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Comprehensive analysis of cytokines in depression: independent data from patient plasma and post-mortem ventromedial prefrontal cortex

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ABSTRACT

Preclinical and clinical evidence has implicated inflammation in the pathophysiology of depression. Abnormal cytokine levels in blood, cerebrospinal fluid, and post-mortem brain samples have been associated with depression. To our knowledge, however, a comprehensive analysis of cytokine protein levels in brain samples from patients with depression has yet to be conducted in major components of the limbic system such as the ventromedial prefrontal cortex (vmPFC). This region plays a crucial role in depression, impacting cognitive control, emotional regulation, and executive functions. In the current exploratory study, we performed a comprehensive profiling of 72 cytokines, chemokines and growth factors in well-characterized vmPFC samples from 34 depressed suicides and 14 matched sudden-death controls. A human antibody array (RayBio®, chemiluminescent detection) was used to measure all markers. In depressed suicide samples, no significant increase in any cytokine, chemokine or growth factor was detected compared to controls. In comparison, in an independent cohort we measured the levels of 43 inflammatory markers in plasma samples from 141 depressed living subjects and 36 controls using the Mesoscale Discovery V-plex assay. Our analyses indicated no significant difference in the levels of pro- or anti-inflammatory markers in the plasma of cases vs controls. We also conducted a detailed morphological analysis of Iba1-immunostained microglia in vmPFC gray matter samples from 28 depressed suicides and 13 healthy controls. The distributions of the various morphological phenotypes assessed were similar between groups, suggesting that microglia/macrophages do not display signs of morphological changes in the vmPFC of depressed suicides. Taken together, these complementary experiments do not provide evidence of depression-associated neuroinflammatory changes in the vmPFC, at least in the samples analyzed.

1. Introduction

The association between neuroimmune activation and depression (Smith, 1991) was first convincingly shown in patients receiving interferon treatment for chronic viral hepatitis (Capuron et al., 2002, 2003; Capuron and Miller, 2004). The measurement of pro-inflammatory markers has also mostly supported this association. In major depressive disorder (MDD) increased circulating pro-inflammatory markers have been reported, at least in subsets of patients (Miller and Raison, 2015; Raison and Miller, 2013). This phenomenon has been found to be especially robust in patients with concurrent inflammatory diseases such as inflammatory bowel disease or rheumatoid arthritis (Fakhfouri et al.,

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2024). Interestingly, low-grade peripheral inflammation has been associated with treatment-resistant depression (Chamberlain et al., 2019; Strawbridge et al., 2015). Studies have reported elevated levels of inflammatory markers in the post-mortem brains of depressed suicide patients (Pandey et al., 2019). Pandey and colleagues showed increased expression of pro-inflammatory cytokines, IL-1β, IL-6 and TNF-α, in the prefrontal cortex (PFC) of teenage suicides (Pandey et al., 2012) while IL-4 and IL-13 expression was reported to be increased in the orbitofrontal cortex of adult depressed suicides (Tonelli et al., 2008). Furthermore, using gene array to analyze post-mortem anterior prefrontal cortex samples, Shelton et al. provided evidence of local inflammatory, apoptotic, and oxidative stress in MDD (Shelton et al., 2011). Moreover, a recent comprehensive meta-analysis revealed increased levels of cytokines in blood, cerebrospinal fluid (CSF), and brains of suicide victims (Black and Miller, 2015; Kappelmann et al., 2021). These authors found that the levels of IL-1β and IL-6 were strongly associated with suicidality. They proposed that these cytokines might be useful as biomarkers to distinguish suicidal from non-suicidal patients (Black and Miller, 2015; Kappelmann et al., 2021). Lastly, Holmes and colleagues measured significantly higher TSPO availability during a moderate to severe major depressive episode in anterior cingulate cortex (ACC) of MDD patients compared to healthy controls. This observation suggests increased microglial activation in brains of depressed subjects (Holmes et al., 2018).

Investigations have associated dysregulations in circulating pro- and anti-inflammatory cytokines with functional changes in brain regions regulating emotion, motivation, and reward (Serafini et al., 2023). In the brain, pro-inflammatory cytokines interact with pathways and systems implicated in the pathophysiology of depression. These include neurotransmitter metabolism, neuroendocrine function, and synaptic plasticity (Miller et al., 2009; Raison et al., 2006). By affecting these pathways, abnormal cytokine levels may contribute to the development or worsening of depressive symptoms. Indeed, a relationship between plasma and CSF inflammatory markers and depressive symptoms, including anhedonia and reduced motivation, has been reported (Felger et al., 2020), and clusters of CSF inflammatory markers found to correlate with depressive symptom severity (Felger et al., 2020).

Despite substantial evidence suggesting a role for neuroinflammation in MDD, at least in some patients, comprehensive post-mortem measurements of cytokines at the protein level are lacking in MDD. The current exploratory study aimed to fill this gap by using an unbiased cytokine array method to profile protein levels of a large number of cytokines, chemokines and growth factors comprehensively in ventromedial prefrontal cortex (vmPFC) gray matter (GM) of well-characterized post-mortem samples from adult depressed suicides and matched psychiatrically healthy individuals. We focused on the vmPFC (Brodmann areas 11 and 12) given its implication in MDD (Hiser and Koenigs, 2018). In parallel, we performed a morphological analysis of vmPFC gray matter microglia in cases and controls. Finally, in an independent cohort, we measured several inflammatory markers in plasma of depressed patients and healthy controls to obtain a complementary assessment of inflammation in the blood of depressed patients. Our main hypothesis was that the protein profile of canonical pro-inflammatory markers would be altered in depression, in both brain and plasma.

2. Materials and methods

2.1. Brain samples

Post-mortem vmPFC samples were provided by the Douglas-Bell Canada Brain Bank. Brain donation was possible thanks to familial informed consent. Subject groups consisted of adult depressed suicides and matched sudden-death controls. Controls died with no psychiatric, immunological nor neurological illness. Cases died by suicide during a depressive episode. A subset of cases had a history of severe childhood abuse, as determined with psychological autopsies with next-of-kin, using an adapted Childhood Experience of Care and Abuse (CECA) questionnaire, assessing experiences of sexual and physical abuse, as well as of neglect (Lutz et al., 2017).

The case and control groups were matched for age, postmortem interval (PMI), pH and sex. The samples provided were either unfixed fresh frozen (Supplementary Table 1) for cytokine array, or long-term fixed (Supplementary Table 2) for cell morphological studies. For the latter, fixed tissue blocks were transferred to 30% sucrose solution and stored at 4 °C for 4-6 days. When tissues sank to the bottom of the solution, they were snap-frozen for 20-30 s at approximately −30 to −40 °C. The samples were then kept at −80 °C until cut into 40-μm-thick sections with a cryostat. Finally, sections were stored in cryoprotectant solution and kept at −20 °C. For the cytokine array we included samples from 14 controls and 34 depressed suicides. For the morphological analyses, we included samples from 13 controls and 28 depressed suicides.

2.2. Plasma samples

Plasma samples were taken from participants of the Biological Classification of Mental Disorders (BeCOME) study (ClincalTrials.gov: NCT03984084) (Brückl et al., 2020; Sun et al., 2024) (n = 106) and the OPtimized Treatment Identification at the MAx Planck Institute (OPTIMA) study (ClinicalTrials.gov: NCT03287362 (Kopf-Beck et al., 2020),) (n = 71). The sample included 141 participants with either a threshold or subthreshold (falling short of one DSM-IV criterion) major depression diagnosis within the last 12 months, as assessed by the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) (Wittchen and Pfister, 1997; Wittchen et al., 1995; Wittchen et al., 1995; Wittchen and Pfister, 1997) and 36 controls without any DIA-X/M-CIDI diagnosis. Detailed information on sex, age, BMI and somatic medication status (available for BeCOME only) is provided in Supplementary Table 3.

2.3. Cytokine arrays on vmPFC samples

Human antibody array (RayBio® C-Series, Human Cytokine Antibody Array C5) was used to measure pro-inflammatory cytokines, anti-inflammatory cytokine, chemokines and growth factors in vmPFC samples. This array allows the semi-quantitative detection of several human proteins in serum, plasma, cell culture media, and tissue lysate at the same time. Antibody array screening improves the chances of discovering key factors, disease mechanisms, or biomarkers related to cytokine signaling. Moreover, this array has a better precision and detection range in comparison to other methods such as ELISA. The inter-array Coefficient of Variation (CV) of spot signal intensities is 5-10%, comparing favorably with ELISA testing (CV = 10-15%). The sensitivity of a Human Cytokine Array C5 kit is typically in the picogram per milliliter range. This makes it highly sensitive for detecting relative expression levels of 72 different human cytokines, chemokines, and growth factors in a single sample. The available sensitivity levels for some of markers in the Human Cytokine Antibody Array C5 are provided in Supplementary Table 4.

For this array, protein lysate was obtained by homogenization of 50 mg of frozen human vmPFC GM in 1X Cell Lysis Buffer (included in the Ray Biotech kit) supplemented with protease inhibitor cocktail (Roche). Protein concentration was determined for each sample using the BCA Protein Assay (Thermo Fisher Scientific).

Antibody arrays were removed carefully from the plastic packaging and each membrane (printed side up) was placed into a well of the incubation tray. 2 ml of blocking buffer was pipetted into each well and membranes were incubated for 2 h at room temperature. After blocking, 1 ml of diluted sample (150 μg protein in 1 ml of blocking each membrane) was added to each well. The wells were incubated overnight at 4 °C on a shaker. Samples were washed with 2 ml of two different wash buffers (5 times in total) for 5 min at room temperature. One ml of the

prepared biotinylated antibody cocktail was pipetted into each well and membranes were incubated overnight at 4 °C. All membranes were washed again as described. Two ml of 1X HRP-streptavidin was added into each well and membranes were incubated for 2 h at room temperature. Following the last series of wash, chemiluminescence detection was completed using detection buffers provided by kit. The density of dots on each membrane was analyzed by Fiji software. The expression of different cytokines and chemokines on each membrane was calculated relative to the positive control.

2.4. Morphological study of microglia in vmPFC gray matter

Ionized calcium-binding adaptor protein-1 (Iba1) immunostaining (DAB) was performed in conjunction with a citrate buffer antigen retrieval on each vmPFC section. Iba1 is expressed in all microglia subtypes, regardless of their phenotype or activation state allowing optimal conditions for morphological assessment (Wittekindt et al., 2022). For each subject, a minimum of five sections were processed for antigen retrieval by incubation in citrate buffer for 15 min at 90-95 °C. After cooling to room temperature and rinsing in 3 changes of dH2O, the slides were incubated in 3% H2O2 in PBS for 10 min before blocking in 2% normal goat serum (Vector Laboratories, S-1000) in PBS + 0.2% Triton X-100 (Fisher Bioreagents, BP151) for 1 h. The sections were then incubated with an Iba1 rabbit primary antibody (Wako, Product Number 019-19741) at a 1:500 concentration diluted in 5% NGS and PBS with 0.2% Triton X-100 for 48h at 4 °C on a shaker. Next, a 1:500 concentration of biotinylated goat anti-rabbit secondary antibody (Vector Laboratories, BA-1000) diluted in PBS with 0.2% Triton X-100 was used to incubate the vmPFC sections for 1 h at room temperature. Following this incubation, the samples were treated with the Vectastain ABC kit (Vector Laboratories, PK-4000) protocol for 30 min. The staining was then developed in DAB (Vector Laboratories, SK-4100) prepared in dH2O. Finally, after drying overnight in a fume hood, samples were dehydrated with 70%, 95% and 100% ethanol twice for 2 min each, followed by two 2-min xylene washes and coverslipping with permount. Between each step described above, sections were rinsed in PBS 3x5 min.

2.5. Quantitative assessment of microglia morphology

For quantitative analysis of microglial morphology, we used Stereo Investigator (MBF Bioscience) to estimate microglial subpopulations based on morphology from representative vmPFC sections. Specifically, an optical fractionator probe was used to analyze thicker sections to estimate phenotypic populations from representative sites in the samples (mbfbioscience.com/products/stereo-investigator). The region of interest (ROI) pertained only to the GM within each vmPFC section. Each ROI was traced in Stereo Investigator's optical fractionator probe using a 4x objective. Imperfections in the tissue were contoured and excluded from ROIs. Then, the software determined a systematic randomly sampled (SRS) set of counting frames depending on the percentage of the ROI being counted. 2% of each section was sampled with 100 μm × 100 μm representative sites from an SRS grid size of 707 μm × 707 μm. Each site had an optical height of 18 μm with top and bottom guard zones of 1 μm each. Using a 60x objective, the contour of each section was sampled to yield countable probe runs. At every site, the thickness of the area was measured manually by finding the topmost and bottommost points of focus within the optical height. Then, using stereological markers provided in the probe, cell bodies were marked at their topmost point along the z-axis. Only cells with their cell body within the counting frame or on the green border were considered. Cell bodies in contact with the red border or outside the frame were ignored. Each phenotype had specific morphological features described previously for ramified, primed, reactive, and amoeboid microglia (Torres-Platas et al., 2014). In brief, and as illustrated in Fig. 4, ramified microglia were identified as having spherical cell bodies between 2.5 and 4.9 μm in the shortest axis with highly ramified cellular processes and at least 16 ends. Primed microglia had an ellipsoid cell body with their shortest axis between 5 and 7 μm. They also had at least 2 processes and 7 ends. Reactive and amoeboid microglia displayed a swollen amoeboid-shaped cell body, but the phenotypic requirements for size and processes differed. Reactive cell bodies were 5-21 μm in the shortest axis with 2 or fewer processes that were longer than the cell body, with more than 3 ends. Amoeboid cell bodies were described as being between 6 and 27 μm in the shortest axis with 2 or fewer processes shorter than the cell body and unramified. After probe runs were finished for a subject, a Cavalieri estimator was used to determine the area of the ROI. An estimated sampling volume was produced by multiplying the area by the mean counted thickness for each subject. Then densities were calculated for all four morphological phenotypes by dividing the total number of cells per phenotype by the calculated total sampling volume.

2.6. Cytokine measurement in plasma samples

Plasma cytokine measurements were performed as described in Hagenberg et al. (2025). In brief, the V-PLEX Human Biomarker 54-Plex Kit (Meso Scale Diagnostics (MSD), Rockville, USA, Cat. No. K15248G-2) was used to measure the cytokines. MSD method relies on electrochemiluminescence, where biomarkers are captured on pre-coated, multi-spot plates and detected with labeled antibodies. Furthermore, enzyme-linked immunosorbent assay (ELISA) was utilized to measure high-sensitivity C-reactive protein (hsCRP, Tecan Group Ltd., Männedorf, Switzerland, Cat. No. EU59151), cortisol (Tecan Group Ltd., Männedorf, Switzerland, Cat No. RE52061), interleukin (IL)-6 (Thermo Fisher Scientific, Waltham, USA, Cat. No. BMS213HS), IL-6 soluble receptor (sIL-6R, Thermo Fisher Scientific, Waltham, USA, Cat. No. BMS214) and IL-13 (Thermo Fisher Scientific, Waltham, USA, Cat. No. BMS231-3). Cytokines with a missingness of more than 16% or with a high sensitivity measurement available were excluded. For an overview of the cytokines and the number of missing values see Supplementary Table 5. The working flow of the methodology and our brain and plasma cohorts has been summarized in Fig. 1.

2.7. Statistical analysis

2.7.1. vmPFC

Analyses were performed using R version 4.0.2. The cytokine concentrations were quantile-normalized, meaning that the observations were ordered according to their value and mapped to the according quantiles of a standard normal distribution. To test the effect of the case/control status on the cytokine concentrations, a linear model including status, age, sex, BMI, PMI, pH value and medication status of any psychotropic medication was used. For the stratified analyses, the linear model additionally included an interaction term between the case-control status and either medication status, sex or BMI. Microglia morphology subtype densities were analyzed with a linear model in the same way as the cytokine data. To control for multiple testing, the Benjamini-Hochberg procedure was applied with a significance threshold of 0.05. A post-hoc minimum detectable effect analysis for the regression coefficient of status was performed assuming a significance threshold of 0.05 (two-sided test) and a power of 0.8.

2.7.2. Plasma

Cytokine concentrations were adjusted for a storage batch variable by regressing out the variable with a linear model and the residuals were used for subsequent analyses. Analyses for the cytokine data were performed as described for the brain data, except that the linear model included the status, age, sex, BMI and medication status of any psychotrophic medication. For the stratified analyses the linear model additionally included an interaction term between the case-control status and either medication status, sex or BMI. To control for multiple testing, the Benjamini-Hochberg procedure was applied with a

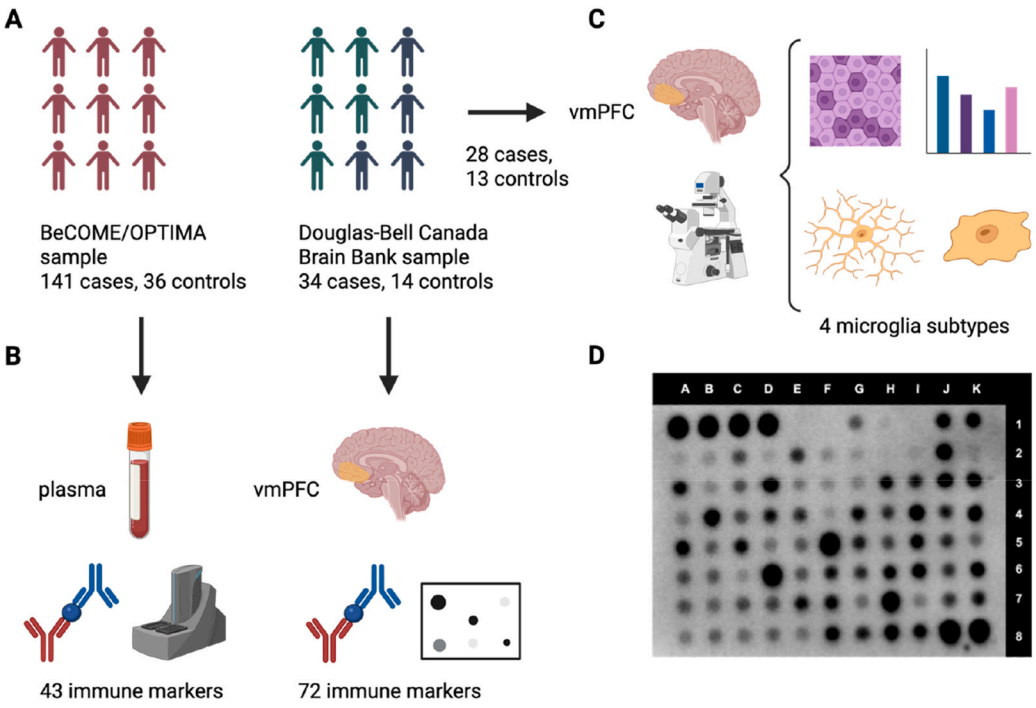

Fig. 1. Analysis overview. (A) The sample for the blood-based analysis comprised 141 cases with depression and 36 controls. The sample for the brain-based analysis comprised 34 cases with depression and 14 controls (unfixed fresh-frozen tissue) and 28 cases and 13 controls (fixed tissue) from the ventromedial prefrontal cortex (vmPFC). (B) Immune markers in plasma were measured with Meso Scale Diagnostics and ELISA assays, while immune markers in brain tissue were measured semi-quantitively with RayBio antibody arrays. (C) For microglial morphology, fixed tissue was stained for Iba1, and immunostained cells categorized into four subtypes. Density estimates were generated with an optical fractionator probe. (D) Example of an antibody array.

significance threshold of 0.05.

3. Results

3.1. Cytokine, chemokine and growth factor levels

The details of our brain and plasma cohort and workflow of our experiments are summarized in Fig. 1A–C. A global and unbiased semi-quantitative assessment of cytokine, chemokine and growth factor protein levels (Fig. 1D) in vmPFC of controls and depressed suicides (DS) was generated with antibody arrays. To control for possible confounding variables, we tested case/control differences in a linear model that included age, sex, BMI, medication status and the PMI and brain pH for the brain derived data. As illustrated in Fig. 2 and Supplementary Fig. 1, no cytokine, chemokine or growth factor was significantly different in samples from cases vs. controls (p-values listed in Supplementary Table 6). A post-hoc minimum detectable effect analysis showed that all observed effect sizes were smaller than the minimum detectable effects assuming a power of 0.8. The parallel analyses conducted in plasma samples in depressed vs control individuals from the BeCOME and OPTIMA studies revealed, as in brain, comparable levels in cases and controls of all markers tested (Fig. 3, Supplementary Fig. 2 and Supplementary Table 7). This included the acute phase C-reactive protein (CRP). We repeated the analyses for brain and plasma and separately included an interaction term between the case-control and either medication status, sex or BMI. No interaction was significant. While both brain and blood measurements were not significantly different between cases and controls, the correlation between the different cytokines differed across the tissues. The markers measured in brain tissue were moderately to highly positively correlated with each other (median Pearson correlation of 0.49). In contrast, the markers measured in plasma showed a lower correlation (median Pearson correlation of 0.14, Supplementary Fig. 3A–B).

3.2. Microglial morphology

The morphological classification used in this study is based on distinct microglial subtypes as defined previously: ramified, primed, reactive, and amoeboid microglia (Fig. 4A) (Torres-Platas et al., 2014). The stereological analysis conducted in vmPFC GM revealed a similar distribution of subtypes between groups, with approximately 10% ramified microglia, 30% primed microglia, 35% reactive microglia, and 25% amoeboid microglia (Fig. 4B). To control for age, sex, BMI, PMI and pH, a linear model was used to compare between groups the density of microglia subtypes. There were no significant differences between cases and controls for any microglial subtype (Fig. 4C and Supplementary Table 8).

4. Discussion

This is the first study to assess the protein levels of a broad panel of cytokines, chemokines and growth factors in the vmPFC, a major limbic region in depressed patients. To date, most post-mortem studies have focused on cytokine transcripts. Measuring proteins is important given post-transcriptional regulation of cytokines and chemokines (Anderson, 2008). Data were complemented with a morphological analysis of microglial subtypes in the same brain region, as well as with measurements of plasma cytokines from an independent patient cohort. None of these analyses suggested the presence of depression-associated neuroinflammation in the vmPFC nor in the plasma. This observation is consistent with our recent single-nucleus RNA sequencing study of dlPFC samples from depressed suicides (Nagy et al., 2020), also indicating an absence of a neuroinflammatory signature in the PFC. In fact, the results of these investigations revealed an overall downregulation of pro- and anti-inflammatory immune signaling pathway gene sets (Maitra et al., 2023; Nagy et al., 2020). Such an immune downregulation in depression was also observed in our most recent transcriptomic analysis of intact vmPFC microvessels from depressed suicides, in which

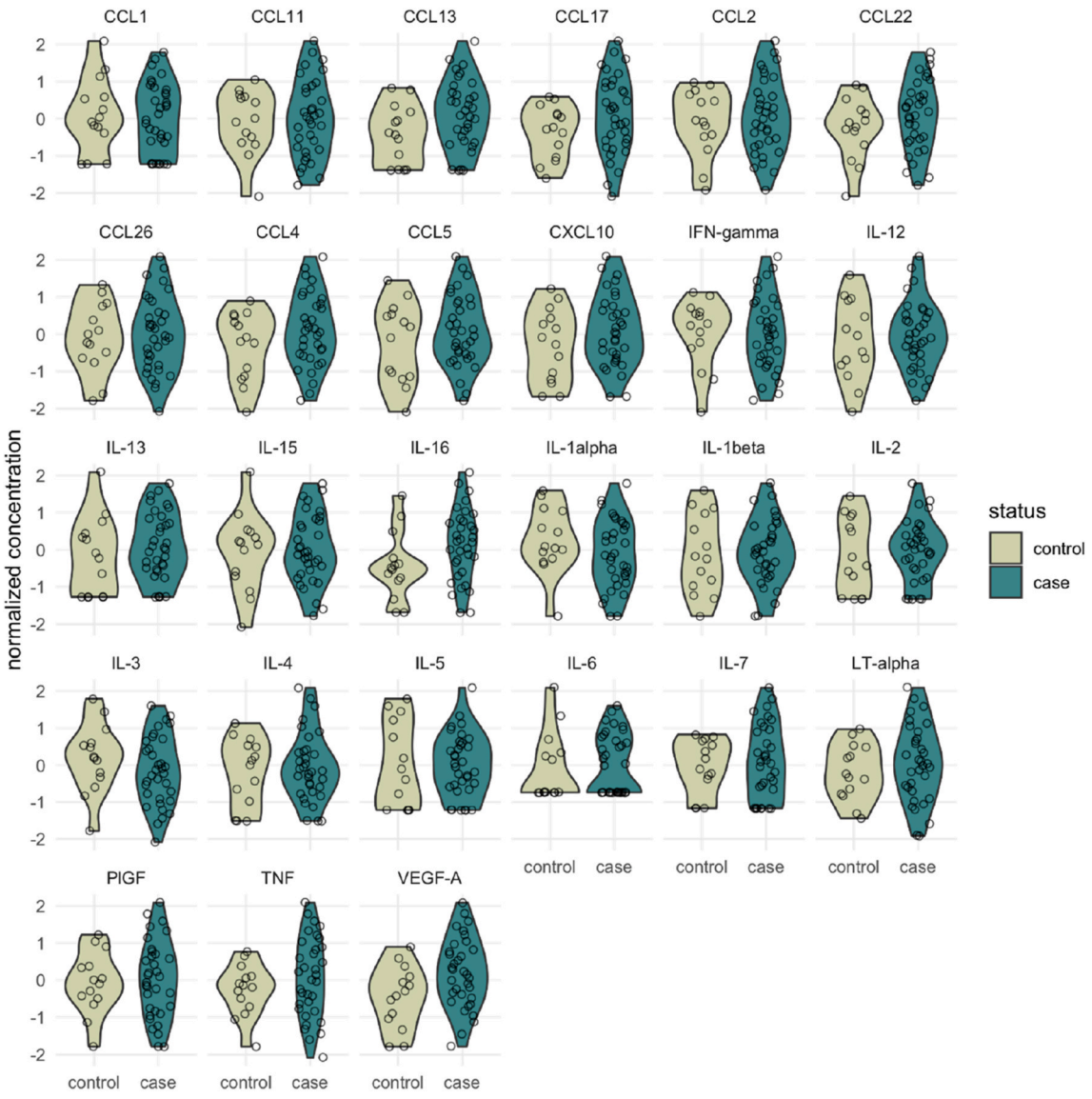

Fig. 2. Violin plots of the normalized immune marker concentrations measured in vmPFC. 27 out of 72 markers are shown, the remaining are depicted in Fig. S1. N = 34 cases and 14 controls.

female samples displayed global immune suppression (Wakid et al., 2026). Similarly, in an independent single cell RNA sequencing study of acutely isolated post-mortem microglia, Scheepstra and colleagues found an immune-suppressed gray matter microglial phenotype in the occipital cortex of medicated MDD patients (Scheepstra et al., 2023). Altogether, these high-throughput transcriptomic analyses suggest a suppression of the immune system in the brain of depressed patients, which could potentially be reflected at the protein level.

Our morphological analysis with the pan microglia/macrophage marker (Iba-1) indicated a similar distribution of microglial morphologies in the vmPFC of cases and controls. A previous study from our group had suggested some microglial priming in the ACC white matter of depressed suicides (Torres-Platas et al., 2014). The fact that the current study did not observe any such morphological evidence of priming or activation would suggest region-specific differences in microglial responses, with vmPFC being more tolerant or adaptable to adverse conditions. It must be mentioned, however, that microglial morphology-based classification does not necessarily correlate with microglial functional state (Paolicelli et al., 2022). In addition, the response of these cells to stress is complex and shaped by many factors, including sex, age, brain region, and the type, timing and duration of the stressor (Rahimian et al., 2019, 2022; Sequeira and Bolton, 2023). Therefore, although our cell morphology findings concord with our molecular data, their interpretation come with the aforementioned caveats.

In the current study, we did not quantify resident microglial cells expressing functional activation markers such as MHC-II, CD68 and TMEM119 in the vmPFC. However, we recently quantified microglial cells that co-express CD68 and TMEM119 using immunofluorescence and measured CD68 with ELISA in vmPFC gray matter samples from depressed suicides and matched controls, and no significant group differences were found (Belliveau et al., 2025).

Regional heterogeneity in the brain's susceptibility to inflammation has been previously reported. The underlying mechanisms might include regional differences in brain cell populations, the local neurovascular unit, and the expression of inflammation-related genes (Kim et al., 2000; Menard et al., 2017; Rahimian et al., 2021; Wakid et al., 2026). These variations might contribute to neuroinflammatory changes reported in regions such as the ACC, vmPFC and OFC in depression. In this context, microglial cells are worth mentioning. Under physiological and pathological conditions, microglia display spatial heterogeneity in density, morphology, turnover rate, pruning, metabolism, and

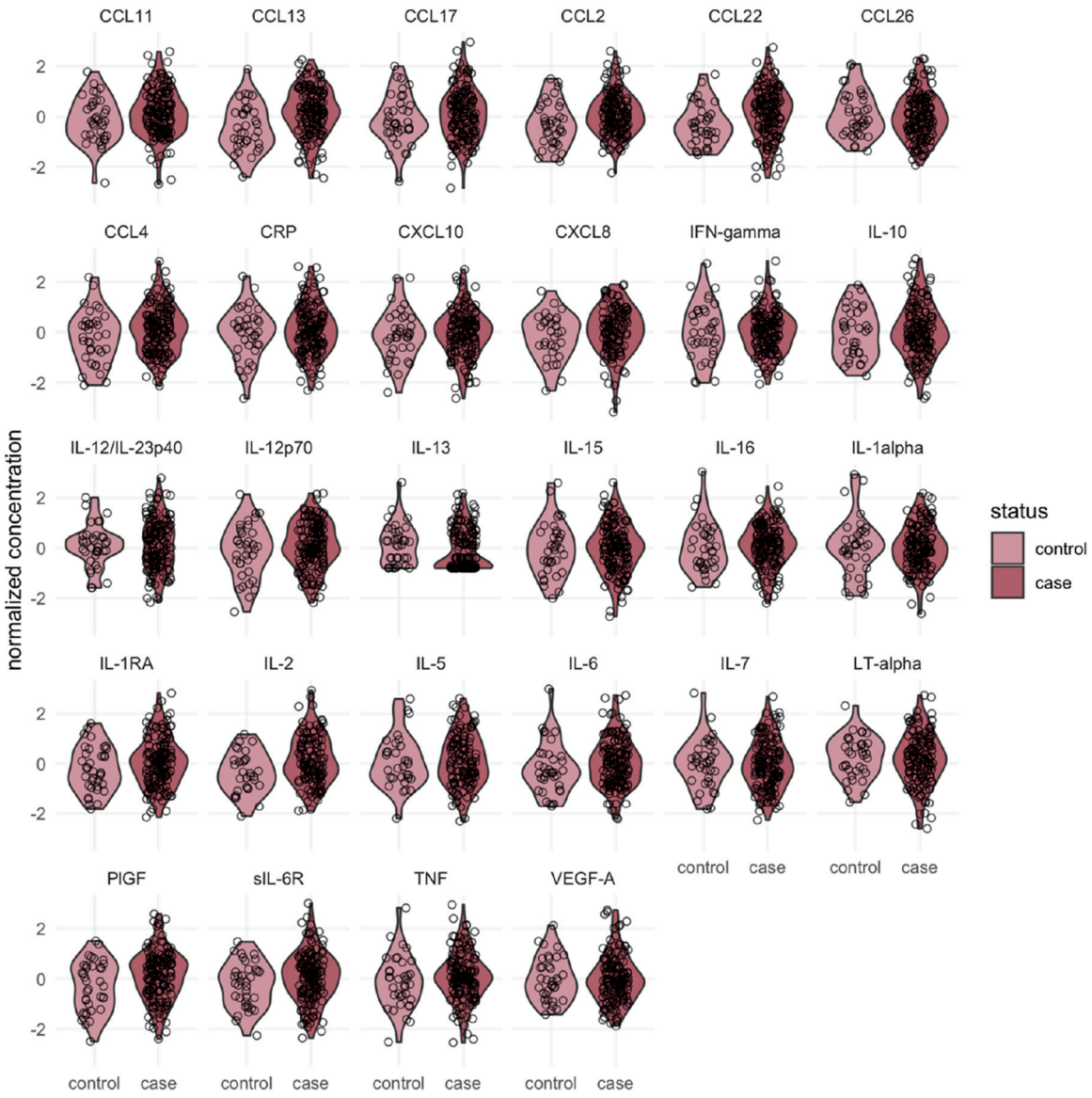

Fig. 3. Violin plots of the normalized immune marker concentrations measured in plasma. 28 out of 43 markers are shown, the remaining are depicted in Fig. S2. N = 141 cases and 36 controls.

molecular signature, which might ultimately translate to diverse regional inflammatory profiles (Rahimian et al., 2021). For example, Kim and colleagues reported that mesencephalic neurons are significantly more susceptible than hippocampal or cortical neurons to inflammation-associated changes in gene expression (Kim et al., 2000). This susceptibility may be attributable to differences in the abundance of microglia within a specific brain region (Kim et al., 2000). Furthermore, recently developed transcriptomic approaches have allowed the characterization of heterogeneity and context-dependent properties of microglial cells in modulation of inflammatory responses across different brain regions (Rahimian et al., 2021).

Similar to our post-mortem brain results, the patient plasma results did not show any significant difference between cases and controls. In particular, the average CRP level did not differ between groups. This result is at odds with previous investigations indicating higher blood CRP levels associated with greater depressive symptom severity and a worse response to treatment (Orsolini et al., 2022). It is also in conflict with higher CRP levels observed in depressed patients relative to controls in a UK biobank study (Pitharouli et al., 2021). It should be mentioned that depression is biologically heterogeneous, and certain patients may exhibit an inflammatory subtype of depression. These discrepancies might be due to the smaller sample size, sample heterogeneity, detection sensitivity, and statistical power of our study.

Given the hypothesis that inflammation plays an aetiological role in a subset of patients with depression (Luning Prak et al., 2022; Mondelli et al., 2017; Rahimian et al., 2021), a large sample size might be required to detect the presence of such a subgroup. Indeed, Lynall et al. have shown a distinct immunological profile for inflamed and non-inflamed depression, with the inflamed group displaying elevated levels of blood neutrophils, monocytes, $CD4^+$ T cells, IL-6 and CRP (Lynall et al., 2020). Similarly, we previously reported that individuals with depression symptoms and a higher BMI had increased levels of CRP and other cytokines (Hagenberg et al., 2025). These findings suggest that individualized anti-inflammatory treatments should be considered only for MDD patients according to baseline plasma cytokine levels and pre-existing inflammatory condition, as highlighted previously (Luning Prak et al., 2022; Lynall et al., 2020).

Therapeutics targeting inflammation in depression with a more global strategy have not proven efficient. This includes clinical trials combining anti-inflammatory drugs as an add-on therapy to

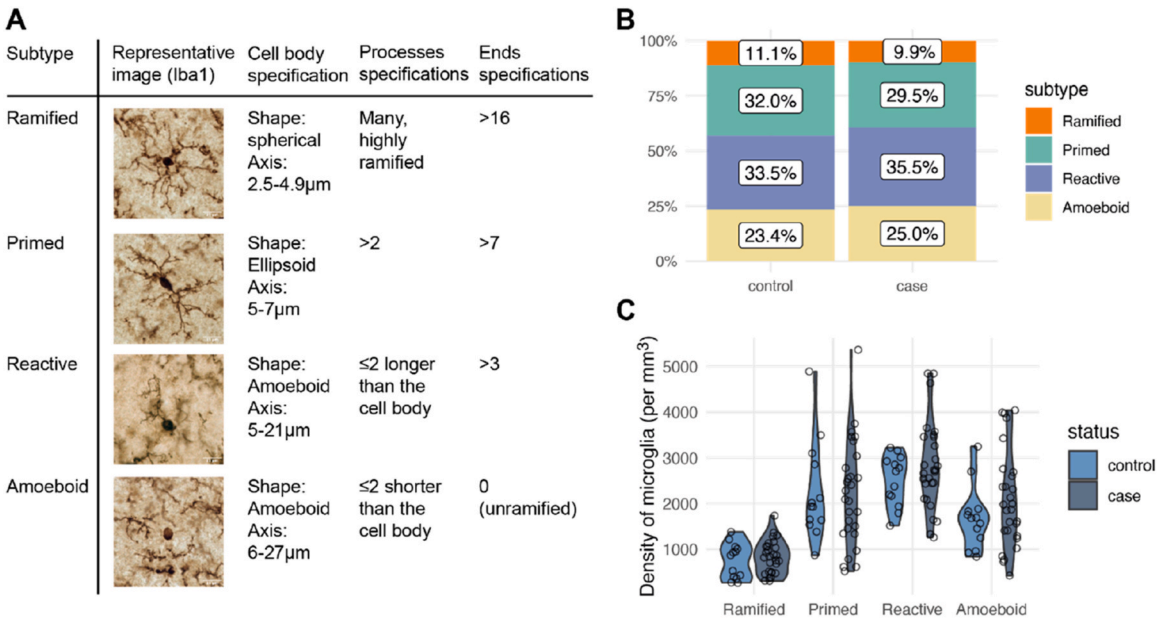

Fig. 4. (A) Overview about the criteria for the microglia subtype classification. (B) Percentage of microglia subtypes summarized across all samples separated by cases and controls. (C) Density of the different microglia subtypes separated by cases and controls. N = 28 cases and 13 controls.

antidepressants. While there is some evidence for some beneficial effects (Hagenberg et al., 2025; Köhler-Forsberg et al., 2019; Nettis et al., 2021), most studies have failed to find a difference compared to placebo (Hellmann-Regen et al., 2022; Husain et al., 2020), even when stratified by CRP (Baune et al., 2021). Luning Prak and colleagues did not observe a significant difference in inflammatory markers between MDD patients and controls. Moreover, when MDD patients received an anti-inflammatory selective COX2 inhibitor (Celecoxib) as an add-on to escitalopram, depression scores and cytokine levels did not decrease more than with escitalopram alone (Luning Prak et al., 2022). These findings contradict the results of some studies, in which cytokine elevations in MDD patients have been reported (Dowlati et al., 2010; Howren et al., 2009; Köhler et al., 2017; Liu et al., 2012; Papakostas et al., 2013; Stewart et al., 2009). However, in the latter studies, patients were not excluded based on peripheral inflammatory illnesses.

Antidepressants can modulate brain immune response and therefore regulate the expression of several cytokines and chemokines (Rahimian et al., 2021). Possible effects of antidepressants, particularly SSRIs, on brain immune function have been well-documented. It is well established that SSRIs can regulate the secretory profile of cerebral glial cells (Su et al., 2015; Tynan et al., 2012). Indeed, SSRIs can directly modulate neuroglial secretory function. In addition, they can indirectly increase availability of serotonin to glial cells that express functional serotonin receptors coupled to different signaling pathways (Rahimian et al., 2021). Furthermore, antidepressants can induce adaptive changes in central monoaminergic neurotransmission and expression of central glucocorticoid receptors, which modulate central actions of cytokines (Castanon et al., 2002). In our study, some cases received different antidepressant medications in their last 3 months of life, and for some subjects, compliance was confirmed by toxicological analysis. However, including medication as a covariate in the regression models on the case-control differences of cytokine levels did not reveal any influence of antidepressants. This suggests, at least for our samples, that antidepressants do not significantly influence peripheral or central inflammation.

Our study is not without limitations, and several factors might have a role in the non-inflammatory phenotype we observed in gray matter vmPFC and plasma of depressed patients. First, given the relatively small number of brain samples and the large number of markers tested, the statistical power may be insufficient even after multiple-comparison correction, making it possible that small but genuine effects were not detected. Second, sample heterogeneity and detection sensitivity may underlie the absence of inflammatory changes we report, especially in vmPFC samples. For instance, the RayBio® antibody array is as semi-quantitative assay with limited sensitivity and low-level signals may have remained below the detection threshold. Third, heterogeneity related to medication status in the plasma cohort could have influenced cytokine levels. The cohort included both medicated and unmedicated depressed individuals. In the BeCOME study, most participants were unmedicated and only a minority (approximately 24%) used anti-inflammatory medication, whereas individuals in the Optima study were primarily medicated with psychotic drugs. While such variability might partly contribute to peripheral cytokine variability, our consistent findings across these subgroups suggest that the lack of significant cytokine difference is unlikely driven by medication status. Fourth, cytokine proteins may degrade post-mortem, possibly leading to a loss of signal. For example, IL-6 levels were very low in some control and MDD vmPFC samples, possibly reflecting post-mortem degradation. Moreover, cytokines show a very dynamic pattern of expression in the brain, whereas our study only provides a cross-sectional measurement. In this context the insufficient sensitivity of protein-assays we used cannot be excluded. Fifth, the brain and blood cohorts were independent and two different methods were used to profile cytokines in brain and plasma. Therefore, the absence of correlation between plasma and brain cytokines cannot be interpreted as a lack of brain-blood concordance. While there was no complete overlap of cytokines, 22 cytokines were measured in both types os samples, including TNF and IL-6. Sixth, all depressed individuals in the brain cohort died by suicide. Recent investigations have also suggested that the immune system may be affected by suicide. In this context, García-Gutiérrez et al. analyzed changes in gene and protein expression of proinflammatory cytokines, IL-6 and TGF-β, and anti-inflammatory cytokine, IL-10, in the dorsolateral prefrontal cortex of suicides with no clinical psychiatric history or treatment with anxiolytics or antidepressants and matched controls (García-Gutiérrez et al., 2025). Therefore, in our vmPFC findings, it was not possible to disentangle the effect of suicide and depression on inflammatory markers. Seventh, our molecular and morphological analyses were conducted in a single region, and results are likely not representative of the entire brain. Finally, our female sample size was too small to allow to identify possible sex-specific differences.

With these limitations in mind, our findings are meaningful in that they do not provide evidence of depression-associated neuroinflammatory changes in the vmPFC. As discussed above, this interpretation is consistent with previous high-throughput studies from our group and others suggesting that, unlike other brain regions, the PFC might not be impacted by neuroinflammation in depression, at least not with the same magnitude.

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CRediT authorship contribution statement

Reza Rahimian: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Jonas Hagenberg:** Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Claudia Belliveau:** Formal analysis, Investigation, Methodology. **Rebecca Chen:** Investigation, Methodology. **Stephanie Théberge:** Investigation, Methodology. **Gohar Fakhfouri:** Formal analysis, Software, Writing – review & editing. **Marina Wakid:** Conceptualization, Writing – review & editing. **Elisabeth Binder:** Supervision, Writing – review & editing. **Gustavo Turecki:** Resources, Writing – review & editing. **Janine Knauer-Arloth:** Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. **Naguib Mechawar:** Conceptualization, Funding acquisition, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2026.101245.

Data availability

Data will be made available on request.

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