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Full-length Article

Inflammatory markers (IL-6 and CRP) in childhood and their association with brain structure and psychotic experiences in adulthood

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A B S T R A C T

Aims: Inflammation is a risk factor for psychosis, yet the mechanisms underlying this association remain unclear. Elevated levels of the inflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6) in childhood have been associated with increased risk of developing later psychotic experiences (PEs) and psychotic disorders. This study investigates whether CRP and IL-6 levels at age 9 are associated with brain grey matter volume at age 20, and whether this association differs between individuals with and without PEs. We hypothesise that childhood inflammation will be linked to altered grey matter volumes in adulthood, and this association will be strongest among those who develop PEs.

Methods: In the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, MRI scans were acquired at age 20 years in participants with PEs (n = 71) and controls without PEs (n = 173). Voxel-based morphometry examined the association between childhood CRP or IL-6 and grey matter volume in adulthood, with interaction analyses testing for group differences by PEs status.

Results: In all participants (PEs and controls) elevated IL-6 in childhood was associated with smaller grey matter volume in adulthood, in several cortical regions which did not reach significance. After excluding 4 subjects with potential acute infection, IL-6 was associated with smaller grey matter volume in the left supramarginal gyrus (pFWE = 0.028, Z = 4.24, family-wise error (FWE) corrected), right parahippocampal gyrus (pFWE = 0.047; Z = 4.21; 292 voxels), and left precuneus (pFWE = 0.035; Z = 3.65). No interaction between IL-6 and PEs group on grey matter volume was found.

A significant interaction between CRP and PEs group was observed on grey matter volume (pFWE = 0.013, Z = 4.13). Elevated CRP levels in childhood were associated with larger right superior frontal gyrus volume in individuals with PEs, whereas CRP did not impact grey matter volume in controls. Effect sizes reduced after excluding 5 subjects with potential acute infection.

Conclusions: These findings suggest that individuals who go on to develop PEs were more vulnerable to the effects of circulating CRP on grey matter volume, consistent with a possible disease-specific pathway linking inflammation to psychosis. In contrast, IL-6 was associated with smaller volume in regions of the default mode network regardless of PEs, suggesting a more general effect on brain development.

1. Introduction

The causes of schizophrenia and psychotic disorders are multifactorial, arising from a complex interplay between genetic predisposition, environmental exposures, and immune system dysregulation (Oliver et al., 2024). Meta-analyses report elevated levels of

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peripheral inflammatory markers in individuals with psychotic disorders, particularly interleukin-6 (IL-6) and C-reactive protein (CRP) (Upthegrove et al., 2014; Pillinger et al., 2019; Misiak et al., 2021). Moreover, a meta-analysis reports longitudinal associations, as higher premorbid CRP levels are associated with an increased risk of developing later psychosis (Osimo et al., 2021). However, the biological mechanisms by which inflammation increases the risk of psychosis remain poorly understood. It is hypothesised that inflammation influences brain structure and function to predispose individuals to develop mental disorders (Kose et al., 2021). However, longitudinal studies assessing the impact of early inflammation on later brain structure are lacking.

Childhood may represent a critical period during which inflammation could influence the risk of developing psychosis. Central nervous system (CNS) infections in childhood are associated with an almost twofold increase in the risk of adult schizophrenia (Leask et al., 2002; Koponen et al., 2004; Khandaker et al., 2012; Dalman et al., 2008). Similarly, findings from the Avon Longitudinal Study of Parents and Children (ALSPAC) show that elevated CRP (Palmer et al., 2024), and IL-6 (Perry et al., 2021; Khandaker et al., 2014) levels at age 9 increase the likelihood of developing psychotic experiences (PEs) and psychotic disorders in early adulthood. Childhood may represent a particularly sensitive period, as it coincides with major neurodevelopmental changes in the brain (Merritt et al., 2021).

Psychotic disorders are associated with characteristic changes in brain structure, particularly reductions in grey matter volume (Merritt et al., 2023; Fonville et al., 2019; Drakesmith et al., 2016; Si et al., 2024; Liloia et al., 2021; van Erp et al., 2018; García-San-Martín et al., 2025). However, the contribution of inflammatory processes to these volume alterations is not well understood. Peripheral inflammatory markers can directly enter the brain (Nusslock and Miller, 2016; Khandaker and Dantzer, 2016). Once in the CNS, circulating cytokines can activate microglia, which play a role in oxidative stress and synaptic pruning in neurodevelopment, potentially impacting grey matter volume (Khandaker and Dantzer, 2016). Research into how inflammation affects the brain is an emerging field with mixed findings to date. Elevated levels of inflammatory markers in the blood are associated with both increased and decreased brain volume and thickness, suggesting that the effect of inflammation varies by brain region, the specific inflammatory marker studied, and also by an individual's age or diagnostic status (Orellana et al., 2024; Williams et al., 2022).

Analyses of the UK Biobank population sample (average age ~ 60 years) have examined the effects of both serum and genetically predicted levels of IL-6 and CRP on the brain. Elevated serum CRP was associated with increased cortical thickness in extensive fronto-parietal brain regions, with reduced thickness identified in fewer areas, including temporal and primary motor cortex, and subcortical regions in the pallidum, thalamus and insula (Orellana et al., 2024). Similarly, genetically predicted levels of CRP were associated with larger cortical volume in the superior frontal cortex, though this did not survive correction for multiple comparisons (Upthegrove et al., 2014). A different pattern of results was seen for IL6: genetically predicted levels of IL-6 was associated with reduced thickness in the superior frontal region and increased volume and cortical thickness in the middle temporal gyrus (Williams et al., 2022). In contrast, serum IL-6 levels were not associated with volume increases, but rather with reductions predominantly in subcortical regions (thalamus, hippocampus, basal ganglia) and to a lesser extent in the cortex (fusiform cortex) (Zhao et al., 2024).

In patients with established psychotic disorders, inflammation is often associated with brain volume reductions: CRP is most consistently associated with reduced cortical thickness in frontal (Jacomb et al., 2018; North et al., 2021; Cannon et al., 2015) and temporal brain regions (Jacomb et al., 2018; Lizano et al., 2021), but some studies find reductions in insula (Jacomb et al., 2018) or parietal and occipital lobe (Lizano et al., 2021), and larger putamen volume (Lizano et al., 2021). In a study of bipolar disorder, a significant CRP-by-diagnosis interaction was found in frontal (Vai et al., 2022) and temporal regions, whereby higher CRP was associated with lower volume and thickness metrics in the bipolar group but higher metrics in controls (Shao et al., 2023). Serum IL-6 and IL-6 mRNA were associated with smaller left hippocampal volume in first-episode psychosis patients (Mondelli et al., 2011; Miller et al., 2021), whilst one study found increased cortical thickness in the temporal and inferior frontal gyrus (Wu et al., 2019). A longitudinal study following youth at clinical high risk of psychosis found that prefrontal thinning associated with transition to psychosis was most severe in those with high levels of baseline proinflammatory cytokines, indicating that brain structure may be differentially affected by cytokines based on timing and disease stage (Cannon et al., 2015).

The majority of MRI studies to date have employed cross-sectional designs that measure inflammation and brain structure at a single timepoint, which cannot establish temporal relationships. Additionally, many large-scale studies have focused on older adult populations, missing earlier neurodevelopmental stages that may be critical to understanding psychosis onset. Studies in patients with schizophrenia may capture grey matter volume changes associated with chronicity of disease, such as antipsychotic treatment, rather than changes associated with inflammatory processes.

The current study addresses these gaps by examining whether early-life inflammation—measured at age 9—is longitudinally associated with brain structure at age 20, and whether this association differs between individuals who report psychotic experiences (PEs) and those who do not. PEs are subclinical psychotic symptoms which occur in 5–10% of the general population and are associated with an increased risk of developing later mental disorders including psychosis (Sullivan et al., 2020). Based on previous reports, we hypothesise that high levels of IL-6 and CRP at age 9 will be associated with significant changes in grey matter volume in adulthood, and these associations could be moderated by the presence/absence of PEs.

2. Methods

Participants were drawn from the UK ALSPAC; a population-based birth cohort from the Southwest of England (http://www.bristol.ac.uk/alspac/) (Boyd et al., 2013; Fraser et al., 2013; Niarchou et al., 2015; Northstone et al., 2019). Pregnant women resident in Avon, UK with expected dates of delivery between 1st April 1991 and 31st December 1992 were invited to take part in the study. Of the initial number of pregnancies (n = 15,447), 14,901 children were alive at 1 year of age.

IL-6 and CRP measures were derived from blood plasma collected at age 9 in the ALSPAC sample. IL-6 was measured by enzyme-linked immunosorbent assay (ELISA, R&D Systems). High-sensitivity CRP was measured by automated particle-enhanced immunoturbidimetric assay (Roche). CRP (mg/L) and IL-6 (pg/mL) were $\log_2$ transformed for all inferential analyses.

PEs were assessed at age 17–18 years by a psychologist using the Psychosis-Like Symptom Interview (Zammit et al., 2013), based on the Schedules for Clinical Assessment in Neuropsychiatry version 2.0 (WHO, 1994). PEs status was binarised into 'absent' or 'present' psychotic experiences: the PEs categories of 'suspected' (n = 22), 'definitely present' (n = 31) and 'psychotic disorder' (n = 18) were combined into the 'present' PEs group (n = 71) and compared to participants with absent PEs (n = 173). PEs excluded those that were attributable to the effects of sleep or fever.

This study combines MRI data from a neuroimaging study recruiting ALSPAC participants based on PEs (David study n = 252: 126 with PEs and 126 without PEs) (Merritt et al., 2023; Fonville et al., 2019; Drakesmith et al., 2016; Drakesmith et al., 2016; Drakesmith et al., 2015; Fonville et al., 2015) plus participants from an overlapping study sample recruiting ALSPAC participants on the basis of high or low polygenic risk scores for schizophrenia (Linden study n = 196, 12 with PEs and 149

without PEs, with 14 participants taking part in both studies) (Lancaster et al., 2019). Recruitment processes were otherwise identical and magnetic resonance imaging was carried out on the same scanner at age 20 years in 138 participants with PEs and 275 individuals without PEs serving as controls.

Written informed consent was obtained prior to scanning, and participants received financial compensation. Approval was granted by Cardiff University, the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Participants can contact the study team at any time to retrospectively withdraw consent for their data to be used. Study participation is voluntary and during all data collection sweeps, information was provided on the intended use of data.

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Bristol (Harris et al., 2009). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. The study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool http://www.bristol.ac.uk/alspac/researchers/our-data/.

2.1. MRI

MRI data were acquired at the Cardiff University Brain Imaging Centre (CUBRIC) on a 3T scanner (Signa HDx;GE Medical Systems) using an 8-channel head coil for radiofrequency reception. A high-resolution, 3D fast spoiled gradient-echo (FSPGR) T1-weighted isotropic image was oriented to the AC–PC line (TR = 7.8 ms, TE = 3 ms, inversion time = 450 ms, flip angle = 20°, field of view = 256 mm × 256 mm × 192 mm, 1 mm isotropic resolution) to assess grey matter volume.

2.2. Voxel-based morphometry (VBM) and statistical analyses

We conducted image preprocessing including segmentation and DARTEL normalisation using the Computational Anatomy Toolbox (CAT12, http://dbm.neuro.uni-jena.de/cat12/) for Statistical Parametric Mapping (SPM 12). 'Modulated' images corrected for non-linear deformations were used for analyses. Spatial smoothing used a Gaussian kernel of 8 mm full width at half maximum using SPM 12 standard routines.

Voxel-wise comparisons of modulated T1-segmented grey matter images were performed using two general linear models: (1) Interaction model: To determine whether IL-6 or CRP (continuous scale, $\log_2$ transformed) had differential effects on grey matter volume depending on PEs group (binary: no PEs/PEs), we tested the IL-6 × PEs and CRP × PEs interaction terms. (2) Main-effects model: To examine the association between IL-6 or CRP levels at age 9 and grey matter volume at age 20 across all participants, we tested each biomarker as a main effect. For VBM analysis, thresholds were set at $p < 0.001$ uncorrected at the voxel level, together with a family-wise error (FWE) correction for multiple comparisons at pFWE < 0.05 at the cluster level.

VBM models included the following covariates: age, sex, study (David or Linden), total intracranial volume (TIV) and maternal occupation at the time of child's birth (coded using OPCS job codes) as a measure of socioeconomic status (SES). In addition, interaction models included their respective main effects (CRP/IL-6 and PEs). Body mass index (BMI) at age 9 was added as a covariate as part of secondary analyses, as BMI at age 9 was not available for every participant. Similarly, antipsychotic medication use was added as a covariate as part of secondary analyses.

To minimise potential confounding by acute inflammation or infection, we repeated the original analyses after excluding participants with baseline CRP levels >10 mg/L, as this threshold is widely used as an indicator of suspected infection in clinical settings. However, there is no established clinical cut-off for IL-6 for this purpose. Therefore, we repeated analyses excluding values >4 standard deviations from the mean IL-6 concentration.

Significant cluster volumes from VBM analyses were extracted using the SPM toolbox 'MarsBaR' and were plotted using R (R Core Team. R, 2021) (version 4.4.2) and the package 'ggplot2'. The R script is available at github.com/katemerritt/inflammation/. For clusters showing significant interactions between IL-6/CRP and PEs status on grey matter volume, post-hoc analyses were conducted using the 'emtrends' function in R. This approach estimates the slope of IL-6/CRP on cluster volume within each PEs group, testing whether the slope differs significantly from zero while controlling for covariates. Regression plots adjusted for covariates were generated using the 'ggeffects' package to visualise the predicted slopes for each group. Images were edited using GIMP (GNU Image Manipulation Program) to remove backgrounds for visualisation purposes.

Inferential statistics on associations between PEs and demographic/inflammatory variables were conducted in R using Chi square (χ^2) for sex, t-tests for age, TIV and BMI. Logistic regression was used to examine associations between $\log_2$-transformed IL-6/CRP levels and PEs group status, with models run both unadjusted and adjusted for sex, BMI at age 9, and maternal SES.

3. Results:

MRI data were available for a total of 434 participants. 21 participants did not complete PEs assessments and were excluded. In the remaining sample, CRP and IL-6 data at age 9 were available for 244 participants ($n = 173$ without PEs, $n = 71$ with PEs). In the Supplement, see flow diagram (Fig. S1) and Table S1 to compare demographics between the full MRI sample and MRI sub-sample with CRP data available. While both biomarkers were available for 244 individuals, the samples differed slightly: one participant had CRP but not IL-6 data, and one had IL-6 data but not CRP. BMI was available for 242 of 244 participants for the CRP sample (2 missing), and 241 of 244 participants for the IL-6 sample (3 missing). Sample demographics are reported in Table 1. The PEs group were slightly younger at the time of scanning compared to controls without PEs ($p < 0.001$).

Table 1
Participant demographics and association between psychotic experiences (PEs) and inflammatory markers; C-reactive protein (CRP) and interleukin-6 (IL-6). Means and standard deviations shown. CRP and IL-6 were $\log_2$-transformed for all inferential analyses. X^2 = Chi-square statistic, df = degrees of freedom, OR = Odds Ratio (CRP was $\log_2$-transformed prior to analysis so the OR represents the change in odds of PEs per doubling of CRP concentration), 95% CI = 95% confidence interval.

	Control n = 173	PEs n = 71	Inferential statistics
Age at MRI	21.6 (1.5)	20.3 (1.1)	t = 7.73, df = 174.87, p < 0.001
Sex	77 male, 96 female	23 male, 48 female	X^2 = 2.57, p = 0.11
Total intracranial volume (TIV)	1454.01 (141.50)	1425.54 (166.61)	t = 1.26, df = 113.53, p = 0.21
BMI – Age 9	17.31 (2.39) n = 171	17.79 (3.20) n = 71	t = -1.13, df = 103.84, p = 0.26
Taking antipsychotic medication	n = 0	n = 4	
IL-6 (pg/mL) – Age 9	1.41 (1.77)	1.79 (2.33)	Unadjusted OR 1.13 [95% CI 0.93–1.39], p = 0.23
CRP (mg/L) – Age 9	0.91 (2.65)	1.10 (2.45)	Unadjusted OR 1.15 [95% CI 1.00–1.33], p = 0.05

3.1. Association between inflammatory markers and psychotic experiences

In the MRI sample, CRP at age 9 was elevated in those who went on to report PEs compared to controls (unadjusted OR 1.15 [95% CI 1.00–1.33], p = 0.05, Table 1), which attenuated after adjusting for sex, BMI at age 9 and maternal SES (OR 1.12 [95% CI 0.96–1.31], p = 0.16).

In the MRI sample, IL-6 at age 9 was not associated with later PEs (unadjusted OR 1.13 [95% CI 0.93–1.39], p = 0.23, Table 1 and adjusted OR 1.09 [95% CI 0.88–1.35], p = 0.42).

Inflammatory markers and grey matter volume

3.2. IL-6

No statistically significant interaction between IL-6 at age 9 and PEs on grey matter volume was observed (all clusters *p*FWE < 0.551). Therefore, we examined the main effect of IL-6 at age 9 on grey matter volume at age 20 across all participants. IL-6 was associated with reduced grey matter volume at age 20, although these effects did not reach significance (all clusters *p*FWE < 0.156; affected regions included parietal and hippocampal areas). Sensitivity analyses including BMI as a covariate did not alter the results (n = 241; BMI at age 9 was not available for all participants). Sensitivity analyses including antipsychotic medication as a covariate did not alter the results (4 subjects were receiving antipsychotic medication).

After excluding four subjects with potential infection at baseline (IL-6 values > 4 SD from the mean), a significant main effect of IL-6 on grey matter volume was observed in several cortical regions: elevated IL-6 was associated with smaller volume in the left supramarginal gyrus (*p*FWE = 0.028; −48, −36, 33; *Z* = 4.24; 328 voxels, Fig. 1), right parahippocampal gyrus (*p*FWE = 0.047; 24, –22, −26; *Z* = 4.21; 292 voxels), and left precuneus (*p*FWE = 0.035; 0, −42, 57; *Z* = 3.65; 313 voxels). There was no evidence for an interaction between IL-6 and PEs group (all clusters *p*FWE < 0.143).

3.3. CRP

To assess whether the effect of CRP on grey matter volume differed by PEs status, we examined the CRP × PEs interaction. A significant interaction was observed in the right superior frontal gyrus (*p*FWE = 0.013; 12, 42, 50; *Z* = 4.13; 389 voxels, Fig. 2). Post-hoc analyses showed that among participants with PEs, higher CRP levels were associated with larger superior frontal gyrus volume (β = 0.0093, p < 0.001, 95% CI: 0.0048, 0.0137), whereas in controls, CRP was not associated with volume in this region (β = –0.0019, p = 0.201, 95% CI: –0.0047, 0.0010).

There was no statistically significant main effect of CRP at age 9 on grey matter volume at age 20 across all participants (all clusters pFWE < 0.218).

Sensitivity analyses including BMI at age 9 as a covariate did not alter the results (n = 242, BMI was not available for all participants). Sensitivity analyses including antipsychotic medication as a covariate did not alter the results (4 subjects were receiving antipsychotic medication). After excluding five subjects with potential infection at baseline (CRP > 10 mg/L), the interaction remained significant after false discovery rate (FDR) correction (*p*FDR = 0.010) and approached significance after FWE correction (*p*FWE = 0.098; 12, 44, 51; *Z* = 3.82; 248 voxels).

4. Discussion

This study examined the association between childhood inflammatory markers (IL-6 and CRP) and grey matter volume in early adulthood. After excluding subjects with potential infection, elevated IL-6 levels at age 9 were associated with smaller grey matter volumes at age 20 in regions of the default mode network (DMN), specifically the precuneus, parahippocampal and supramarginal gyri. In contrast, the effects of CRP on grey matter volume varied according to psychotic experiences (PEs) status: among individuals who developed PEs, elevated childhood CRP

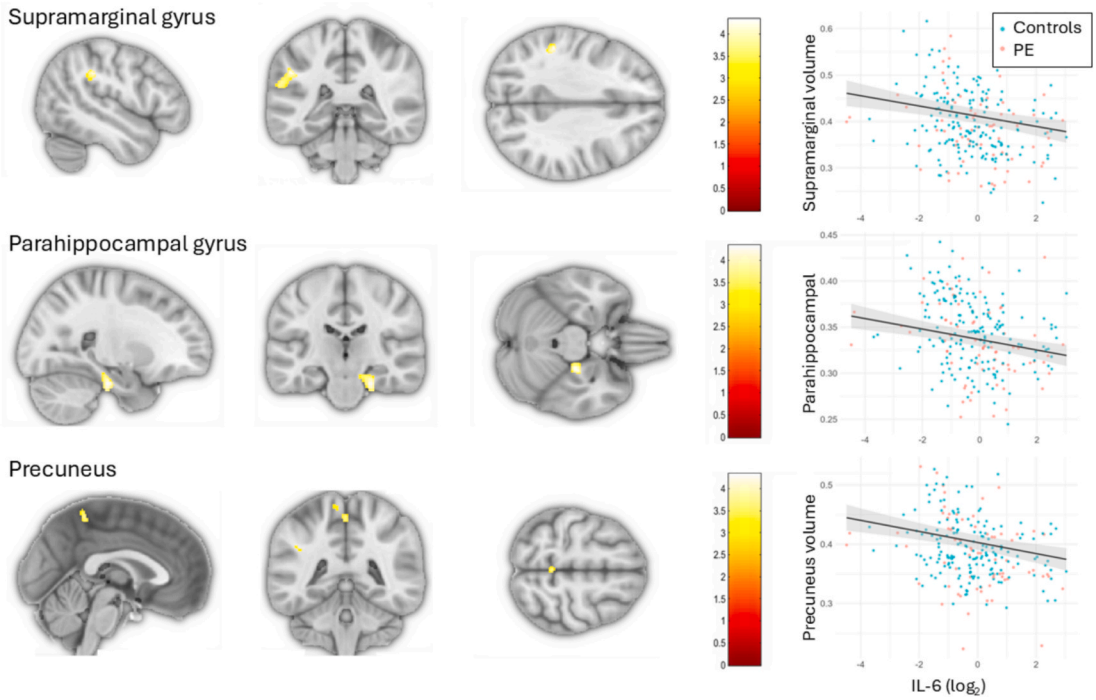

Fig. 1. Main effect of IL-6 on grey matter volume across all participants. Elevated IL-6 levels at age 9 were associated with significantly smaller gey matter volume at age 20 in the left supramarginal gyrus (pFWE = 0.028), right parahippocampal gyrus (pFWE = 0.047), and left precuneus (pFWE = 0.035). Colour bars (white–yellow–red) indicate Z-score effect sizes. Grey matter volume at age 20 is plotted against IL-6 (log2-transformed) for each significant cluster. Regression lines show predicted values from the covariate-adjusted model, and the shaded area represents the 95% confidence interval around these predictions. Raw data points are overlaid for reference where controls are shown in blue and participants with PEs shown in red.

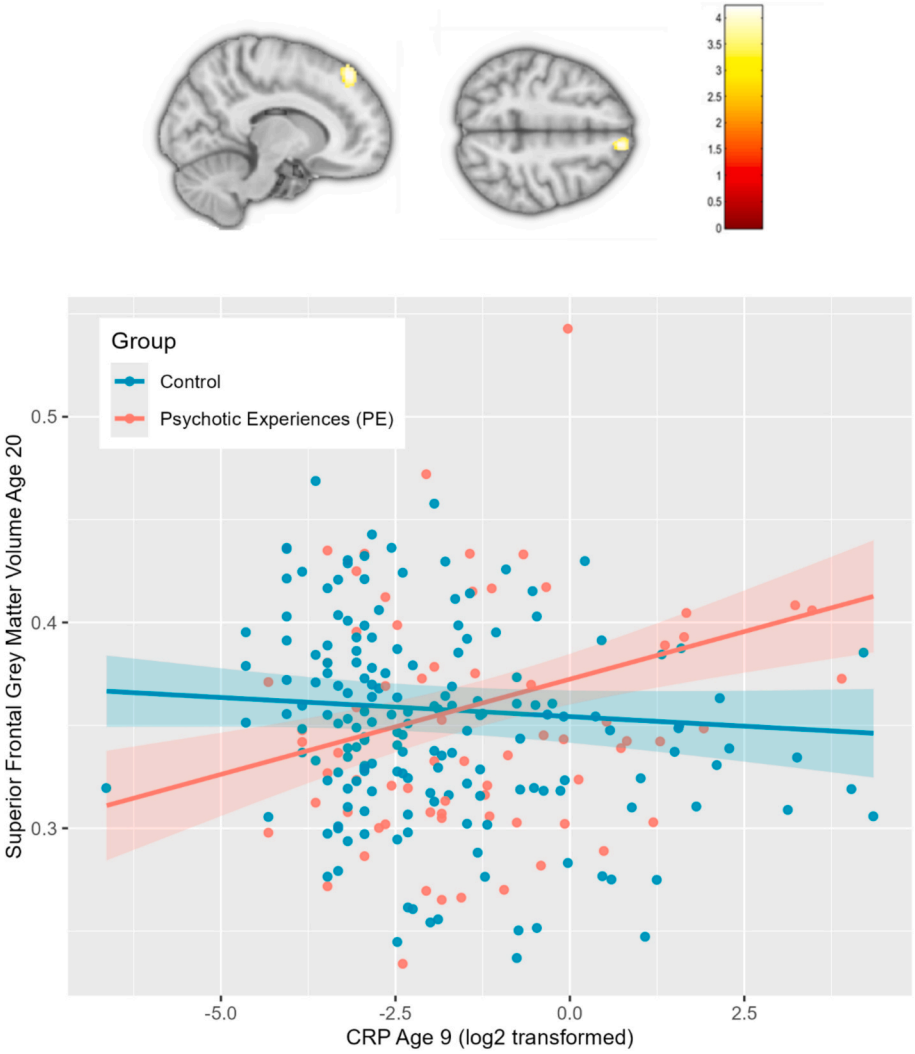

Fig. 2. Significant interaction between CRP level and psychotic experiences (PEs) in the right superior frontal gyrus. Elevated CRP was associated with larger superior frontal gyrus volume in those with PEs (shown in red), whereas CRP was not associated with superior frontal gyrus volume in controls (shown in blue). Heatmap colour bars (white–yellow–red) indicate Z-score effect sizes. Predicted superior frontal grey matter volume at age 20 is plotted against CRP levels at age 9 (log2-transformed) for each group (controls or PEs). Regression lines show predicted values from the covariate-adjusted model, and the shaded area represents the 95% confidence interval around these predictions. Raw data points are overlaid for reference.

was linked to larger volume in the superior frontal gyrus, whereas CRP had no effect on grey matter volume in controls. These findings suggest a potential dynamic neurobiological pathway through which childhood inflammation may contribute to the later development of psychotic disorders.

Our finding that IL-6 is associated with smaller grey matter volume (precuneus, parahippocampal and supramarginal gyri) is consistent with findings from the UK Biobank: genetically predicted levels of IL-6 were linked to reduced cortical thickness in medial fronto-parietal brain regions, including the precuneus (Williams et al., 2022) and serum levels of IL-6 were associated with smaller hippocampal volume (Zhao et al., 2024). Other studies in adults also report an association between IL-6 and reduced parahippocampal gyrus volume (Marsland et al., 2008), and mouse models with transgenic elevation of CNS IL-6 show impaired hippocampal neurogenesis (Vallières et al., 2002).

The link between childhood IL-6 and alterations in DMN regions is also consistent with evidence from psychosis-spectrum patients, where a high-inflammatory subgroup demonstrated reduced anterior DMN connectivity, which was further associated with cognitive deficits (Lizano et al., 2023). Altered DMN connectivity is implicated in several mental disorders (Doucet et al., 2020) , including schizophrenia (Hu et al., 2016). Structural changes in the parahippocampal gyrus (critical for memory encoding and retrieval) (Ward et al., 2014), precuneus (involved in self-referential thought (Narasimha et al., 2019) and executive functions) (Ahmed et al., 2018), and the supramarginal gyrus (language processing including inner speech) (Geva et al., 2011) provide a plausible mechanistic pathway by which inflammation-driven alterations in brain development may contribute to clinical phenomenology in psychosis.

For CRP, elevated childhood levels were associated with larger superior frontal gyrus volume in individuals with PEs, whereas no association was seen in controls. The superior frontal gyrus supports higher-order functions including self-referential processing (Lemogne et al., 2009), working memory (du Boisgueheneuc et al., 2006), language (Ren et al., 2023), impulse control (Hu et al., 2016) and mood regulation (Lemogne et al., 2009). Our findings in those with PEs align with findings in the UK Biobank, where serum CRP was associated with increased cortical thickness in fronto-occipital areas, including the superior frontal gyrus (Orellana et al., 2024), while another study found that genetically predicted CRP was associated with larger superior frontal gyrus volume, the same region identified in our analysis (Williams et al., 2022). Volume increases may reflect an acute inflammatory effect of CRP on brain

structure in older participants (mean age ~60 years in UK Biobank), whereas in our younger cohort they may instead reflect pathological or compensatory processes associated with PEs. One possibility is that inflammatory proteins more readily penetrate the brain in individuals with genetic vulnerability to PE (Pollak et al., 2018; Futtrup et al., 2020) or in older adults (van Engelen et al., 1992) due to a compromised blood–brain barrier (BBB).

The association between CRP and larger superior frontal gyrus volume in those with PEs contrasts with most neuroimaging studies in schizophrenia, which typically report inflammation-related volume *reductions* (Jacomb et al., 2018). This discrepancy may reflect differences in illness stage and neurodevelopmental timing. Early developmental insults such as childhood inflammation may have a priming effect on microglia in the brain, which may increase microglial activation and psychosis risk following subsequent infections (Frank et al., 2007; Frank et al., 2011). Inflammation during the prodromal phase of psychosis may initially drive volume increases (Kitzbichler et al., 2021), potentially reflecting inefficient pruning during neurodevelopment, whereas in later stages of the illness it may contribute to grey matter loss. Supporting this, one study of clinical high-risk individuals found that elevated proinflammatory markers predicted a greater rate of prefrontal cortical thinning in those who subsequently developed psychosis (Cannon et al., 2015). This trajectory appears to continue into chronic illness, where more pronounced cortical reductions are observed (Merritt et al., 2021). Consistent with this, CRP has been linked to reduced superior frontal gyrus thickness in patients with chronic schizophrenia (Jacomb et al., 2018), and a post-mortem study similarly found that 'high inflammation' patients (based on mRNA expression of SERPINA3, IL-6, IL-8, and IL-1β in the brain) had reduced superior frontal gyrus volume compared to those with 'low inflammation' (Zhang et al., 2016).

This study found differential effects of CRP and IL-6 on brain grey matter volume. It is important to recognize that both IL-6 and CRP play complex roles in pro- and anti-inflammatory pathways. IL-6 can signal via classic pathways, predominantly mediating metabolic regulation and tissue repair, or via *trans*-signalling, which drives pro-inflammatory responses. Similarly, CRP exists in two isoforms: pentameric CRP (pCRP), which largely promotes inflammation resolution and tissue maintenance, and monomeric CRP (mCRP), which is pro-inflammatory and amplifies local inflammatory responses. These distinctions highlight that moderate elevations in IL-6 or CRP do not necessarily indicate ongoing low-grade inflammation, but may instead reflect adaptive allocation of resources toward somatic maintenance and repair (Del Giudice and Gangestad, 2018). In addition these measures are from a single timepoint and so it is difficult to comment on the chronicity of exposure.

Our study has a number of limitations. Previous studies in the full ALSPAC sample report that higher childhood levels of CRP and IL-6 are associated with an increased likelihood of developing later psychotic experiences (PEs). In our smaller MRI subsample, we replicate the association between CRP and PEs in unadjusted analyses, but not for IL-6. This discrepancy is likely due to our substantially smaller sample size (one-tenth the size of the ALSPAC sample used in previous papers) (Palmer et al., 2024; Perry et al., 2021; Khandaker et al., 2014). Assessing the association between CRP and PEs was not the aim of our paper, but this loss of association may subsequently limit power to detect inflammation-related grey matter volume alterations linked to later PEs.

The impact of removing participants with potential acute infection varied depending on the inflammatory marker. For IL-6, reductions in parahippocampal and parietal volumes were evident after excluding individuals with very high levels of IL-6 (indicative of acute infection at the time of blood sampling), although these clusters were at threshold significance when individuals with infection were included. Whereas for CRP, effect sizes reduced after excluding participants with potential acute infection, although clusters remained significant after FDR correction. In terms of confounders, although we controlled for BMI and SES, we may have missed other confounders shown to affect levels of inflammation in childhood, such as early puberty (Shanahan et al., 2013).

Immunity and inflammation are complex systems involving numerous cytokines, chemokines and acute phase proteins. Our study focused on the proinflammatory cytokine IL-6 and the acute phase protein CRP, as these have been most consistently associated with psychosis, particularly when elevated in childhood (Palmer et al., 2024; Perry et al., 2021; Khandaker et al., 2014). It is important to note that we did not examine the many other proinflammatory cytokines, nor did we examine anti-inflammatory cytokines. Nonetheless, other cytokines such as TNF-α and IL-1β may also play important roles in brain development and the emergence of psychopathology (Upthegrove et al., 2014).

The presence of PEs also predicts the development of non-psychotic disorders in later adulthood, such as depression and anxiety. Our finding that individuals with PEs are more vulnerable to the effects of CRP on the brain may therefore reflect a mechanistic pathway linking inflammation not only to psychosis risk but also to an increased likelihood of developing depression.

Finally, regarding causality: we frame this paper with the hypothesis that peripheral inflammation affects brain structure. However, it is also conceivable that brain-based processes, particularly involving the HPA axis, drive inflammatory activity in the periphery (Nusslock and Miller, 2016). The HPA axis frequently acts as a negative feedback mechanism to suppress immune and inflammatory responses, and this process may be disrupted by psychosocial stressors (Kronfol and Remick, 2000). We attempted to mitigate this through a temporally ordered analysis (childhood inflammation predicting in grey matter volume adulthood), but we cannot rule out the possibility that pre-existing grey matter alterations in childhood influence circulating inflammatory markers.

In conclusion, elevated IL-6 levels in childhood are associated with later grey matter volume reductions in regions involved in the DMN, namely the precuneus, parahippocampal and supramarginal gyri. Notably, high IL-6 levels did not show a distinct effect on grey matter in individuals who later developed psychotic experiences (PEs), suggesting a more general neurodevelopmental impact rather than a PE-specific trajectory. In contrast, those who develop PEs may be more vulnerable to effects of CRP on the brain, perhaps due to greater compromised BBB or other predisposing factors. Environmental risk factors experienced at higher rates in schizophrenia, such as maternal infection, obstetric complications, smoking, epilepsy, and childhood trauma (Oliver et al., 2024), are each linked to increased BBB permeability (Pollak et al., 2018). Genetic loci associated with schizophrenia may also impact the BBB (Lv and Luo, 2025). Once disrupted, a permeable BBB may render individuals more susceptible to the adverse effects of peripheral inflammation.

These findings highlight potential neurobiological mechanisms through which early-life inflammation may contribute to vulnerability for PEs, with IL-6 and CRP affecting grey matter volume in brain regions involved in working memory, language and self-referential processing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2025.106247.

Data availability

R script available at github.com/katemerritt/inflammation/. Informed consent from ALSPAC participants does not allow data to be made available through any third party maintained public repository.

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