fractional anisotropy in UHRs and controls might be in line with individual characteristics of the stress system, which in turn might be a marker for vulnerability.[11]

In agreement with our findings of right lateralized effects for stress are reports showing that the reaction of the brain structure to stress is lateralized in such a way that severe stress activates the right medial prefrontal cortex.[66] Restraint stress also has been reported to have more severe effects on the right than the left prelimbic cortex within the prefrontal cortex.[67] Interestingly, the effect of stress in the right hemisphere increases variance in white matter fractional anisotropy and might explain why the difference between UHRs and controls in our study was only observed in the right hemisphere when early-life adversity was additionally taken into account.

Limitations

Limitations of the present study are that early-life adversity was assessed retrospectively. It also has to be mentioned that abuse, particularly sexual abuse, remains underreported in healthy individuals.[68] Nevertheless, we found significant effects of early-life adversity on DTI parameters even when most of the participants had little experience with early-life

Table 3: Fractional anisotropy values of the uncinate fasciculus, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and fornix for healthy controls with and without a first-degree relative with major depressive disorder and with and without early childhood adversity

Tractography	Group; mean (SD) fractional anisotropy value				$F_{1,39}$	*p* value
	UHR with ELA	UHR without ELA	Control with ELA	Control without ELA		
Left UF	0.442 (0.0138)	0.439 (0.0153)	0.436 (0.0172)	0.443 (0.0163)	0.2	0.66*
Right UF	0.436 (0.0160)	0.442 (0.0226)	0.426 (0.0332)	0.435 (0.0267)	1.7	0.20*
Left IFO	0.488 (0.0127)	0.488 (0.0160)	0.481 (0.0187)	0.489 (0.0163)	1.0	0.34*
Right IFO	0.492 (0.0129)	0.504 (0.0188)	0.486 (0.0173)	0.498 (0.0166)	4.0	0.048*
Left fornix	0.394 (0.0180)	0.394 (0.200)	0.389 (0.0166)	0.403 (0.0178)	3.7	0.06†
Right fornix	0.414 (0.0257)	0.425 (0.0217)	0.410 (0.0149)	0.405 (0.0228)	5.8	0.020*
Left SLF	0.461 (0.0179)	0.476 (0.0177)	0.452 (0.020)	0.462 (0.0259)	5.7	0.022*
Right SLF	0.475 (0.0279)	0.470 (0.0265)	0.464 (0.0266)	0.476 (0.0257)	1.3	0.26†

ELA = early-life adversity; IFO = inferior fronto-occipital fasciculus; NS = not significant; SD = standard deviation; SLF = superior longitudinal fasciculus; UF = uncinate fasciculus; UHR = unaffected first-degree relatives of patients with major depressive disorder.
*UHR > control.
†Post hoc: lower fractional anisotropy in controls with early-life adversity compared with controls without early-life adversity.

adversity. Another limitation is that the high-risk study design may have led to the selection of participants with a first-degree relative with MDD from treated populations, thereby selecting families with an increased rate of illness. To overcome this issue it would have been necessary to use register linkage, as performed previously in larger population-based studies.[69] Moreover, we did not study participants' strategies for coping with early-life adversity or their resilience behaviourally (e.g., with respect to current stressors), so we were not able to investigate the association between increased fractional anisotropy and coping mechanisms. White matter fibre crossing is always an issue in DTI studies, TBSS are limited to investigating local changes in white matter integrity, and interpreting differences in regions of crossing fibres can be complex.[70] Considerable areas of fibre crossing exist, for example, in the centrum semiovale, UF and transpontine fibres, which have corresponding low fractional anisotropy and are difficult to investigate. Thus, it is difficult to relate significant areas back to specific fibre tracts. In the present study, we were able to observe changes in the IFO, SLF and fornix using tractography; however, evidence for changes in the UF could not be replicated with tractography. Fewer white matter crossings are seen in the corpus callosum;[71] therefore, our results for the corpus callosum do not seem to be influenced by fibre crossings.

Conclusion

Effects of early-life adversity and family risk on fractional anisotropy values and volumes of frontotemporal fibre tracts were demonstrated in the present study. Our findings highlight the importance of stress–gene interactions. Whether the stronger fibre connections might be associated with resilience and might render participants more stable against environmental stressors needs further investigation in studies with longitudinal designs.

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