Changes in Default-Mode Network Associated with Childhood Trauma in Schizophrenia

Short Title: Childhood trauma and default-mode network in schizophrenia

MR Dauvermann[1,2], D Mothersill[3,1], KI Rokita[1], S King[1], L Holleran[1], R Kane[1], DP McKernan[4], JP Kelly[4], DW Morris[1,5], A Corvin[6], B Hallahan[1,7], C McDonald[1,7], G Donohoe[1]

[1] Centre for Neuroimaging, Cognition & Genomics (NICOG), School of Psychology, National University of Ireland Galway, Ireland
[2] McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, USA
[3] Dept of Psychology, National College of Ireland, Dublin, Ireland
[4] Pharmacology & Therapeutics, National University of Ireland Galway, Ireland
[5] School of Natural Sciences, National University of Ireland Galway, Ireland
[6] Department of Psychiatry, Trinity Centre for Health Sciences, St. James's Hospital, Dublin, Ireland
[7] Department of Psychiatry, Clinical Science Institute, National University of Ireland Galway, Ireland

*Corresponding author:

Prof. Gary Donohoe

Centre for Neuroimaging and Cognitive Genomics (NICOG)

School of Psychology

National University of Ireland Galway

University Road, Galway, Ireland

gary.donohoe@nuigalway.ie

Tel. +353 (0)91 495 122

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Abbreviation list

ACC	Anterior Cingulate Cortex
BOLD	Blood oxygen level-dependent
CSF	Cerebral spinal fluid
CT	Childhood trauma
CTQ	Childhood Trauma Questionnaire
DMN	Default-mode network
DSM-IV	Diagnostic Statistical Manual - IV
EPI	Echo planar imaging
fMRI	Functional Magnetic Resonance Imaging
GM	Grey matter
IPL	Intraparietal lobe
LP	Lateral Parietal Lobe
MDD	Major depressive disorder
MRI	Magnetic Resonance Imaging
PANSS	Positive and Negative Syndrome Scale
PCC	Posterior Cingulate Cortex
PFC	Prefrontal Cortex
PTSD	Posttraumatic stress disorder
Eyes task	Reading the Mind in the Eyes
rs-fMRI	Resting-state fMRI
CANTAB SWM	CANTAB Spatial working memory
SD	Standard deviation
SZ	Schizophrenia
SZA	Schizo-affective disorder
ToM	Theory of Mind
WAIS	Wechsler Adult Scale of Intelligence
WM	White matter

Abstract

Background

There is considerable evidence of dysconnectivity within the default-mode network (DMN) in schizophrenia, as measured during resting-state functional MRI (rs-fMRI). History of childhood trauma (CT) is observed at a higher frequency in schizophrenia than in the general population, but its relationship to DMN functional connectivity has yet to be investigated.

Methods

CT history and rs-fMRI data were collected in 65 individuals with schizophrenia and 132 healthy controls. Seed-based functional connectivity between each of four *a priori* defined seeds of the DMN (medial prefrontal cortex, right and left lateral parietal lobes, and the posterior cingulate cortex) and all other voxels of the brain were compared across groups. Effects of CT on functional connectivity were examined using multiple regression analyses. Where significant associations were observed, regression analyses were further used to determine whether variance in behavioral measures of Theory of Mind (ToM), previously associated with DMN recruitment, were explained by these associations.

Results

Seed-based analyses revealed evidence of widespread reductions in functional connectivity in patients versus controls, including between the left/right parietal lobe (LP) and multiple other regions, including the parietal operculum bilaterally. Across all subjects, increased CT scores were associated with reduced prefrontal-parietal connectivity and, in patients, with increased prefrontal-cerebellar connectivity also. These CT-associated differences in DMN connectivity also predicted variation in behavioral measures of ToM.

Conclusions

These findings suggest that CT history is associated with variation in DMN connectivity during rs-fMRI in patients with schizophrenia and healthy participants, which may partly mediate associations observed between early life adversity and cognitive performance.

Introduction

It is well established that individuals with schizophrenia (SZ) show aberrant resting-state functional connectivity (i.e. temporal correlations between different brain regions) across several large-scale functional networks, including the default-mode network (DMN) (1–3). The DMN is a functional network of interconnected regional brain activity observable both when the brain is at rest (4–6) and during internally orientated processes, such as self-reflection (7,8). In schizophrenia, dysconnectivity involving the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), thalamus and the cerebellum has repeatedly been observed during resting-state functional Magnetic Resonance Imaging (rs-fMRI) (6,9,10). However, inconsistent findings of both hyper- and hypoconnectivity between key regions of the DMN have also been reported (3,9,11–13), which may relate to differences in acquisition parameters and illness heterogeneity (9).

Although potential genetic causes of DMN functional dysconnectivity have received attention (23), the impact of childhood trauma (CT) on DMN in schizophrenia has not, despite its well-established association with schizophrenia - whether as a causal risk factor (24–28) or a moderating factor (29–34). CT includes experience of physical abuse, physical neglect, emotional abuse, emotional neglect and sexual abuse (35). The neural effects of CT have been widely studied using structural and functional MRI in the general population (15,30,36–43), in patients with major depressive disorder (MDD) (44,45) and posttraumatic stress disorder (PTSD) (46–48), but are only beginning to receive attention in schizophrenia. Across studies of the general population, MDD and PTSD, evidence of DMN dysconnectivity during rs-fMRI following CT has been widely reported (15,30,36,49–51), suggesting reduced connectivity of the DMN.

In schizophrenia, evidence of neural effects of CT is supported by a range of structural and functional imaging studies. Structural imaging studies showed that CT leads to reduced total cerebral grey matter (GM) volumes, including the dorsolateral prefrontal cortex (DLPFC) (52,53) as well as changes in white matter (WM) integrity in the inferior and superior longitudinal fasciculus among other regions (31,53). Recent fMRI studies of SZ and childhood trauma reported increased blood oxygenated level–dependent (BOLD) responses in cortical regions overlapping with the DMN during cognitive task performance. Specifically, increased activity of the left intra-parietal lobule (IPL) during a working memory task (54) and increased activation of the PCC/precuneus during a ToM task were both positively associated with CT (55). The same group (95) also reported that trauma exposure was associated with poorer behavioural performance when performing a ToM task offline, in the absence of other cognitive associations. In a study of negative vs. positive emotional material, Aas et al. (96) found evidence of increased trauma-related activation in the parietal lobe. Finally, Cancel et al. (56) observed decreased functional connectivity between the amygdala and the PCC/precuneus during an emotion processing task in SZ and a history of CT.

Whether or how DMN recruitment during rs-fMRI is associated with the experience of CT in schizophrenia has not yet been investigated. Myin-Germeys and Os (102) have previously hypothesized that stress exposure may increase SZ risk via either an affective or cognitive pathway to SZ. In terms of a cognitive pathway, we have recently presented evidence that CT exposure, is associated with poorer performance on measures of cognition and social cognition in Schizophrenia (97,98). We have interpreted this association as reflecting CT's moderation of other causal factors (e.g. genetic variation) associated with SZ risk and cognitive deficits. Greater deactivation of the DMN during rs-fMRI has been associated with better performance on measures of Theory of Mind (ToM) (16), the capacity to accurately infer the mental state of others (17,18). In schizophrenia, aberrant DMN recruitment have been associated with deficits

in ToM performance (11,18,19). ToM task performance deficits are widely reported in schizophrenia, and predictive of social and occupational function (20–22).

Here, we investigated the association between CT and DMN connectivity during rs-fMRI in SZ and healthy controls in a large sample. We based our analysis on four well-established regions of interest within the DMN, namely the mPFC, right lateral parietal lobe (LP), left LP and the PCC (3,6,57). Furthermore, we used seed-based functional connectivity analysis as one of the most robust techniques for measuring functional connectivity (2,3,9). Based on the literature reviewed above for both SZ and healthy participants with a history of CT, we formulated the following hypotheses: Firstly, that *both* SZ and controls with a history of CT will display comparable alterations in DMN functional connectivity during rs-fMRI. Secondly, following evidence of DMN dysconnectivity in SZ, that patients diagnosed with SZ who have a history of CT would show additional dysconnectivity within the DMN compared to controls with a history of CT. Additionally, we characterized the functional effects of CT-associated DMN connectivity on ToM task performance, expecting that any such association would have a negative impact on behavioral task performance.

2. Methods and Materials

2.1 Study participants

One hundred and eighty-nine participants took part in this study. Sixty-five individuals with SZ or schizoaffective disorder (SZA) were recruited in Galway and Dublin through community mental health services. All patients had a chronic illness history, a diagnosis of SZ or SZA confirmed using the Structured Clinical Interview for Diagnostic Statistical Manual-IV (58), and were clinically stable at the time of assessment in the opinion of their treatment team. Positive and Negative syndrome scale scores (PANSS; 58) and chlorpromazine equivalent (CPZ) scores, a measure for antipsychotic use in SZ, were available for n=41 of the 65 patients. The Hamilton Rating Scale for Depression (HDRS) (99) was used to measure severity of depressive symptoms, in both patients and controls. Further inclusion criteria for patients were that they would be aged between 18 and 65 years. Exclusion criteria included the presence of a documented history of neurological disorders (e.g., epilepsy), comorbid axis I mental health disorders, an estimated intelligence quotient (IQ) less than 70, a lifetime history of head injury causing loss of consciousness for more than one minute, evidence of substance use disorder within the past month, reported pregnancy or lactation, and contra-indication for MRI scanning (e.g., metal implants or claustrophobia).

In addition, 132 sex and age-matched healthy controls were recruited via local and national media advertising in the same regions of Galway and Dublin. Controls were included if in addition to the criteria for patients above, they met the criteria of having no documented lifetime personal history of axis I mental health disorder or substance use disorder in the last six months, or a first-degree relative with a psychotic disorder, or substance abuse in the last six months (based on self-report). Eight SZ and 16 controls were excluded due to either missing CT data (n = 6), missing rs-fMRI data (n = 5), excessive movement in the scanner (n = 3), or scanner artifacts (n = 9).

All participants provided written informed consent in accordance with the guidelines of the local Ethics Committees of the Galway University Hospitals, National University of Ireland Galway and Tallaght Hospital.

2.2 Data collection

2.2.1 Childhood trauma

CT was retrospectively assessed using the Childhood Trauma Questionnaire (CTQ) – Short Form (35), a widely-used self-report questionnaire comprising five subscales of physical abuse, physical neglect, emotional abuse, emotional neglect and sexual abuse. Each subscale includes five items, and individuals are requested to answer whether they had experienced the event on a Likert scale ranging from '1' for 'never true' to '5' for 'very often true'. Please see the supplemental information for details. Following on our earlier behaviour study (98), both to Total CTQ scores and physical neglect CTQ scores - employed as continuous variables - were used to index childhood trauma in this study.

2.2.2 Neuropsychological assessment

The Reading the Mind in the Eyes task (Eyes task) was used to measure ToM performance (61). This task required participants to recognize complex emotional expressions on the basis of information that is provided by the eye region of adult faces. More specifically, this Eyes Task evaluates the participants ability to infer emotions and mental states of others by asking them to identify emotional expressions by selecting labels that describe distinct emotional states. The abbreviated version of the Wechsler Adult Scale of Intelligence version III (WAIS – III) (62) was also used to provide an estimate of IQ. Please see the supplemental information for further details.

2.2.3 Neuroimaging data acquisition

Brain imaging was carried out on a 3 Tesla Philips Achieva MR system (Philips Medical Systems, Best, The Netherlands) equipped with gradient strength 80 mT/m and slew rate 200 T/m/s using an 8-channel receive-only head coil at the Centre for Advanced Medical Imaging, St. James's Hospital, Dublin, Ireland.

2.2.4.1 Structural Magnetic Resonance Imaging

A 3D Inversion Recovery prepared Spoiled Gradient Recalled echo (IR-SPGR) sequence was used to obtain high resolution T_1-weighted images of the brain, with: FOV = 256 x 256 x 160 mm^3, spatial resolution 1 mm^3, TR/TE = 8.5/3.9 ms, TI =1060 ms, flip angle = 8°, SENSE factor = 1.5, acquisition time = 7 min 30 s. In addition, T_2-weighted images were acquired using a turbo spin echo (TSE) sequence with turbo factor 15 and with: FOV = 230 x 184 x 149 mm^3, spatial resolution 0.57 x 0.72 x 4 mm^3, 30 slices with1 mm gap, TR/TE = 3000/80 ms, with no SENSE parallel imaging employed, acquisition time = 1 min 48 s.

2.2.4.2 Resting-state functional Magnetic Resonance Imaging

Rs-fMRI data was acquired using a SE-EPI sequence with a dynamic scan time of 2000 ms, with: FOV = 240 x 240 x 132 mm, spatial resolution = 3 x 3 x 3.2 mm, 38 slices with interslice gap = 0.3 mm, TR/TE = 2000 / 28 ms, SENSE factor = 2, with SPIR fat suppression and dynamic stabilization. In total, 210 volumes were acquired for the resting state experiment in an acquisition time of 7 min 12 s. Participants were instructed to keep their eyes open and fixated on a crosshair.

2.3 Neuroimaging data analysis

2.3.1 Pre-processing

Images were pre-processed in SPM12 (developed by theWellcome Department of Cognitive Neurology, Institute of Neurology, London, UK, http://www.filion.ucl.ac.uk/spm/software/spm12) running in Matlab (version 2016a). The first five EPI scans were discarded. EPI scans were pre-processed, including the following steps of head motion correction, slice-time correction, co-registration to native space of the structural data, segmentation and normalization to MNI space. Consistent with prior rs-fMRI studies in schizophrenia, no spatial smoothing was applied to the EPI scans (63).

To limit the effects of head motion, rs-fMRI scans underwent 'motion scrubbing'. Structural WM and cerebrospinal fluid (CSF) masks were used to create regressors as part of the anatomical component-based noise correction method (aCompCor) as implemented in CONN. This method has been shown to be effective at reducing the effects of head movement of functional estimates (64). Then, regressors corresponding to the six motion correction parameters and their first temporal derivatives (including GM, WM and CSF) were included to remove variance related to head motion with functional data band-pass filtered (.01 - .10 Hz). There was no significant difference in head motion between patients and controls ($T_{(171)} = 0.22$, $p = 0.828$).

2.3.2 Functional connectivity analysis

Seed-based functional connectivity was run in CONN-fMRI Functional Connectivity toolbox (57) (version 18a) to assess functional connectivity of four *a priori* seeds of the DMN, namely the medial PFC, right LP, left LP and PCC according to the Harvard-Oxford Cortical and Subcortical Atlas (http://www.cma.mgh.harvard.edu/fsl_atlas.html) as implemented in CONN (STable 1). Mean BOLD time series were extracted for each of the four seeds and entered as

predictors in a multiple regression general linear model to create functional connectivity maps. For statistical analyses in CONN, functional connectivity maps were entered into a one-sample t-test for the total sample and two-sample t-tests for patients and controls to examine functional connectivity of the DMN in the absence of CT data. Then, to test the individual effects of CT severity on functional connectivity of the DMN, a series of regression analyses was carried out for all participants, and for patients and controls separately. CT was entered as the independent variable. Individual functional connectivity coefficients for all significant seed-based findings were each, in turn, included as dependent variables indexing functional connectivity. Symptom severity (measured using PANSS total scores) was included as a covariate. Results were thresholded at $P_{FWE} < .05$ for both the cluster-level and height threshold to account for multiple comparisons (3; 57). Finally, a one-way ANCOVA was performed to statistically compare regression findings between patients and controls.

2.2.3 Statistical Analysis of demographic and cognitive variables

All statistical analyses were performed using Statistical Package for Social Sciences Version 25.0 (SPSS Inc., IBM, Chicago, IL). Group comparisons for age, sex, level of education, handedness, CT, IQ and the ToM task were assessed with two-tailed independent samples *t*-tests and Chi-square (χ^2) tests, where appropriate. To investigate the potential confounding influence of medication dosage in the SZ sample, a pearson correlation coefficient was used to assess the relationships between the CPZ measure and these variables of interest. No significant associations were observed and CPZ was therefore not included as a covariate in further analyses.

To investigate the mediating role of individual functional connectivity measures between CT and the Eyes Task, a moderated mediation analysis was carried out using PROCESS macro, model 59 (100). The outcome variable was the Eyes Task total score and the independent variables were CTQ total scores or CTQ physical neglect scores as a continuous variable.

Functional connectivity coefficients observed to be both a) significantly different between patients and controls and b significantly associated with CT were included as potential mediation variables and diagnosis (patient versus control) was included as a potential moderation.

3. Results

3.1 Demographic, clinical, environmental and neuropsychological data

Demographic, clinical, environmental and neuropsychological data are presented in Table 1. No significant differences between patients and controls were observed for either age (patients, mean = 43.61 years, standard deviation (SD) $\pm$ 11.51; controls, mean = 40.15 years, SD $\pm$ 11.27; $T_{(171)} = 1.889$, $p = .061$) or sex (patients, 22.5% male; controls, 41.6% male; $\chi^2 = .671$, $p = .413$).

For patients, PANSS total scores indicated a low level of current symptom severity (mean 38.66; SD $\pm$ 8.89), as expected for a clinically stable outpatient group. Patients reported higher total scores of CT (mean 42.44; SD $\pm$ 14.80) than controls (mean 36.23; SD $\pm$ 11.89) ($T_{(171)} = 2.97$, $p = .003$), and higher total scores of CT-physical neglect ($T_{(171)} = 2.868$, $p = .005$). HDRS total scores indicated that the entire sample had low a level of current depressive symptom severity score, with no significant difference between patients (mean 3.61; SD 3.88) and controls (mean 2.88; SD 3.64). In terms of CT, a significant positive relationship between the total CTQ score and both total PANSS scores (n=41, r = .345, $p < .027$) and total positive symptoms (n=41, r = .427, $p = .005$) was found. We did not observe any significant associations between CT and either PANSS negative (n=41, r = .221, $p = .154$) or general symptoms (n=41, r = .255, $p < .098$). As expected, patients performed worse on the social cognitive performance task, i.e., the Eyes Task (ToM measure), compared to controls ($T_{(170)} = -3.11$, $p = .002$)

Insert Table 1 here

3.2 Functional connectivity of the Default-mode network in patients and controls

Seed-based functional connectivity between each of the four DMN seed regions (medial PFC, right LP, left LP and the PCC) and the rest of the brain are shown for patients and controls in SuppFigure 1 (See supplemental information for details).

Comparisons between patients and controls showed no significant differences between groups for the medial PFC seed at the *a priori* defined statistical threshold of cluster-level $P_{FWE} < .05$ for both the cluster-level and height threshold. This is in keeping with findings of some systematic reviews and meta-analyses (65), but not others (2,12,64). We did, however, observe differences in functional connectivity of the DMN in patients versus controls between the left LP seed and the precuneus, right parietal operculum, right superior frontal gyrus, left postcentral gyrus and cerebellum (Figure 1 and Table 2), confirming previously reported findings (1,65,66,68). For the right LP seed, functional connectivity differences between patients and controls were also observed between the precuneus and the left parietal operculum. Finally, functional connectivity differences were also observed between the PCC seed and the brain stem in patients compared to controls.

Insert Figure 1

Insert Table 2

3.3 Functional connectivity of the DMN and childhood trauma

In regression analyses, higher total CT scores were associated with significantly reduced functional connectivity between the mPFC and the precuneus across the total participant sample ($r = -.342$, $p < .001$; $T_{(171)} = 3.14$, cluster-level $P_{FWE} < .05$ and $P_{FWE} < .05$ height threshold) (Figure 3 and Table 3). Higher CT scores were also associated with significantly decreased functional connectivity between the right LP and the precuneus across all participants ($r = -.358$, $p < .001$; $T_{(171)} = 3.14$, cluster-level $P_{FWE} < .05$ and $P_{FWE} < .05$ height threshold). No significant group difference (HC versus SZ) was observed following statistical comparison of regression analysis findings for CT severity at either the cluster-level or height threshold at $P_{FWE} < .05$.

Insert Figure 2

Insert Table 3

In addition, within patients, higher CT scores were also associated with significantly increased functional connectivity between the medial PFC and the cerebellum (r = .562, $p < .001$; $T_{(55)} = 3.25$, cluster-level $P_{FWE} < .05$ and $P_{FWE} < .05$ height threshold) (Figure 3 and Table 4). Re-running this analysis with PANSS total scores included as a covariate did not change the significance of this association. In contrast, no significant associations were found that were specific to the control group alone.

Insert Figure 3

Insert Table 4

3.4 CT-related functional connectivity of the DMN and cognitive task performance

Given that CT exposure was significantly associated with decreased connectivity, we tested whether CT associated connectivity coefficients mediated our previously reported behavioral finding of association between CT and theory of mind performance (98). The correlation coefficient for RLP-precuneus connectivity was used to index resting state connectivity in this analysis, on the basis that this variable showed evidence of both case control differences and an association with CTQ. Using PROCESS, a moderated mediation analysis was carried out in which CT was included as the independent variable, right LP/precuneus connectivity was included as the mediating variable, Eyes task performance was included as the dependent measure of theory of mind, and IQ was included as a covariate. In the full sample, the CT-DMN correlation coefficient for the right LP explained 5.7% of the variation in Eyes task performance ($F_{(1, 171)} = 10.296$, $p < .002$; 95% CI range based on 5000 boot strapped samples: -.0912 to -.0084). Diagnosis did not moderate this association (ß=−0.0709, SE=0.1414, 95%CI:−0.3459 to

0.2089). Re-running these analyses by using the physical neglect subscale to index CT (the CT variable most strongly correlated with social cognition in our behavioral study) and replacing IQ with educational attainment as the covariate did not change the significance of these findings. See Figure 4.

Insert Figure 4 here

4. Discussion

4.1 Summary of main findings

The aim of this study was to investigate the effects of CT on rs-fMRI DMN recruitment in SZ compared to healthy controls and explore the relevance of this relationship to cognitive performance. We found that *both* patients and controls with a history of CT displayed altered functional connectivity in the DMN. Specifically, we observed that higher CT scores were associated with *reduced* functional connectivity between the (i) medial PFC and PCC/precuneus and (ii) right LP and PCC/precuneus in both groups. In addition, in the patient group only, we found evidence that higher CT scores were associated with *increased* functional connectivity between the medial PFC and the cerebellum. These differences remained significant after controlling for clinical symptom severity. In contrast, no changes in DMN recruitment were observed that were specific to controls. Finally, reduced functional connectivity between the right LP and the precuneus were observed to partly mediate the relationship between CT and variation in ToM task performance.

4.2. Childhood trauma, functional connectivity and cognitive performance

These combined findings are consistent with our hypothesis that CT-related DMN dysconnectivity would be comparable between patients and controls. This is in keeping with literature reporting similar neural effects of CT on DMN connectivity during rs-fMRI in healthy participants (15,36) and in MDD and PTSD (30,49–51). For example, the association between CT and connectivity between the medial PFC and the precuneus is one of the most commonly reported findings in patients with MDD, PTSD and controls with CT experience (49). This connection is widely known to be affected by chronic stress (e.g. via the hypothalamic-pituitary-adrenal axis (69) and CT (70,71)) with known hormonal (30,52,72–74) and cytokine (75–77) alterations. While we are unable to draw any causal inferences, the evidence for largely comparable effects of CT on DMN connectivity in patients and controls makes it unlikely that

CT increases SZ risk via this neural pathway. Instead, the observed association between CT and DMN recruitment may serve to impact upon aspects of illness presentation (e.g. clinical and cognitive function) in those with pre-existing susceptibility. In this context, it is interesting to speculate about whether the SZ-group specific association – between the medial PFC and the cerebellum – may reflect an interaction between CT and illness risk given that this was only observed in patients. The significance of dysconnectivity between these regions has previously been highlighted in schizophrenia (78,79), including during working memory performance (80,81), but not as part of the stress circuit noted above.

Evidence of the functional significance of the association between CT and DMN connectivity derives in part from the associations observed with cognitive function. In a larger dataset of which the present sample represents a subset, we recently report that CT was associated with poorer social cognitive performance in both patients and healthy controls (98). In our mediation analysis, the correlation coefficient for RLP-precuneus connectivity was used to index resting state connectivity. This was on the basis that this variable showed evidence of both case-control differences and an association with CTQ. On this basis, the results of this study showed that changes in functional connectivity between the right LP and the precuneus partly mediated the relationship between CT and variation in ToM task performance across the whole sample. Regarding the direction of this association, CT-related DMN connectivity coefficients were associated with poorer task performance in both patients and healthy participants. Activation of both the mPFC and precuneus/PCC is widely reported during both ToM (11,16,18,31). As noted above, given that this association was observed across both patients and healthy participants, we do not interpret these associations as causal of cognitive deficits in schizophrenia. Instead, we interpret these associations as suggesting at least one cortical pathway by which childhood trauma may interact with causal effects associated with other environmental or biological factors (e.g. genetic vulnerability) on cognition.

4.3 Limitations and suggestions for further studies

The findings presented here should be considered in light of some limitations. Firstly, while the CTQ is widely used, the issues of recollection bias and subjectively in retrospective measures of CT are widely acknowledged, and factors including personality and temperament are known to play a role in what people remember. It is noteworthy, however, that recent studies comparing retrospective and prospective recall of CT found moderate correlations between these measures and that both explained a similar amount of variation in negative life outcomes (93). Furthermore, subjective reports of these experiences are noted to predict risk for psychopathology more strongly than objective measures (e.g. court reports; 94). Replicating these findings in samples for which prospective CT data is available will provide important confirmation of our observations. Similarly, it will also be important to examine the staging and length of CT exposure using measures sensitive to these factors (85)

Secondly, the associations between DMN dysconnectivity and CT scores may have been influenced by relatively high CT scores observed in the control group (41). This may reflect the recruitment strategy, whereby controls were attracted to participation in a CT study if they had personal experience of CT. By comparison, CTQ scores of patients in the study were comparable to those previously reported in SZ, as was performance on cognitive tasks used (86). CT scores were positively associated with positive but not negative symptoms; however, these findings were based on an analysis of only a subgroup of patients for whom PANSS data was available (n=41 of the total sample of 65 patients) and required replication in larger samples.

Thirdly, associations between CT exposure and aberrant DMN functional connectivity presented here were based on total CTQ scores and (for our ToM analyses) total physical neglect (PN) scores. Future studies will need to consider the impact of severity levels of CT (for example, low

versus high levels) and other individual CT subtype differences (for example, abuse versus neglect) (87), given the likelihood that individual CT subtypes, severity and the developmental timing of when they occurred (30,88,89) may enable parsing of these effects on network connectivity. These additional analyses were not carried out as part of the present study owing to the multiple testing burden involved, and the risk of inflating our type I error. Of note here, although we employed a relatively conservative threshold for statistical significance, it could be argued that an even more stringent threshold might have been set given the four seed regions used, i.e. FWR p= 0.0125. However, we considered that doing so would unduly inflate the risk of inflating our type II error. Either approach risks misrepresenting the significance of our findings, and underlines the importance of replication of our results.

Finally, we assessed functional connectivity of the DMN as the most robust network for rs-fMRI. However, we have not analyzed other networks that are known to be deactivated during rs-fMRI, such as task-positive networks of the executive control network and salience network. Recent work in controls and MDD suggests that the interplay between task-negative and task-positive networks during rs-fMRI can yield novel insights of how brain networks are affected by CT (36,67,90,91). Similarly, we have not investigated whether and how known stress response measures, such as hormonal and cytokine levels, may mediate the relationship between CT and functional large-scale brain networks as has been recently shown in MDD (37,92). Future studies using longitudinal study designs, mechanistic paradigms and modelling approaches to fMRI data are needed to establish the causal effects of CT on functional large-scale networks in schizophrenia. Doing so will likely advance our understanding of how to combine genetic and environmental factors that may regulate functional connectivity and dysconnectivity.

4.4 Conclusion

To our knowledge, this is the first study providing evidence of an association between CT and altered DMN connectivity during rs-fMRI in patients with SZ. Our findings suggest that CT exposure is associated with variability DMN connectivity during rs-fMRI in patients in a manner comparable to controls, and in so doing may mediate the relationship previously reported between CT and cognitive performance. We conclude that the dysregulated DMN connectivity, already widely associated with susceptibility to SZ, is likely to be further **impacted by** CT exposure. Requiring confirmation in longitudinal studies, this suggests that DMN connectivity may be part of the mechanism by which early life adversity may exerts deleterious effects on cognitive performance. Continuing to develop biological models explaining how environmental exposure (e.g., CT) moderates biological (e.g., genetic) susceptibility to result in the cortical network connectivity changes observed – for example, via an altered immune response - represents important next steps arising from this work.

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Author contributions

Conceptualisation and study design: MRD, DM, GD. Investigation: MRD, DM, KIR, LH, SK, RK, BH. Analysis: MRD, SK. Manuscript: MRD, SK, GD. Manuscript review: MRD, SK, DM, KIR, LH, RK, DMK, JK, DM, AC, BH, CMD, GD. Project coordination: MRD, GD. All authors contributed to and approved the final version of the manuscript.

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Figure Legend

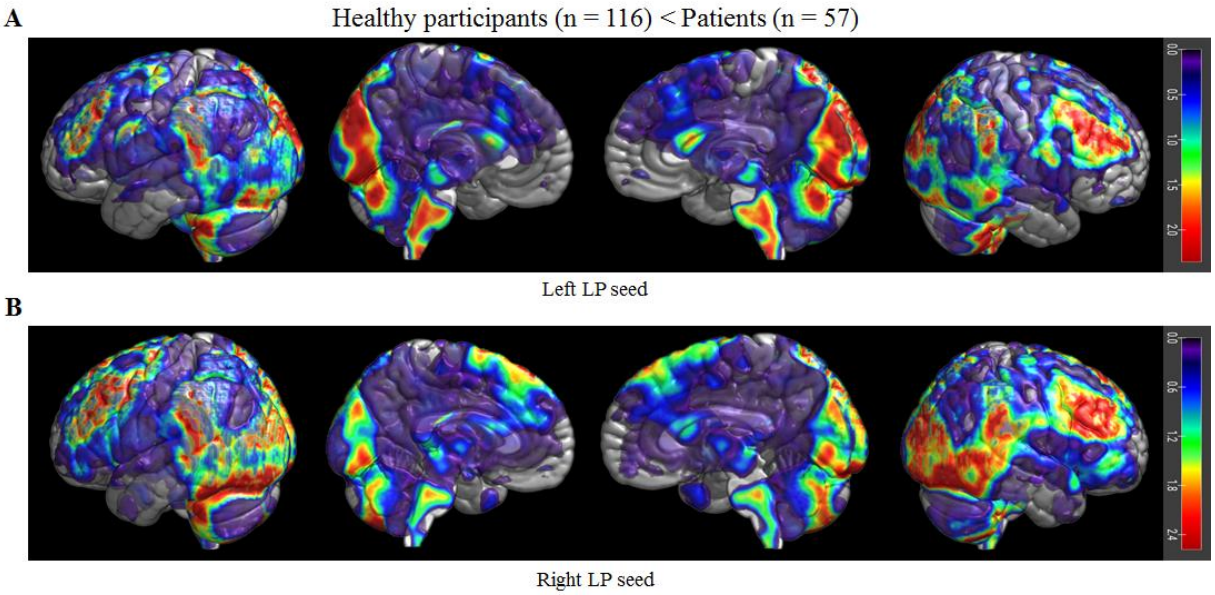


Figure 1. Group differences in functional connectivity of the default-mode network

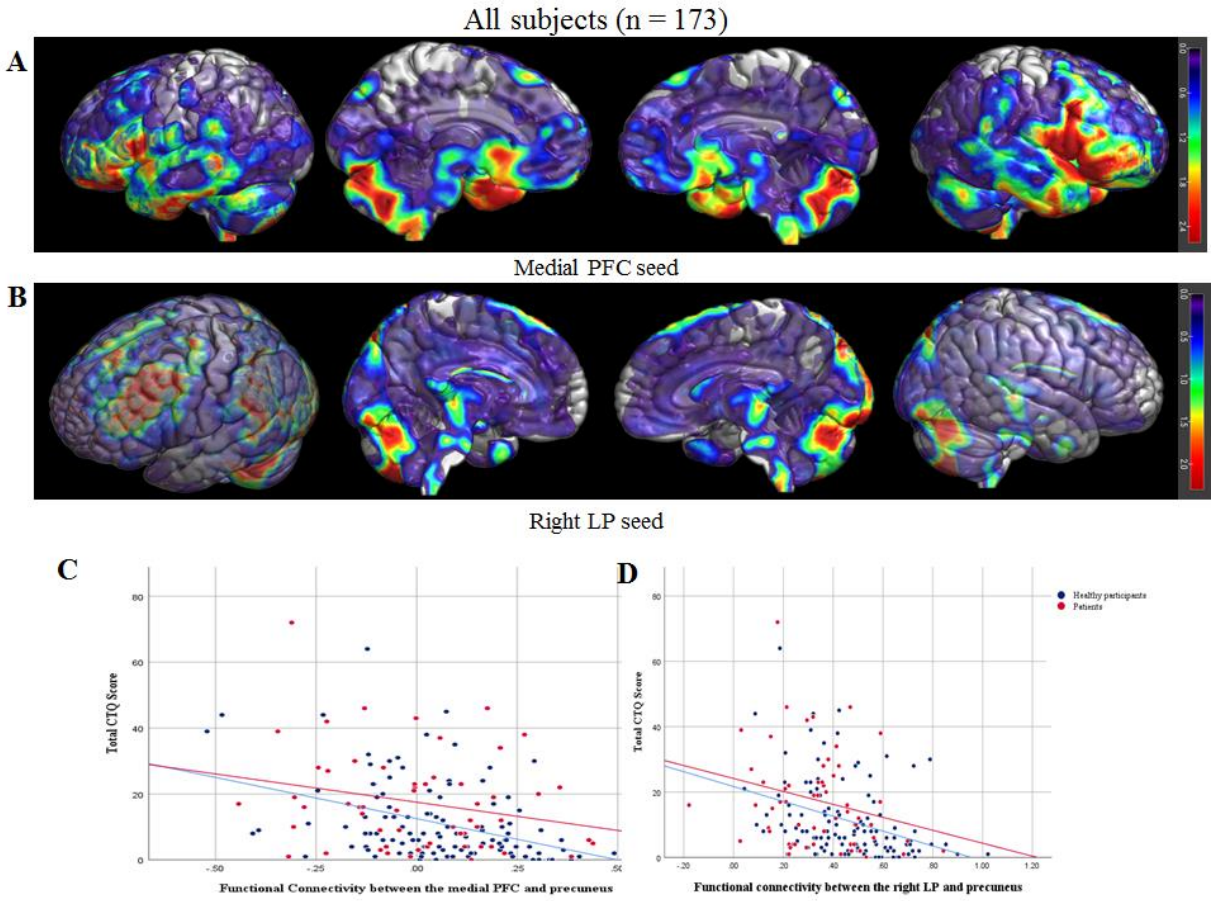
A. Greater reduced functional connectivity between the left Lateral Parietal seed and the precuneus, right parietal operculum, right superior frontal gyrus, and left postcentral gyrus (Healthy participants < Patients with schizophrenia).

B. Greater reduced functional connectivity between the right Lateral Parietal seed and the precuneus and left parietal operculum (Healthy participants < Patients with schizophrenia).

All results thresholded at cluster-level corrected $P_{FWE} < .05$ and $P_{FWE} < .05$ height threshold).

Abbreviations. LP, Lateral Parietal Lobe.

Figure 2. Functional connectivity and childhood trauma across all participants



A. For the medial PFC seed, we found a negative association between childhood trauma and reduced functional connectivity with the precuneus across all participants. Results thresholded at cluster-level corrected $P_{FWE} < .05$ and $P_{FWE} < .05$ height threshold).

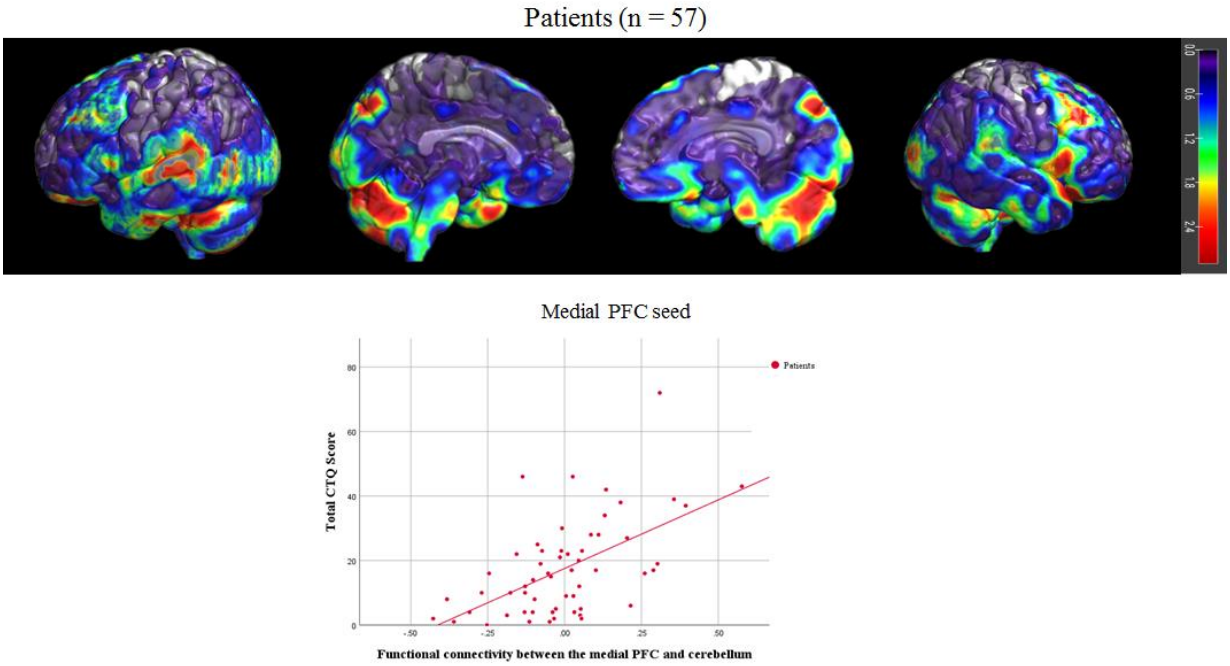
B. For the right Lateral Parietal seed, we found a negative association between childhood trauma and reduced functional connectivity with the precuneus across all participants. Results thresholded at cluster-level corrected $P_{FWE} < .05$ and $P_{FWE} < .05$ height threshold).

C. Functional connectivity between the medial PFC seed and precuneus inversely correlated with the total CTQ score across all participants (r = -.342, $p < .001$).

D. Functional connectivity between the right Lateral Parietal seed and precuneus was negatively correlated with the total CTQ score across all participants (r = -.358, $p < .001$).

Abbreviations. CTQ, Childhood Trauma Questionnaire; LP, Lateral Parietal Lobe; PFC, Prefrontal Cortex.

Figure 3. Functional connectivity and childhood trauma in patients with schizophrenia

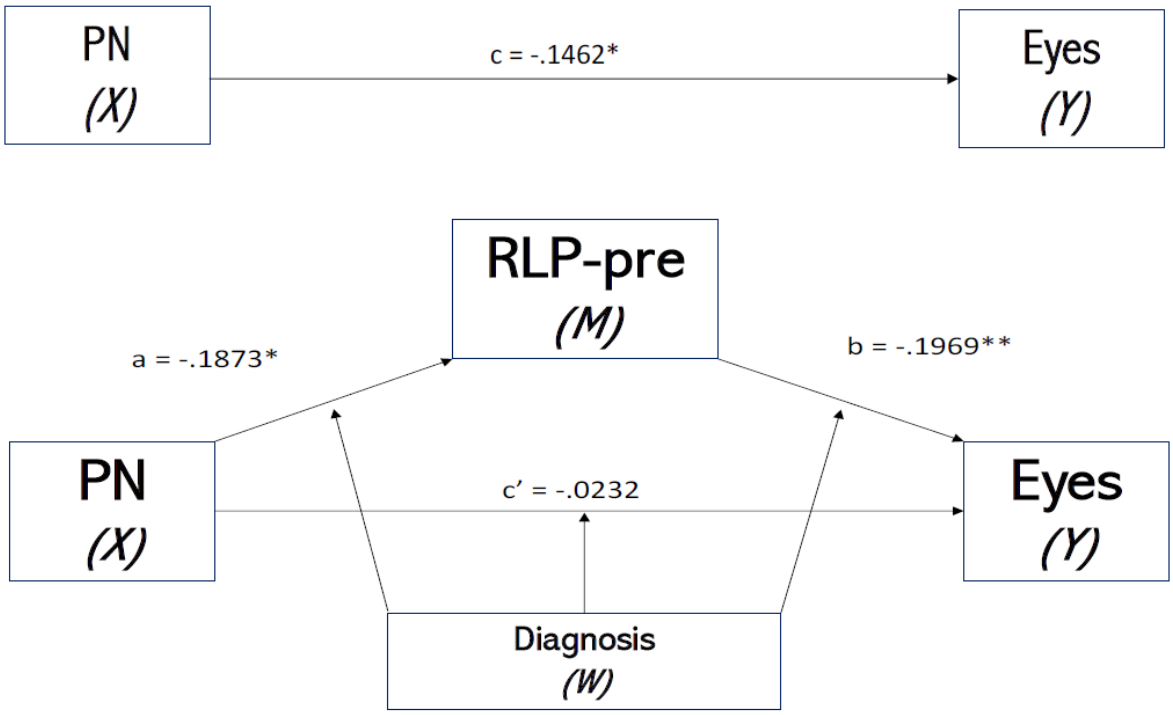


A. For the medial PFC seed, we found a positive association between childhood trauma and increased functional connectivity with the cerebellum in patients with schizophrenia. Results thresholded at cluster-level corrected $P_{FWE} < .05$ and $P_{FWE} < .05$ height threshold).

B. Functional connectivity between the right medial PFC seed and cerebellum was positively correlated with the total CTQ score in patients with schizophrenia (r = .562, $p < .001$).

Abbreviations. CTQ, Childhood Trauma Questionnaire; PFC, Prefrontal Cortex.

Figure 4. Moderated mediation analysis of CTQ, DMN activation, and Theory of Mind performance, with diagnosis as moderator.



* $P < .05$

** $P < .001$

Independent (X) variable =CTQ-physical neglect (PN) total scores; Mediating (M) variable = right lateral parietal cortex – precuneus (RLP-pre) connectivity coefficients; Dependent (Y) variable = Reading the Mind in the Eyes(Eyes) total scores; Moderating (W) variable = Diagnosis.

Table 1. Means scores for demographic, clinical, and cognitive variables.

Characteristics	Patients (N = 57)	Healthy participants (N = 116)	Statistics	
			t/ χ^2	*P*
	Mean (SD)	Mean (SD)		
Gender (male : female)	39 : 18	72: 44	χ^2 = .671	.413
Age (years)	43.61 (11.51)	40.15 (11.27)	$t_{(171)}$ = 1.889	.061
Handedness N (right : left)	51 : 6	105 : 10	χ^2 = .646	.724
Years of education[a]	14.58 (2.57)	17.17 (3.77)	$t_{(161)}$ = -4.356	< .001**
Total CTQ Score	42.44 (14.80)	36.23 (11.89)	$t_{(171)}$ = 2.972	.003**
Emotional Abuse	10.04 (5.16)	8.47 (4.18)	$t_{(171)}$ = 1.987	.06
Physical Abuse	7.39 (4.42)	6.55 (6.37)	$t_{(171)}$ = 1.311	.194
Sexual Abuse	6.58 (4.36)	5.56 (2.03)	$t_{(171)}$ = 1.677	.098
Emotional Neglect	9.22 (4.35)	5.61 (4.58)	$t_{(171)}$ = 1.905	.06
Physical Neglect	7.82 (3.25)	6.42 (2.49)	$t_{(171)}$ = 2.868	.0005**
Total WASI IQ[b]	95.39 (17.53)	110.27 (15.69)	$t_{(171)}$ = -5.640	< .001**
Eyes Task (total score)[c]	24.51 (4.70)	26.79 (4.45)	$t_{(170)}$ = -3.110	.002**
Diagnosis (SZ : SZA)	45 : 12	-	-	-
Duration of Illness (years)[f]	18.42 (11.80)	-	-	-
HDRS depressive symptom severity	2.88 (3.64)	3.61 (3.88)	$t_{(147)}$ = -1.604	.214
PANSS Total Score[g]	38.66 (8.89)	-	-	-
PANSS Positive Symptoms	8.51 (2.22)	-	-	-
PANSS Negative Symptoms	9.95 (4.15)	-	-	-
PANSS General Symptoms	20.20 (4.12)	-	-	-
Primary antipsychotic medication[h,i]	(a) 4; (b) 11; (c) 1; (d) 11; (e) 2; (f) 4; (g) 5	-	-	-
Additional antipsychotic medication[j]	(a) 5; (b) 3; (c) 10; (d) 0; (e) 2; (f) 1; (g) 1	-	-	-
Other medication[k]	(a) 6	-	-	-

* Significant at $p < 0.05$

** Significant at $p < 0.005$

[a] Missing data in 9 patients and 1 healthy control

[b] Abbreviated WASI

[c] Missing data in 1 HC

[d] Missing data in 4 patients and 8 HC

[e] Missing data in 13 patients and 2 HC

[f] Missing data in 26 patients

[g] Missing data in 16 patients

[h] Missing data in 15 patients

[i] Primary antipsychotic medication: (a) Aripiprazole, (b) Clozapine, (c) Fluphenazine, (d) Olanzapine, (e) Paliperidone, (f) Quetiapine, (g) Risperidone/Risperidone Consta depot

[j] Additional antipsychotic medication: (a) Aripiprazole, (b) Chlorpromazine, (c) Clopixol, (d) Paliperidone, (e) Quetiapine, (f) Risperidone, (g) Ziprasidone

[k] Other medication: (a) Antidepressant

Abbreviations. CANTAB SWM, CANTAB spatial working memory task; CTQ, Childhood Trauma Questionnaires; Eyes task, Reading the Mind in the Eyes; PANSS, Positive and Negative Syndrome Scale; WASI, Wechsler Adult Scale of Intelligence.

Table 2. Group differences in functional connectivity of default-mode network seeds at cluster-level corrected $P_{(FWE)} = .05$ – Healthy Participants < Patients with Schizophrenia

Brain Area	MNI x	MNI y	MNI z	Voxels	Peak T	Height threshold P_{FDR} value
L Lateral Parietal Seed – Healthy Participants < Patients with Schizophrenia						
Precuneus (BA7)	-4	-46	52	1459	-5.48	<.05
	-48	-17	50	106		
	40	-22	55	104		
R Parietal Operculum (BA40)	66	-26	28	407	-4.40	<.05
R Superior Frontal Gyrus	16	-2	72	472	-5.10	<.05
L Postcentral Gyrus	-46	-26	36	544	-3.23	<.05
R Lateral Parietal Seed – Healthy Participants < Patients with Schizophrenia						
Precuneus (BA7)	0	-50	52	395	-4.35	<.05
L Parietal Operculum (BA40)	-48	-24	34	242	-3.56	<.05
Posterior Cingulate Cortex Seed – Healthy Participants < Patients with Schizophrenia						
Brain Stem	-6	-22	-28	505	-4.01	<.05
Medial PFC Seed - – Healthy Participants < Patients with Schizophrenia						
No significant clusters						

No significant findings for the contrast Healthy Participants > Patients with Schizophrenia for any of the four seeds.

Abbreviations. BA, Brodman area; L, Left; PFC, Prefrontal Cortex; R, Right.

Table 3. Functional connectivity and childhood trauma across all participants

Abbreviations. BA, Brodman area; L, Left; PFC, Prefrontal Cortex; R, Right.

Brain Area	MNI			Voxels	Peak T	Height threshold *P* value uncorrected
	x	y	z			
Medial PFC Seed and Childhood Trauma – All Subjects						
Precuneus (BA7)	-12	-48	48	968	-4.76	<.05 (FWE)
R Lateral Parietal Seed and Childhood Trauma – All Subjects						
Precuneus (BA7)	-12	-66	28	1234	-5.01	<.001

Table 4. Functional connectivity and childhood trauma in patients with schizophrenia

Abbreviations. L, Left; PFC, Prefrontal Cortex.

Brain Area	MNI			Voxels	Peak T	Height threshold *P* value uncorrected
	x	y	z			
L Medial PFC Seed and Childhood Trauma – Patients with schizophrenia						
Cerebellum	-10	-78	-26	2484	5.04	<.001