Altered White Matter Connectivity in Young People Exposed to Childhood Abuse: A Tract-Based Spatial Statistic (TBSS) and Tractography Study

Journal:	*Journal of Psychiatry and Neuroscience*
Manuscript ID	JPN-17-0241.R2
Manuscript Type:	Research
Date Submitted by the Author:	n/a
Complete List of Authors:	Lim, Lena; King's College london, Department of Child & Adolescent Psychiatry; Imperial College London - Nanyang Technological University Singapore, Lee Kong Chian School of Medicine Hart, Heledd; King's College London, Department of Child & Adolescent Psychiatry Howells, Henrietta ; Institute of Psychiatry, Psychology & Neuroscience, King's College London, Department of Forensic and Neurodevelopmental Sciences Mehta, Mitul; King's College London, Department of Neuroimaging Simmons, Andrew; King's College London, Institute of Psychiatry, Department of Neuroimaging Mirza, Kah ; Institute of Psychiatry, Psychology & Neuroscience, King's College London, Department of Child & Adolescent Psychiatry Rubia, Katya; Institute of Psychiatry, Department of Child & Adolescent Psychiatry
Keywords:	Adolescent psychiatry < Clinical Psychiatry, Trauma victims < Clinical Psychiatry, Brain imaging (MRI) < Neuroscience, Stress < Clinical Psychiatry

Word count

Abstract: 249

Main text: 4000

Tables: 3

Figures: 2

Supplementary materials: 1

Altered White Matter Connectivity in Young People Exposed to Childhood Abuse: A Tract-Based Spatial Statistic (TBSS) and Tractography Study

Lena Lim, PhD[1,2 *]; Heledd Hart, PhD[1 *]; Henrietta Howells, PhD[3]; Mitul A. Mehta, PhD[4]; Andrew Simmons, PhD[4]; Kah Mirza, MBBS, FRCPsych[1]; Katya Rubia, PhD[1]

[1]Department of Child & Adolescent Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [2]Lee Kong Chian School of Medicine, Imperial College - Nanyang Technological University Singapore, Singapore; [3]NatBrainLab, Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [4]Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK.

* Dr. Lim and Dr. Hart contributed equally to this work.

Corresponding author:

Dr Lena Lim
Lee Kong Chian School of Medicine
Imperial College London - Nanyang Technological University Singapore
Experimental Medicine Building Level 7,
59 Nanyang Drive
Singapore 636921
Email: Lena.lim@ntu.edu.sg / Lena.lim@kcl.ac.uk

Abstract

Background: Childhood abuse is associated with structural brain abnormalities. Few studies have investigated white matter tract abnormalities in medication-naïve drug-free individuals with childhood abuse or controlled for psychiatric comorbidities. This study examines the association between childhood abuse and abnormalities in white matter tracts metrics in medication-naïve, drug-free youth, controlling for psychiatric comorbidities.

Methods: Diffusion tensor imaging data were collected on 20 age-and gender-matched youth with childhood abuse, 18 psychiatric controls matched for psychiatric diagnoses and 25 healthy controls. Tract-specific analysis was conducted using Tractography. Tract-based spatial statistic (TBSS) was used to assess group differences in fractional anisotropy at the whole-brain level.

Results: Tractography analysis showed abuse-specific reduced tract volume in the inferior longitudinal fasciculus (ILF) and inferior frontal-occipital fasciculus (IFOF) in the abuse group relative to both healthy and psychiatric controls. Furthermore, abnormalities in the left IFOF were associated with greater abuse severity in the abuse group. TBSS analysis revealed significantly reduced fractional anisotropy in a left-hemispheric cluster comprising ILF, IFOF and corpus callosum splenium in the abuse group relative to healthy and psychiatric controls.

Limitations: It is unclear to what extent pubertal development, malnutrition and prenatal drug exposure may have influenced the findings.

Conclusion: Childhood abuse is associated with altered structure of neural pathways connecting the frontal, temporal and occipital cortices that are known to mediate affect and cognitive control. The abuse-specific deficits in the ILF and IFOF suggest that fibre tracts presumably involved in conveying and processing the adverse abusive experience are specifically compromised in this population.

Keywords: Childhood adversity, early-life stress, childhood maltreatment, diffusion tensor imaging, DTI

Introduction

Brain development is a complex process that is regulated by genes and sculpted by environmental experiences. Although experiential influences affect brain structure and function throughout the life span, early childhood experience is particularly crucial; where early stress and exposure to traumatic events have been shown to adversely affect the nature and trajectory of normal brain development[1].

Childhood maltreatment, which includes physical, sexual and emotional abuse and neglect, is common in the UK with paediatric prevalence rates of 7-10%[2]. It has been associated with a host of adverse consequences, such as low IQ, abnormal error processing[3], along with impaired attention, inhibition, emotion and reward processing[4,5]. Large-scale epidemiological studies found that childhood maltreatment is significantly associated with first onsets of various psychiatric disorders, such as depression and post-traumatic stress disorders (PTSD)[6]. The psychopathological outcomes associated with childhood maltreatment may be mediated by the disruption of neural underpinnings[7].

Structural MRI studies show that childhood maltreatment is associated with grey matter volume (GMV) abnormalities in several relatively late-developing brain regions particularly the orbitofrontal cortex (OFC)[8-10] and temporal lobes[11,12], as well as in the visual cortex[8,13,14]. Our meta-analysis of voxel-based morphometry studies showed that childhood maltreatment is associated with GMV reduction in OFC-limbic-temporal regions and inferior frontal cortices that mediate top-down affect and cognitive control, respectively; and in the left motor-somatosensory cortex that mediate sensory functions[10].

Compared to the extensive research on GMV abnormalities in childhood maltreatment, fewer studies have examined white matter (WM) tracts in this population. Brain regions do not

function independently; they are interconnected through a complex system of short-and long-range WM tracts[15]. WM connectivity regulates the speed and timing of activation across neural networks, which are essential for optimal performance of higher-order tasks that rely on integrated information processing[16].

DTI measures the restricted diffusion of water molecules and provides a more detailed assessment of fibre tracts than conventional MRI, and has emerged as a powerful technique for examining structural connectivity[17]. Fractional anisotropy (FA), a DTI-derived metric, describes the directionality of water diffusion and may reflect aspects of membrane integrity and myelin thickness, where decreased FA is usually associated with WM disruption[18]. Tractography facilitates the reconstruction of 3D trajectories of specific WM tracts and probe their microstructure, which allows a more detailed analysis of specific subpopulations of fibres and indirect volumetric indices (e.g. number of streamlines and tract volume)[19]. These volumetric indices can be indicative of the speed of communication between different brain regions. Tract-based spatial statistics (TBSS), on the other hand, is a fully automated approach that permits a whole-brain analysis of WM in a voxel-wise manner, which allows the identification of WM differences in specific regions beyond *a priori* defined tracts[20]. Therefore, we used these two complementary methods to examine atypical WM tracts in youth exposed to childhood abuse.

Stress can affect WM tract development as corticosteroids can suppress the final mitosis of glial cells necessary for myelination[21]. Moreover, given the protracted postnatal development timeline of WM[22], it may be particularly vulnerable to the neurotoxic impact of childhood trauma, especially during certain sensitive periods. Several DTI studies reported that childhood maltreatment is associated with reduced FA in various large WM tracts particularly the inferior fronto-occipital fasciculus (IFOF), which is a direct pathway connecting the occipital, posterior temporal and the OFC areas[23-25]; the inferior longitudinal fasciculus (ILF) connecting the

occipital with the anterior temporal cortex[23,26,27], which is considered to be an indirect pathway essentially connecting similar brain areas as the IFOF and anteriorly joins the uncinate fasciculus to relay information to the OFC; the superior longitudinal fasciculus (SLF) connecting Broca's area with Wernicke's area[24,25,27]; the corpus callosum (splenium) connecting the (posterior) left and right cerebral hemispheres[24,25]; and the uncinate fasciculus connecting the anterior temporal lobe with the medial and lateral OFC[28].

Given that childhood maltreatment is associated with the development of psychiatric complications[29], it is crucial to control for these in order to disentangle the effects of maltreatment from psychiatric comorbidities[10]. So far, only three DTI studies included a psychiatric group without childhood maltreatment[25,30,31]; however, they were on adult samples and focused only on depression which limits the generalizability of their findings to other psychiatric comorbidities. Furthermore, a number of DTI studies have not measured and/or controlled for drug abuse[23,28] and medication use[23,26-28,30], which are known to affect brain structure[32].

Therefore, the aim of this study was to examine the association between childhood abuse and WM tract abnormalities by conducting tract-specific and whole-brain analyses in medication-naïve, drug-free youth with documented childhood physical abuse compared to healthy controls. To assess the specificity of the association with abuse, we included a third group of psychiatric controls that was matched with the abuse group on psychiatric comorbidities. Sexual abuse was excluded because it has different effects on brain structure[33] and different behavioural and psychiatric consequences[34]. It has also been argued that childhood sexual abuse is associated with experiences unique to sexual victimisation relative to other abuse experiences; for example, traumatic sexualisation, betrayal, stigmatisation as well as feelings of guilt and shame may impact sexual abuse victims differently than victims of other abuse experiences[35]. For these

reasons, and in order to obtain a more homogenous group, we only included youth exposed to childhood physical abuse. Nevertheless, it is unrealistic to separate physical abuse from typically co-occurring emotional abuse and neglect since psychological maltreatment would be present in *almost all* cases of physical maltreatment[36]. Hence, it is unlikely for the abused victim to experience *severe* physical abuse without experiencing at least moderate levels of emotional abuse and neglect concurrently; but physical abuse does not always co-occur with sexual abuse.

Given that childhood maltreatment is associated with GMV deficits in OFC-limbic-temporal and occipital visual regions[8,10,13,14], along with abnormalities in the WM tracts connecting these regions[23-27], we hypothesized that the abuse group would have WM tract abnormalities, particularly of the IFOF and ILF, relative to both healthy and psychiatric groups. We also investigated atypical FA in regions beyond our priori-defined tracts with a whole-brain TBSS analysis.

Methods

Participants

Seventy (23 childhood abuse, 20 psychiatric controls, 27 healthy controls) right-handed, medication-naïve, drug-free and age-and-gender matched youth were assessed by a child psychiatrist (KM) using the Development and Well-Being Assessment (DAWBA)[37], designed to generate ICD-10 and DSM-IV psychiatric diagnoses. The Strengths and Difficulties Questionnaires (SDQ)[38] and Beck's Depression Inventory (BDI)[39] were also used to provide symptom scores on psychopathology. IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI)[40]. The Childhood Trauma Questionnaire (CTQ)[41] was used to measure the severity of childhood physical, sexual and emotional abuse, and physical and emotional neglect. Socioeconomic status (SES) was measured by two non-sensitive items (on housing tenure and room occupancy) from the Family Affluence Scale (FAS)[42].

Exclusion criteria for all participants were childhood sexual abuse, drug abuse, learning disability, neurological abnormalities, epilepsy, IQ < 70 and MRI contraindications. Urine screening for recent drug use was conducted with 10-panel urine drug test integrated cups (T-Cup; http://www.testfield.co.uk). Participants were also asked about drug use in the past 4 weeks. Most of them did not use any drugs in the last 4 weeks before the scan and there were no significant group differences (see Table S1). All participants, or their guardians if they were under the age of 18, provided written informed consent to participate in the study. The study was approved by the local NHS Research Ethics Committee.

The 23 youth who experienced physical abuse before the age of 12 were first recruited through social services and psychiatric clinics. They or their guardians were first asked to provide signed permission to contact their social services for written confirmation of official records of physical abuse. The Childhood Experience of Care and Abuse (CECA) interview[43] was used to corroborate the CTQ and provide additional information including the age of onset and duration of abuse. Participants scored ≥ 13 (i.e. the cut-off for severe/extreme physical abuse)[41] on the CTQ physical abuse subscale, and information from the CECA interview and the CTQ were consistent with the official records. Common psychiatric comorbidities included PTSD, depression, anxiety and conduct disorder (Table 1). Three participants were excluded due to MRI motion artefacts, leaving a final sample of 20 participants.

The 20 psychiatric patients that were matched with the abuse group on psychiatric comorbidities but with no history of childhood maltreatment (scoring below the cut-offs for the respective CTQ subscales)[41] were recruited through psychiatric clinics and social services. PTSD patients experienced non-abuse related trauma (e.g. witnessed a murder, experienced a car

accident or the death of a loved one). Two participants were excluded due to motion artefacts, leaving a final sample of 18 patients (Table 1).

Participants in the childhood abuse and psychiatric control groups who were recruited from social services did not have any psychiatric diagnosis beforehand and their GPs were subsequently notified by the child psychiatrist (KM). For those that were recruited from clinics, they were new clinical cases that had not yet started on any treatment, and the diagnoses made using the DAWBA were consistent with the patients' diagnoses in the clinics. None of the participants was receiving any treatment at the time of recruitment and scanning.

The 27 healthy controls with no history of psychiatric illness and childhood maltreatment (scoring below the same cut-offs for the respective CTQ subscales) were recruited through advertisements in the same geographic areas of South London to ensure similar socioeconomic background. Two participants were excluded due to motion artefacts, leaving a final sample of 25 participants (Table 1).

DTI Acquisition and Processing

The DTI acquisition procedures are described in the supplementary materials. Diffusion data were preprocessed using ExploreDTI (www.exploredti.org) (Supplementary materials).

We assessed group differences in head motion, as this may affect quantitative diffusion measurements. We quantified head motion as the mean volume-by-volume translation and rotation. This was calculated as the average across the translation or rotation component of the affine registration performed between each volume and the first volume, and t-tests were then performed between the two groups for each of the two motion measures. There were no

significant group differences in mean translation ($F(2,60)=0.8$, $p=0.45$) and rotation ($F(2,60)=2.2$, $p=0.1$); hence, motion was not used as a nuisance regressor in our results.

Outlier profiles of each diffusion scan were generated using ExploreDTI during the quality check stage of preprocessing, with no difference between groups observed ($F(2,60)=1.20$, $p>0.05$). All scans were then corrected for head motion using ExploreDTI.

Tractography

We performed virtual dissections of the left and right ILF and IFOF according to previous studies [19] (Fig.1). Regions of interest (ROIs) were delineated in the FA maps of each participant in native space using previously described anatomical guidelines to constrain the whole-brain tractogram[19]. Two-ROI approaches were used for each tract to show the full extent of WM streamlines running through each ROI. Specifically, the ILF was dissected to show streamlines running between the occipital lobe (one ROI in the coronal plane within the WM of the occipital lobe) and the temporal pole (one ROI in the coronal plane within the WM of the anterior temporal lobe). The IFOF was dissected using the same occipital lobe ROI as used for the ILF, and a second ROI delineated in the coronal plane within the external capsule.

Group differences were examined for each measurement (i.e. streamline count, tract volume, FA, mean diffusivity and radial diffusivity) using ANOVA with SPSS24 (SPSS, Inc., Chicago) controlling for IQ, age and gender. Comparisons for specific tracts were considered as statistically significant if they survived Bonferroni correction for multiple comparisons ($p<0.0125$, two tracts for each hemisphere).

TBSS

Each participant's FA map was transformed into standard stereotactic space (using FMRIB58 template) and a mean FA map for the whole sample was used to create the average core 'skeleton'. Skeleton images of each participant's FA map were then produced and projected onto the mean skeleton to identify voxels where FA value differs significantly between these skeletons using General Linear Model[20]. The design matrix used IQ, age and gender as covariates. Five thousand permutations were applied. The statistical threshold was set at $p<0.05$, fully corrected for multiple comparison using threshold-free cluster enhancement (TFCE) across all WM tracts in the whole-brain analysis.

Exploratory Correlational Analysis

Finally, Pearson correlations were used to explore possible associations between tract-specific measurements and SDQ within each group, and with abuse measures (severity, age of onset and duration of abuse) within the abuse group.

Results

Subject Characteristics

The groups did not differ significantly in age, gender, ethnicity and SES, but differed in IQ which was expected as this is typical for these populations[44] (Table 1). Participants in the childhood abuse group did not mention any head trauma injuries or loss of consciousness from the abuse in the CECA interview. All MRI brain scans were also reviewed by a radiologist and no traumatic brain injury or incidental findings were discovered. Hence, mild traumatic brain injury is unlikely to be a factor in the findings. Although we selected participants with severe childhood physical abuse, they also experienced marked/severe emotional abuse and neglect (Table 1), which typically co-occur with physical abuse, and hence they seem to represent adequately the childhood abuse population[36].

The healthy controls scored significantly lower than the abuse group on BDI (p<0.01) and all SDQ difficulties subscales (p<0.01), and lower than psychiatric controls on BDI (p<0.001) and all SDQ difficulties subscales (p<0.05) except for SDQ conduct problems. The abuse group scored significantly higher than psychiatric controls, who did not differ from healthy controls, on the SDQ conduct problems subscale (p<0.01) (Table 1).

Tractography Analysis

The abuse group had significantly lower tract volume of the left ILF, right ILF and left IFOF relative to both healthy (p<0.01) and psychiatric controls (p<0.01) (Table 2, Fig 1), and lower streamline count of the right ILF and left IFOF relative to both healthy (p<0.01) and psychiatric controls (p<0.01), as well as lower FA of the left IFOF relative to healthy controls (p=0.01) (Table 2). There were no significant differences between the healthy and psychiatric controls.

TBSS Analysis

The abuse group, relative to healthy controls, had significantly reduced FA in a left-hemispheric posterior region comprising the ILF, IFOF, splenium of the corpus callosum and the SLF (p=0.02, TFCE-corrected) (Table 3, Fig. 2). Mean FA values of this region were extracted for comparison between the abuse and psychiatric groups using ANOVA with SPSS24 controlling for IQ, age and gender. The abuse group had significantly reduced FA relative to psychiatric controls (F(1,36) =16.4, p<0.001), which suggests that compromised microstructure of this region may be abuse-specific. The psychiatric controls had marginally lower FA compared to health controls in this region (F(1,41) =3.89, p=0.06). There were no significant regions with increased FA for the abuse versus healthy and psychiatric groups.

Exploratory Correlational Analysis

Reduced FA of the left IFOF was significantly associated with higher CTQ physical neglect (r = -0.52, p<0.05), emotional neglect (r = -0.48, p<0.05) and CTQ total score (r = -0.50, p<0.05) within the abuse group (Figure S1). For the healthy controls, lower left IFOF FA was significantly associated with higher SDQ emotion (r = -0.61, p<0.05) and peer (r = -0.46, p<0.05) problems and SDQ total score (r = -0.51, p<0.05). Lower left ILF tract volume was significantly associated with higher SDQ peer (r = -0.67, p<0.05) and hyperactivity (r = -0.69, p<0.05) problems and SDQ total score (r = -0.63, p<0.05) within the psychiatric control group. There were no significant correlations between SDQ and tract measurements within the abuse group. As the correlational analyses were exploratory, we did not correct for multiple comparisons which would have rendered the findings non-significant.

Discussion

To our knowledge, this is the first DTI study to examine the association between documented childhood abuse and alterations in the structure of neural pathways in medication-naïve, drug-free youth controlling for psychiatric comorbidities by the inclusion of a psychiatric control group. This is crucial to elucidate the effects of abuse independently from effects associated with psychiatric comorbidities or medication and drug abuse[10].

As hypothesized, the abuse group had significantly reduced WM tract volume in bilateral ILF and left IFOF compared to both healthy and psychiatric controls. At the whole-brain level, the abuse group also had significantly reduced FA in a left-hemispheric posterior region comprising the ILF, IFOF, splenium of the corpus callosum and SLF relative to both healthy and psychiatric controls. Reduced FA of the left IFOF, which was also found in the tractography results, furthermore correlated with greater abuse severity in the abuse group. This suggests differences exist both at the microstructural level as measured by FA, but also at the volumetric

level of the entire tract. Thus, differences in the WM of the ILF and IFOF, particularly in the left hemisphere, was specifically related to the abuse experience. Moreover, reduced FA of the left IFOF was significantly associated with higher SDQ emotion and peer problems in the healthy controls, reinforcing the association between the IFOF and emotional and social behaviours.

The ILF is a ventral associative bundle that mediates the fast transfer of visual signals from the visual areas to the amygdala and hippocampus, and neuromodulatory back-projections from the amygdala to early visual areas, enhancing the visual processing of emotionally significant stimuli[45]. It is a key component of the visual-limbic pathway involved in facial affect recognition[46] and visual perception[47]. The finding of an abuse-specific reduced WM microstructure of the ILF extends earlier studies that found decreased FA of the ILF in adolescents exposed to early neglect[23] and in young adults with childhood maltreatment[26,27], where the decreased FA was furthermore related to poorer visual learning and memory in neglected adolescents[23] and with longer duration of abuse[26].

The right hemisphere is particularly dominant for negative emotional processing in most individuals[48]. Thus, it seems that abuse exposure affects corticolimbic regions involved in emotional regulation and specifically targets the visual-limbic pathway involved in the emotional processing of (aversive) visual information. Given that the abuse experience has both visual and auditory components, the left ILF may also have been compromised as it is involved in language processing[49]. Interestingly, studies suggest that fearful facial expressions alone activate the right amygdala, while fearful facial expressions combined with fearful voices activate the left medial temporal gyrus[50]. Hence, the combined exposure to fearful faces and voices during a typical severe abuse episode may have disrupted the normal development of both the left and right ILF.

The IFOF, which overlaps spatially and functionally with the ILF, connects the ventral occipital, posterior temporo-basal areas to the frontal lobe (inferior frontal, dorsolateral prefrontal and emotion-related OFC regions) and runs parallel to the ILF in its occipital course[51]. Hence, it is also involved in facial affect recognition[46], visual and semantic processing, as well as in multimodal sensory-motor integration[52]. Altered microstructure of the IFOF is also consistent with earlier studies that reported lower FA of the IFOF in adolescents exposed to early neglect[23] and in individuals with childhood maltreatment[24,25]. The association between abuse experience and microstructure of the IFOF is further underpinned by the current findings of significant negative correlation between abuse severity and FA of the left IFOF.

The splenium of the corpus callosum interconnects the left and right occipital and inferior temporal cortices[51]. These regions form the ventral visual stream with reciprocal connections with the hippocampus and emotion-related structures such as the amygdala and OFC[53]. The splenium has a protracted myelination trajectory from birth to early adulthood with an accelerated growth during middle childhood which accompanies the development of visual-spatial integration[54]. It is involved in the integration of somatosensory and emotional visual information in the two hemispheres[55]. Our findings also support earlier studies that found reduced FA of the splenium in individuals exposed to childhood maltreatment[24,25].

Childhood maltreatment has been associated with abnormal development of the sensory systems that relay adverse sensory experiences. For instance, studies reported structural deficits in the occipital-lingual regions in children with maltreatment[56] and psychosocial deprivation[57], in women who experienced childhood sexual/physical abuse[13], and in young adults who witnessed domestic violence during childhood[14]. These findings suggest that the sensory systems that process and interpret adverse sensory inputs may be altered by the abuse experience, reflecting an

adaptive response of the developing brain to protect the child from highly hostile environmental conditions by gating sensory experiences and processing related to the abuse[33].

Similarly, childhood maltreatment is associated with structural deficits in the emotion-related OFC[8-10] and amygdala regions[58], along with functional abnormalities in fronto-limbic regions while processing fearful or angry faces[59,60]. Therefore, besides impairment in these individual regions, the findings of WM alterations in the ILF and IFOF tracts further suggest disruptions in visual-limbic-OFC pathways mediating sensory integration and cognitive or emotion regulation to sensory stimuli, which may also possibly underlie the neuropsychological deficits in emotion and reward processing[61,62] observed in childhood maltreatment.

Given that large-scale epidemiological and longitudinal studies have consistently shown that childhood maltreatment is linked developmentally to psychiatric disorders[29], it is crucial to control for these in order to disentangle the effects of maltreatment from psychiatric comorbidities[10]. Therefore, the specificity of the present findings of differences in the ILF and IFOF at both the microstructural and volumetric levels relative to a psychiatric control group in particular extends previous studies and suggests that these neural pathways are specifically compromised in abused individuals.

The human brain is a highly plastic organ that is continually modified by experience and undergoes changes across the lifespan. The individual neural regions and circuits mature at different rates and have different windows of vulnerability to effects of traumatic stress, with increased vulnerability ascribed to a period of rapid maturation[63]. Studies suggest that the maturation of neuronal circuits of the human visual cortex may extend beyond infancy into childhood, with significant development in visual spatial integration between 5 and 14 years of age[54]. Given that the ILF, IFOF and splenium show rapid development from childhood with FA

increase peaking at early adulthood[64], the visual-limbic pathways may possibly be more susceptible to impairment in individuals with early adversities. Thus, our findings of an association between childhood maltreatment and altered structure of these late developing visual-emotional processing tracts suggests an environmentally triggered disturbance in the normal development of these pathways that may underlie the emotional problems that develop as a consequence of early adversities.

Limitations

Among the strengths of this study are that all participants were medication-naïve and drug-free, and their abuse experience was carefully assessed and corroborated by social service records. Also, we included a psychiatric control group to determine the specificity of childhood abuse in our findings. The inclusion of a childhood abuse group without any psychiatric disorders would have provided a more robust means of determining abuse-specific abnormalities; however, such a "pure" group would not be representative of the general childhood abuse populations, as large-scale epidemiological and longitudinal studies have consistently reported that childhood maltreatment is linked developmentally to psychiatric disorders[29], and a meta-analysis further reported a causal relationship between non-sexual childhood maltreatment and a range of mental disorders[65]. For the tractography analysis, multiple comparison correction was performed for the number of tracts only and not for the number of diffusion measures as these are not independent from each other and Bonferroni correction would thus have been too conservative. It is unclear to what extent pubertal development, malnutrition, prenatal drug exposure and presence of current life stressors may have influenced the findings. The moderate sample size of the present study warrants replication in larger samples of youth in future studies. The SES measure used is limited, as it does not provide information on parents' income and education; however, youth often have difficulties in reporting this information[42]. Although we recruited participants exposed to childhood physical abuse, it is unrealistic to separate physical abuse from typically co-

occurring emotional abuse and neglect; hence, many participants in the abuse group also suffered from emotional abuse and neglect[36].

Conclusion

In summary, using medication-naïve, drug-free, carefully assessed age-and-gender-matched groups of youth exposed to childhood abuse and psychiatric controls matched on psychiatric comorbidities, we found that childhood abuse is associated with altered microstructure of neural pathways connecting the OFC-limbic, temporal and occipital visual regions. The abuse-specific abnormalities of the ILF and IFOF visual-limbic pathways may possibly underlie the abnormal emotional regulation to sensory stimuli in victims of abuse.

Acknowledgments

This study, LL and HH were supported by the Reta Lila Weston Trust for Medical Research and the Kids Company UK. LL was also supported by the Lee Kong Chian School of Medicine, Nanyang Technological University Singapore Fellowship Grant (grant number L0491050). HHowells was supported by the Wellcome Trust (grant number 103759/Z/14/Z). AS and KR received research support from the UK Department of Health via the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) for Mental Health at South London and the Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology and Neuroscience, King's College London.

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

We thank all the individuals and their families who participated in this study. We also thank the staff of Kids Company London for their help with recruitment.

Financial Disclosures

KR has received speaker's honoraria from Lilly and Shire. MM has acted as a consultant for Cambridge Cognition and Lundbeck and has received fees from Shire for contribution towards education. KM has received research and educational grants from Glaxo Smith Kline and Shire pharmaceuticals and has served on the advisory boards of Janssen, Eli Lilly and Shire pharmaceuticals. KM has also received honoraria for speaking at conferences organized by Janssen, Eli Lilly and Shire pharmaceuticals. LL, HHart, HHowells and AS reported no financial interests or potential conflicts of interest.

References

1. Pechtel P, Pizzagalli DA. Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology* 2011;214(1):55-70.
2. NSPCC. *Child abuse and neglect in the UK today*. 2011, 2012.
3. Lim L, Hart H, Mehta MA, et al. Neural correlates of error processing in young people with a history of severe childhood abuse: An fMRI study. *Am J Psychiatry* 2015;172:892-900.
4. De Bellis MD, Zisk A. The biological effects of childhood trauma. *Child Adolesc Psychiatr Clin N Am* 2014;23(2):185-222, vii.
5. Lim L, Hart H, Mehta MA, et al. Neurofunctional abnormalities during sustained attention in severe childhood abuse. *PLoS ONE* 2016;11(11):e0165547.
6. Green J, McLaughlin KA, Berglund PA, et al. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication i: Associations with first onset of dsm-iv disorders. *Arch Gen Psychiatry* 2010;67(2):113-123.
7. Bremner JD, Vermetten E. Stress and development: behavioral and biological consequences. *Dev psychopathol* 2001;13(3):473-489.
8. Edmiston EE, Wang F, Mazure CM, et al. Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. *Arch Pediatr Adolesc Med* 2011;165(12):1069-1077.
9. Hodel AS, Hunt RH, Cowell RA, et al. Duration of early adversity and structural brain development in post-institutionalized adolescents. *NeuroImage* 2015;105:112-119.
10. Lim L, Radua J, Rubia K. Gray matter abnormalities in childhood maltreatment: A voxel-wise meta-analysis. *Am J Psychiatry* 2014; 171:854-863.
11. De Bellis MD, Keshavan MS, Frustaci K, et al. Superior temporal gyrus volumes in maltreated children and adolescents with PTSD. *Biol Psychiatry* 2002;51(7):544-552.
12. Tomoda A, Sheu YS, Rabi K, et al. Exposure to parental verbal abuse is associated with increased gray matter volume in superior temporal gyrus. *NeuroImage* 2011;54 Suppl 1:S280-286.
13. Tomoda A, Navalta CP, Polcari A, Sadato N, Teicher MH. Childhood sexual abuse is associated with reduced gray matter volume in visual cortex of young women. *Biol Psychiatry* 2009;66(7):642-648.
14. Tomoda A, Polcari A, Anderson CM, et al. Reduced Visual Cortex Gray Matter Volume and Thickness in Young Adults Who Witnessed Domestic Violence during Childhood. *PLoS ONE* 2012;7(12):e52528.
15. Catani M, Bambini V. A model for social communication and language evolution and development (SCALED). *Curr Opin Neurobiol* 2014;28:165-171.
16. Fields RD. White matter in learning, cognition and psychiatric disorders. *Trends Neurosci* 2008;31(7):361-370.
17. Catani M. Diffusion tensor magnetic resonance imaging tractography in cognitive disorders. *Current Opin Neurol* 2006;19(6):599-606.
18. Beaulieu C. The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed* 2002;15(7-8):435-455.
19. Catani M, Dell'Acqua F, Budisavljevic S, et al. Frontal networks in adults with autism spectrum disorder. *Brain* 2016;139(2):616-630.
20. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage* 2006;31(4):1487-1505.
21. Jauregui-Huerta F, Ruvalcaba-Delgadillo Y, Gonzalez-Castañeda R, Garcia-Estrada J, Gonzalez-Perez O, Luquin S. Responses of glial cells to stress and glucocorticoids. *Current Immunology Rev* 2010;6(3):195-204.
22. Walhovd KB, Westlye LT, Amlien I, et al. Consistent neuroanatomical age-related volume differences across multiple samples. *Neurobiol Aging* 2011;32(5):916-932.

23. Hanson J, Adluru N, Chung M, et al. Early neglect is associated with alterations in white matter integrity and cognitive functioning. *Child Dev* 2013;84(5):1566-1578.
24. Huang H, Gundapuneedi T, Rao U. White matter disruptions in adolescents exposed to childhood maltreatment and vulnerability to psychopathology. *Neuropsychopharmacology* 2012;37(12):2693-2701.
25. Frodl T, Carballedo A, Fagan AJ, et al. Effects of early-life adversity on white matter diffusivity changes in patients at risk for major depression. *J Psychiatry Neurosci* 2012;37(1):37-45.
26. Choi J, Jeong B, Polcari A, et al. Reduced fractional anisotropy in the visual limbic pathway of young adults witnessing domestic violence in childhood. *NeuroImage* 2012;59(2):1071-1079.
27. Poletti S, Mazza E, Bollettini I, et al. Adverse childhood experiences influence white matter microstructure in patients with schizophrenia. *Psychiatry Res* 2015;234(1):35-43.
28. Govindan RM, Behen ME, Helder E, et al. Altered water diffusivity in cortical association tracts in children with early deprivation identified with Tract-Based Spatial Statistics (TBSS). *Cereb Cortex* 2010;20(3):561-569.
29. MacMillan HL, Tanaka M, Duku E, et al. Child physical and sexual abuse in a community sample of young adults: Results from the Ontario Child Health Study. *Child Abuse Negl* 2013;37(1):14-21.
30. Ugwu ID, Amico F, Carballedo A, et al. Childhood adversity, depression, age and gender effects on white matter microstructure: a DTI study. *Brain Struct Funct* 2015;220(4):1997-2009.
31. Tatham EL, Ramasubbu R, Gaxiola-Valdez I, et al. White matter integrity in major depressive disorder: Implications of childhood trauma, 5-HTTLPR and BDNF polymorphisms. *Psychiatry Res* 2016;253:15-25.
32. Ersche KD, Williams GB, Robbins TW, et al. Meta-analysis of structural brain abnormalities associated with stimulant drug dependence and neuroimaging of addiction vulnerability and resilience. *Current Opin Neurobiol* 2013;23(4):615-624.
33. Heim CM, Mayberg HS, Mletzko T, et al. Decreased cortical representation of genital somatosensory field after childhood sexual abuse. *Am J Psychiatry* 2013;170(6):616-623.
34. Lewis T, McElroy E, Harlaar N, et al. Does the impact of child sexual abuse differ from maltreated but non-sexually abused children? A prospective examination of the impact of child sexual abuse on internalizing and externalizing behavior problems. *Child abuse & neglect.* 2016;51:31-40.
35. Feiring C, Taska L, Lewis M. A process model for understanding adaptation to sexual abuse: the role of shame in defining stigmatization. *Child Abuse Negl* 1996;20(8):767-782.
36. Claussen AH, Crittenden PM. Physical and psychological maltreatment: relations among types of maltreatment. *Child Abuse Negl.* 1991;15(1-2):5-18.
37. Goodman R, Ford T, Richards H, et al. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry* 2000;41(5):645-655.
38. Goodman R. The strengths and difficulties questionnaire: A research note. *J Child Psychol Psychiatry* 1997;38(5):581-586.
39. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. *J Consul Clin Psychol* 1988;56(6):893-897.
40. Wechsler D. *Wechsler Abbreviated Scale of Intelligence.* San Antonio, Texas: The Psychological Corporation; 1999.
41. Bernstein DP, Fink L. *Childhood Trauma Questionnaire: A retrospective self-report manual San Antonio, TX:* The Psychological Corporation. 1998.
42. Currie CE, Elton RA, Todd J, et al. Indicators of socioeconomic status for adolescents: the WHO Health Behaviour in School-aged Children Survey. *Health Edu Res* 1997;12(3):385-397.

43. Bifulco A, Brown GW, Harris TO. Childhood Experience of Care and Abuse (CECA): a retrospective interview measure. *J Child Psychol Psychiatry* 1994;35(8):1419-1435.
44. Geoffroy MC, Pinto Pereira S, Li L, et al. Child neglect and maltreatment and childhood-to-adulthood cognition and mental health in a prospective birth cohort. *J Am Acad Child Adolesc Psychiatry* 2016;55(1):33-40.e33.
45. Catani M, Jones DK, Donato R, et al. Occipito-temporal connections in the human brain. *Brain* 2003;126:2093-2107.
46. Genova HM, Rajagopalan V, Chiaravalloti N, et al. Facial affect recognition linked to damage in specific white matter tracts in traumatic brain injury. *Soc Neurosci* 2015;10(1):27-34.
47. Ffytche DH. The hodology of hallucinations. *Cortex* 2008;44(8):1067-1083.
48. Schiffer F, Teicher MH, Anderson C, et al. Determination of hemispheric emotional valence in individual subjects: A new approach with research and therapeutic implications. *Behav Brain Funct* 2007;3(1):13.
49. Mandonnet E, Nouet A, Gatignol P, et al. Does the left inferior longitudinal fasciculus play a role in language? A brain stimulation study. *Brain* 2007;130(3):623-629.
50. Ethofer T, Anders S, Erb M, et al. Impact of voice on emotional judgment of faces: An event-related fMRI study. *Hum Brain Mapp* 2006;27(9):707-714.
51. Catani M, Thiebaut de Schotten M. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex* 2008;44(8):1105-1132.
52. Martino J, Brogna C, Robles SG, et al. Anatomic dissection of the inferior fronto-occipital fasciculus revisited in the lights of brain stimulation data. *Cortex* 2010;46(5):691-699.
53. Rudrauf D, David O, Lachaux J-P, et al. Rapid Interactions between the ventral visual stream and emotion-related structures rely on a two-pathway architecture. *J Neurosci* 2008;28(11):2793.
54. Kovács I, Kozma P, Fehér Á, et al. Late maturation of visual spatial integration in humans. *Proc Natl Acad Sci USA* 1999;96(21):12204-12209.
55. Tamietto M, Latini Corazzini L, de Gelder B, et al. Functional asymmetry and interhemispheric cooperation in the perception of emotions from facial expressions. *Exp Brain Res* 2006;171(3):389-404.
56. Kelly PA, Viding E, Wallace GL, et al. Cortical thickness, surface area, and gyrification abnormalities in children exposed to maltreatment: neural markers of vulnerability? *Biol Psychiatry* 2013;74(11):845-852.
57. McLaughlin KA, Sheridan MA, Winter W, et al. Widespread reductions in cortical thickness following severe early-life deprivation: A neurodevelopmental pathway to ADHD. *Biol Psychiatry* 2014;76(8):629-638.
58. Tottenham N, Hare TA, Quinn BT, et al. Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Dev Sci* 2010;13(1):46-61.
59. McCrory EJ, De Brito SA, Kelly PA, et al. Amygdala activation in maltreated children during pre-attentive emotional processing. *Br J Psychiatry* 2013;202(4):269-276.
60. Dannlowski U, Stuhrmann A, Beutelmann V, et al. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biol Psychiatry* 2012;71(4):286-293.
61. Pine DS, Mogg K, Bradley BP, et al. Attention bias to threat in maltreated children: implications for vulnerability to stress-related psychopathology. *Am J Psychiatry* 2005;162(2):291-296.
62. Weller JA, Fisher PA. Decision-making deficits among maltreated children. *Child Maltreatment* 2013;18(3):184-194.
63. Tottenham N. The importance of early experiences for neuro-affective development. *Curr Top Behav Neurosci* 2014;16:109-129.

64. Lebel C, Gee M, Camicioli R, et al. Diffusion tensor imaging of white matter tract evolution over the lifespan. *NeuroImage* 2012;60(1):340-352.
65. Norman RE, Byambaa M, De R, et al. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. *PLoS Med* 2012;9(11):e1001349.

Table 1: Demographic characteristics of 20 young people exposed to childhood abuse, 18 psychiatric controls and 25 healthy controls

	Childhood Abuse (N=20)		Psychiatric Controls (N= 18)		Healthy Controls (N=25)		Analysis		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F(2, 60)**	***p* (corr.)**	**Between Groups**
Age (years) [age range 13-20]	17.1	2.52	16.8	2.65	17.75	1.61	0.85	ns	-
Socioeconomic status	2.81	0.70	3.00	0.69	3.28	0.74	2.59	ns	-
IQ	92.1	15.5	92.8	12.8	105.3	10.5	7.56	0.001	CA, PC < HC
Strengths and Difficulties Questionnaire:									
Emotional problems	4.35	2.82	5.00	3.03	2.09	1.56	7.94	0.001	CA, PC > HC
Conduct problems	4.10	2.17	2.33	2.20	1.83	1.59	7.55	0.001	CA > PC, HC
Hyperactivity	5.40	2.28	4.72	2.72	3.00	2.13	5.93	0.005	CA, PC > HC
Peer problems	3.65	1.51	2.61	1.98	1.22	1.78	9.56	<0.001	CA, PC > HC
Prosocial	7.30	1.72	8.50	1.79	8.04	1.46	2.59	ns	-
Total difficulties score	17.5	6.75	14.7	6.31	8.13	5.67	12.9	<0.001	CA, PC > HC
Beck's Depression Inventory	15.6	10.8	19.9	10.3	5.92	6.09	8.03	0.001	CA, PC > HC
Childhood Trauma Questionnaire:									
Physical abuse	20.2	5.53	6.00	1.50	5.52	0.96	133.9	<0.001	CA > PC, HC
Emotional abuse	17.3	4.76	6.89	1.84	6.60	2.63	69.5	<0.001	CA > PC, HC
Sexual abuse	5.05	0.22	5.28	0.56	5.05	0.28	2.08	ns	-
Physical neglect	13.4	5.40	6.72	2.22	6.08	2.41	26.3	<0.001	CA > PC, HC
Emotional neglect	17.8	4.73	9.00	3.68	8.40	3.67	33.2	<0.001	CA > PC, HC
Age at onset of (physical) abuse (years)	3.85	2.80	-	-	-	-	-	-	-

Duration of (physical) abuse (years)	8.00	3.15	-	-	-	-	-	-	-
	N	**%**	**N**	**%**	**N**	**%**	χ^2	***p***	**Between Groups**
Gender (Males)	12	65	8	45	16	76	4.52	ns	-
Ethnicity:							7.98	ns	-
Caucasian	10	50	3	17	12	48			
Afro-Caribbean	7	35	9	50	11	44			
Others (Asian/mixed)	3	15	6	33	2	8			
DSM-IV Psychiatric diagnosis:									
PTSD	10	50	11	61	-				
Depression	5	25	5	28	-				
Anxiety disorders	4	20	5	27	-				
Social phobia	2	10	2	11	-				
Panic disorder	1	5	1	6	-				
ADHD	1	5	1	6	-				
ODD/CD/Other disruptive behaviours	4	20	3	17	-				

Abbreviations: CA=Childhood Abuse group; PC=Psychiatric Controls; HC=Healthy Controls; corr=Bonferroni corrected; ADHD=Attention Deficit Hyperactivity Disorder; PTSD=Post-Traumatic Stress Disorder; ODD=Oppositional Defiant Disorder; CD=Conduct Disorder; ns=non-significant

Table 2: Tract-specific measurements of the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus tracts

Tracts	Childhood Abuse (N=20)		Psychiatric Controls (N= 18)		Healthy Controls (N=25)		CA vs HC comparisons					CA vs PC comparisons		
	Mean	SD	Mean	SD	Mean	SD	*F*(2, 57)	*p*	F(1,40)	*p*		F(1,33)	*p*	
Left ILF														
Streamlines	426	270	614	364	726	396	3.23	0.047	4.47	0.041	CA<HC	4.58	0.040	CA<PC
Tract Vol	1465	544	1953	673	2149	591	6.23	0.004*	9.02	0.005	CA<HC	10.4	0.003	CA<PC
FA	0.495	0.021	0.499	0.022	0.501	0.021	0.42	ns	0.45	ns	-	1.01	ns	-
MD	0.793	0.026	0.790	0.033	0.786	0.021	1.35	ns	3.66	ns	-	0.19	ns	-
RD	0.553	0.027	0.547	0.0316	0.543	0.0250	0.96	ns	2.29	ns	-	0.62	ns	-
Right ILF														
Streamlines	339	282	666	393	719	404	7.15	0.002*	11.9	0.001	CA<HC	11.2	0.002	CA<PC
Tract Vol	1180	684	2091	695	2132	650	12.2	<0.001*	16.7	<0.001	CA<HC	19.3	<0.001	CA<PC
FA	0.480	0.040	0.486	0.023	0.493	0.022	0.76	ns	1.13	ns	-	0.37	ns	-
MD	0.792	0.027	0.786	0.032	0.780	0.020	0.67	ns	1.54	ns	-	0.43	ns	-
RD	0.561	0.037	0.553	0.033	0.545	0.024	1.14	ns	2.16	ns	-	0.75	ns	-
Left IFOF														
Streamlines	406	330	849	436	960	509	10.0	<0.001*	12.6	0.001	CA<HC	13.9	0.001	CA<PC
Tract Vol	1762	872	2776	599	2860	677	14.3	<0.001*	14.8	<0.001	CA<HC	17.7	<0.001	CA<PC
FA	0.499	0.027	0.510	0.026	0.516	0.024	3.20	0.048	7.41	0.010	CA<HC	2.08	ns	-
MD	0.810	0.029	0.794	0.032	0.796	0.020	3.05	0.05	5.93	0.020	CA>HC	3.65	0.065	CA>PC
RD	0.561	0.036	0.542	0.036	0.540	0.027	3.74	0.03	8.46	0.006	CA>HC	3.37	0.075	CA>PC
Right IFOF														
Streamlines	409	332	676	384	706	356	2.74	0.07	2.14	ns	-	6.04	0.019	CA<PC

Tract Vol	1694	831	2352	830	2390	733	3.61	0.03	2.91	ns	-	7.04	0.012	CA<PC
FA	0.496	0.017	0.502	0.022	0.509	0.022	1.59	ns	3.57	ns	-	1.33	ns	-
MD	0.801	0.030	0.802	0.037	0.793	0.020	0.20	ns	0.47	ns	-	0.02	ns	-
RD	0.558	0.026	0.554	0.035	0.543	0.023	0.74	ns	2.25	ns	-	0.18	ns	-

Abbreviations: SD=Standard Deviation; CA=Childhood Abuse group; HC=Healthy Control group; PC=Psychiatric Control group; Vol=Volume; FA=Fractional Anisotropy; MD=Mean Diffusivity; RD=Radial Diffusivity; ILF= Inferior Longitudinal Fasciculus; IFOF=Inferior Fronto-Occipital Fasciculus; ns=non-significant; * indicates values that survive Bonferroni correction for multiple comparisons

Table 3: Cluster of reduced white matter fractional anisotropy in the childhood abuse group compared with healthy controls (p<0.05, TFCE-corrected)

	MNI Coord. (x,y,z)	Cluster size	*p* value
Left Inferior longitudinal fasciculus/ Inferior fronto-occipital fasciculus/ Splenium of the corpus callosum/ Superior longitudinal fasciculus	-31,-69,-1	678	0.02

Abbreviations: MNI=Montreal Neurological Institute; TFCE=Threshold-Free Cluster Enhancement

Figure Legend

Fig. 1: (A) Tractography reconstructions of the Inferior Longitudinal Fasciculus (ILF) and Inferior Fronto-Occipital Fasciculus (IFOF) tracts. (B) Differences in the tract volume of the ILF and IFOF between the childhood abuse group, psychiatric controls and healthy controls. Statistically significant differences between the childhood abuse group and psychiatric and healthy control groups within each tract are indicated with asterisks (*p<0.05; **$p < 0.01$).

Fig. 2: Whole-brain TBSS analysis of differences in FA values between the childhood abuse group and healthy controls (p<0.05, TFCE-corrected). Sagittal, coronal and transversal axial sections of the white matter skeleton (green) superimposed on the mean FA brain template. Red regions indicate significantly reduced FA values in the abuse group compared to healthy controls. The x,y z-coordinates are in standard MNI space. Images are in radiological convention (The *right* side of the image corresponds with the *left* hemisphere of the brain and vice versa). TBSS=Tract-Based Spatial Statistics; FA=Fractional Anisotropy; TFCE=Threshold-Free Cluster Enhancement; MNI=Montreal Neurological Institute.

Fig. 1

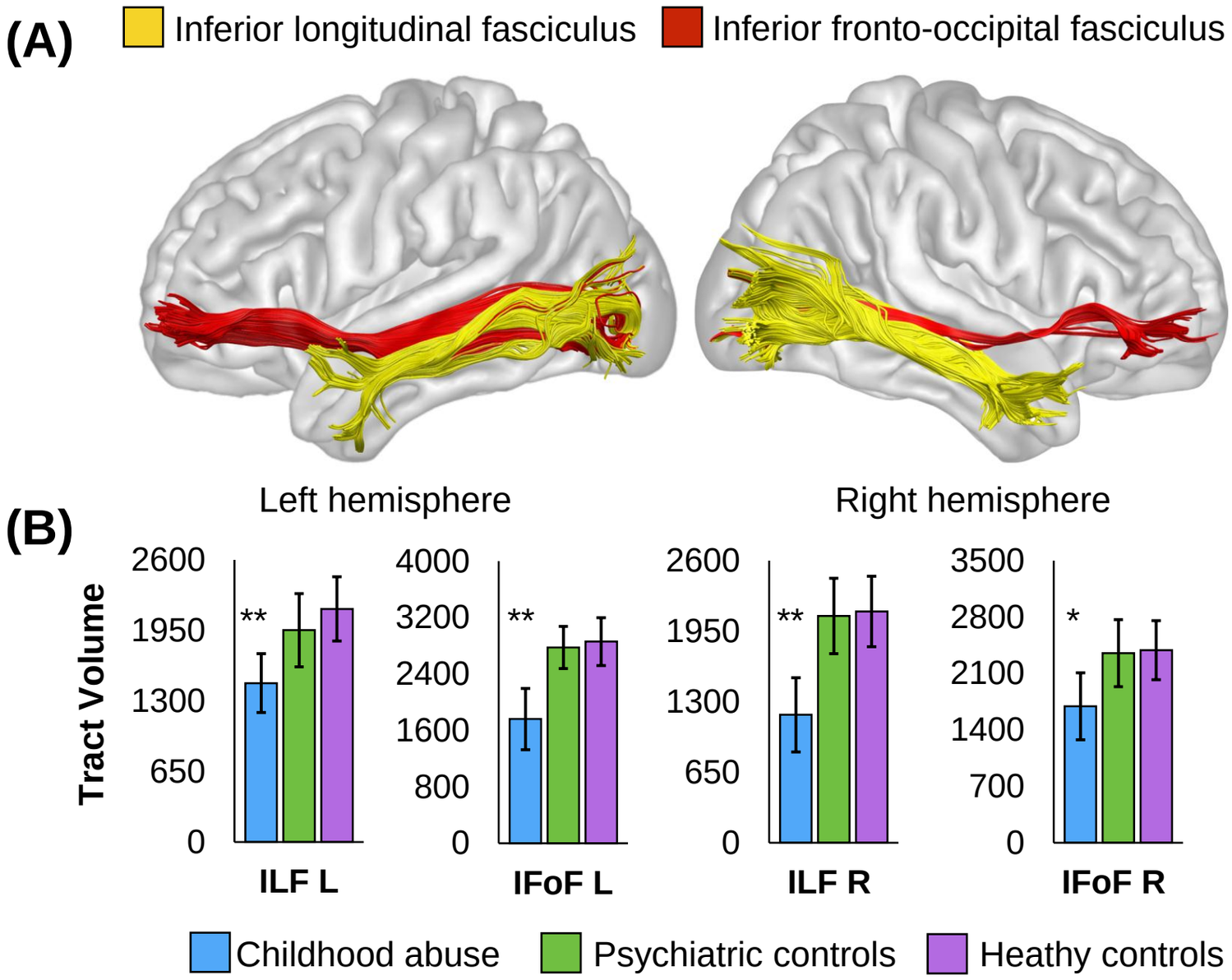
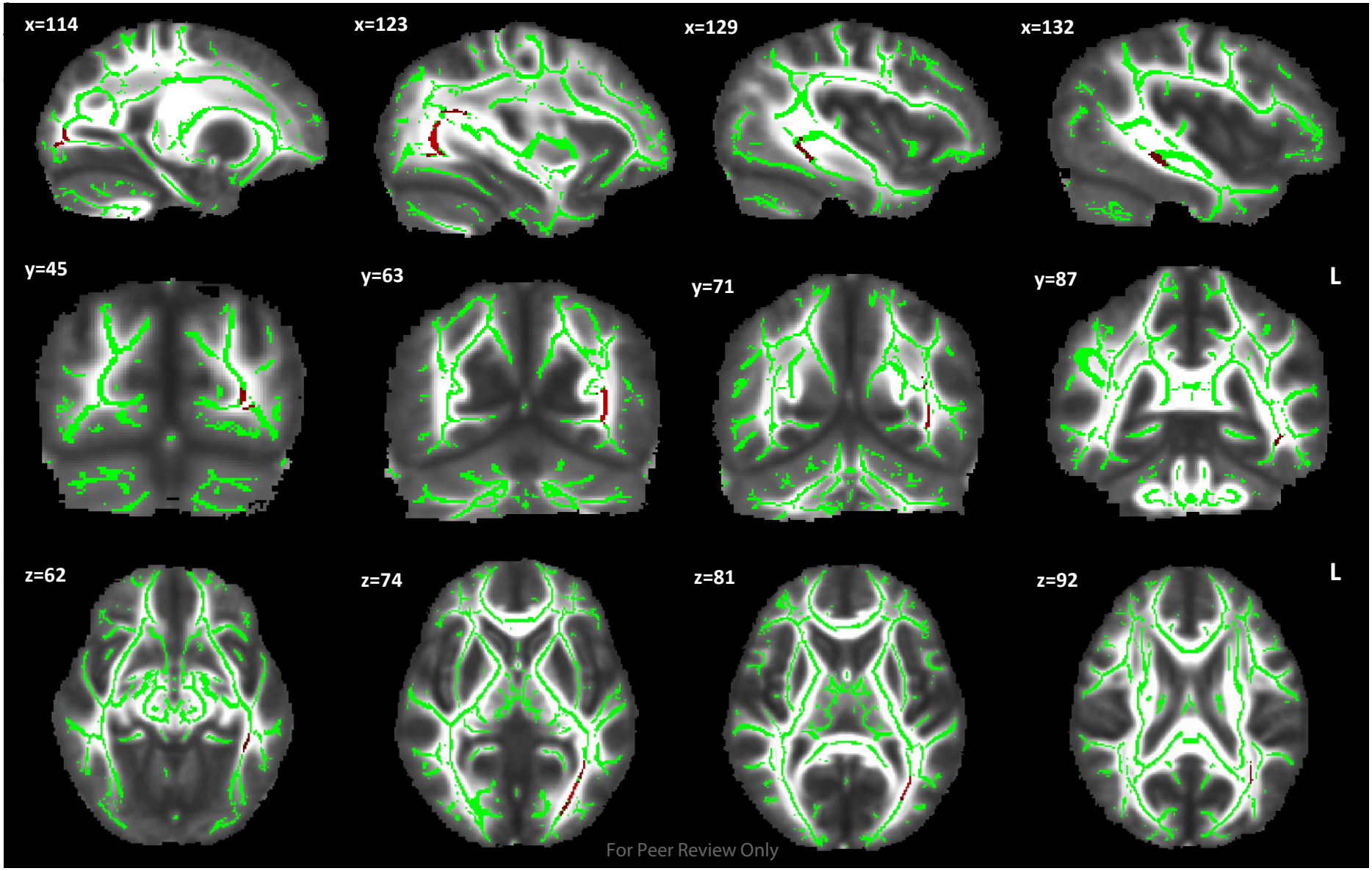

(A)
Inferior longitudinal fasciculus
Inferior fronto-occipital fasciculus
Left hemisphere
Right hemisphere
(B)
Tract Volume
2600
1950
1300
650
0
4000
3200
2400
1600
800
3500
2800
2100
1400
700
**
*
ILF L
IFoF L
ILF R
IFoF R
Childhood abuse
Psychiatric controls
Heathy controls

Fig. 2



Supplementary Materials

Participants

Besides undergoing a urine test for drug abuse, participants were also asked as part of the DAWBA assessment if they had used any drugs (cannabis, ecstasy, solvents, amphetamines, tranquillisers, cocaine, crack, opiates, other drugs) in the past 4 weeks, on a scale of 0 (No), 1 (Occasionally), 2 (Only at weekends), 3 (Most days), 4 (Every day). As shown on the table below, most of the participants did not use any drugs in the last 4 weeks before the scan and there were no significant differences between the 3 groups.

Table S1. Drugs used in the past 4 weeks in the childhood abuse, psychiatric control and healthy control groups.

Drugs	Childhood abuse Mean (SD)	Psychiatric Controls Mean (SD)	Healthy Controls Mean (SD)	F(2, 60)	*P* value
Cannabis	0.25(0.44)	0(0)	0.37(0.95)	1.74	0.19
Ecstasy	0(0)	0(0)	0.11(0.32)	2.11	0.13
Solvents	0(0)	0(0)	0(0)	-	-
Amphetamines	0(0)	0(0)	0(0)	-	-
Tranquillisers	0(0)	0(0)	0.05(0.22)	1.00	0.38
Cocaine	0(0)	0(0)	0(0)	-	-
Crack	0(0)	0(0)	0(0)	-	-
Opiates	0(0)	0(0)	0(0)	-	-
Other drugs	0(0)	0(0)	0(0)	-	-

MRI Data Acquisition

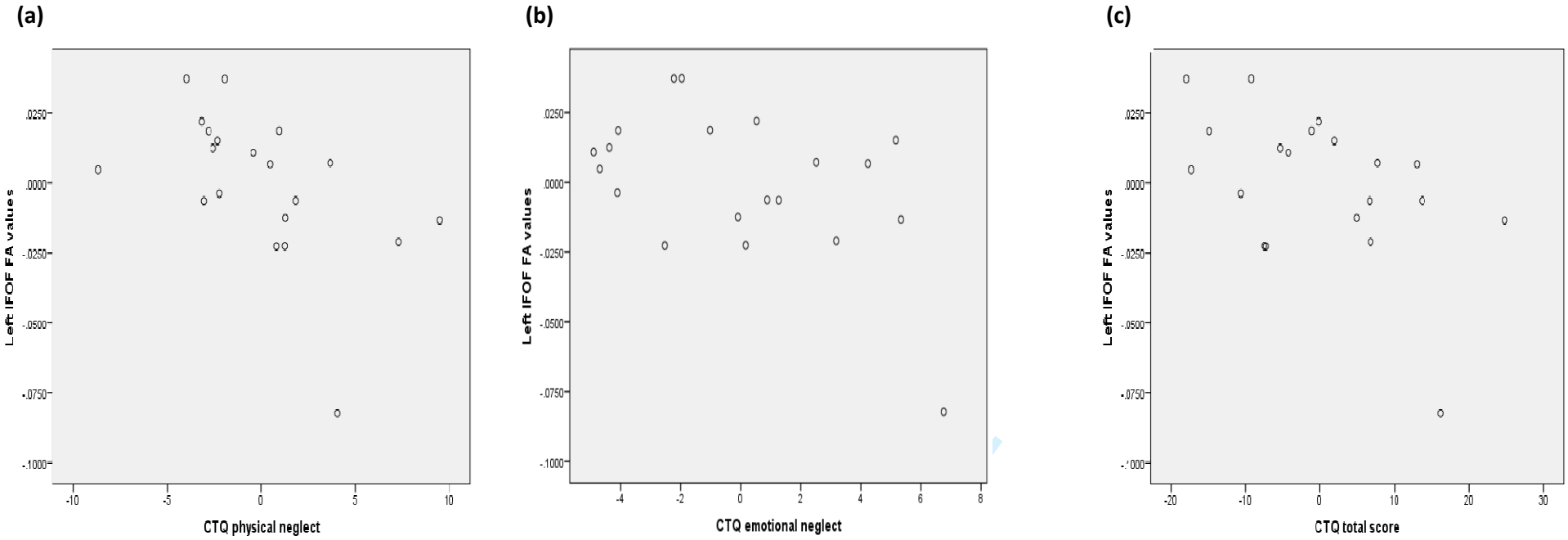
MRI data were acquired using a 3T GE Signa HDx system (General Electric, USA) at the Centre for Neuroimaging Sciences, King's College London, UK. The body coil was used for radio frequency (RF) transmission and an eight-channel head coil for RF reception allowing a parallel imaging (ASSET) speed up factor of 2. High-resolution structural three-dimensional (3D) T1-weighted images were acquired with full head-coverage, 166 contiguous slices, 1.2 mm thickness, a 256 x 256 x 166 matrix and a repetition time/echo time of 7/2.8 ms (field of view 260 mm). Consistent image quality was ensured by a semi-automated quality control procedure. DTI-MRI data were acquired using a spin-echo echo-planar imaging double refocused sequence providing

whole head coverage with isotropic image resolution (2.4 x 2.4 x 2.4 mm; 32 diffusion-weighted volumes with different non-collinear diffusion directions with b-factor 1300 s/mm^2, and four non-diffusion-weighted volumes; 60 slices without slice gap; echo time = 104.5 ms; repetition time = 20 R-R intervals; 128 x 128 acquisition matrix; field of view 307 x 307 mm). The acquisition was gated to the cardiac cycle using a digital pulse oximeter placed on participants' forefinger.

Diffusion Tensor MRI Preprocessing

Diffusion tensor imaging data were preprocessed using ExploreDTI (www.exploredti.org) and corrected for eddy current and motion artefacts through iterative correction to the four non-diffusion weighted volumes. For each participant, the raw data set was examined in a slice-wise manner to exclude subject movement during the scan. In compliance with the study protocol, participants who generated corrupted images on more than two diffusion-weighted imaging volumes would have been excluded. Seven participants had to be excluded after inspection. The b-matrix was reoriented (Leemans and Jones, 2009), and the tensor was estimated using a non-linear least square approach in StarTrack software (Jones and Basser, 2004, www.natbrainlab.com). Tractography maps were generated, including fractional anisotropy (FA), mean diffusivity and radial diffusivity. Whole brain tractography was performed by selecting all seed voxels with FA > 0.2. Streamlines were propagated using Euler integration (Basser et al 2000), and a step size of 1mm. The algorithm stopped tracking where FA < 0.2 or when the angle between two consecutive tracking steps was > 35^o. Finally, diffusion tensor maps and whole brain tractography were exported to Trackvis (Wang et al 2007) for virtual manual dissection of the tracts, which was performed with the assistance of a white matter atlas (Catani & Thiebaut de Schotten, 2012) and a skilled anatomist (H.Howells).

Figure S1. Associations between left Inferior Fronto-Occipital Fasciculus (IFOF) FA values and **(a)** CTQ physical neglect, **(b)** CTQ emotional neglect and **(c)** CTQ total score within the abuse group.



References

Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A (2000): In vivo fiber tractography using DT-MRI data. *Magn Reson Med 44:* 625–32.

Catani M, Thiebaut De Schotten, M (2012): *Atlas of Human Brain Connections*. Oxford: Oxford University Press.

Jones DK, Basser PJ (2004): "Squashing peanuts and smashing pumpkins": how noise distorts diffusion-weighted MR data. *Magn Reson Med 52:* 979–93.

Leemans A, Jones DK (2009): The B-matrix must be rotated when correcting for subject motion in DTI data. *Magn Reson Med 61*: 1336–49.

Wang R, Benner T, Sorensen A, Wedeen V (2007): Diffusion toolkit: a software package for diffusion imaging data processing and tractography. *Proc Int Soc Magn Reson Med 15:* 3720.