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DOI:
10.1016/j.pscychresns.2023.111616

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Dauvermann, MR, Costello, L, Tronchin, G, Holleran, L, Mothersill, D, Rokita, KI, Kane, R, Hallahan, B, Corvin, A, Morris, D, McKernan, DP, Kelly, J, McDonald, C, Donohoe, G & Cannon, DM 2023, 'Childhood trauma is associated with altered white matter microstructural organization in schizophrenia', *Psychiatry Research Neuroimaging*, vol. 330, 111616. https://doi.org/10.1016/j.pscychresns.2023.111616

Psychiatry Research: Neuroimaging 330 (2023) 111616

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Childhood trauma is associated with altered white matter microstructural organization in schizophrenia

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ARTICLE INFO

Keywords:
Schizophrenia
Childhood trauma
Childhood trauma severity
Fractional anisotropy
Diffusion-weighted magnetic resonance imaging
Tract-based spatial statistic

ABSTRACT

It has been reported that childhood trauma (CT) is associated with reductions in fractional anisotropy (FA) in individuals with schizophrenia (SZ). Here, we hypothesized that SZ with high levels of CT will show the greatest reductions in FA in frontolimbic and frontoparietal regions compared to healthy controls (HC) with high trauma levels and participants with no/low levels of CT. Thirty-seven SZ and 129 HC with CT experience were dichotomized into groups of 'none/low' or 'high' levels. Participants underwent diffusion-weighted MRI, and Tract-based spatial statistics were employed to assess the main effect of diagnosis, main effect of CT severity irrespective of diagnosis, and interaction between diagnosis and CT severity. SZ showed FA reductions in the corpus callosum and corona radiata compared to HC. Irrespective of a diagnosis, high CT levels ($n = 48$) were related to FA reductions in frontolimbic and frontoparietal regions compared to those with none/low levels of CT ($n = 118$). However, no significant interaction between diagnosis and high levels of CT was found ($n = 13$). Across all participants, we observed effects of CT on late developing frontolimbic and frontoparietal regions, suggesting that the effects of CT severity on white matter organization may be independent of schizophrenia.

1. Introduction

The association between the experience of childhood trauma (CT) and developing schizophrenia is well established (Bendall et al., 2007; Kelleher et al., 2013; Morgan and Fisher, 2006; Popovic et al., 2019; Varese et al., 2012). CT encompasses early-life stressors, including instances of abuse (physical, emotional, and sexual), and neglect (physical or emotional). Evidence indicates a relationship between greater severity of CT and increased prevalence of schizophrenia in early adulthood (Morgan and Fisher, 2006; Quidé et al., 2020; Trauelsen et al., 2015). In addition, history of CT is often associated with greater symptom severity in individuals with established schizophrenia (SZ) (Bailey et al., 2018), greater cognitive deficits (Aas et al., 2012; Dauvermann and Donohoe, 2019; Quidé et al., 2020) and poorer functional outcomes (Copeland et al., 2018). Therefore, there is a need to shed light on the nature of associations between the occurrence and severity of CT and related brain alterations in SZ since it is known that early developmental insults may impact typical maturation patterns of white matter (WM) development (Heim and Nemeroff, 1999; McLaughlin et al., 2019).

It has been proposed that the diathesis-stress model may explain the greater probability of developing schizophrenia after the experience of CT compared to other individuals (Pruessner et al., 2017; Walker et al., 2008; Walker and Diforio, 1997). According to this vulnerability stress model, existing neurobiological vulnerabilities interact with additional environmental stressors, such as CT, which may result in a cascade of early neurodevelopmental disruptions and trigger the emergence of psychotic symptoms compared to other individuals (Pruessner et al.,

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https://doi.org/10.1016/j.pscychresns.2023.111616
Received 9 December 2022; Received in revised form 2 February 2023; Accepted 15 February 2023
Available online 21 February 2023

2017; Walker et al., 2008; Walker and Diforio, 1997).

Findings from Diffusion Tensor Imaging (DTI) studies demonstrate consistent and widespread reductions in fractional anisotropy (FA) throughout the brain in SZ (Ellison-Wright and Bullmore, 2009; Kelly et al., 2018; Keshavan et al., 2020; Samartzis et al., 2014). FA is a metric of DTI that is widely used as an indirect measure of WM microstructural organization since it is sensitive to changes in biophysical tissue properties, (i.e., axonal orientation) (Basser and Pierpaoli, 2011; Beaulieu and Allen, 1994). Support for the role of CT on both increases and decreases of FA has been reported in individuals with neuropsychiatric disorders and healthy controls (HC) without a psychiatric diagnosis (Lim et al., 2020; Teicher et al., 2016). In schizophrenia, findings from three DTI studies propose an emerging pattern of associations between lower FA in SZ and high CT levels (Supplemental Table 1). Two studies found that childhood adversity in individuals with first-episode schizophrenia (FES) and SZ was associated with FA reductions in the superior longitudinal fasciculus (SLF), forceps major, inferior longitudinal fasciculus (ILF) and the inferior frontooccipital fasciculus (IFOF) (Asmal et al., 2019; Poletti et al., 2015), while Asmal *et al.* (2019) also reported a significant negative relationship in FES compared to HC with high levels of CT (Asmal et al., 2019). Further support for lower FA in SZ comes from Molina et al. (2018), who selected physical neglect as one subtype of CT, and demonstrated an inverse correlation between history of physical neglect and lower FA in WM connections between the left superior-medial prefrontal cortex and the left hippocampus in SZ compared to HC (Molina et al., 2018b). Despite this general trend of reduced FA, the extent of clinical differences (i.e., different stages of schizophrenia) and methodological differences between the studies (i.e., different CT and childhood adversity types; total CT or subtype measures) limit the interpretability and generalisability of the findings (Cancel et al., 2019). In summary, no prior study has examined reductions in FA between trauma-exposed SZ relative to HC by taking severity levels into account as well as unexposed individuals.

The aims of the study were to examine the association between CT and WM microstructural reductions in SZ relative to HC using an unbiased and data-driven approach of tract-based spatial statistics (TBSS). We investigated whether a history and severity of trauma in SZ was associated with more pronounced reductions in FA within deep WM voxels relative to trauma-exposed HC and participants irrespective of diagnosis of schizophrenia categorized as having none/low levels of trauma. Firstly, we hypothesized that having a diagnosis of schizophrenia would be associated with widespread reductions in FA across the brain compared to HC. Secondly, we predicted that high levels of trauma will be associated with voxel-based reductions in FA, particularly in frontolimbic and frontoparietal pathways irrespective of diagnosis. Finally, compared to the exposure and severity of CT or diagnosis, we assumed that the greatest reductions in FA in late developing frontolimbic and frontoparietal regions will be evident in SZ who reported high levels of trauma relative to trauma-exposed HC with high levels of trauma, and participants with none/low levels of trauma independent of a diagnosis.

2. Methods

2.1. Subjects

Participants were pooled from a subset of participants recruited as part of the Immune Response & Social Cognition in Schizophrenia project and the Social Cognition study in schizophrenia with identical eligibility criteria, questionnaires and scanning procedures (please see Supplemental Figure 1 for study flow). The Ethics Committees of the following institutions approved both studies: National University of Ireland Galway, University Hospital Galway, and Tallaght Hospital, Dublin. Written informed consent was obtained prior to the initiation of any study-related procedures.

HC without a psychiatric condition were recruited from public advertisements placed in County Galway and Dublin. Clinically stable SZ were recruited from hospital outpatient clinics or community-based mental health programmes in St. James's Hospital Dublin or University Hospital Galway via referrals from a trained clinical psychiatrist. Typical inclusion and exclusion criteria have been defined (please see Supplementary Material for details on inclusion and exclusion criteria).

2.2. Procedures

2.2.1. Clinical measures

Severity of symptomatology in SZ was measured using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), which is a 30-item semi-structured interview containing three subscales, including the positive symptoms scale (seven items), negative symptom scale (seven items), and general psychopathology scale (16 items). PANSS items are rated on a 7-point scale with items on each subscale range from '1′ ('absent') to '7′ ('extreme'). To reflect 'absence' scores, we used the re-scaled Likert scale ranging from '0′ ('absent') to '6′ ('extreme') resulting in a total score ranging from '0′ to '138′ (Leucht et al., 2010). PANSS assessment was only available for SZ. Current and lifetime cumulative medication use was recorded and converted into chlorpromazine equivalents (CPZ – mg/d), calculated using methods described in detail elsewhere (Andreasen et al., 2010; Leucht et al., 2015).

2.2.2. Assessment of childhood trauma

Self-reported experiences of trauma during childhood and adolescence were retrospectively assessed using the 28 - item Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). The CTQ is a Likert scale questionnaire that assesses five subtypes of abuse (emotional, physical, and sexual) and/or neglect (emotional and physical) that may have occurred between the ages of 0 - 18 years (Bernstein et al., 2003). The items on each subscale range from '1′ ('never true') to '5′ ('very often true'). We rescaled the first scoring option '1′ ('never true') to reflect the 'absence' of scores, and thus, responses ranged from '0′ ('never true') to '4′ ('very often true'). Therefore, scores summarised across all five subscales provide a total score ranging from '0 – 100′ instead of '25 – 125′, with higher scores indicating more severe traumatic experiences (Bernstein et al., 2003). The validated CTQ-manual cut-off scores (rescaled) were used to rate the presence and severity of abuse and neglect as either none, low, moderate or severe (Bernstein et al., 2003). Severity for each subscale was calculated individually using the thresholds in the manual and adapted for the rescaled scores. Furthermore, we also added the total and subtype CTQ scores using the original '1 - 7′ scaling system to allow for easier comparison with existing and future literature (please see details in Supplementary Material).

Participants were dichotomized into the groups of either 'high levels of trauma' or 'none-low levels of trauma'. High levels of trauma were defined as the presence of moderate or severe abuse with or without moderate or severe neglect. In contrast, none or low levels of trauma was defined when participants met the criteria for none or low levels across each of the five CTQ subscales or had a single case of moderate or severe neglect (Table 1). The justification for using the dichotomized scores lies in the lack of evidence of the effect of childhood trauma severity on brain structure and function, including the general population (Teicher et al., 2022) and individuals with schizophrenia (Dauvermann et al., 2021) although it has been suggested that more severe childhood trauma levels may be associated with greater clinical symptomatology in people with psychotic disorders (Quidé et al., 2020). Simultaneously, milder severity levels may be more prevalent in individuals without mental health problems (Church et al., 2017). Please see supplemental material for details for an overview of total CTQ and subtype scores for HC and SZ, including scores with the '1 - 7′ scaling system (Supplemental Table 2) and trauma severity categorization across each of the five CTQ subtypes (Supplemental Table 3).

Table 1
Demographic and clinical characteristics of all participants stratified by study group and trauma severity ($n = 166$).

Demographic and Clinical Characteristics	Study groups		Statistical comparison Between Groups ($U/\chi 2$, p-value)	Severity Categorisation of trauma severity		Statistical comparison Between Groups ($U/\chi 2$, p-value)
	Healthy Controls	Individuals with schizophrenia		None/Low	High	
Sample Size, *n*	129	37		118	48	
Age (years), Mean ± SD	34±11	44.0 ± 11	$U = 1248.5$, $p < 0.001$*	35±11	39±14	$U = 2379.5$, $p = 0.11$
Sex, Female (*n*,%)/Males (*n*,%)	70 (54.3%) / 59 (45.7%)	26 (70.3%) / 11 (29.7%)	χ^2=3.02, $p = 0.08$	73 (61.9%) / 45 (38.1%)	23 (47.9%) / 25 (52.1%)	χ^2=2.72, $p = 0.10$
Handedness, Right (*n*, %)/Left (*n*,%)	122 (94.6%) / 7 (5.4%)	35 (94.6%) / 2 (5.4%)	χ^2=0.58, $p = 0.75$	111 (94.1%) / 7 (5.9%)	46 (95.8%) / 2 (4.2%)	χ^2=1.05, $p = 0.59$
Years of Education (years), Mean ± SD#	16.8 ± 4.1	13.8 ± 4.4	$U = 977.5$, $p = 0.00003$*	16.0 ± 4.3	16.8 ± 4.3	$U = 2065.0$, $p = 0.18$
CTQ total (0–100), Mean ± SD	11.53±12.02	18.05±14.6	$U = 1516.0$, $p = 0.001$*	7.07±5.78	27.5 ± 14.0	$U = 402.0$, $p = 4.52 \times 10^{-18}$*
Emotional Abuse (0–20), Mean ± SD	3.47±4.20	5.22±4.81	$U = 1778.0$, $p = 0.02$*	2.0 ± 2.04	8.44±5.21	$U = 718.0$, $p = 2.77 \times 10^{-14}$*
Physical Abuse (0–20), Mean ± SD	1.43±2.29	2.81±4.37	$U = 1962.0$, $p = 0.08$	0.73±1.16	4.23±4.22	$U = 1086.0$, $p = 2.96 \times 10^{-11}$*
Sexual Abuse (0–20), Mean ± SD	0.96±2.95	1.70±4.44	$U = 2319.5$, $p = 0.69$	0.09±0.43	3.69±5.41	$U = 1557.5$, $p = 6.85 \times 10^{-12}$*
Emotional Neglect (0–20), Mean ± SD	1.54±2.64	3.08±3.39	$U = 1609.5$, $p = 0.002$*	3.46±3.58	7.35±5.02	$U = 1459.0$, $p = 8.46 \times 10^{-7}$*
Physical Neglect (0 - 20), Mean ± SD	0.63±0.94	0.51±0.93	$U = 1483.0$, $p = 0.002$*	1.08±1.74	3.85±4.02	$U = 1552.5$, $p = 1.0 \times 10^{-6}$*
HAM-D (0 - 17), Mean ± SD#	3.0 ± 3.61	4.06±4.26	$U = 1262.5$, $p = 0.20$	4.25±4.58	3.73±3.80	$U = 1505.5$, $p = 0.32$
Duration of illness (years) #	–	19±11	–	16±9.10	23±12.70	$U = 59.0$, $p = 0.15$
PANSS, Positive (7 - 49), Mean ± SD#	–	8.44±2.20	–	7.85±1.53	9.64±2.8	$U = 86.0$, $p = 0.25$
PANSS, Negative (7 - 49), Mean ± SD#	–	9.84±4.10	–	9.85±4.15	10.09±4.21	$U = 106.0$, $p = 0.73$
PANSS, Total (30 - 210), Mean ± SD#	–	38.78±9.16	–	37.75±7.38	40.8 ± 12.24	$U = 103.5$, $p = 0.64$
CPZ equivalents, Mean ± SD#	–	517.3 ± 357.9	–	438.6 ± 326.1	643.4 ± 387.1	$U = 52.0$, $p = 0.15$

	Categorisation of trauma severity across study groups				Statistical comparison between groups ($H/\chi 2$, p-value)
	Healthy Control: None/Low	Healthy Control: High	Schizophrenia: None/ Low	Schizophrenia: High	
Sample Size, *n*	94	35	24	13	
Age (years), Mean ± SD	33±11	36±13	42±9	47±14	$H(3)$=21.18, $p = 0.00009$*
Sex, Males/ Female (*n*,%)	55 (58.5%) / 39 (41.5%)	15 (42.9%) / 20 (57.1%)	18 (75.0%) / 6 (25.0%)	8 (61.5%) / 5 (38.4%)	X^2=6.21, $p = 0.10$
Handedness, Right/Left (*n*,%)	89 (94.6%) / 5 (5.4%)	33 (94.3%) / 2 (5.7%)	22 (91.7%) / 2 (8.3%)	13 (100%) / 0 (0%)	X^2=2.70, $p = 0.84$
Years of Education (years), Mean ± SD	16.4 ± 4.4	17.9 ± 3.17	14.1 ± 3.8	13.1 ± 5.5	$H(3)$=20.4, $p = 0.0001$*
CTQ total-RS (0 - 100), Mean ± SD	6.18±5.5	25.89±13.12	10.54±5.83	31.9 ± 15.83	$H(3)$=82.55, $p = 8.72 \times 10^{-18}$*
Emotional Abuse (0 - 20), Mean ± SD	1.73±1.84	8.14±5.12	3.04±2.44	9.23±5.58	$H = 62.11$, $p = 2.08 \times 10^{-13}$*
Physical Abuse (0 - 20), Mean ± SD	0.67±1.08	3.49±3.25	0.96±1.43	6.23±5.82	$H = 46.52$, $p = 4.39 \times 10^{-10}$*
Sexual Abuse (0 - 20), Mean ± SD	0.09±0.44	3.31±4.94	0.08±0.41	4.69±6.63	$H = 47.10$, $p = 3.33 \times 10^{-10}$*
Emotional Neglect (0 - 20), Mean ± SD	2.81±3.08	7.54±5.13	6.0 ± 4.30	6.85±4.86	$H = 35.69$, $p = 8.71 \times 10^{-8}$*
Physical Neglect (0 - 20), Mean ± SD	0.85±4	3.40±3.87	2.0 ± 2.17	5.08±4.33	$H = 35.36$, $p = 1.02 \times 10^{-7}$*

Demographic and clinical characteristics presented for all participants and stratified according to either study groups (HC or SZ), severity level of trauma independent of diagnosis (high levels of trauma or none/low levels of trauma) resulting in the following groups: (i) HC; (ii) SZ; (iii) none/low levels of trauma; (iv) high level of trauma; (v) HC with none/low levels of trauma; (vi) HC with high levels of trauma; (vii) SZ none/low levels of trauma; (viii) SZ high levels of trauma.
Abbreviations. CTQ, Childhood Trauma Questionnaire; HC, healthy controls; SD, standard deviation; SZ, individuals with schizophrenia.

2.3. Magnetic resonance imaging data acquisition and analyses

Diffusion-weighted MR images (DWI) were acquired for all participants at the Wellcome Trust Health Research Board National Centre for Advanced Medical Imaging (CAMI) at St. James's Hospital Dublin, Ireland, using a 3.0 Tesla Achieva scanner (Philips Medical Systems, Best, The Netherlands). DWI was acquired using a SE-EPI sequence with a 32-direction Stejskal-Tanner diffusion encoding scheme. Please see Supplementary Material for image acquisition parameters and DWI processing details. At this stage, ten individuals were removed from all subsequent analyses (four HC and six SZ).

2.3.1. Tract-based spatial statistics

TBSS was performed to assess group differences in FA within deep WM voxels (FSL v6.0.1; Smith et al., 2006). Firstly, all native FA maps were nonlinearly registered to $1 \times 1 \times 1$ mm ^{3} MNI152 template, which resulted in a standard space version of each FA image. Following this, the FA maps were individually registered to a subject-specific target to

create a 'mean FA' map which was subsequently 'thinned' to create a WM' skeleton' image which represented the centre of all deep WM voxels common to all subjects (i.e., the highest local FA value perpendicular to each voxel of the skeleton was projected onto the WM skeleton). A FA value of 0.2 was used to threshold the WM skeleton to exclude voxels containing grey-matter, CSF, and peripheral WM tracts on the edges of the cortex where significant inter-subject variability exists (Bach et al., 2014). Manual visual inspection was carried out at each step in the processing pipeline according to an established quality control protocol to check for alignment and registration inaccuracies, which resulted in the removal of thirty-two individuals from all subsequent analyses (17 HC and 15 SZ).

2.4. Statistical analyses

Non-voxel-wise analysis was conducted to examine differences across clinical and demographic variables (age, sex, handedness, years of education, CTQ scores). Specifically, a Mann-Whitney *U* tested for group differences across continuous variables was run, whilst a Chi-square test was used to test for group differences with categorical variables. A two-tailed significance level of $p < 0.05$ denotes significance in all statistical analyses undertaken (SPSS v25).

Between-group comparisons in FA within deep WM voxels across the whole-brain were tested using a general linear model (GLM) in FSL randomise tool (Winkler et al., 2014). The GLM was designed as a Multivariate Analysis of Covariance (MANCOVA) covarying for age and sex to test three main contrasts. The first contrast examined the main effect of diagnosis on FA. The second contrast examined the main effect of trauma severity, i.e., whether high levels of CT would be associated with reductions in FA compared to those with none/low levels of trauma in both SZ and HC. The third contrast, the interaction between trauma severity and a diagnosis of schizophrenia, was run to test the hypothesis that reductions in FA would be greatest in SZ with high levels of trauma relative to HC with high levels of CT and unexposed SZ and HC. These analyses were performed separately for both the dichotomized and continuous CTQ scores.

Voxel-wise statistics were computed using permutation-based analysis (5000 iterations), and the results were thresholded using threshold-free cluster enhancement (TFCE) and *p* FWE-corrected <0.05. Results were visualised using fslview (FSL v6.0.1) (Jenkinson et al., 2012) and the John Hopkins University (JHU) ICBM_DTI_81 WM labels atlas was used for stereotactic reporting of anatomical regions (Mori et al., 2008). FA was extracted from significant clusters of masked voxels using the *fslmeants* cluster tool (FSL v6.0.1) (Jenkinson et al., 2012).

3. Results

3.1. Clinical and demographic characteristics

Thirty-seven individuals with a current diagnosis of established schizophrenia ($n = 30$) or schizoaffective disorder ($n = 7$) and 129 HC were included in this study (Table 1). SZ and HC differed in age but were matched for sex and handedness. All included SZ were taking atypical antipsychotic medication and were clinically stable at the time of assessment with mild positive and negative symptoms.

The number of participants meeting the criteria for moderate or severe trauma across each of the five CTQ subtypes was as follows: emotional abuse (HC = 20, SZ = 8), physical abuse (HC = 12, SZ = 6), sexual abuse (HC = 16, SZ = 6), emotional neglect (HC = 12, SZ = 2), physical neglect (HC = 10, SZ = 7). Forty-eight participants were classified as having experienced high levels of trauma, while 118 participants were classified as having none/low levels of trauma. Individuals with and without reported experiences of trauma were matched for age, sex, and handedness ($p > 0.05$, Table 1). Non-parametric Mann-Whitney *U* demonstrated no sex or age differences in the severity of CT although we found a significant difference in total CTQ scores between none/low and moderate/high trauma groups ($p > 0.05$, Table 1).

The categorization of CT severity for the groups was balanced across each of the five CTQ subscales as follows emotional abuse ($\chi^2 = 0.70$, $p = 0.28$), physical abuse ($\chi^2 = 1.42$, $p = 0.23$), sexual abuse ($\chi^2 = 0.36$, $p = 0.55$), emotional neglect ($\chi^2 = 0.56$, $p = 0.45$), physical neglect ($\chi^2 = 3.90$, $p = 0.05$). Furthermore, across the four groups, no significant differences were detected across either sex, handedness, or clinical variables ($p > 0.05$, Table 1). However, there was a significant difference in age between the four groups, with SZ being older than HC (ten years older on average; ($p < 0.05$, Table 1).

3.2. Voxel-wise statistical analysis of white matter microstructure (TBSS)

3.2.1. Fractional anisotropy

After accounting for age and sex, the voxel-wise TBSS analyses revealed two clusters of lower FA in SZ compared to HC (Fig. 1, Supplemental Table 4), which encompassed the genu and body of the corpus callosum as well as the left anterior, superior, and posterior corona radiata ($p < 0.05$, TFCE).

Irrespective of diagnosis, group comparisons of voxel-wise differences in FA identified one significant cluster of lower FA in the group with high levels of trauma relative to the group with none/low levels of trauma. In the group with high levels of CT, we observed a significant group difference in deep WM voxels in a cluster involving the genu, body, and splenium of the corpus callosum, fornix, bilateral anterior, superior, and posterior corona radiata, anterior, posterior and retrolenticular limb of the internal capsule, cingulum (hippocampal part), superior longitudinal fasciculus, external capsule, posterior thalamic radiation, tapetum, left cerebral peduncle, and the right sagittal stratum (Fig. 2, Supplemental Table 5). We detected no statistically significant clusters of increased FA in either of the trauma groups ($p > 0.05$, TFCE).

When examining the interaction between CT and diagnosis, no significant increases or decreases in FA within deep WM voxels was observed across SZ with high levels of CT, HC with high levels of trauma, nor SZ or HC reporting none/low levels of exposure ($p > 0.05$, TFCE, Fig. 2C).

While our main analyses were based on treating CTQ scores as a categorical variable, we confirm that when the analyses were repeated using participants' total CTQ scores as a continuous variable, the results did not differ across either the 1) main effect of diagnosis, 2) main effect of trauma or 3) the interaction between diagnosis and trauma.

4. Discussion

This study examined whether and how occurrence and higher severity of CT were associated with WM microstructural alterations in SZ relative to HC. We reported WM reductions in the corpus callosum and corona radiata in SZ compared to HC. Across all participants, we observed that high levels of CT were associated with widespread reductions in WM microstructural organization involving late developing regions interconnecting frontolimbic and frontoparietal pathways. In contrast to previous studies, however, exposure to CT was not specifically associated with any of the observed microstructural differences in SZ relative to the HC group.

SZ showed reductions in FA within a WM cluster involving the corpus callosum (body, genu, and splenium) and corona radiata (anterior, superior, and posterior) compared to HC. These findings are in keeping with prior research demonstrating dysfunctional communication between interhemispheric and medial frontal regions in the pathophysiology of schizophrenia (Ellison-Wright and Bullmore, 2009; Kelly et al., 2018; Keshavan et al., 2020). In contrast, we observed fewer differences in FA in SZ relative to HC, such as microstructural reductions in the fornix, cingulum bundle, superior longitudinal fasciculus, uncinate fasciculus and the anterior limb of the internal capsule. Such discrepancies may partly reflect the heterogeneous clinical presentation of SZ between studies as well as the role of genetics or differences in analytical

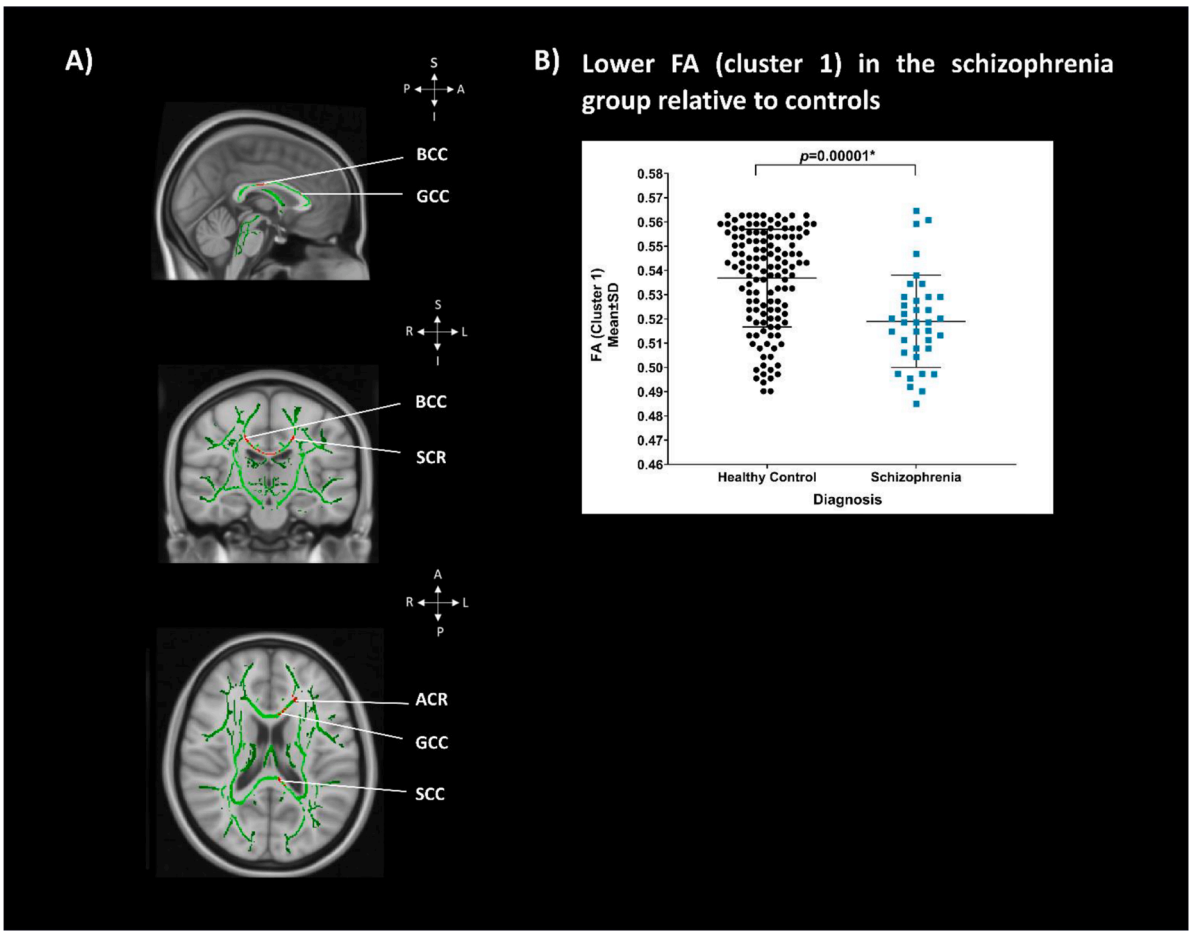

Fig. 1. Between-group differences in fractional anisotropy. A) Significant differences in FA between SZ relative to HC in a cluster encompassing the GCC, BCC, left ACR, SCR, and PCR ($p < 0.05$, cluster 1, TFCE). Significance denoted in a red ($p = 0.05$) to yellow (lowest p-value) colour intensity scale ($x = 90$, $y = 108$, $z = 90$). **B)** Scatterplot shows extracted FA values from significant cluster 1 (A) plotted across both HC and SZ. Significance of post-hoc group differences between the extracted FA cluster and the study groups ($p < 0.05$, MANCOVA). Error bars represent mean and standard deviation and the 95% confidence intervals for all groups. **Abbreviations.** ACR, anterior corona radiata; BCC**,** body of the corpus callosum; FA, fractional anisotropy; GCC, genu of the corpus callosum; HC, healthy controls; PCR, posterior corona radiata; SCR, superior corona radiata; SZ, individuals with schizophrenia; TFCE, threshold-free cluster enhancement.

techniques used (van Os and Kapur, 2009).

In addition, we found that high levels of CT were associated with reductions in WM microstructure, particularly in voxels encompassing stress-sensitive interhemispheric, frontoparietal and frontolimbic regions, across both SZ and HC groups. These findings are consistent with a significant body of work displaying the effects of CT on the cytoarchitecture of WM in other neuropsychiatric conditions as well as non-clinical populations with a history of CT (Lim et al., 2020; Teicher et al., 2016). Moreover, previous findings from our research group suggest that the experience of CT is associated with brain changes across different modalities in both SZ and HC. For example, we observed that increased CT scores were significantly related to reduced functional connectivity during resting-state functional MRI between prefrontal and parietal regions across all participants, which also mediated emotion recognition performance (Dauvermann et al., 2021). Furthermore, we found reduced functional connectivity across networks during working memory, which was significantly associated with increased CT levels in both HC and SZ (Dauvermann et al., 2019). Here, we extend these findings by demonstrating an association between high levels of CT and microstructural reductions in overlapping frontolimbic and frontoparietal regions. Collectively, these findings suggest that high CT severity may confer microstructural reductions in the integrated network of anatomical regions underpinning processes of emotional reactivity, emotion regulation and working memory irrespective of diagnosis (Cancel et al., 2019; Etkin et al., 2015). These findings raise questions that neuroanatomical differences may reflect adaptive or compensatory brain changes that enable individuals to build resilience by maintaining mental well-being and cognitive functioning (Dazzan, 2018; Roeckner et al., 2021). Future research should aim to explore these hypotheses by examining the mediating and moderating roles of various biological and psychosocial markers of risk and resilience after the experience of CT on brain markers longitudinally.

We did not observe a trauma level by diagnosis effect, which is inconsistent with our hypothesis. The contrasting findings compared to previous studies may be due to differences in clinical characteristics in our cohort of SZ and methodological details. SZ in this study were clinically stable and had a comparably long duration of illness (mean = 19 years). Furthermore, previous studies examined childhood adversity in contrast to CT, which encompass additional stressful and traumatic events to CT and may reflect a different stress exposure (Poletti et al., 2015), assessed the occurrence of CT but not severity levels (Molina et al., 2018b; Poletti et al., 2015) or included FES but not SZ (Asmal et al., 2019; Molina et al., 2018b). We speculate that the association between CT exposure, high severity level of CT and WM alterations in schizophrenia may be more pronounced in the earlier stages than later stages of the disorder. Alternatively, we suggest that we did not detect microstructural differences in regions of the SLF, ILF, and IFOF due to the protracted developmental trajectory of these long-range association pathways (Dubois et al., 2014; Lebel and Beaulieu, 2011), and variations in developmental timing alongside the severity and frequency of CT

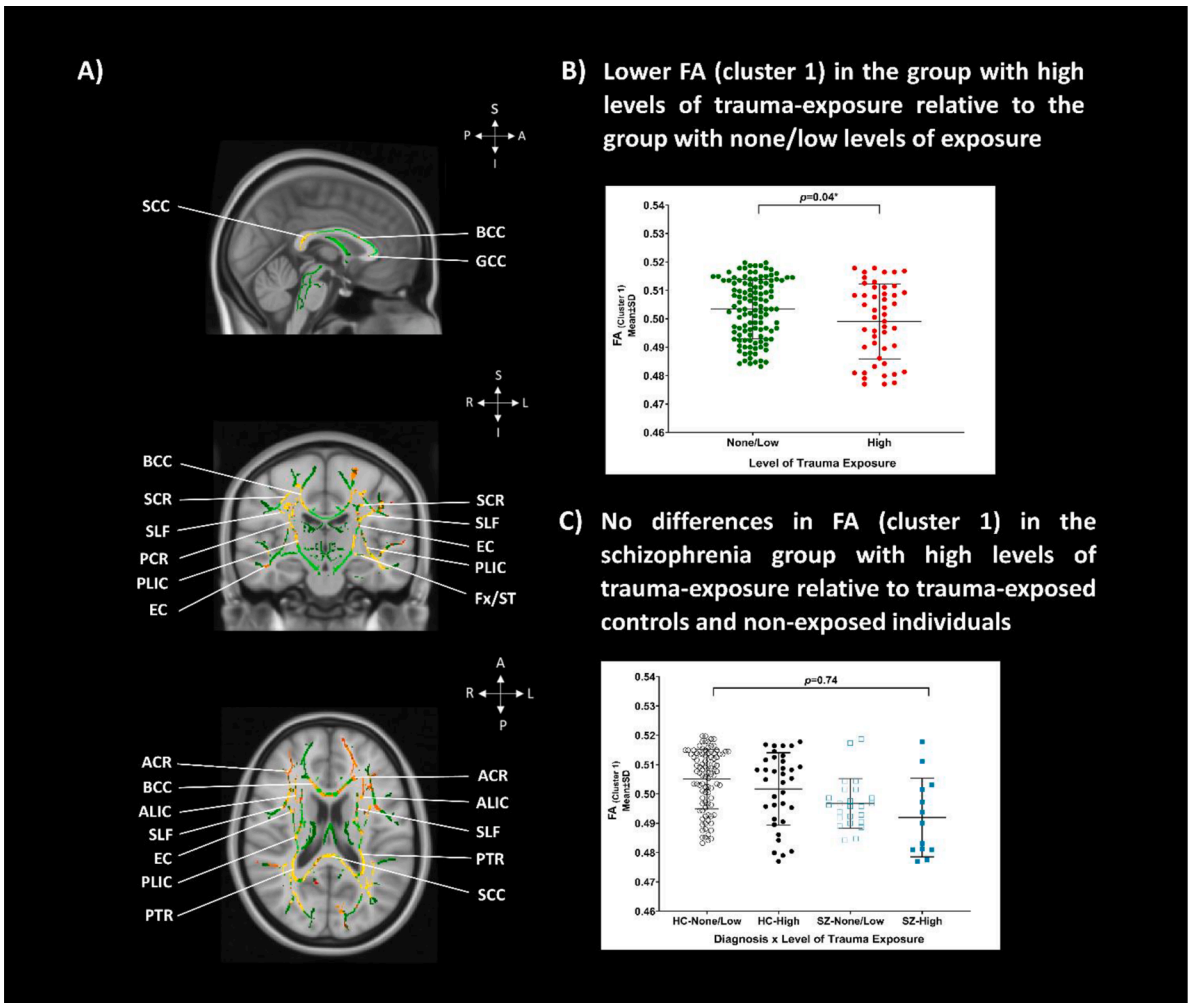

Fig. 2. Associations between high levels of trauma and lower fractional anisotropy in frontolimbic regions (cluster 1). A) Across all participants, significant association between high levels relative to none/low levels of trauma with significant differences in FA in a cluster of regions involving the GCC, SCC, BCC, PCR, RLIC, PTR, and SLP ($p < 0.05$, TFCE). Significant differences in FA are denoted in a red ($p = 0.05$) to yellow (lowest p-value) colour intensity scale ($x = 90$, $y = 108$, $z = 90$). **B)** Scatterplot illustrates differences in FA between high levels relative to none/low levels of trauma with extracted FA values from significant cluster 1 (A) ($p < 0.05$, cluster 1, TFCE) for visualisation purposes. **C)** A separate diagnosis x trauma contrast was not significant ($p > 0.05$, TFCE). The FA values plotted in Figure C (cluster 1) are plotted across the four groups for visualisation purposes. All p values noted above the graphs B and C are the results of post-hoc analyses between the extracted FA cluster and the main effect of trauma (B, cluster 1, $p < 0.05$, MANCOVA) and the respective study group x trauma interaction (C, $p > 0.05$, MANCOVA). Error bars represent mean and standard deviation and the 95% confidence intervals for all groups ($p < 0.05$).

Abbreviations. BCC, body of the corpus callosum; FA, fractional anisotropy; GCC, genu of the corpus callosum; HC, healthy controls; PCR, posterior corona radiata; PTR, posterior thalamic radiation; RLIC, retrolenticular limb of the internal capsule; SCC, splenium of the corpus callosum; SCR, superior corona radiata; SLF, superior longitudinal fasciculus; SZ, individuals with schizophrenia; TFCE, threshold-free cluster enhancement; WM, white matter.

(Croft et al., 2019; Fisher et al., 2010). Taken together, we propose that the association between CT history, CT severity and WM differences in SZ is more likely to be underpinned by multifactorial effects than a singular factor (see McCarthy-Jones *et al.* 2018), despite observed WM reductions in individuals with high levels of CT independent of a diagnosis. Future studies should aim to replicate these findings and incorporate more complex vulnerability and neurobiological models, such as stress and immune response models (Quidé et al., 2020).

This study has notable strengths, including the use of an unbiased voxel-based approach combined with a subject-specific template registration to improve the anatomical specificity of the findings (Bach et al., 2014; Keihaninejad et al., 2012). However, several limitations of this study must also be acknowledged. Firstly, the relatively small cohort of trauma-exposed SZ with high CT levels may have been underpowered to detect subtle group differences. Secondly, the assessment of CT is retrospective and based on self-report, which may have introduced the possibility of recall bias (Baldwin et al., 2019). However, we opted for the CTQ in this study as it is the most widely used assessment for CT, allowing for comparability across studies. Thirdly, while there was no evidence for an association between age or duration of illness in this study, we cannot rule out the possibility that some of the findings may have been confounded by age-related effects due to the broad age range of our cohort (between 18 - 65 years). Fourthly, acknowledge limitations in the use of a trauma dichotomous measure across both abuse and neglect experiences as it may be an oversimplification of a multidimensional construct, which may be associated with a loss of information about individual differences (Altman and Royston, 2006). Therefore, we repeated our analyses with the continuous scores as previously suggested (Fassler et al., 2005), which resulted in the same findings. Lastly, FA is a highly sensitive but nonspecific indicator of cellular differences at the tissue level (Assaf et al., 2019; Beaulieu, 2002). Traditional tensor metrics may reflect a weighted average of both cellular and extracellular processes, thus obscuring the true measure of FA present in the tissue (Beaulieu, 2014). Future studies might benefit from the application of free water modelling approaches to derive free-water corrected measures of FA at a cellular level (Pasternak et al., 2009).

In conclusion, we observed that high levels of CT were associated with widespread reductions in FA within WM regions interconnecting later developing frontolimbic and frontoparietal pathways across both SZ and HC. We speculate that the effects of CT on WM microstructure may reflect compensatory or adaptive mechanisms, which require future research. Longitudinal studies may consider examining a multifactorial vulnerability and neurobiological model to increase insight into the role of CT on brain alterations in schizophrenia.

CRediT authorship contribution statement

Conceptualization and study design (MRD, LC, GD, DMC), acquisition of data (MRD, LC, LH, DM, KIR, RK, BH), analysis of the data (MRD, LC, GT, LH, KIR), interpretation of the work (MRD, LC, GD, DMC), writing the manuscript (MRD, LC, DCM) or revising the manuscript (all authors), final approval of the work (all authors), and agreement to be accountable for the work (all authors).

Declaration of Competing Interest

The authors report no biomedical financial interests or potential conflicts of interest.

Acknowledgements

This work was supported by the European Research Council (ERC/2015-STG-677467 to G.D.); and by Science Foundation Ireland (SFI-16/ERCS/3787 to G.D.). We are grateful to the Irish Research Council PhD Scholarship for funding L.C. We thank all participants who participated in both studies. We would also like to thank Michael Gill, Caroline Cullen, Niamh Daly Ryan, Laura McHugh, Ainé McNicholas, Marta Grzywacz, Cathal Ó Curraoin, Catherine O'Donoghue and Angela Ambrosio.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2023.111616.

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