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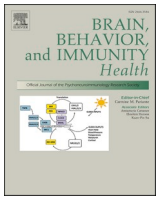

Childhood trauma and inflammatory biomarker effects on cortical thinning in schizophrenia spectrum disorders

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A B S T R A C T

Patients with schizophrenia spectrum disorders (SSD) have higher risks for early and adult life traumatic events and suffer from a heightened body response to stress and increased inflammatory activities. We hypothesize that in SSD, the effect of stress is associated with prolonged activation of the inflammatory system and causes elevation in immune markers. We examined the effects of childhood trauma and adult stressful life events on a C-reactive protein (CRP) and their combined contribution to cortical thickness thinning in 49 SSD patients and 26 healthy controls. Participants with SSD reported higher levels of childhood trauma ($p = 0.015$) and lifetime stressful experiences as measured by a Major Life Event scale ($p = 0.00005$). Participants with SSD had significantly lower cortical thickness in multiple brain regions but showed no significant elevation in the CRP levels. Only childhood trauma appears to have consistent and significant impacts on multiple cortical regions after accounting for age, sex, CRP and disease effects. These findings may point to the disproportional role of childhood stress in impeding early cortical development.

1. Introduction

Schizophrenia spectrum disorder (SSD) is a severe mental disorder that affects about 1 % of the population and is characterized by the presence of psychosis and cognitive deficits. SSD has complex and heterogenous pathological mechanisms (Kahn et al., 2015; Stępnicki et al., 2018; Tandon et al., 2009). People with SSD experience cortical thinning (Chiappelli et al., 2015; Shenton et al., 2001), reduction in white matter integrity (Shenton et al., 2001) and many other brain structural and functional deficits (Li et al.). Decreased cortical thickness in people with schizophrenia have been found in the frontal, temporal, occipital and some parietal regions of the brain (Rimol et al., 2010), which has been linked to inflammation and stress in numerous studies (Ji et al., 2022; Kang et al., 2024; North et al., 2021), although the underlying mechanism remains largely unknown. Several lines of evidence point to chronic inflammation, including elevated cytokines in the blood and cerebrospinal fluid (Baumeister et al., 2016), immune cell abnormalities (Foiselle et al., 2023), and altered inflammatory genes (Hennah et al., 2006), playing a causal role in the development of SSD. Chronic stress and/or abnormal stress regulations may also be among the possible mechanisms of the elevated neuroinflammatory process in schizophrenia (Chiappelli et al., 2015; Nugent et al., 2015; Stępnicki et al., 2018) (see Fig. 1).

There are several hypotheses on the causal link from stress/trauma and inflammation to schizophrenia (Chiappelli et al., 2016; Miller et al., 2011; Mongan et al., 2020). In rats, social isolation rearing as a developmental stress model induced significantly increased levels of inflammatory molecules (Ko and Liu, 2015). In humans with and without mental illness, childhood trauma has been linked to pro-inflammatory phenotypes (Dennison et al., 2012). Increased levels of C-reactive protein (CRP) have been found in patients with depression (Pace et al., 2006) and schizophrenia who have a history of childhood trauma (Quidé et al., 2019). Proposed theories include chronic stress leading to interference in cortisol's regulatory function in the immune system (Miller et al., 2007) and epigenetic changes in genes related to the hypothalamic-pituitary-adrenal (HPA) axis, leading to immune dysregulation in adulthood (Chen et al., 2021). Additionally, lower levels of brain-derived neurotrophic factor mRNA in the leukocytes of first-episode psychosis patients who have experienced psychosocial stressors have been found to be associated with decreased left hippocampal volume (Mondelli et al., 2011). It is hypothesized that this is likely through an increase in IL-6 expression (Mondelli et al., 2011).

CRP is one of the most common clinical generic indices for inflammatory processes, although the mechanisms linking CRP to different conditions are complex and not fully understood. It is hypothesized to be involved in many immune and non-immune functions from host defense,

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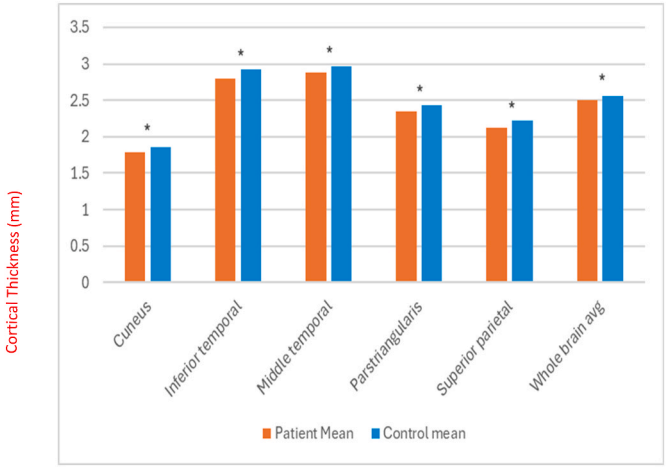

Fig. 1. Group Differences in Cortical Thickness. *Significant diagnosis effects based on linear regression from Table 3.

aiding early defense against infection, and enhancement of the innate immune response to inhibition of fibrinolysis and regulation of endothelial nitric oxide release (Du Clos, 2000; Singh and Chaudhuri, 2014; Sproston and Ashworth, 2018). Elevated levels of CRP have been found in schizophrenia although the findings are not consistent (Delaney et al., 2019; Perry et al., 2021; Singh and Chaudhuri, 2014). The increased inflammatory signaling based on CRP and other proinflammatory cytokines are thought to be related to abnormal microglial, neuronal, and glutamatergic neurotransmitter functions in schizophrenia (Williams et al., 2022). In addition, evidence has pointed to increased levels of CRP leading to reduced cortical thickness in people with schizophrenia (Chiappelli et al., 2017; Jacomb et al., 2018).

The role of neuroinflammation on brain abnormalities including abnormal grey matter volumes and cortical thinning found in most patients with schizophrenia has been hypothesized or examined (Fond et al., 2022; Liu et al., 2024). For example, elevated IL-6 has been related to decreased hippocampal volume in healthy (Marsland et al., 2008) and first episode psychosis patients (Mondelli et al., 2011). Similarly, increased levels of CRP are associated with decreased thickness in various cortical regions in patients with schizophrenia (Jacomb et al., 2018; North et al., 2021; Quidé et al., 2021). Childhood trauma has also been associated with structural and functional brain alterations (Grauduszus et al., 2024; Juruena et al., 2020; Quidé et al., 2021). However, it is unclear if trauma and inflammatory changes separately contribute to grey matter loss in schizophrenia. In this study, we tested whether the relationship between childhood trauma and increased inflammation can be replicated, and if so, whether they jointly or independently contribute to cortical changes in schizophrenia.

2. Materials and methods

2.1. Participants

The study included 124 SSD patients and 71 healthy controls with CRP data available (Table 1). Among them, 107 SSD and 56 controls also completed structural brain imaging. In addition, childhood trauma questionnaire (CTQ) measure was collected in 72 SSD and 39 controls and major life event (MLE) in 107 SSD and 61 controls, but only 49 SSD and 26 controls who had all whole-brain cortical thickness averages, CRP, CTQ and MLE measures available. Patients were recruited from the Maryland Psychiatric Research Center outpatient clinics and several neighboring mental health clinics in the Baltimore area. Controls were recruited from local media advertisements. Diagnoses in patients and absence of current DSM-IV or 5 Axis I diagnoses in controls were confirmed by the Structured Clinical Interview for DSM-IV or 5.

Table 1
Demographic and clinical characteristics.

	Schizophrenia n = 124	Healthy controls n = 70	t, F or χ^2	p
Age (years) (±SD)	37.11 ± 13.7	41.61 ± 15.79	4.31	0.04
Male/Female	90/34	34/36	11.74	0.0007
BPRS total score	36.02 ± 10.48	–	–	–
BNSS total score	27.09 ± 16.34	–	–	–
Antipsychotic Medication				
Typical only	20	–	–	–
Atypical only	90	–	–	–
Typical & Atypica	9			
Medication-free	5	–	–	–
CPZ equivalents (mg)	493.09	–	–	–
GAF total score	168.26 ± 51.42	280.21 ± 26.37	142.8	<0.001
CTQ total score	39.99 ± 19.85	33.69 ± 13.10	3.61	0.06
MLE total score	4.76 ± 2.31	3.63 ± 2.16	12.88	0.0004
Serum CRP	4.18 ± 5.12	2.18 ± 2.06	6.17	0.41
Race				
African American	57	35		
White	53	27		
Asian	7	4		
Hawaiian	0	1		
American Indian	1	1		
Other	4	3		

BPRS: brief psychiatric rating scale. BNSS: brief negative symptom scale. CPZ: Chlorpromazine. GAF: global assessment of functioning. CTQ: childhood trauma questionnairre. MLE: major life events. CRP: C-reactive protein. Five patients took both typical and atypical antipsychotic medications. Variance is measured by standard deviation.

Exclusion criteria were major medical and neurological illnesses, head injury, and substance dependence or substance abuse (except nicotine). Regarding antipsychotic medication, five SSD patients were not taking any antipsychotic medications, 90 were taking atypical, 20 were taking typical, and 9 were taking both atypical and typical antipsychotics (Table 1). All subjects gave their written informed consent approved by the local Institutional Review Board. People with SSD were evaluated for competence to understand the study before they gave written informed consent.

2.2. Assessments of symptoms and functioning

Overall clinical symptoms were assessed by the 20-item Brief Psychiatric Rating Scale (BPRS). Positive symptom score was obtained by the summation of sub-items (i.e., item 4, 7, 8, 11, 12, 15, and 20) of the 20-item version of the BPRS. The Brief Negative Symptom Scale (BNSS) was used to assess negative symptoms. The BNSS is a 13-item clinician-rated scale validated for the assessment of negative symptoms in SSD patients (Strauss et al., 2012). All BPRS and BNSS raters were formally trained until raters achieved acceptable reliability. The Mental Illness Research, Education, and Clinical Center (MIRECC) version of the Global Assessment of Functioning (GAF) was adopted for measuring global functioning.

2.3. Assessments of trauma and stress

Experiences of past childhood trauma were measured by the Childhood Trauma Questionnaire, the 28-item version (Bernstein et al., 2003). It categorizes childhood trauma into five subtypes: physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse. Each item was scored on a scale of 1–5. Total and subtype scores were obtained for each participant.

A self-report questionnaire was used to quantify lifetime major

negative stressful life events (Ma et al., 2023). Ten types of events were evaluated: 1) death of a family member or significant other, 2) experience of serious illness or injury, 3) significant other experience of serious illness or injury, 4) divorce or breakup of a relationship (you or your parents), 5) unusual, extreme stress at work or school, 6) experienced robbery, sexual assault or violence, 7) loss of primary job or substantial financial loss (you or your parent), 8) experienced legal disputes, 9) hospitalization due to physical or mental illness, and 10) other serious life event not listed. For each event, participants indicated the time at which they experienced the event (over 10 years ago, within 1–10 years, within 1 year or within 6 months), as well as their age at the time of the event. Total major life events (MLEs) were defined as the number of MLE types that the participant endorsed as ever experiencing.

2.4. Imaging data acquisition

A subset of participants (107 SSD and 56 controls) also completed structural brain imaging. All imaging was performed at the University of Maryland Center for Brain Imaging Research using a Siemens 3T Prisma MRI system (Erlangen, Germany) equipped with a 64-channel phase array head coil as previously described (Chiappelli et al., 2017). High-resolution, T1-weighted, 3D Turbo-flash sequence with an adiabatic inversion contrast pulse with the following scan parameters: TR/TI/TE = 2100/785/3.04 ms, flip angle = 13°, voxel size (isotropic) = 0.8 mm. To obtain high resolution cortical data, each subject was consecutively scanned two or more times using the same protocol, and a single image was obtained by linearly coregistering these images and computing the average that included a retrospective motion correction for quality control (Kochunov et al., 2006). The T1W image processing was conducted using the FreeSurfer software package. The analysis followed the procedures described by Fischl and Dale (2000). Computationally, cortical thickness was determined by measuring the distance between grey matter and white matter polygonal meshes. The grey matter thickness was measured as the Euclidian distance from the white matter mesh vertex to corresponding vertex on the grey matter mesh. We divided the cortical areas into 33 regions per hemisphere as described in van Erp et al. (2018) and Chiappelli et al. (Chiappelli et al., 2017). The primary measures are the whole-brain cortical thickness measurement that was obtained by averaging all regions.

2.5. Measurement of C-reactive protein

Blood samples were collected by venipuncture in gel barrier tubes by a certified phlebotomist at the Maryland Psychiatric Research Center. Blood samples were then assayed by CLIA lab for quantitative C-reactive protein, as measured by latex immunoturbidimetry. The minimum detectable limit is 0.1 mg/L.

2.6. Statistical analysis

Group differences in childhood trauma, stressful life events, and CRP were examined using analysis of covariance (ANCOVA) corrected for age and sex. To detect group differences, a minimum sample size of N = 64 per group (total N = 128) is needed to detect a medium effect size (Cohen's d = 0.5) with a power of 80 % at alpha = 0.05, suggesting adequate power for some but not all of the analyses. Correlations between CRP and stressful life events were examined using Kendall's correlation. To detect a significant Kendall's correlation, a sample size of N = 38 is needed to detect a Kendall's tau of 0.15 with a 95 % confidence interval of a width of 0.01, suggesting adequate power for most of correlation analyses. Each brain region was examined using the linear regression model *cortical thickness* ~ *Age* + *sex* + *childhood trauma* + *MLE* + *CRP* + *diagnosis*. To detect a significant association between cortical thickness, childhood trauma, MLEs, CRP or diagnosis, a sample size of N = 55 is needed to detect a medium effect size ($f^2 = 0.15$) with a power of 80 % at alpha = 0.05. For models that were significant after correction for multiple comparisons (at $p < 0.05/34 \sim 0.002$), we reported any predictors of interest (childhood trauma, MLE, CRP, diagnosis) that were significant (at $p < 0.05$). If diagnosis and childhood trauma, MLE or CRP were significant, we also explored whether there was diagnosis interaction with childhood trauma, MLE and/or CRP by adding an interaction term to the model, followed by examination of patient and control groups separately. Exploratory correlation analyses were performed between Global Assessment of Functioning total score, CPZ equivalents, BPRS total score and positive symptom scores and BNSS total score.

3. Results

3.1. Group differences in stress experience

There were significant differences in age and sex ratio in the patient vs. control groups (Table 1). For childhood trauma, SSD patients (N = 72) had higher CTQ total scores than controls (p = 0.06) (N = 39), though not significant. However, subscale scores for the SSD group revealed significantly higher CTQ scores for physical abuse (p = 0.004), sexual abuse (p = 0.006), and emotional abuse (p = 0.020), but physical neglect (p = 0.06) and emotional neglect (p = 0.23) were not significantly different compared to healthy controls. Only physical abuse and sexual abuse were significant after Bonferroni correction for multiple comparisons on subscale scores, which were summed together for a childhood physical/sexual trauma score (PST score) that was treated as the primary childhood trauma measures in subsequent analyses.

SSD patients (N = 107) also reported a significantly higher number of major life events (MLE score) compared to healthy controls (N = 61) (p = 0.0004).

3.2. Group differences in CRP

CRP data were log-transformed to achieve a normal distribution. There was no significant difference between SSD patients (N = 124) and healthy controls (N = 71) in log-transformed CRP (F = 0.68, p = 0.41) after controlling for age and sex.

3.3. Relationship between stress and CRP

Childhood trauma as measured by CTQ total score, and all subscale scores showed nominally significant positive correlations with CRP levels in both patients (N = 72) and controls (N = 39). After Bonferroni correction for multiple comparisons, childhood physical abuse and sexual abuse are significantly positively correlated with higher adulthood CRP levels in patients (Table 2). The primary childhood PST score was significantly correlated with CRP in SSD (N = 72) and but not in controls (N = 39). No significant correlation was found in any other trauma measures in the controls after correction for multiple

Table 2
Relationship between stress and C-reactive protein.

	Schizophrenia		Healthy controls	
	tau[c]	p	tau[c]	p
Emotional Abuse	0.13	0.04[a]	0.18	0.05[a]
Physical Abuse	0.20	0.003[b]	0.21	0.03[a]
Sexual Abuse	0.20	0.005[b]	0.22	0.03[a]
Physical + Sexual Abuse	0.23	0.01	−0.03	0.79
Emotional Neglect	0.15	0.03[a]	0.17	0.05[a]
Physical Neglect	0.14	0.04[a]	0.18	0.05[a]
Total CTQ	0.17	0.009[a]	0.18	0.05[a]
Total MLEs	0.12	0.1	0.12	0.2

[a] Nominally significant.
[b] Significant after Bonferroni correction for multiple comparisons.
[c] Statistics were analyzed with a nonparametric test. Tau is the statistic from Kendall's test.

comparisons. The MLE score was not significantly correlated with levels of CRP in patients or controls (Table 2).

3.4. Contributions of trauma, CRP and diagnosis on cortical thickness

Our primary analysis was on whole-brain cortical thickness averages, conducted in 49 SSD and 26 controls with all imaging, CRP, PST and MLE measures available. Linear regression that covaried for age and sex showed that patients had significantly reduced whole-brain cortical thickness compared with controls ($t = -3.27$, $p = 0.002$). We then added CRP, PST or MLE one at a time to a hierarchal regression analysis to identify potential moderating variables and found that adding CRP ($t = -0.40$, $p = 0.67$) or MLE ($t = -1.43$, $p = 0.16$) did not explain a significant proportion of the variance in the whole-brain cortical thickness and did not significantly change the diagnosis effect ($t = -2.28$, $p = 0.03$). However, adding PST showed that higher PST was significantly contributed to whole-brain cortical thickness ($t = -2.30$, $p = 0.024$) while the diagnosis effect on cortical thickness was reduced ($t = -2.45$, $p = 0.017$), suggesting that PST (but not MLE or CRP) explained a significant proportion of the variance of whole-brain thickness when included in the model. Finally, to examine whether PST was moderating the effect of diagnosis on cortical thickness, we added a diagnosis × PST interaction term to the model. There was no significant diagnosis × PST interaction ($t = 0.95$, $p = 0.35$).

We repeated the above regression analyses on each of the 33 regions to explore regional specific effects and found 5 regions that showed significant diagnosis effects after covarying for age and sex and after correction for multiple comparison ($p \leq 0.002$) (Table 3, Fig 1). We then added CRP, MLE and PST one at a time to the regression analysis on these 5 regions and found that MLEs and CRP were not significant in any of these models. However, PST was significant in 2 of the 5 significant regions: the middle and inferior temporal cortices (Table 3). The SSD diagnosis effect on cortical thickness was also reduced (from $t = -3.16$, $p = 0.002$ and $t = -3.78$, $p = 0.0003$) without PST to ($t = -2.39$, $p = 0.02$ and $t = -2.81$, $p = 0.006$) after adding PST, suggesting that PST may be a moderator of the diagnosis effects on the middle and inferior temporal cortices. To formally test for these moderating effects, we added a diagnosis × PST interaction term to the model, and there was no significant diagnosis × PST interaction ($t = 1.22$, $p = 0.23$ and $t = -0.19$, $p = 0.85$, respectively) on cortical thickness for middle or inferior temporal cortices.

To further explore if cortical thinning in patients was due to diagnosis and/or childhood trauma history, we performed a median split of patients by CTQ total score. Patients with low CTQ (≤38) showed nominally significant correlation between cortical thickness and trauma history in the pericalcarine only ($R = 0.96$, $p = 0.04$, uncorrected). However, patients with high CTQ (>38) showed nominally significant correlations with trauma history in the lingual ($R = -0.74$, $p = 0.01$), parsorbitalis ($R = -0.68$, $p = 0.03$), parstriangularis ($R = -0.68$, $p = 0.03$), rostral anterior cingulate ($R = -0.79$, $p = 0.006$) and superior parietal ($R = -0.81$, $p = 0.004$) regions, suggesting that the effects were mostly in patients experiencing higher levels of adversities in childhood.

Given the generally higher rates of sexual abuse reported in females, we also explored whether there was a significant difference in the relationship between current CRP and childhood sexual abuse in patient and control males and females. We found that there were no significant sex differences in the relationship between current CRP and reported childhood sexual abuse based on CTQ.

3.5. Relationship to symptoms and antipsychotic medications

CRP was significantly correlated with GAF total score ($N = 72$, $r = -0.25$, $p = 0.04$) in patients. However, CRP was not significantly correlated with BPRS total score ($N = 71$, $r = 0.12$, $p = 0.34$), the positive symptom subscale of BPRS ($r = 0.22$, $p = 0.08$) or BNSS total score ($N = 67$, $r = 0.05$, $p = 0.68$) in patients. CTQ total score was significantly correlated with BPRS total score ($r = 0.27$, $p = 0.04$), but not the positive symptom subscale of BPRS ($p = 0.09$), GAF total score ($r = -0.12$, $p = 0.33$) or BNSS total score ($p = 0.60$). The PST score from the CTQ was significantly correlated with BPRS positive symptoms ($r = 0.32$, $p = 0.01$), but not BPRS total score ($r = 0.21$, $p = 0.09$), GAF total score ($r = -0.12$, $p = 0.33$) or BNSS total score ($r = -0.10$, $p = 0.43$). The total number of MLEs was significantly correlated with BPRS total score ($r = 0.48$, $p = 0.0003$) and the positive symptom subscale of BPRS ($r = 0.44$, $p = 0.0009$), but not BNSS total score ($r = 0.04$, $p = 0.79$) or GAF total score ($r = -0.09$, $p = 0.51$).

CPZ equivalent was not significantly correlated with CTQ total score ($p = 0.06$), PST score ($p = 1$), MLE score ($p = 1$) or CRP ($p = 0.83$).

4. Discussion

In this study, we explored the relationship between history of severe stress (childhood trauma and major life events) and inflammation (using CRP as the immune marker) in adulthood, and their potential contributions to brain cortical thickness in SSD patients and healthy controls. We found that patients had significantly more childhood trauma, more major life events, and reduced whole-brain and multiple regional cortical thickness. Childhood trauma, specifically childhood physical abuse and sexual abuse, was positively correlated with CRP level in adult patients and negatively associated with whole-brain cortical thickness and in several brain regions.

We originally considered that the relationship between childhood trauma and the brain changes found in SSD are mediated by inflammation (Baumeister et al., 2016; Dennison et al., 2012; Grauduszus et al., 2024; Jacomb et al., 2018). Chronic stress-related inflammations could act like inflammatory conditions from infection during fetal development and childhood that have been found to increase the risk of developing a psychotic illness during adulthood (Khandaker et al., 2013, 2014). Early life adversity is known to increase inflammatory cytokines in SSD through epigenetic changes (Løkhammer et al., 2022) and by altering the relationship between the brain and the immune system (Danese and J Lewis, 2017). However, we found no significant associations between CRP and cortical thickness, although this lack of association cannot rule out the inflammation link, as stress-related inflammatory effects may occur during the post-trauma early development, but direct evidence may be less obvious in adulthood;

Table 3
Contributions of Childhood Physical/Sexual Trauma (PST score), CRP and Diagnosis on Cortical Thickness. Statistics were based on linear regression models using diagnosis as the predictor; for significant models, CRP, PST or MLE were added.

	Diagnosis Only		Adding CRP		Adding PST		Adding MLE	
	t	p	t	p	t	p	t	p
Whole brain average	−3.27	0.002*	−0.40	0.67	−2.3	0.02*	−1.43	0.16
Parstriangularis	−3.37	0.001*	−0.09	0.93	−1.45	0.15	−0.72	0.47
Superior parietal	−3.73	0.0004*	−0.69	0.49	−0.82	0.41	−0.93	0.36
Cuneus	−3.43	0.001*	−1.01	0.31	1.32	0.19	0.02	0.98
Middle temporal	−3.16	0.002*	−0.16	0.87	−2.06	0.04*	−0.91	0.37
Inferior temporal	−3.78	0.0003*	0.04	0.97	−3.07	0.003*	−0.82	0.41

alternatively, CRP may not be a sensitive enough marker to capture this process or may be affected by the anti-inflammatory effect of antipsychotic medications.

We found that SSD had significantly reduced whole-brain cortical thickness, with regional analysis showing the strongest thinning at pars triangularis, the superior parietal lobule, the cuneus, and the middle and inferior temporal cortex. Pars triangularis is the part of the inferior frontal lobe that is involved in communication functions from language semantic processing tofacial expression to modulation of speech tone (Beharelle and Small, 2016). The superior parietal lobule is involved in diverse functions from visuospatial processing to working memory and multiple executive functions (Koenigs et al., 2009). The cuneus is part of the occipital cortex posteriorly adjacent to the temporoparietal cortices, serving many visual and object recognition functions (Harvey et al., 2011), and its volume or thickness has been found to be reduced in SSD (Koenigs et al., 2009; Reavis et al., 2017; Rimol et al., 2010). Reduced middle and inferior temporal cortical volumes have long been observed as one of the most prominent abnormalities in schizophrenia brain imaging studies, occurring even at disease onset, and thought to be related to language and semantic memory, visual perception, and multimodal sensory integration abnormalities in SSD (Løkhammer et al., 2022; Tang et al., 2012).

The primary findings were that contributions of specific childhood adversity, i.e., physical/sexual trauma, reported by SSD patients appeared to have significant associations with the thinning of whole-brain cortical thickness. We found that, after covarying for age and sex in the regression model, both SSD and physical/sexual trauma history significantly contributed to whole-brain and inferior and middle temporal cortical thinning. There were no significant diagnosis by trauma history interactions, and the effect by SSD diagnosis is partially moderated by the trauma history, but SSD still significantly affects cortical thinning independent of the trauma history (Table 3).

The middle and inferior temporal cortex is located on the lateral and ventral surface of the temporal lobe and has been suggested to be associated with language and semantic memory processing (Cabeza and Nyberg, 2000), multimodal sensory integration (Mesulam, 1998), and visual and object perception processing (Ishai et al., 1999). Decreased grey matter volume in the temporal gyrus in SSD was associated with auditory hallucinations (Barta et al., 1990; Onitsuka et al., 2004; Rimol et al., 2010) and deficits in cognitive domains associated with the middle and inferior temporal gyrus, such as language (Stephane et al., 2007), semantic memory (Tan et al., 2020) and complex visual perception (Phillipson and Harris, 1985) have been reported in schizophrenia. Adding to these, our data suggested that the middle and inferior temporal gyri are particularly vulnerable to the 'double-hit' of schizophrenia and childhood physical and sexual trauma, although these effects were also seen globally based on the whole-brain average data.

We also found that PST scores were positively correlated with positive symptoms, as measured by the BPRS. While this may be indicative of childhood physical and sexual abuse increasing positive symptoms in adulthood, it is also possible that positive symptoms of psychosis can lead to biased recall and reporting of childhood events. In order to differentiate the order of these factors, methods other than retrospective self-reporting may need to be utilized in the future to better gauge trauma history of those with SSD.

The study has several limitations. Due to the nature of human subject research, not all study components were completed by each participant. Because of this, the full sample size of 124 patients and 71 controls with CRP data was reduced to 49 patients and 26 controls for the primary analysis of cortical thickness, CRP, CTQ and MLEs. The patient and control samples were not matched for sex and age, which may introduce potential confounding effects not fully correctable by using them as covariates. The study is cross-sectional, and the stress measures are based on retrospective self-report, precluding a causal inference on the relationship between past stress and current cortical thickness measures. Ideally, future studies will need to be conducted to determine the directionality of the relationship of CRP, childhood trauma and cortical thickness through prospective study designs. The use of CRP as a sole marker of inflammation may be somewhat unreliable due to inconsistencies in the literature regarding increased CRP in those with SSD, however it was the only inflammatory marker collected for the present study. For future studies, adding additional inflammatory markers such as interleukins and tumor necrosis factor-alpha may prove to be beneficial to clearly assess inflammatory effects. Because we found a relationship between PST and whole brain cortical thickness but not CRP and MLE, future studies will be needed to determine if there are other mechanisms in which PST may impact cortical thinning. For example, one may explore HPA axis dysfunction through cortisol or adrenocorticotropic hormone and other biomarkers such as blood and cerebrospinal fluid levels of brain-derived neurotrophic factor. Additionally, our population of SSD patients are not medication-naïve, which may affect inflammatory markers due to antipsychotic medications' effect on inflammation in the body. We were able to calculate average CPZ equivalent dosing for patients on medication, which was not significantly correlated with CRP. However, we were unable to obtain average time participants were on these medications due to irregular and unreliable self-reporting. Time on medication and the chronicity of the disorder may be another factor that can affect inflammation in this population. In the future, our goal will be to collect time diagnosed and time on medication to better control for these confounds.

In conclusion, our study highlighted the disproportional detrimental roles of childhood physical and sexual trauma on the cortical thinning that may add to the disease effects in patients with schizophrenia spectrum disorders.

CRediT authorship contribution statement

Samantha Narvaez: Writing – review & editing, Visualization, Investigation, Data curation, Writing – original draft, Resources, Formal analysis, Conceptualization. **Yizhou Ma:** Writing – review & editing, Data curation. **Joshua Chiappelli:** Writing – review & editing, Conceptualization. **Hemalatha Sampath:** Formal analysis, Data curation. **Alia Warner:** Writing – review & editing. **Peter Kochunov:** Writing – review & editing, Data curation, Software. **Giselli Scaini:** Writing – review & editing. **Anilkumar Pillai:** Writing – review & editing. **L. Elliot Hong:** Writing – original draft, Resources, Funding acquisition, Writing – review & editing, Supervision, Methodology, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: LEH has received or plans to receive research funding or consulting fees on research projects from Mitsubishi, Your Energy Systems LLC, Neuralstem, Taisho, Heptares, Pfizer, Luye Pharma, Sound Pharma, IGC Pharma, Takeda, Regeneron, and Alto Neuroscience. None of these entities was involved in the design, analysis, or outcomes of the study. All other authors have no conflicts of interest to disclose, financial or otherwise.

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Data availability

Data will be made available on request.

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