Research Paper

Large-scale evidence for an association between low-grade peripheral inflammation and brain structural alterations in major depression in the BiDirect study

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Background: Preliminary research suggests that major depressive disorder (MDD) is associated with structural alterations in the brain; as well as with low-grade peripheral inflammation. However, even though a link between inflammatory processes and altered brain structural integrity has been purported by experimental research, well-powered studies to confirm this hypothesis in patients with MDD have been lacking. We aimed to investigate the potential association between structural brain alterations and low-grade inflammation as interrelated biological correlates of MDD. **Methods:** In this cross-sectional study, 514 patients with MDD and 359 healthy controls underwent structural MRI. We used voxel-based morphometry to study local differences in grey matter volume. We also assessed serum levels of high-sensitivity C-reactive protein (hsCRP) in each participant. **Results:** Compared with healthy controls (age [mean ± standard deviation] 52.57 ± 7.94 yr; 50% male), patients with MDD (49.14 ± 7.28 yr, 39% male) exhibited significantly increased hsCRP levels (Z = –5.562, $p < 0.001$) and significantly decreased grey matter volume in the prefrontal cortex and the insula. Prefrontal grey matter volume reductions were significantly associated with higher hsCRP levels in patients with MDD (x = 50, y = 50, z = 8; $t_{1,501}$ = 5.15; k = 92; $p_{FWE} <$ 0.001). In the MDD sample, the significant negative association between hsCRP and grey matter appeared independent of age, sex, body mass index, current smoking status, antidepressant load, hospitalization and medical comorbidities. **Limitations:** This study had a cross-sectional design. **Conclusion:** The present study highlights the role of reduced grey matter volume and low-grade peripheral inflammation as interrelated biological correlates of MDD. The reported inverse association between peripheral low-grade inflammation and brain structural integrity in patients with MDD translates current knowledge from experimental studies to the bedside.

Introduction

Major depressive disorder (MDD) is one of the most debilitating disorders worldwide.[1] Neurobiological research on MDD has identified both peripheral low-grade inflammation and structural brain alterations as promising candidates for biomarkers that might enhance prevention and treatment in affective disorders.[2–4] The importance of peripheral inflammatory processes in affective disorders is supported by a cumulative meta-analysis by Haapakoski and colleagues, which demonstrated a significant association between C-reactive protein (CRP) serum levels and MDD in 14 studies.[5]

The consistency of these findings in recent years has encouraged researchers to begin exploring both mono- and polytherapeutic treatment strategies that target not only potential monoamine neurotransmitter abnormalities, but also chronic low-grade fluctuations in peripheral inflammatory markers such as CRP.[6,7]

Meta-analyses have also been performed to investigate structural abnormalities in MDD, collating neuroimaging results for MDD and confirming associations between MDD and alterations in the orbitofrontal cortex, insula, cingulate cortex, temporal cortex and hippocampus.[4,8] Given the role of these brain regions in neurocognitive domains such as reward processing and emotion regulation, their contribution to the development of MDD appears highly suggestive.[9] However, despite the increasing number of studies demonstrating effects of genetic[10,11] and environmental risk

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factors[12,13] on MRI-detectable alterations in these brain regions, the biological processes underlying the association between MDD and brain structural alterations are still poorly understood.

An important question in this context is whether chronic low-grade peripheral inflammation might contribute to observed structural abnormalities in MDD. Preliminary support for the contribution of inflammation stems from animal research[14] and from reports on associations between inflammation and structural brain alterations in humans in nonpsychiatric fields of research;[15–17] only a few studies have directly investigated the association between inflammation and brain structural alterations in patients with MDD.[18–20] Frodl and colleagues[21] demonstrated an inverse association between interleukin-6 and hippocampal volumes in a sample of 40 patients with MDD. Two further studies have investigated associations between differing immune markers and cortical thickness: van Velzen and colleagues[20] reported an inverse association between CRP and the thickness of the rostral anterior cingulate cortex in 283 participants (including healthy controls and patients with MDD and anxiety disorders); Meier and colleagues[22] found that CRP was correlated with decreased thickness of the dorsal anterior cingulate cortex (Brodmann area 32) in a mixed sample made up of both healthy participants and patients with unmedicated depression.

Taken together, the results of previous research suggest a link between inflammation and brain structure in general. However, findings from the few existing studies came from small or heterogeneous study samples that applied differing inflammatory markers and neuroimaging approaches, all relying on a priori selection of diverging regions of interest. The scope of the present study was to investigate the potential link between inflammation and brain structure in MDD by taking into account these limitations. First, we studied a well-powered, homogeneous sample of patients with MDD. Second, we investigated high-sensitivity CRP (hsCRP) levels, a serum marker that has frequently been shown to provide reliable assessments of peripheral inflammation in MDD[23] as well as in other psychiatric disorders, such as bipolar disorder[24] and psychosis,[25] and that has repeatedly been associated with brain structural alterations.[16,20,22,26] Third, we used a voxel-based morphometry approach, which does not rely on a priori selection of regions of interest, allowing us to investigate structural alterations across the entire brain.

We hypothesized that patients with MDD would be characterized by increased serum hsCRP levels and by decreased grey matter volume compared with healthy controls, and that grey matter volume in brain regions associated with MDD would be negatively associated with hsCRP levels in patients with MDD.

Methods

Data set and clinical outcomes

The BiDirect study is an ongoing study that comprises 3 distinct cohorts: patients hospitalized for an acute episode of major depression, patients 2 to 4 months after an acute cardiac event and healthy controls randomly drawn from the population register of the city of Münster, Germany.[27] In line with our hypotheses, the present work included only data from the MDD and healthy control cohorts of the BiDirect study. Baseline examination of all participants included a structural MRI of the brain, a computer-assisted face-to-face interview about sociodemographic characteristics, a medical history, an extensive psychiatric assessment and collection of blood samples.

Inclusion criteria for the present study were availability of completed baseline MRI and hsCRP data. Participants with a lifetime history of stroke, Parkinson disease, a neuroinflammatory disorder, epilepsy, meningitis, myocardial infarction or cancer were excluded from the present study to prevent bias from severe neurologic and medical conditions, leaving 514 patients with MDD and 359 healthy controls suitable for analysis. We calculated a comorbidity index by summing all remaining medical comorbidities (for details, see Appendix 1, Table S1, available at jpn.ca/18208-a1). After exclusion of 9 participants because of poor MRI quality, a final sample of 864 participants (MDD 506, controls 358) remained for analyses.

All patients with MDD in the present study had an episode of major depression at the time of recruitment and were either currently hospitalized (> 90%) or had been hospitalized for depression at least once during the 12 months before inclusion in the study (< 10%). We confirmed MDD diagnosis according to ICD-10 criteria (discharge diagnosis) in all patients with MDD. All included patients with MDD were free of a lifetime history of substance use disorders. We obtained participants' lifetime number of hospitalizations for a depressive episode as an indicator of disease course severity. We also assessed the total number of lifetime depressive episodes and lifetime disease duration. To assess participants' current symptom and severity status, we administered the Mini-International Neuropsychiatric Interview (German version 5.0.0),[28] the Hamilton Depression Rating Scale,[29] and the Center for Epidemiologic Studies Depression Scale.[30] We also assessed for the presence of atypical depressive symptoms in all BiDirect participants with MDD using 6 items of the Inventory of Depressive Symptomatology (items 8, 12, 14, 27, 29 and 30)[31] and summing them to yield a single score that reflected the presence and extent of atypical symptoms.

We acquired information about the presence or absence of antidepressant medication, as well as the type of medication, for each patient with MDD (12.9% of patients were unmedicated). Building on this, we computed a score reflecting antidepressant load by summing the number of different antidepressant agents regularly taken at the time of examination.

For all control participants, exclusion criteria were the presence or any lifetime history of a psychiatric disorder (including depressive disorder, anxiety disorders, substance use disorders, psychosis), as well as the presence of severe depressive symptoms according to the Center for Epidemiologic Studies Depression Scale (cutoff ≥ 15).

We calculated body mass index from directly measured height and weight (kg/m^2). We assessed current smoking status as a binary variable based on self-report (current smoker or nonsmoker).

The study was approved by the ethics committee of the University of Münster and the Westphalian Chamber of Physicians in Münster. All participants provided written informed consent. Further details on the rationale, design and recruitment procedures of the BiDirect study have been described previously.[27]

Biochemical analyses of hsCRP levels

We assessed serum levels of high-sensitivity CRP (hsCRP) using CardioPhase hsCRP, an in vitro diagnostic reagent for the measurement of CRP in human serum, heparin and EDTA samples. CardioPhase hsCRP uses particle-enhanced immunonephelometry and is composed of a suspension of polystyrene particles coated with mouse monoclonal antibodies to CRP (www.framinghamheartstudy.org/share/protocols/crp1_7s_protocol.pdf). Because hsCRP serum levels were not normally distributed (Kolmogorow–Smirnow test: $p < 0.001$), we used logarithmic-transformed hsCRP (log hsCRP) values for all analyses of variance, including all imaging analyses.

Structural MRI methods

Image acquisition
We acquired T_1 structural images at a single 3.0 T MRI scanner (Intera with Achieva update; Philips Medical Systems) using a 3-dimensional fast gradient echo sequence (repetition time 7.26 ms, echo time 3.56 ms, flip angle 9°, 2 signal averages, inversion prepulse every 404 ms, field of view of 256 × 256 mm, phase encoding anterior–posterior and right–left, reconstructed to voxels of 1 mm × 1 mm × 1 mm).

Voxel-based morphometry
We used the CAT12-toolbox (www.neuro.uni-jena.de/cat/) for preprocessing of the structural images using default parameters. Briefly, images were bias-corrected, tissue-classified, and normalized to Montreal Neurological Institute space using linear (12-parameter affine) and nonlinear transformations in a unified model that included high-dimensional DARTEL normalization. The modulated grey matter images were smoothed with a Gaussian kernel of 8 mm full width at half maximum. We used absolute threshold masking with a threshold value of 0.1 for all second-level analyses, as recommended for voxel-based morphometry analyses (www.neuro.uni-jena.de/cat/). We assessed image quality by visual inspection, as well as by using the check for homogeneity function implemented in the CAT12 toolbox. Nine participants were excluded owing to poor image quality (mean correlation < 2 SD) or anatomic artifacts, leaving a total of 864 (MDD 506, controls 358) for all analyses.

Statistical analyses

We used SPM12 (www.fil.ion.ucl.ac.uk/spm) for all imaging analyses. Further statistical analyses were performed using SPSS version 25 (IBM). To address our hypotheses, we carried out the following analyses.

High-sensitivity CRP
To investigate possible group differences in hsCRP levels between patients with MDD and controls, we applied a non-parametric Mann–Whitney *U* test. We also investigated group differences in log hsCRP levels using a 2-tailed *t* test.

Voxel-based morphometry
First, to investigate group differences in grey matter volume between patients with MDD and controls, we performed whole-brain voxel-based morphometry analyses, including age, sex and total intracranial volume as nuisance covariates for the entire cerebrum. We set a cluster-level, family-wise error (FWE)–corrected significance threshold for multiple testing at $p < 0.05$ and a cluster-forming threshold of $p < 0.001$.

Second, to investigate potential associations between peripheral inflammation and MDD-related structural brain alterations, we performed a multiple regression analysis of log hsCRP levels on grey matter volume in the MDD group, again including age, sex and total intracranial volume as covariates. For this step, following our aim to investigate the influence of log hsCRP on decreases in MDD-related grey matter, we used a region-of-interest analysis based on a mask that included all significant clusters of the preceding analyses on whole-brain grey matter, applying rigorous FWE correction in this region of interest at $p < 0.05$ at the voxel level. To rule out a specific contribution of potentially relevant confounding variables, such as antidepressant load, hospitalization, medical comorbidity, smoking status and body mass index, we repeated the regression analysis by separately adding each of these variables as nuisance regressors of no interest into a new regression model.

In the control sample, we performed multiple regression analysis of log hsCRP levels on grey matter volume using the same process.

We performed anatomic labelling using AAL-Toolbox.[32]

Results

High-sensitivity CRP

Results of the Mann–Whitney *U* test indicated significant group differences in hsCRP levels between the healthy control and MDD groups ($Z = -5.562$; $p < 0.001$), showing increased hsCRP levels in patients with MDD (range 0.02–3.80 mg/dL, geometric mean 0.15 mg/dL, mean ± SD 0.28 ± 0.41 mg/dL) compared with controls (range 0.02–2.20 mg/dL, geometric mean 0.10 mg/dL, mean ± SD 0.17 ± 0.25 mg/dL). Similarly, the 2-tailed *t* test confirmed increased log hsCRP levels in patients with MDD compared with controls ($t_{1,862} = 5.63$, $p < 0.001$; Table 1 and Fig. 1).

To rule out the possibility that this observation was substantially biased by age, sex, body mass index or smoking status, we conducted an analysis of covariance including those variables as nuisance covariates and confirmed the significant group differences in log hsCRP serum levels between controls and patients with MDD ($F_{1,856} = 7.48$, $p = 0.006$).

Additional exploratory regression analyses between hsCRP levels and all available clinical variables (Hamilton

Depression Rating Scale, Center for Epidemiologic Studies Depression Scale, Inventory of Depressive Symptomatology sum score, hospitalization, lifetime depressive episodes, disease duration) revealed a significant positive association between log hsCRP levels and hospitalization as measured by the number of inpatient depressive episodes ($\beta = 0.154$, $p = 0.001$) controlling for age and sex; we detected no further significant association between log hsCRP levels and any other clinical variable. Details of these exploratory analyses can be found in Appendix 1.

Voxel-based morphometry

The whole-brain voxel-based morphometry analysis of group differences yielded significant grey matter reductions in patients with MDD compared with healthy controls in a total of 3 clusters. Clusters comprised voxels in the right insula, the right superior and middle temporal cortex, and several prefrontal brain regions, including areas in the left and right orbitofrontal cortex, the left middle frontal gyrus and the right middle frontal gyrus (Table 2 and Fig. 2). We observed no significant increase in grey matter volume in patients with MDD compared with controls at the applied thresholds.

Regression analysis of log hsCRP levels on MDD-associated grey matter ($k = 3479$, $x = 60$, $y = -24$, $z = -6$; $k = 1764$, $x = -8$, $y = 68$, $z = 8$; $k = 1109$, $x = 38$, $y = 52$, $z = 27$) yielded a significant volume decrease in the prefrontal cortex within the right middle frontal gyrus ($x = 50$, $y = 50$, $z = 8$; $t_{1,501} = 5.15$; $k = 92$; $p_{FWE} < 0.001$) in the MDD group (Fig. 3, Appendix 1, Figs. S1 and S2).

To control for the potential effect of antidepressant medication, we repeated the analysis but added antidepressant load as a nuisance regressor. The same pattern of results emerged, with a significant negative association between log hsCRP levels and prefrontal grey matter volume ($x = 50$, $y = 50$, $z = 8$; $t_{1,500} = 4.90$; $k = 73$; $p_{FWE} < 0.001$).

Table 1: Summary statistics, final study sample

Characteristic*	MDD ($n = 506$)†	Healthy controls ($n = 358$)	p
Sex (male/female), no.	198/308	180/178	< 0.001
Age, yr	49.14 ± 7.28 (30.91–65.48)	52.57 ± 7.94 (35.55–65.61)	0.014
hsCRP, mg/dL	0.28 ± 0.41 (0.02–3.80)	0.17 ± 0.25 (0.02–2.20)	< 0.001
Hamilton Depression Rating Scale, score	13.74 ± 6.61 (0.00–33.00)	NA	NA
Comorbidity index, score	1.65 ± 0.81 (0.00–5.00)	0.37 ± 0.61 (0.00–3.00)	< 0.001
Center for Epidemiologic Studies Depression Scale, total score	27.58 ± 12.16 (0.00–56.00)	6.3 ± 4.09 (0.00–15.00)	< 0.001
Inpatient episodes, no.	1.61 ± 1.32 (0.00–10.00)	NA	NA
Depressive episodes, no.	6.22 ± 10.85 (1.00–99.00)	NA	NA
Disease duration, mo	80.71 ± 95.30 (2.00–506.00)	NA	NA
Inventory of Depressive Symptomatology, sum score	3.99 ± 2.86 (0.00–15.00)	NA	NA
Body mass index, kg/m^2	28.41 ± 5.39 (17.70–50.10)	26.50 ± 3.93 (16.70–41.30)	< 0.001

hsCRP = high-sensitivity C-reactive protein; MDD = major depressive disorder; NA = not applicable.
*Unless otherwise specified, results are presented as mean ± standard deviation (range); p-values derived from χ^2, Mann–Whitney U and t-tests.
†In the MDD group, for Hamilton Rating Scale for Depression, $n = 504$; for comorbidity index, $n = 505$; for Center for Epidemiologic Studies Depression Scale total, $n = 500$; for inpatient episodes, $n = 498$; for depressive episodes, $n = 467$; for disease duration, $n = 501$; for Inventory of Depressive Symptomatology sum score, $n = 500$.

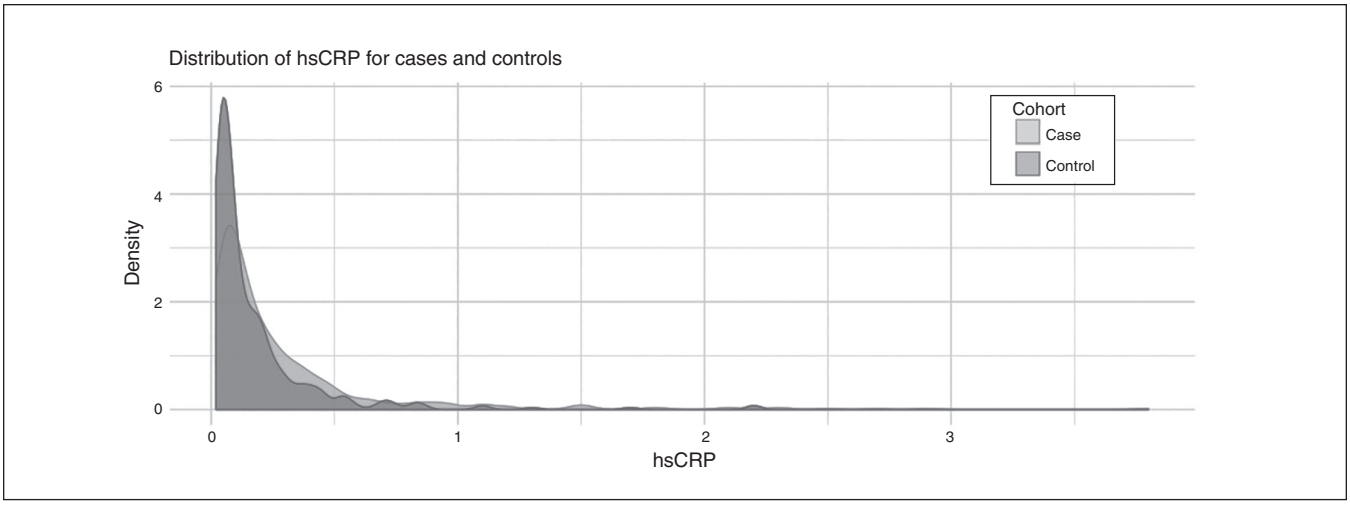

Fig. 1: Density plot depicting the distribution of hsCRP values in mg/dL in healthy controls and patients with MDD (cases). hsCRP = high-sensitivity C-reactive protein; MDD = major depressive disorder.

Analogously, we aimed to control for the potential influence of hospitalization (which was correlated with log hsCRP levels in the MDD group) by including the number of inpatient depressive episodes as an additional covariate in the model. Still, the same pattern of significant negative association between log hsCRP levels and prefrontal grey matter volume emerged ($x = 50$, $y = 50$, $z = 8$; $t_{1,500} = 5.06$; $k = 87$; $p_{FWE} < 0.001$). Moreover, we observed similar results after controlling for medical comorbidities by including comorbidity index values as an additional covariate in the model ($x = 50$, $y = 50$, $z = 8$; $t_{1,499} = 4.58$; $k = 49$, $p_{FWE} = 0.002$). Similarly, analyses controlling for smoking status confirmed the association between log hsCRP and prefrontal grey matter ($x = 50$, $y = 50$, $z = 8$; $t_{1,499} = 5.31$; $k = 101$; $p_{FWE} < 0.001$). Analyses controlling for body mass index yielded a strongly diminished cluster size, but we still detected a FWE-corrected significant association between log hsCRP and prefrontal grey matter ($x = 50$, $y = 50$, $z = 8$; $t_{1,500} = 3.66$; $k = 1$; $p_{FWE} = 0.046$; Appendix 1, Fig. S3).

Additional whole-brain analyses indicated that the negative association between log hsCRP and prefrontal grey matter volume would survive even a most conservative voxel-wise FWE correction for the entire cerebrum ($x = 50$, $y = 50$, $z = 8$; $t_{1,501} = 5.15$; $k = 9$; $p_{FWE} = 0.005$), while no further suprathreshold clusters could be detected at this rigorous threshold. No further negative or positive associations between log hsCRP and whole-brain grey matter emerged at an exploratory threshold of $p < 0.001$, $k > 400$. We observed no significant association between antidepressant load and whole-brain grey matter at the applied thresholds in patients with MDD. Even at an exploratory threshold of $p < 0.001$, $k > 400$, no association between antidepressant load and grey matter emerged in the MDD group.

Additional exploratory analyses in the MDD group did not yield any significant associations between prefrontal grey-matter volume and clinical variables, including total number of depressive episodes, duration of illness or presence of atypical symptoms (Appendix 1).

Table 2: Results for group comparisons between patients with MDD healthy controls*

Brain region	Cluster size, *k*	MNI (at peak), *x, y, z*	Side	*t*	p_{FWE}
Insula/superior temporal gyrus/middle temporal gyrus/ rolandic operculum	3479	60, –24, –6	Right	4.86	< 0.001
Superior frontal gyrus/medial frontal gyrus, orbital part/ middle frontal gyrus/superior frontal gyrus, medial part	1764	–8, 68, 8	Left	4.78	0.002
Middle frontal gyrus/inferior frontal gyrus, orbital part/ middle frontal gyrus, orbital part	1109	38, 52, 27	Right	4.69	0.014

FWE = family-wise error; MDD = major depressive disorder; MNI = Montreal Neurological Institute.
*Including age, sex and total intracranial volume as nuisance regressors.

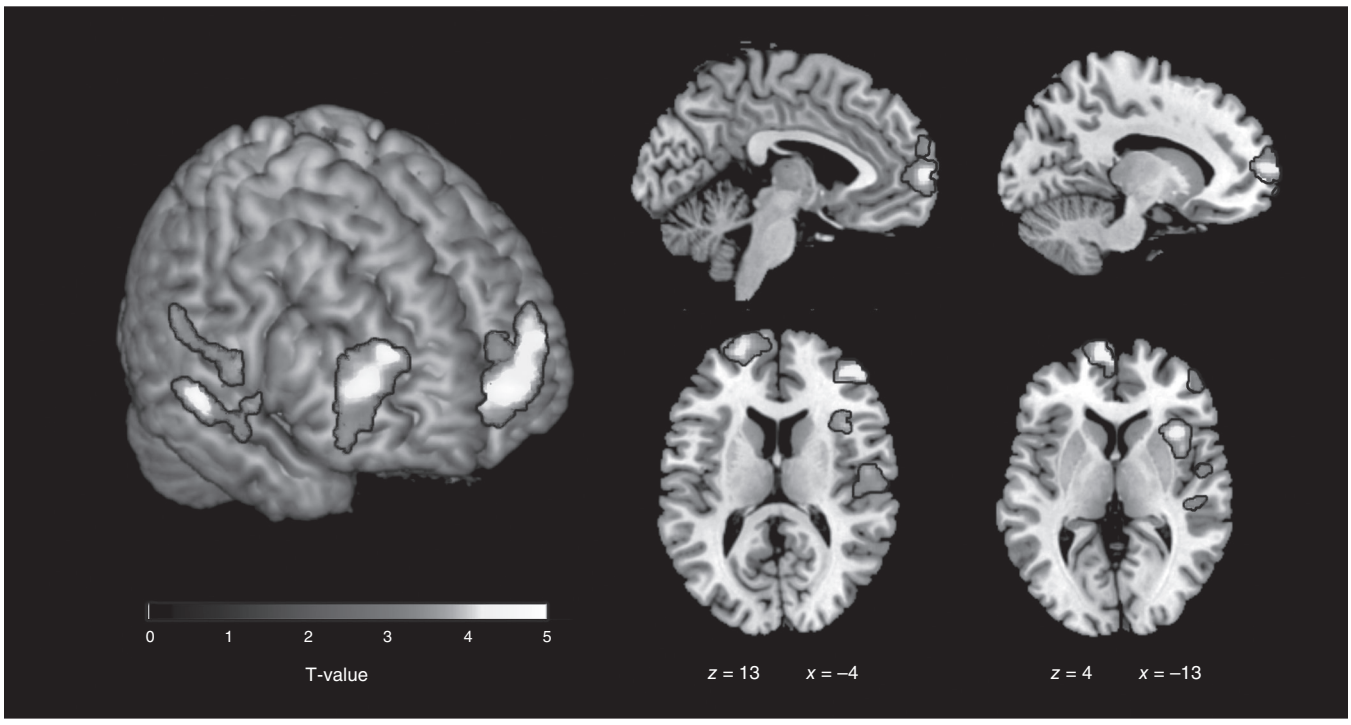

Fig. 2: Results of group comparisons for whole brain grey matter, displaying significantly decreased grey matter in patients with MDD compared with healthy controls. For display reasons, uncorrected results are presented at voxel threshold $p < 0.001$, minimum cluster volume threshold $k \geq 1000$. hsCRP = high-sensitivity C-reactive protein; MDD = major depressive disorder.

In the control group, we detected no significant association between log hsCRP levels and grey matter at the applied thresholds. No negative or positive association between log hsCRP and whole-brain grey matter emerged at an exploratory threshold of $p < 0.001$, $k > 400$.

Discussion

With the present study, we provide large-scale evidence for a relationship between peripheral low-grade inflammation and grey-matter reductions in the prefrontal cortex in patients with MDD. Importantly, our analysis directly confirms that these inflammatory-related neurostructural alterations occur in brain areas with regional specificity for MDD in a large sample of patients with depression. These findings support previous evidence for an interplay between peripheral inflammation and brain structure from experimental research,[33,34] and our corresponding finding of this association in a large sample of patients with MDD translates these insights into the clinic.

As expected, our findings support previous reports that the pathophysiology of MDD is associated with low-grade inflammation.[2,35] Interestingly, the reported positive association between peripheral inflammation and the number of lifetime hospitalizations in patients with MDD — which can be interpreted as an indicator of disease course severity — points to low-grade inflammation as a feature of a more severe course of the disorder. Considering the distribution of hsCRP levels in patients with MDD in the present study, peripheral inflammation might characterize a clinically distinct subtype of depressive disorder.

In line with our hypothesis and many reports from previous neuroimaging research, patients with MDD exhibited significantly altered brain structural integrity compared with healthy controls in the BiDirect study.[8,9] Grey matter volume reductions in patients with MDD occurred predominantly in the prefrontal cortex, the insula and the temporal cortex, a finding that tightly matches the results from a recent meta-analysis on cortical brain structural alterations in major depression.[4]

Most importantly, we demonstrated that a grey matter decrease in MDD was associated with higher levels of the proinflammatory marker hsCRP. While the reported association between peripheral inflammation and brain structure in MDD matches findings from nonpsychiatric research,[15,16] it is important to acknowledge that no association between brain structure and inflammation was present in the control group in the present study. Diverging exclusion criteria leading to different levels of somatic and psychiatric comorbidities in control samples in previous studies might explain this inconsistency.

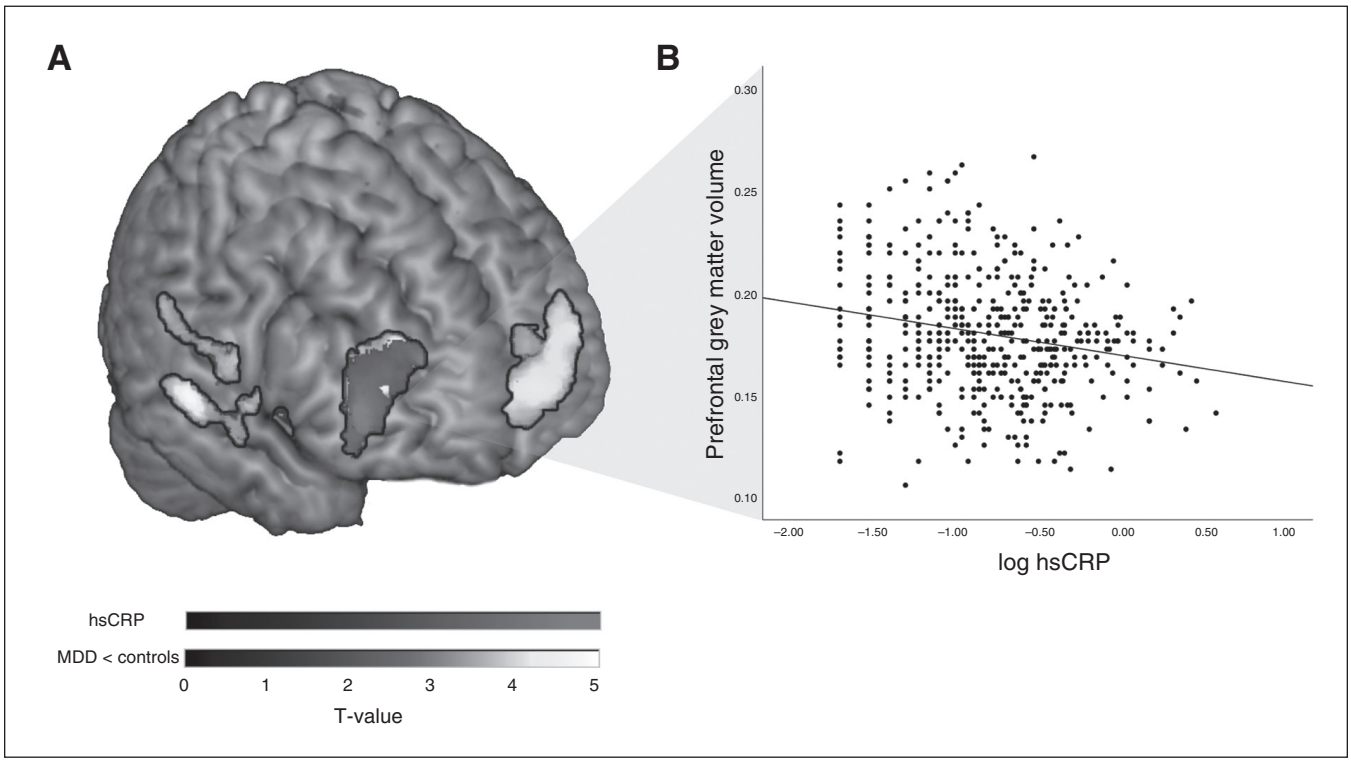

Fig. 3: (A) Association between log hsCRP values and MDD-related grey matter. Results for the log hsCRP analysis are shown in dark grey; the employed mask comprising significant clusters of the preceding whole-brain analyses of group differences between participants with MDD and healthy controls is displayed in light grey. For display reasons, uncorrected results are presented at voxel threshold $p < 0.001$, minimum cluster volume threshold $k \geq 1000$. (B) Plot depicting the negative association between log hsCRP and grey matter volume in MDD participants at $x = 50$, $y = 50$, $z = 8$ (fit line: $r = -0.215$). log hsCRP = logarithmic-transformed high-sensitivity C-reactive protein; MDD = major depressive disorder.

Several findings of the present study support the relevance of the observed relationship between inflammation and brain structure in MDD. First, hsCRP levels had an inverse relation to grey matter in brain regions precisely identical to those in which we observed differences between patients with MDD and controls. Second, the inverse association between hsCRP and grey matter was regionally specific for the prefrontal cortex, a brain region consistently found to be associated with MDD in previous studies.[4,9] Third, the reported association between peripheral inflammation and prefrontal brain structure in MDD was independent of potential confounders such as antidepressant load, hospitalization, body mass index, smoking status and medical comorbidities.

The clinical relevance of this finding is further highlighted by a report from Harrison and colleagues[36] demonstrating that experimentally induced inflammation was associated with mood deterioration, which in turn was correlated with altered functional connectivity between the medial prefrontal cortex and the anterior cingulate cortex in response to emotional stimuli, suggesting that inflammation might lead to mood changes via altered signalling in MDD-specific brain regions.

Regarding a mechanistic explanation for our observations, a plethora of recent evidence supports the notion of a bidirectional communication between the central nervous system and the immune system.[3,37] Chronic peripheral inflammation, as characterized by increased levels of systemic proinflammatory cytokines has been demonstrated to lead to brain microglial activation.[3,38] It has been shown that a proinflammatory environment affects central activation of microglia, which can then impede neurogenesis and the formation of new neuronal circuits — potentially by suppressing neuronal stem cell proliferation, increasing apoptosis of neuronal progenitor cells and decreasing the survival of newly developing neurons and their integration into existing neuronal circuits.[33] This concept might further be underlined by our observation of associations between CRP and grey matter volume in the prefrontal cortex of patients with MDD, a brain region with pronounced structural plasticity and vulnerability to environmental influences.[39]

Because our imaging analyses carefully controlled for the influence of somatic comorbidities that have repeatedly been demonstrated to be highly prevalent in patients with MDD,[40] the contribution of undiscovered clinical disorders to the association between brain structure and inflammation appears unlikely and might not serve as an alternative explanation for the presented findings. Furthermore, the central nervous system itself is thought to exert an influence on peripheral inflammatory processes (for example, via activation of stress signalling pathways in response to external threats or stress).[37] Following this notion of bidirectional communication between the central nervous system and the immune system, it might be that the observed MDD-specific structural alterations could contribute to the maintenance of low-grade inflammation in major depression.

Another important point to consider is that results of the present study might further corroborate the well-documented relationship between affective and cardiovascular disorders[41–44] by demonstrating low-grade inflammation as a characteristic of patients with MDD and by pointing to associations between MDD diagnosis and brain structural alterations in the insula. This is a finding that is well in line with the literature[4] and that might further elucidate the aforementioned link between MDD and cardiovascular disease, considering the critical importance of the insular cortex for cardiorespiratory interoception and regulation of the sympathetic nervous system.[45,46]

Limitations

Limitations of the present study include its cross-sectional design, which prevented us from drawing conclusions about the causal relationship between inflammation and brain structure in MDD. Considering reports from previous studies about the influence of genetic and early environmental risk factors on both inflammatory processes and brain structural alterations, it appears likely that earlier onset of the biological mechanisms leading to the observed association between low-grade inflammation and brain structure could precede the onset of depressive symptoms.[10,12,13,21,47] However, this notion remains speculative, because the direction of the observed association is unknown.

Furthermore, our findings do not allow us to infer specificity for MDD. In light of multiple reports on similar associations between low-grade inflammation and brain structural alterations in other neuropsychiatric disorders, such as bipolar disorder[48,49] and schizophrenia,[25,50] this question is highly relevant and should be addressed in future research.

Furthermore, in line with the literature,[4,9] the present study demonstrated bilateral grey matter volume reductions in patients with MDD; in contrast, associations between hsCRP and grey matter were restricted to the right hemisphere. While this finding appears to be in line with 2 previous studies reporting right-sided associations between inflammatory markers and cortical thickness in the cingulate cortex,[20,22] the potential underpinnings of the laterality of inflammation-related brain changes remain poorly understood and should be targeted by future studies.

Another limitation lies in the observed inconsistency of the studied clinical variables, reflecting disease course before the study that might have been the subject of recall bias. Results of analyses based on these variables should be regarded as exploratory and interpreted with caution.

Major strengths of the present work include the large sample size in both cohorts and the availability of serum- and MRI-derived biomarker data. This allowed us to combine information from different levels of biological abstraction using measures already established in clinical routine (structural MRI and CRP serum levels), enabling easy application.

Conclusion

Our results point to peripheral inflammation and altered brain structural integrity as interrelated biological correlates in patients with MDD. By providing robust evidence for an inverse relationship between inflammation and

brain structure in patients with MDD, the present study translates current knowledge from experimental studies to the bedside.

To further investigate this suggested pathophysiology, longitudinal and interventional studies should test whether both inflammation and anti-inflammatory treatments prospectively lead to brain structural changes over time in patients with MDD, and whether or not these molecular and structural markers are robust predictors of subsequent response to clinically relevant anti-inflammatory/antidepressant augmentation strategies.

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