Brain, Behavior, & Immunity - Health 26 (2022) 100540

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Childhood trauma, IL-6 and weaker suppression of the default mode network (DMN) during theory of mind (ToM) performance in schizophrenia

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A B S T R A C T

Background: Both low-grade systemic inflammation and functional connectivity of the default mode network (DMN) *during rest* have recently been observed to mediate the association between childhood trauma (CT) and behavioural performance on an emotion recognition task. Whether inflammation also mediates the association between CT and functional connectivity of the DMN *during social cognitive task performance* is unknown.

Methods: 51 patients with schizophrenia (SZ) or schizoaffective disorder (SZA) and 176 healthy participants completed a theory of mind (ToM) task during fMRI. IL-6 was measured in plasma using ELISA. DMN connectivity was measured during performance of the fMRI ToM task. To examine DMN connectivity, we selected 4 a priori seeds of the DMN, i.e., the medial prefrontal cortex (PFC), right lateral parietal (LP), left LP, and posterior cingulate cortex (PCC) according to the Harvard-Oxford Cortical and Subcortical Atlas (http://www.cma.mgh.harvard.edu/fsl_atlas.html) as implemented in CONN.

Results: Patients showed significantly increased DMN connectivity compared to healthy participants between each of the four seeds of the DMN and with other clusters in the brain. Across the entire sample, higher levels of IL-6 predicted increased connectivity between the mPFC and regions encompassing the cerebellum (<0.001 FWE). IL-6 mediated the association between physical neglect and weaker suppression of the posterior cingulate cortex (PCC) DMN seed -left precentral and postcentral gyrus ($\beta_{INDIRECT}$ = .0170, CI: 0.0008 to.0506) connectivity during ToM performance.

Discussion: This is the first study to our knowledge that provides evidence that higher plasma IL-6 mediates the association between higher childhood neglect and increased DMN connectivity during ToM task performance. Consistent with our previous study that IL-6 mediated the association between early life stress exposure and reduced connectivity of the DMN during rest, here IL-6 mediated the association between early life stress and increased connectivity of the DMN during ToM based cognitive processing. These findings suggest a biological mechanism for how chronic stress impacts social cognitive processing.

1. Introduction

Functional network connectivity within the brain refers to a pattern of statistical dependencies that likely reflect brain regions working together in support of complex behaviour and cognition (Sporns, 2013). Recent studies demonstrate disruptions to several brain networks in individuals with schizophrenia, including networks that play an important role in core social cognitive functions, such as theory of mind (ToM) - the ability to make inferences about the mental states of others (Bora et al., 2009; Brüne, 2003; Fornito et al., 2012; Mothersill et al., 2017; Zhou et al., 2016). Among these, the default mode network (DMN) is a neural network encompassing the prefrontal cortex, the cingulate cortex and the inferior parietal cortex, and is associated with social cognitive performance and other forms of self-generated thought. The DMN is *typically* deactivated during the performance of an externally oriented attention-demanding task (Alves et al., 2019; Anticevic et al., 2012; Fox et al., 2006) and activated when individuals are focused on their internal mental-state processes during rest (Dauvermann et al., 2021; Spreng and Grady, 2010). Importantly, greater deactivation of the DMN during task based activity has been found to be associated with better cognitive and behavioural performance (Anticevic et al., 2012), suggesting that the ability to suppress the DMN during tasks is critical

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https://doi.org/10.1016/j.bbih.2022.100540
Received 5 July 2022; Received in revised form 21 October 2022; Accepted 22 October 2022
Available online 27 October 2022

for optimal cognition.

There is abundant evidence that childhood trauma has a deleterious effect on the structure, function and connectivity of DMN brain regions and on social cognitive performance in neuropsychiatric disorders (Rokita et al., 2019). We recently found evidence that childhood trauma was significantly associated with atypically decreased network connectivity between the lateral parietal cortex and precuneus during resting state, which in turn correlated with poorer performance on a behavioural measure of emotional recognition (Dauvermann et al., 2021). We have previously shown that resting state DMN dysconnectivity (using the precuneus as the seed region) was associated with lower behavioural performance on a theory of mind task (Mothersill et al., 2017). Similarly, in an fMRI whole brain analysis during theory of mind task performance, Quide and colleagues found evidence of increased activation of the posterior cingulate cortex (PCC)/precuneus and dorsal medial prefrontal cortex (dmPFC) (Quidé et al., 2017). The biological mechanism by which childhood trauma causes alterations in the DMN is still unclear, but may be at least partially associated with immune dysfunction.

Childhood trauma has been shown in many cross-sectional and longitudinal studies to predict low grade systemic inflammation in adults (Baumeister et al., 2016; Danese et al., 2007). We recently reported an association between the pro-inflammatory cytokine interleukin 6 (IL-6), an indicator of systemic inflammation, and resting state functional connectivity within the DMN, in a manner which sequentially mediated the association between early life stress and lower behavioural performance of an emotion recognition task (King et al., 2021). These data suggest that inflammation and DMN dysconnectivity during rest, may represent at least one mechanism via which childhood trauma may exert an impact on social cognition. Further support of this hypothesis requires demonstration of the same associations between childhood trauma, inflammation, and DMN connectivity during social cognitive task performance within the scanner.

The aim of this study was to examine associations between childhood trauma, IL-6 and DMN connectivity during performance of a theory of mind (ToM) processing task in patients and healthy participants. Specifically, we sought to (1) examine DMN connectivity differences between both patients and healthy participants during a theory of mind task. Here, we hypothesised that increased connectivity/weaker suppression of DMN would be observed in patients, compared to healthy participants. Next, following on from our resting state DMN findings described above, i.e., showing that higher childhood trauma predicted reduced DMN rs-FC, we tested whether (2) higher childhood trauma predicted increased DMN connectivity during ToM. Our hypothesis was that childhood trauma would predict increased DMN alterations during the ToM task across the full sample. Finally, we aimed to (3) investigate whether IL-6 mediated the association between childhood trauma and DMN dysconnectivity during task performance. We hypothesised that the association between higher childhood trauma and higher DMN activation during task performance would be partially mediated by higher levels of IL-6 plasma.

2. Methods

2.1. Participants

Two hundred and twenty-seven participants took part in this study. Fifty one individuals with SZ or SZA were recruited for the Immune Response and Social Cognition (iRELATE) project, as described in our previous studies (King et al., 2021). Briefly, all participants were recruited in Galway and Dublin through community mental health services. All patients had a diagnosis of SZ or SZA confirmed using the Structured Clinical Interview for Diagnostic Statistical Manual-IV, and were clinically stable at the time of assessment. Exclusion criteria included (i) the presence of a documented history of neurological disorders (e.g., epilepsy) (ii) comorbid axis I mental health disorders (iii) an estimated intelligence quotient (IQ) of less than 70 (iv) a lifetime history of head injury causing loss of consciousness for more than 1 min (v) evidence of substance use disorder within the past month (vi) reported pregnancy or lactation (vii) contra-indication for MRI scanning (e.g., metal implants or claustrophobia) (viii) the presence of chronic inflammatory illness and (ix) use of non-steroidal anti-inflammatory drugs (NSAIDs) in the past 24 h. In addition, one hundred and seventy six healthy participants were recruited via local and national media advertising in the same regions of Galway and Dublin. Healthy participants were included if they met the criteria of having no documented lifetime personal history of axis I mental health disorder or substance use disorder in the last 6 months, or a first-degree relative with a psychotic disorder, or substance abuse in the last 6 months (based on self-report). 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. Plasma isolation and whole blood culture

Plasma isolation and analysis was carried out as described in (King et al., 2021). Briefly, blood samples were taken at approximately the same time of day (9.30am) from each participant in a 6 mL EDTA tube (BD367873). Basal plasma levels of IL-6 were measured using a quantikine high sensitivity enzyme-linked immunosorbent assay (ELISA) (Bio-Techne Catalog Number HS600C) which has an assay sensitivity of 0.09 pg/mL and range of 0.156–10 pg/mL, and read at 450 nm.

2.3. Childhood trauma

Childhood trauma (CT) was retrospectively assessed using the Childhood Trauma Questionnaire (CTQ)—Short Form (Bernstein et al., 1994), a widely used self-report questionnaire comprising 5 subscales of physical abuse, physical neglect, emotional abuse, emotional neglect and sexual abuse. Each subscale includes 5 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.”

2.4. Neuroimaging data acquisition

Brain imaging was carried out on a 3 T 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.

2.5. Structural magnetic resonance imaging

High resolution T1-weighted images were obtained using a 3D magnetisation-prepared rapid acquisition with gradient echo (MPRAGE) sequence. The following parameters were used: FOV = 240 × 220 × 162 mm^3, spatial resolution 0.83 × 0.83 × 0.9 mm3, TR/TE = 6.7/3.1 ms, TI = 808.239929 ms, flip angle = 8°, acquisition time = 5 min 18.8 s.

2.5.1. Resting-state functional magnetic resonance imaging during the theory of mind task

During the cartoon ToM task, functional MRI data were acquired during the task using a SE-EPI sequence with a dynamic scan time of 3 s, with: FOV = 240 × 240 × 131 mm, REC voxel MPS (mm) = 3 × 3 x 3.2, 37 slices with interslice gap = 0.349999905 mm, TR/TE = 3000/28 ms, and flip angle = 90°. For the cartoon ToM task, 160 vol were acquired, taking 8 min and 11.9 s.

2.6. Neuroimaging data analysis

2.6.1. Pre-processing

Images were pre-processed in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and MATLAB R2019b 64-bit (v9.7.0.1296695). All pre-processing steps were carried out as described in our previous study (King et al. under review). Briefly, the functional MRI spatial pre-processing included (1) Realignment Estimate and Re-slice (2) Co-registration between the T1 image and the re-sliced mean functional image (3) Segmentation and normalization: into grey matter (GM), white matter (WM), and CSF (CSF) tissue classes (Ashburner and Friston, 2005) and (4) Smoothing of the normalised functional images with an 8 mm full-width half maximum (FWHM) Gaussian kernel.

2.7. Functional connectivity analysis

Seed-based functional connectivity was carried out in CONN-fMRI Functional Connectivity toolbox (version 20b) to assess functional connectivity of 4 a priori seeds of the DMN, i.e., 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. To test the differences in connectivity between patients and healthy participants, CONN analysis was performed to statistically compare differences between the four DMN seed and connectivity with the rest of the brain. To test the individual effects of higher IL-6 on functional connectivity of the DMN, a regression analysis was carried out across all participants, and in CONN. Results were thresholded at $P_{FWE} < .001$ for both the cluster-level and height threshold to account for multiple comparisons.

2.8. Brüne theory of mind (ToM) task

To assess functional connectivity of the DMN during social cognitive task-based activity, we used a cartoon ToM task previously reported in Brune et al. (2011). During the fMRI scan, a series of ToM related cartoon stories were presented on a screen, followed by some questions. These cartoon stories were presented in the form of four static pictures displayed in two rows and viewed consecutively from left to right. The participant was asked to think about the answer to each question in their mind for the entire length that each question was displayed on the screen. During the ToM condition, the four pictures were displayed in the correct order and questions were asked about the mental state of the characters. During the non-ToM condition, the pictures were in a mixed-up order and questions were asked about the physical characteristics of the characters' surroundings. In this CONN functional connectivity study, there were six ToM and six non-ToM blocks, each lasting 39 s. Each block involved presentation of the pictures (15 s) and questions (12 s for each question). DMN connectivity was examined during the ToM condition only. ToM behavioural performance (i.e., participants behavioural responses to the fMRI Cartoon task) was compared between patients and healthy participants and assessed with 2-tailed independent samples t-tests.

2.8.1. Statistical analysis of demographic and cognitive variables

Except for the CONN specific analysis described in 2.2.4.1, all remaining statistical analyses were performed using Statistical Package for Social Sciences Version 25.0 (SPSS Inc., IBM). Group comparisons for age, sex, level of education, IQ, CTQ, IL-6 and ToM behavioural performance was assessed with 2-tailed independent samples t-tests and Chi-square (χ^2) tests, where appropriate. Significant associations observed, in our initial group comparison analyses, as well as from our regression analyses (i.e., between IL-6 and DMN) within CONN, were extracted as individual functional connectivity coefficients and imported into SPSS. In order to investigate the relationship between childhood trauma, IL-6, and the significant DMN seeds, we firstly ran a mediation analysis where IL-6 was included as a mediating variable (M), CTQ as the independent variable (IV) and the relevant DMN correlation coefficients as our dependent variable (DV). When examining associations with ToM behavioural performance, we replaced out DMN variable with total scores from the ToM behavioural task, as our DV. False Discovery rate (FDR) analysis was carried out on all bivariate analyses to account for multiple comparisons.

3. Results

3.1. Demographics

Two hundred and twenty seven participants took part in this study. Demographic and clinical characteristics of the study participants are presented in Table 1. Significant differences between patients and healthy participants were observed for age, but not sex. Patients had significantly lower total years of education and IQ compared to healthy participants. Patients reported significantly more childhood trauma experiences compared to healthy individuals, on three separate measures of the childhood trauma (CTQ) questionnaire; i.e., on total CTQ scores, CTQ-sexual abuse scores, and CTQ-physical neglect scores compared to healthy participants. Higher plasma IL-6 levels were observed in patients compared to healthy participants.

Table 1
Demographic, clinical, environmental, immune and behavioural data.

	Total Sample M (SD)/%	Healthy Participants (n = 176) M/% SD	Patients (n = 51) M/% SD	T value/ χ^2 Controls v cases	P value
Demographics					
Sex (female)	33%	33%	30%	2.800	.21
Age	37 (12.1)	36 12.28	42 11.25	3.561	.001
Years of Education	15.1	16.76 3.94	14.94 3.25	−4.085	.001
BMI	25.1 (4.8)	24.58 3.86	29.66 5.89	6.936	.001
IQ	108.1 (18.9)	113.1 15.87	93.2 17.1.	−7.331	.001
Clinical					
PANSS Total Score		…. .	38.53 8.70	…. .	…. .
HAM-D	3.23 (3.65)	2.99 3.41	4.88 4.75	3.618	.001
Childhood Trauma Questionnaire (CTQ)					
CTQ Total Score	37.6. (12.64)	36.61 12.61	41.08 15.50	1.946	.04
Emotional abuse	8.8 (4.54)	8.59 4.39	9.45 4.97	1.232	.22
Emotional neglect	9.58 (4.51)	9.46 4.43	9.98 4.77	.708	.52
Sexual abuse	5.82 (2.7)	5.49 1.6	6.94 4.7	2.207	.02
Physical abuse	6.61 (3.02)	6.49 2.71	6.96 3.61	.858	.49
Physical neglect	6.92 (2.76)	6.46 2.40	7.62 3.34	2.356	.02
Inflammatory marker					
IL-6 Plasma	1.9 (3.2)	1.53 1.59	3.34 6.08	2.16	.03
ToM Behavioural Performance					
ToM Cartoon task	49.5 (8.7)	54.4 6.2	44.5 11.5	.5.56	.001

3.2. Patients exhibit weaker suppression of the DMN compared to healthy participants

Following on from recent study, where DMN connectivity was a) significantly decreased in patients compared to controls during rest (Dauvermann et al., 2021), we next tested whether differences in DMN connectivity were observed between these groups in the same sample, during an fMRI theory of mind (ToM) task.

During ToM performance, patients showed significantly increased DMN connectivity compared to healthy participants between each of the four seeds of the DMN and with other clusters in the brain.

Specifically, there were differences between patients and controls between the mPFC seed and two other clusters of the brain i.e., the mPFC and a cluster encompassing the left frontal cortex (mPFC cluster 1), and the mPFC and the right precentral and postcentral gyrus (mPFC cluster 2). See Table 2. Patients again showed increased DMN connectivity between the LLP and two other clusters i.e., between the LLP and a cluster encompassing the left and right superior frontal gyrus (LLP cluster 1) and between the LLP and a cluster encompassing the right lateral occipital cortex (LLP cluster 2). See Table 2. For the RLP seed, increased connectivity was observed between RLP and a cluster encompassing the left middle temporal gyrus (RLP Cluster 1), and between RLP and left temporal Gyrus (RLP Cluster 2). Increased connectivity of the DMN was also observed in patients compared to healthy individuals when examining the PCC seed. Specifically, increased connectivity was observed between the PCC and the left precentral and postcentral gyrus (PCC Cluster 1). All results were thresholded at <0.0125 FWE (see Table 2).

3.3. Childhood trauma and weaker suppression of the DMN during ToM

We next tested whether childhood trauma also predicted weaker suppression of the DMN during a theory of mind (ToM) task. The CTQ total scores and CTQ-neglect scores were used to index childhood trauma in this analysis, on the basis that both CTQ-neglect was associated with both plasma IL-6 and connectivity within the DMN in our previous studies. We found that neither CTQ-total or CTQ-neglect was associated with the extracted DMN connectivity coefficients observed in 3.2.

3.4. Higher IL-6 and seed-based functional connectivity between each of the 4 DMN seed regions (medial PFC, right LP, left LP, and the PCC) and the rest of the brain during ToM

Higher levels of IL-6 predicted increased connectivity between the mPFC and regions encompassing the cerebellum (<0.001 FWE). Diagnosis did not moderate this significant association (p = .76) (See Table 3).

3.5. IL-6 mediates the association between CTQ and weaker suppression of the DMN during ToM

We next tested whether IL-6 mediated the association between higher CTQ and weaker suppression For this analysis, we used the extracted DMN connectivity coefficients observed above in 3.2. Mediation analyses, based on 5000 bootstrapped samples indicated that higher IL-6 did not mediate the association between higher CTQ and connectivity between the mPFC, LLP, and RLP seeds ($\beta_{INDIRECT}$ = .0170, CI: -.0012 to 0.1141; $\beta_{INDIRECT}$ = .0231, CI: -.0011 to 0.1223; $\beta_{INDIRECT}$ = .0113, CI: -.0112 to 0.1206 respectively). However, IL-6 was found to mediate the association between higher CTQ-physical neglect and weaker suppression of the PCC seed i.e., between PCC and left precentral and postcentral gyrus ($\beta_{INDIRECT}$ = .0170, CI: 0.0008 to.0506) during ToM performance. This finding remains significant after correcting for either age or sex but is no longer significant when correcting for BMI or IQ. When we reran the analysis by replacing our connectivity metrics

Table 2
Differences in DMN connectivity during ToM (patients > healthy participants).

Brain Area	MNI				
	x	y	z	Voxels	P value
Medial PFC Seed (patients > healthy participants)					
mPFC - cluster 1 268 voxels (24%) covering 16% of atlas.FOrb l (Frontal Orbital Cortex Left) 150 voxels (14%) covering 11% of atlas.IC l (Insular Cortex Left) 98 voxels (9%) covering 27% of atlas.PP l (Planum Polare Left) 94 voxels (9%) covering 30% of atlas.HG l (Heschl's Gyrus Left) 76 voxels (7%) covering 3% of atlas.TP l (Temporal Pole Left) 63 voxels (6%) covering 6% of atlas.CO l (Central Opercular Cortex Left) 30 voxels (3%) covering 0% of atlas.FP l (Frontal Pole Left) 29 voxels (3%) covering 5% of atlas.PT l (Planum Temporale Left) 17 voxels (2%) covering 2% of atlas.IFG oper l (Inferior Frontal Gyrus, pars opercularis Left) 13 voxels (1%) covering 5% of atlas.aSTG l (Superior Temporal Gyrus, anterior division Left) 12 voxels (1%) covering 0% of atlas.PreCG l (Precentral Gyrus Left) 9 voxels (1%) covering 2% of atlas.pSTG l (Superior Temporal Gyrus, posterior division Left) 7 voxels (1%) covering 2% of atlas.FO l (Frontal Operculum Cortex Left) 3 voxels (0%) covering 0% of atlas.IFG tri l (Inferior Frontal Gyrus, pars triangularis Left) 236 voxels (21%) covering 0% of atlas.not-labeled	−48	+34	−14	1105	<.0125
mPFC - cluster 2 75 voxels (20%) covering 2% of atlas.PreCG r (Precentral Gyrus Right) 46 voxels (12%) covering 1% of atlas.PostCG r (Postcentral Gyrus Right) 45 voxels (12%) covering 5% of atlas.CO r (Central Opercular Cortex Right) 26 voxels (7%) covering 7% of atlas.PP r (Planum Polare Right) 16 voxels (4%) covering 2% of atlas.IFG oper r (Inferior Frontal Gyrus, pars opercularis Right) 16 voxels (4%) covering 6% of atlas.aSTG r (Superior Temporal Gyrus, anterior division Right) 9 voxels (2%) covering 2% of atlas.PT r (Planum Temporale Right) 1 voxels (0%) covering 0% of atlas.TP r (Temporal Pole Right) 136 voxels (37%) covering 0% of atlas.not-labeled	+54	+02	+16	370	<.0125
L Lateral Parietal Seed (patients > healthy participants)					
LLP - Cluster 1 194 voxels (20%) covering 30% of atlas.SMA L(Juxtapositional Lobule Cortex -formerly Supplementary Motor Cortex-	+24	−02	+54	949	<.0125 (FWE)

(continued on next page)

Table 2 (*continued*)

Brain Area	MNI				
	x	y	z	Voxels	P value
Medial PFC Seed (patients > healthy participants)					
Left) 124 voxels (13%) covering 4% of atlas.SFG l (Superior Frontal Gyrus Left) 110 voxels (12%) covering 4% of atlas.SFG r (Superior Frontal Gyrus Right) 105 voxels (11%) covering 4% of atlas.MidFG r (Middle Frontal Gyrus Right) 52 voxels (5%) covering 7% of atlas.SMA r (Juxtapositional Lobule Cortex -formerly Supplementary Motor Cortex-Right) 10 voxels (1%) covering 0% of atlas.PreCG r (Precentral Gyrus Right) 1 voxels (0%) covering 0% of atlas.MidFG l (Middle Frontal Gyrus Left) 1 voxels (0%) covering 0% of atlas.PreCG l (Precentral Gyrus Left) 352 voxels (37%) covering 0% of atlas.not-labeled					
LLP - Cluster 2 289 voxels (46%) covering 14% of atlas.iLOC r (Lateral Occipital Cortex, inferior division Right) 200 voxels (32%) covering 4% of atlas.sLOC r (Lateral Occipital Cortex, superior division Right) 83 voxels (13%) covering 7% of atlas.toMTG r (Middle Temporal Gyrus, temporooccipital part Right) 26 voxels (4%) covering 2% of atlas.AG r (Angular Gyrus Right) 1 voxels (0%) covering 0% of atlas.pSMG r (Supramarginal Gyrus, posterior division Right) 23 voxels (4%) covering 0% of atlas.not-labeled	+48	−70	+12	622	<.0125 (FWE)
LLP - Cluster 3 173 voxels (43%) covering 18% of atlas.aSMG l (Supramarginal Gyrus, anterior division Left) 97 voxels (24%) covering 9% of atlas.pSMG l (Supramarginal Gyrus, posterior division Left) 10 voxels (2%) covering 1% of atlas.AG l (Angular Gyrus Left) 7 voxels (2%) covering 0% of atlas.SPL l (Superior Parietal Lobule Left) 3 voxels (1%) covering 1% of atlas.PO l (Parietal Operculum Cortex Left) 115 voxels (28%) covering 0% of atlas.not-labeled	−40	−52	+42	405	<.0125 (FWE)
R Lateral Parietal Seed (patients > healthy participants)					
RLP - Cluster 1 217 voxels (23%) covering 16% of atlas.pMTG l (Middle Temporal Gyrus, posterior division Left) 174 voxels (18%) covering 27% of atlas.SMA L(Juxtapositional Lobule Cortex -formerly Supplementary Motor Cortex-Left) 82 voxels (9%) covering 11% of atlas.SMA r (Juxtapositional Lobule Cortex -formerly Supplementary Motor Cortex-Right) 80 voxels (8%) covering 3% of atlas.SFG l (Superior Frontal Gyrus Left)	−02	+00	+56	549	<.0125 (FWE)
RLP – Cluster 2 76 voxels (8%) covering 19% of atlas.pSTG l (Superior Temporal Gyrus, posterior division Left) 28 voxels (3%) covering 1% of atlas.PreCG l (Precentral Gyrus Left) 23 voxels (2%) covering 4% of atlas.PT l (Planum Temporale Left) 2 voxels (0%) covering 0% of atlas.MidFG l (Middle Frontal Gyrus Left) 1 voxels (0%) covering 0% of atlas.PreCG r (Precentral Gyrus Right) 280 voxels (29%) covering 0% of atlas.not-labeled	−52	−32	−04	414	<.0125 (FWE)
Posterior Cingulate Cortex Seed (patients > healthy participants)					
PCC – Cluster.1 246 voxels (36%) covering 6% of atlas.PreCG l (Precentral Gyrus Left) 71 voxels (10%) covering 2% of atlas.PostCG l (Postcentral Gyrus Left) 17 voxels (3%) covering 1% of atlas.AC (Cingulate Gyrus, anterior division) 4 voxels (1%) covering 1% of atlas.SMA L(Juxtapositional Lobule Cortex -formerly Supplementary Motor Cortex-Left) 2 voxels (0%) covering 0% of atlas.MidFG l (Middle Frontal Gyrus Left) 337 voxels (50%) covering 0% of atlas.not-labeled	−32	−10	+38	677	<.0125 (FWE)

during ToM performance with the behavioural scores from the ToM fMRI task, higher IL-6 was again observed to mediate the association between CTQ-physical neglect and lower ToM fMRI behavioural performance (($\beta_{INDIRECT} = -0.0139$, CI: -.0475 to −0.0005). All analysis was assessed for multiple comparisons using false discovery rate (FDR).

4. Discussion

4.1. Summary of main findings

The main aim of the study was to test the hypothesis that IL-6 predicts increased DMN functional connectivity, across the total sample. We found that IL-6 predicted increased functional connectivity between the mPFC and cerebellum. We further aimed to investigate whether higher IL-6 mediated the relationship between retrospective measures of childhood trauma and increased DMN connectivity during ToM task performance. We found that IL-6 mediated the relationship between physical neglect and connectivity between the PCC-left precentral and postcentral gyrus. At a behavioural level we found that higher IL-6 also mediated the association between physical neglect and lower

Table 3
Higher IL-6 and seed-based functional connectivity between each of the 4 DMN seed regions (medial PFC, right LP, left LP, and the PCC) and the rest of the brain.

Brain area	x	y	Z	Voxels	Peak T	P value
Medial PFC Seed and IL-6 – All Subjects						
236 voxels (18%) covering 13% of atlas.Cereb8 l (Cerebelum 8 Left) 228 voxels (17%) covering 10% of atlas. Cereb8 r (Cerebelum 8 Right) 124 voxels (9%) covering 8% of atlas.SPL l (Superior Parietal Lobule Left) 99 voxels (8%) covering 18% of atlas.Caudate l 74 voxels (6%) covering 3% of atlas.Cereb1 l (Cerebelum Crus1 Left) 54 voxels (4%) covering 10% of atlas.Cereb7 l (Cerebelum 7b Left) 52 voxels (4%) covering 6% of atlas.Cereb9 l (Cerebelum 9 Left) 48 voxels (4%) covering 9% of atlas.Caudate r 40 voxels (3%) covering 2% of atlas.Cereb2 l (Cerebelum Crus2 Left) 8 voxels (1%) covering 1% of atlas.Cereb9 r (Cerebelum 9 Right) 354 voxels (27%) covering 0% of atlas.not-labeled	−24	−26	74	887	−4.54	<.001 (FWE)
L Lateral Parietal Seed and IL-6 – All Subjects						
No significant clusters						
R Lateral Parietal Seed and IL-6 – All Subjects						
No significant clusters						
Posterior Cingulate Cortex Seed and IL-6 – All Subjects						
No significant clusters						

performance on the fMRI ToM behavioural task. This is the first study to our knowledge that provides evidence that both higher childhood physical neglect and evidence of low grade systemic inflammation (i.e., higher IL-6) predicts increased DMN functional connectivity during a ToM based cognitive task. Together, both the imaging and behavioural data suggests that altered inflammation is part of the mechanism by which CT exerts a deleterious effect on social cognition via an impact on DMN connectivity.

4.2. Patients exhibit weaker suppression of the DMN compared to healthy participants

We began our study analysis by testing the hypothesis that patients with schizophrenia show increased DMN functional connectivity during a theory of mind (ToM) fMRI task compared to healthy participants. We found that patients showed significantly increased connectivity between all four nodes of the DMN and multiple clusters of the brain. There was significantly increased connectivity observed in patients compared to healthy individuals between the mPFC seed and two other brain regions (i.e., mPFC and a cluster encompassing the left frontal pole and between the mPFC and a cluster encompassing the right precentral gyrus). We also observed significant differences between patients and healthy participants between the LLP seed and several clusters of the brain (i.e., LLP and a cluster encompassing the left motor cortex, LLP seed and a cluster encompassing the left lateral occipital cortex, and between the LLP and a cluster encompassing the left supramarginal gyrus). For the RLP seed, there were significant group differences observed between the RLP seed and two separate clusters (i.e., RLP – left motor cortex and RLP – left precentral gyrus). Lastly, significant differences in DMN connectivity between patients and healthy individuals were also observed between the PCC seed and the left precentral gyrus.

Patients with schizophrenia have consistently been reported to show atypical DMN connectivity compared to healthy individuals, and we have previously shown a relationship between DMN connectivity and lower ToM behavioural performance in patients (Mothersill el. al, 2017). In terms of fMRI activations studies, we have recently shown increased DMN activation in patients compared to controls during a facial emotion recognition task (Mothersill et al., 2014) and others have found a similar pattern of increased DMN activation in patients vs controls, during ToM performance (Quidé et al., 2017). The present study extends these findings by demonstrating that patients have atypically increased connectivity/weaker suppression of specific regions of the DMN compared to healthy participants *during* theory of mind performance. More specifically, significant differences were observed in connectivity between each node of the DMN and multiple clusters of the rest of the brain during ToM, indicating that the DMN is systemically dysregulated in patients during ToM related cognitive processing. Together, we interpret these findings and previous resting state findings (i.e., decreased DMN connectivity in patients compared to healthy participants) as meaning general dysregulation of the DMN both during resting state and task based conditions (Dauvermann et al., 2021; King et al., 2021).

4.3. IL-6 is directly associated with and mediates the association between CTQ-neglect and weaker suppression of the DMN during task based activity

Our observation that higher IL-6 mediates the relationship between physical neglect and weaker suppression of DMN connectivity during ToM performance builds on recent studies in which we observe that both IL-6 and the DMN mediate the effects of physical neglect on behavioural measures of social cognition. The present study extends these previous findings by demonstrating that IL-6 mediates the relationship between childhood trauma and atypical DMN connectivity not only during rest but also during social cognitive task performance in the scanner. This is important because it directly highlights the role of IL-6 in mediating the association between childhood traumatic effects and weaker suppression of DMN during social cognitive processing instead of indirectly via a correlation between DMN resting state connectivity and behavioural social cognitive performance. Our finding showing an association between IL-6 and DMN connectivity during the ToM condition between the mPFC and cerebellum is noteworthy. IL-6 appears to be specifically related to theory of mind processes in a manner directly associated with DMN connectivity with the cerebellum. The cerebellum has historically and primarily known for the regulation of movement. Recent evidence however demonstrates that the cerebellum also plays an important role in remembering emotional experiences (Fastenrath et al., 2022). Furthermore, the fact that the mediating associations of IL-6 between CT and increased connectivity (weaker suppression) between the PCC and left precentral and postcentral gyrus were no longer significant after correcting for both BMI or IQ needs to be highlighted. This finding is consistent with our recent study examining the mediating role of IL-6 between CT and ToM behavioural performance, which was also no longer significant when including BMI as a covariate (King et al., 2021). There is a growing body of evidence demonstrating associations between BMI, inflammation and cognitive performance (Balter et al., 2019; Balter et al., 2018) and the present findings suggests that BMI might be an important contributor towards DMN dysregulation and theory of mind deficits. Future neuroimaging studies are needed to confirm CT and IL-6 effects on DMN dysregulation during different cognitive processes, whilst at the same time correcting for these important confounds.

In summary, together with our earlier studies (King et al., 2021), this evidence suggests that low grade systemic inflammation (as indexed by IL-6) is a key mediator of atypical dysconnectivity of the DMN, i.e. in a manner relevant to social cognition. These studies build upon the growing literature demonstrating previous causal and association evidence of an immune basis for schizophrenia risk and cognitive function (Baumeister et al., 2016; Brydges and Reddaway, 2020; Dennison et al., 2012; Goldsmith et al., 2016; Khandaker et al., 2015; McKernan et al., 2011; Upthegrove and Khandaker, 2020). The association between higher levels of inflammatory markers and CT exposure has been studied across many conditions, including psychosis (Baumeister et al., 2016; Baumeister et al., 2014; Dennison et al., 2012; Goldsmith et al., 2016; McKernan et al., 2011). A meta-analysis of inflammatory markers and associations with CT exposure published in 2016 by Baumeister et al. (2016) found that low-grade systemic inflammation was dependent on the type of CT exposure (Baumeister et al., 2016).

Given the above evidence (described in section 4.2) of differences in both DMN network connectivity and social cognitive performance between patients and healthy participants, the fact that IL-6 was directly associated with and mediated the effects of CT on DMN connectivity and ToM task performance in both patients and healthy participants is noteworthy. Despite the fact that patients presented as expected with higher levels of CT, altered DMN connectivity and reduced social cognitive performance – the mediating effects of lL-6 on the association between CT on social cognition did not differ between the two groups. This suggests that the immune mediated effects of CT on social cognition do not explain schizophrenia-specific cognitive deficits or causal processes, but rather wider developmental effects observed in both patients and non-patients. This is consistent both with our previous studies of IL-6 mediated trauma effects (Dauvermann et al., 2021; King et al., 2021) and with our genetic studies of the complement system, indicating the broad developmental effects of this pathway on memory function that was observed across patients and controls. It is also consistent with our recent mendelian randomisation study of the association between IL-6 and brain structure, in which predicted IL-6 gene expression was associated with grey matter volume in the UK biobank (Williams et al., 2022). In terms of social cognition in schizophrenia, our findings here again suggest that CT associated effects of IL-6 represents a moderator of other potential causal factors of schizophrenia risk, rather than a causal factor in its own right.

4.4. Limitations and future directions

There are a number of limitations in this study which should be acknowledged. The childhood trauma questionnaire (CTQ) is a well-established tool for measuring past experiences of childhood trauma, however, as with all retrospective self-report questionnaires, there are limitations associated with this, due to recollection bias. However, as we discussed previously, there have been a number of studies investigating this problem, by comparing retrospective with prospective recall of traumatic experiences in childhood. The resulting evidence revealed moderate agreement between these measures and that both explained a similar amount of variation in negative life outcomes (Reuben et al., 2016). Furthermore, future studies could benefit from including mode detailed information on traumatic experiences, such as onset and duration.

Regarding some of the measures used in our study, active substance use was not assessed with UDS at study visits (only self-report measures were used) and thus, this could be considered a limitation. NSAIDs were only excluded if used in the 24 h from study visit and therefore this, also could be considered a limitation as the impact of such drugs on the brain may be a confound.

Finally, recent research by Marek and colleagues (2022) suggests that associations between resting-state fMRI measures and cognitive or clinical phenotypes are smaller than previously assumed and may require samples of thousands of individuals to identify. Our total sample of 227 participants is significantly higher than the median neuroimaging sample size, and we examined functional connectivity during a ToM task rather than during rest, which might show stronger associations with ToM behavioural performance. In addition, we cross-checked our findings with our behavioural data, showing a similar effect. Nevertheless, larger samples may be required to identify some of the associations between functional connectivity and cognitive and clinical phenotypes. Future studies should examine these associations in more detail, including the examination of additional immune markers.

5. Conclusion

In conclusion, exposure to early life stress, particularly physical neglect and levels of the pro-inflammatory cytokine IL-6 was found to predict increased DMN connectivity during ToM task performance, with IL-6 observed to mediate the relationship between early life physical neglect and ToM task based DMN connectivity. These findings extend our previous resting-state based DMN findings by demonstrating that IL-6 and early life stress is associated with atypical DMN connectivity during ToM task performance, and also with lower behavioural performance on the same ToM task. Collectively, the associations between childhood trauma, IL-6 levels, and ToM task based DMN connectivity suggest a potential developmental mechanism by which CT might be associated with difficulties with social cognitive ability. Future studies should examine these associations in more detail, including the examination of additional immune markers, BMI and different cognitive tasks.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Data availability

Data will be made available on request.

Acknowledgements

We sincerely thank all participants who took part in the study. We would also like to thank Karolina Rokita, Maria Dauvermann, Ruán Kane, Michael Gill, Laura Costello, Caroline Cullen, Niamh Daly Ryan, Laura McHugh, Ainé McNicholas, Marta Grzywacz, Cathal Ó Curraoin, and Catherine O'Donoghue for their assistance with the project. Conceptualisation and study design: S.K, D.M., G.D. Investigation: S.K Analysis: S.K Manuscript: S.K., D.M., G.D. Project coordination: S.K., G. D. All authors contributed to and approved the final version of the manuscript. S.K, D.M., K.I.R., L.H., R.K., D.P.M., J.P.K., D.W.M., A.C., R. McM., M.K., B.H., C.M., and G.D. reported no biomedical financial interests or potential conflicts of interest. This work was funded by grants to GD from the European Research Council (ERC-2015-STG-677467) and Science Foundation Ireland (SFI-16/ERCS/3787).

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