Are cytokine profiles associated with the cognitive performance of adults with severe major depression?

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1. Introduction

Cognitive performance is often impaired in individuals with major depressive disorder (MDD) (Reppermund et al., 2009; Wagner et al., 2012). This is a major concern for affected individuals since cognitive impairment is associated with severe problems in occupational and social functioning, and daily life (Gupta et al., 2013; Hammar et al., 2022). Owing to this, it has a large impact on the quality of life of an individual with depression (Douglas et al., 2018). Furthermore, a deeper understanding of cognitive impairment in patients with mental disorders is of great clinical significance, as it can limit patients' coping skills. This in turn makes patients more vulnerable to relapse, affecting the success of a treatment protocol (Castaneda et al., 2008).

So far, first-line antidepressant and psychological treatments have only limited positive effects on the patient's cognitive function. This can lead to a persistence of symptoms (Douglas and Porter, 2009; Reppermund et al., 2009; Wagner et al., 2012; Porter et al., 2016). For a treatment to mitigate cognitive impairment, its causes must be more thoroughly investigated in depression (Hammar et al., 2022).

A growing number of studies reported that MDD is associated with a systematic immune activation (Allison and Ditor, 2014; Beurel et al., 2020). However, inflammatory processes are not only linked to the pathophysiology of depression (Köhler et al., 2017; Osimo et al., 2020; Beurel et al., 2020) but also to the pathophysiology of cognitive impairment (Allison and Ditor, 2014; Beurel et al., 2020). It has been suggested that the peripheral immune system may act as a regulator of various brain functions such as learning, memory and attention and that a dysfunction in inflammatory signaling can result in memory and cognitive deficits (Tian et al., 2018). To date, most studies investigating the impact of the immune system on the cognitive performance of

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depressed patients have focused on a limited number of cytokines (Tateishi et al., 2020).

Therefore, the present study aimed to investigate the relationship between 48 peripheral blood cytokines and the cognitive performance in patients with severe unipolar depression using data from an observational study in Augsburg, Germany.

2. Material and methods

2.1. Design and study population

The present study used data from the Depression long-term Augsburg (DELTA) study, a prospective single-center observational study on the long-term management of patients with major depression after an inpatient treatment at the Department of Psychiatry, Psychotherapy and Psychosomatics of the University of Augsburg, Germany (Kirchberger et al., 2019). The work presented here used solely the baseline data of the DELTA study. Baseline assessments were performed from 15/02/2018 to 17/12/2020.

The DELTA study included all adult consecutive hospitalized cases (age range 18–75 years) with the primary discharge diagnosis of severe major depression. The patients were screened based on the hospital information system where diagnoses were coded according the International Classification of Diseases, Tenth Revision (codes: F32.2, F32.3, F33.2, F33.3). Prior to inclusion into the study, diagnoses were confirmed with the Structured Clinical Interview for DSM IV (SCID-I, categories A, B, C, D) criteria (Spitzer et al., 1992). Furthermore, a score above 16 on the Hamilton Depression Rating Scale (Hamilton, 1960) was required. Patients exhibiting (i) mental and behavioral disorders due to primary psychoactive substance use (F.10 to F.19) (ii) disorders of adult personality and behavior (F.60 to F.60.9, F.61) (iii) mental retardation (F.70 to F.79), (iv) dementia (F.00 to F.09), (v) insufficient knowledge of the German language, (vi) comorbidities with a life expectancy less than one year (e.g. terminal cancer) were not included in the study. The study was approved by the Ethics Committee of the Ludwig-Maximilians-Universität München (date of approval: 23 October 2017, reference number: 17–625) and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

A total of 126 patients met the inclusion criteria and were enrolled in the study. Eight patients with a history of either stroke, Parkinson's disease or multiple sclerosis (MS) were excluded from the statistical analysis. Additionally, 18 patients who had not completed any cognitive test or whose blood counts had not been examined were excluded, leaving 100 patients for the statistical analysis.

2.2. Survey data

The data was collected by an interview and a self-reporting questionnaire. The survey included information on socio-demographics, disease history, smoking behavior, and psychotropic drug intake. In order to assess comorbid conditions, the patients were asked whether they were ever diagnosed as having musculoskeletal disorders (e.g. rheumatoid arthritis, back pain), coronary heart disease, myocardial infarction, hypertension, diabetes or cancer. However, the precise proportion of patients with inflammatory or immune conditions among the musculoskeletal disorders is unknown. In addition, standardized questionnaires were used to assess alcohol consumption and depression severity. The severity of depressive symptoms was assessed using two different questionnaires. To quantify the severity of depression symptoms by a third-party rating, study psychologists used the Hamilton Depression Rating Scale (HDRS). The HDRS consists of 17 items resulting in a score ranging from zero to 52. Scores between zero and eight indicate the absence of depressive symptomatology, scores between nine and 16 indicate a mild degree of depressive symptomatology, scores between 17 and 24 indicate a moderately severe degree of depressive symptomatology, and scores over 24 indicate severe depressive symptomatology (Hamilton, 1960; Deutsche Gesellschaft für Psychiatrie und Psychatrie und Psychotherapie, Psychosomatik und Nervenheilkunde (DGPPN), Deutsche Gesellschaft für Suchtforschung und Suchttherapie e.v. (DG-Sucht), 2020; Chai and Ho, 2021). The severity of the depression symptoms was additionally self-rated by the patients using the Beck Depression Inventory (BDI-II). It is composed of 21 items (values range 0–3) resulting in values ranging from zero to 63. Values of less than 13 are considered clinically unremarkable while scores between 13 and 19 indicate a mild degree of depressive symptomatology, scores between 20 and 28 indicate a moderate degree of depressive symptomatology, and values greater than 28 indicate a severe degree of depressive symptomatology (Kühner et al., 2007; Deutsche Gesellschaft für Psychiatrie und Psychatrie und Psychotherapie, Psychosomatik und Nervenheilkunde (DGPPN), 2015). Alcohol consumption was assessed using the Alcohol Use Disorder Identification Test (AUDIT) – C. This questionnaire focuses on identifying hazardous alcohol use in the previous year consisting of ten items. Generally, a cut-off value of five indicates hazardous alcohol use (Sanchez-Roige et al., 2019; Deutsche Gesellschaft für Psychiatrie und Psychatrie und Psychotherapie, Psychosomatik und Nervenheilkunde (DGPPN), Deutsche Gesellschaft für Suchtforschung und Suchttherapie e.v. (DG-Sucht), 2020).

2.3. Assessment of cognitive performance

Cognitive evaluations were conducted by trained psychologists. The evaluation covered memory and executive cognitive functions. Working memory (WM) involves "working with information that is no longer perceptually present" (Diamond, 2013). To test WM the subtests "forward, backward and sequential digit span" from the Wechsler Adult Intelligence Scale (WAIS) IV were performed (Petermann, 2021). For the digit span tests, the examinee is read aloud a sequence of 2–9 numbers. For the forward digit span, the examinee recalls these numbers in the same order, for backward digit span in reverse order and for sequential digit span in ascending order, respectively. The raw scores from each subtest are summed up. Cognitive interference occurs "when the processing of a specific stimulus feature impedes the simultaneous processing of a second stimulus attribute", known as the Stroop Effect (Diamond, 2013). To assess the ability to inhibit cognitive interference (interference control (IC)) the Stroop Color and Word Test (SCWT) with the subtests "word" (W), "color" (C) and "color-word" (CW) was performed (Stroop, 1935; Scarpina and Tagini, 2017; Bäumler, 1985). For subtest "W", the examinee is presented a table of words (green, red, yellow, blue) printed in black color and is asked to read them aloud. For subtest "C" the examinee is presented a table with printed color blocks and is requested to name the color of each block. In subtest "CW" color words are printed in different colors, e.g. the word "green" is printed in red color. The examinees are asked to name the color.

2.4. Biomaterial

A sample of 30 mL venous blood was collected from each patient after study inclusion. The blood samples were drawn in the morning, while patients were in a state of overnight fasting and before the daily medication intake. Processed and aliquoted samples were stored at −80 °C in the biorepository of the Chair of Epidemiology, University Hospital Augsburg. Subjects' cytokine levels were assessed in a small sample of blood serum using the Bio-Plex Pro™ Human Cytokine Screening Panel (Bio-Rad, USA). All assays were performed according to the manufacturer's instructions.

2.5. Data analysis

All analyses were performed using R software (version 4.2.0). Descriptive statistics were used to characterize basic demographic,

psychosocial, and clinical characteristics, cognitive test results and cytokine measurements. The frequency, variety, and severity of cognitive manifestations were investigated by comparing patients' cognitive performance to their expected performance. This analysis was performed in accordance with the respective test manuals. Raw values from the WAIS-IV were transformed into age-corrected standardized value points. Normal distribution with a mean of ten and a standard deviation of three was assumed. Cut-off points were seven for mild or borderline negative alteration of the WM and four for impairment of the WM. Values greater than seven indicated no impairment (Petermann, 2021). The raw values of the SCWT were transformed into t-standardized age corrected values, assuming a normal distribution with a mean of 50 and a standard deviation of ten. Cut-off points were 40 for mild or borderline negative alteration of the inhibition of cognitive interference and 30 for impairment of the inhibition of cognitive interference. Values larger than 40 were interpreted as no impairment recorded (Scarpina and Tagini, 2017).

According to the manufacturer's recommendations, 19 cytokine measurements with 25% or more missing values were excluded from the statistical analysis. The remaining 29 cytokines and their abbreviations are listed in Table 1. If the missing values of cytokines were less than 25%, the limit of detection (LOD) value was imputed. The raw values of the cytokine variables were normalized using the intensity normalization (Olink, 2021) and thereafter $\log_2$-transformed. Outliers were removed from further analysis. Multiple linear regression models were fitted to determine the association between the cytokine levels and the patient's cognitive performance. Potential confounding variables included in the models were chosen based on current literature. The assumptions for multivariable linear regression analyses were tested using scatterplots and Q-Q plots to confirm linearity of associations, normal distribution of the residuals and homoscedasticity. The R package "car" (Fox and Weisberg, 2019) was used to identify multicollinearity. For statistical tests, an alpha level of 0.05 was defined. P-values were corrected for multiple testing using the Benjamini & Hochberg procedure (False Discovery Rate, FDR) (Benjamini, 2010).

Table 1
Measured cytokines with less than 25% missing values.

Cytokine	Abbreviation
Cutaneous T-cell Attracting Chemokine	CTACK
Eotaxin	
Granulocyte Colony Stimulating Factor	G-CSF
Hepatocyte Growth Factor	HGF
Intercellular Adhesion Molecule-1	ICAM-1
Interferon γ	INF-γ
Interleukin-16	IL-16
Interleukin-18	IL-18
Interleukin-1β	IL-1β
Interleukin-2 receptor antagonist	IL-2Ra
Interleukin-4	IL-4
Interleukin-9	IL-9
Interferon γ-induced protein	IP-10
Leukemia inhibitory factor	LIF
Macrophage Colony Stimulating Factor 1	M-CSF
Monocyte Chemoattractant Protein-1	MCP-1
Monokine induced by γ interferon	MIG
Macrophage Inflammatory Protein-1α	MIP-1α
Macrophage Inflammatory Protein-1β	MIP-1β
Platelet-derived growth factor BB	PDGF-BB
Regulated upon activation, normal T cell expressed and secreted	RANTES
Stem cell factor	SCF
Stem Cell Growth Factor β	SCGF-β
Stromal cell-derived factor-1	SDF-1
Tumor necrosis factor α	TNF-α
Tumor necrosis factor β	TNF-β
TNF-Related Apoptosis Inducing Ligand	TRAIL
Vascular cell adhesion protein 1	VCAM-1

3. Results

3.1. Sample characteristics

The demographic and clinical characteristics of the patients are shown in Table 2. The mean (±standard deviation) age of the participants was 42.6 (±13.3) years with 41 (41.0%) men and 59 (59.0%) women. The most common comorbidities were diseases of the musculoskeletal system (e.g. rheumatoid arthritis, back pain) (62.0%), followed by hypertension (36.0%). Prior to hospitalization 80 patients had been treated with psychotropic drugs. The median disease duration was 4.03 years (0.4–8.9). The patients obtained a HDRS Score with a median of 22.5 (19.0–26.0) and a median of 28 (19–37) at the Beck Depression Inventory. Nine (9.1%) patients obtained a score of at least five in the AUDIT-C questionnaire, indicating hazardous alcohol use. Cognitive tests were performed in median 34 days (28–42) after hospital admission. Blood samples were collected in median 28 days (23–34) after hospital admission. The resulting cytokine levels are shown in the Supplementary Table 1.

3.2. Results of the cognitive evaluation

The results of the cognitive tests are displayed in Table 3. Eleven patients (11.0%) obtained a score signaling impairment and 23 (23.0%) patients' scores showed a mild/borderline negative alteration in the WAIS-V test for memory function. Less patients obtained scores that indicated an impairment or negative alterations in the SCWT tests.

Table 2
Demographic and clinical characteristics of the sample (n = 100).

Demographic characteristics	
Age [mean (SD), MIN - MAX, y]	42.6 (13.3), 18-65
Gender	
Female	59
Male	41
Education	
Less than or equal to 9 years of schooling	29
More than 9 years of schooling	69
Other	2
Marital status	
Married	41
Single	38
Divorced	16
Widowed	4
Smoking	
Never-smoker	34
Current smoker	42
Former smoker	24
Clinical characteristics	
Comorbidities (yes)	
Hypertension	36
Coronary heart disease or angina pectoris	5
Heart attack	1
Diabetes	6
Diseases of the musculoskeletal system	62
Cancer	5
Any comorbidity	73
Body Mass Index [median (Q1 – Q3)]	27.0 (24.5–32.4)
Disease History (Depression)	
Psychotropic drug intake (yes)	80
Total disease duration, years [median (Q1 – Q3)]	4.0
Prior hospitalization (yes)	41
Depression Severity	
Hamilton Score [median (Q1 – Q3)]	22.5 (19.0–26.0)
Beck Depression Inventory [median (Q1 – Q3)]	28.0 (19.0–37.0)
Alcohol consumption (AUDIT-C) [median (Q1 – Q3)] (n = 99)	1.0 (0.0–3.0)
≥5: Hazardous alcohol use	9.0

AUDIT: Alcohol Use Disorder Identification Test – C, MIN: minimum, MAX: maximum, SD: standard deviation, y: years, Q1: first quartile, Q3: third quartile, percentages refer to non-missing values.

Table 3
Cognitive evaluation: results of standard cognitive tests on working memory and interference control.

Cognitive tests	n	
WAIS-IV [median (Q1 – Q3)]	100	9 (6.75–11)
≥8: normal		66 (66.0%)
>4 - ≤7: mild/borderline negative alteration		23 (23.0%)
≤4: impairment		11 (11.0%)
SCWT–W [median (Q1 – Q3)]	97	49 (43–55)
≥41: normal		82 (84.5%)
>30 - ≤ 40: mild/borderline negative alteration		12 (12.4%)
≤30: impairment		3 (3.1%)
SCWT–C [median (Q1 – Q3)]	97	50 (46–57)
≥41: normal		89 (91.8%)
>30 - ≤ 40: mild/borderline negative alteration		7 (7.2%)
≤30: impairment		1 (1.0%)
SCWT–CW [median (Q1 – Q3)]	97	52 (48–58)
≥41: normal		91 (93.8%)
>30 - ≤ 40: mild/borderline negative alteration		4 (4.1%)
≤30: impairment		2 (2.1%)

Depending on the SCWT subtest, one and three patients had an impairment and up to 12 patients (12.4%) showed mild/borderline negative alterations.

3.3. Association between serum cytokines and the patients' cognitive performance

Multiple linear regression models were calculated to estimate the relationship between the cytokines and cognitive performance. For each cognitive test and each of the 28 cytokines, one regression model was fitted. Possible confounding variables included in all models were: sex, age, body mass index, AUDIT-C, HDRS score, smoking status, any comorbidities, highest education, and prior psychotropic drug intake. The results of the models are shown in the Supplementary Table 2.

Fig. 1 shows a forest plot compiling the results of the multiple linear regression models fitted for the 28 cytokines for the respective cognitive test. It displays the β-estimate and its confidence interval for each model. Most cytokines were negatively related with cognitive performance. Exceptions were ICAM-1, MIP-1β, SCGF-β and VCAM-1. None of the positive β-estimates generated a significant result in the regression models. In contrast, some of the negatively related cytokines showed significant results.

Elevated levels of the cytokines eotaxin (β: 1.59, 95% CI: 2.70 to −0.48, p-value: 0.0056), IL-4 (β: 1.65, 95% CI: 2.87 to −0.44, p-value: 0.0083), MCP-1 (β: 1.54, 95% CI: 2.68 to −0.40, p-value: 0.0088), IL-1β (β: 1.55, 95% CI: 3.08 to −0.02, p-value: 0.0472), G-CSF (β: 1.61, 95% CI: 2.91 to −0.31, p-value: 0.0159) and PDGF-BB (β: 1.03, 95% CI: 2.03 to −0.03, p-value: 0.0435) were significantly associated with poorer performances in the WAIS-IV test.

Similarly, higher levels of the cytokines eotaxin (β: 3.64, 95% CI: 6.83 to −0.44, p-value: 0.0263), MCP-1 (β: 4.31, 95% CI: 7.53 to −1.09, p-value: 0.0094), SCF (β: 7.60, 95% CI: 13.20 to −1.99, p-value: 0.0085), IL-1β (β: 4.77, 95% CI: 9.07 to −0.47, p-value: 0.0277), IL-4 (β: 3.92, 95% CI: 7.40 to −0.44, p-value: 0.0277), IL-16 (β: 6.56, 95% CI: 11.39 to −1.73, p-value: 0.0083), MIP-1α (β: 2.82, 95% CI: 5.61 to −0.03, p-value: 0.0473), IL-18 (β: 3.09, 95% CI: 5.81 to −0.37, p-value: 0.0266) and G-CSF (β: 4.44, 95% CI: 8.11 to −0.76, p-value: 0.0187) were significantly associated with a poorer performance in the SCWT-C test.

In addition, elevated cytokines levels of eotaxin (β: 3.31, 95% CI: 6.60 to −0.01, p-value: 0.0491), MCP-1 (β: 3.81, 95% CI: 7.14 to −0.48, p-value: 0.0257), IL-16 (β: 7.35, 95% CI: 12.25 to −2.46, p-value: 0.0037), SCF (β: 6.06, 95% CI: 11.89 to −0.21, p-value: 0.0423), and G-

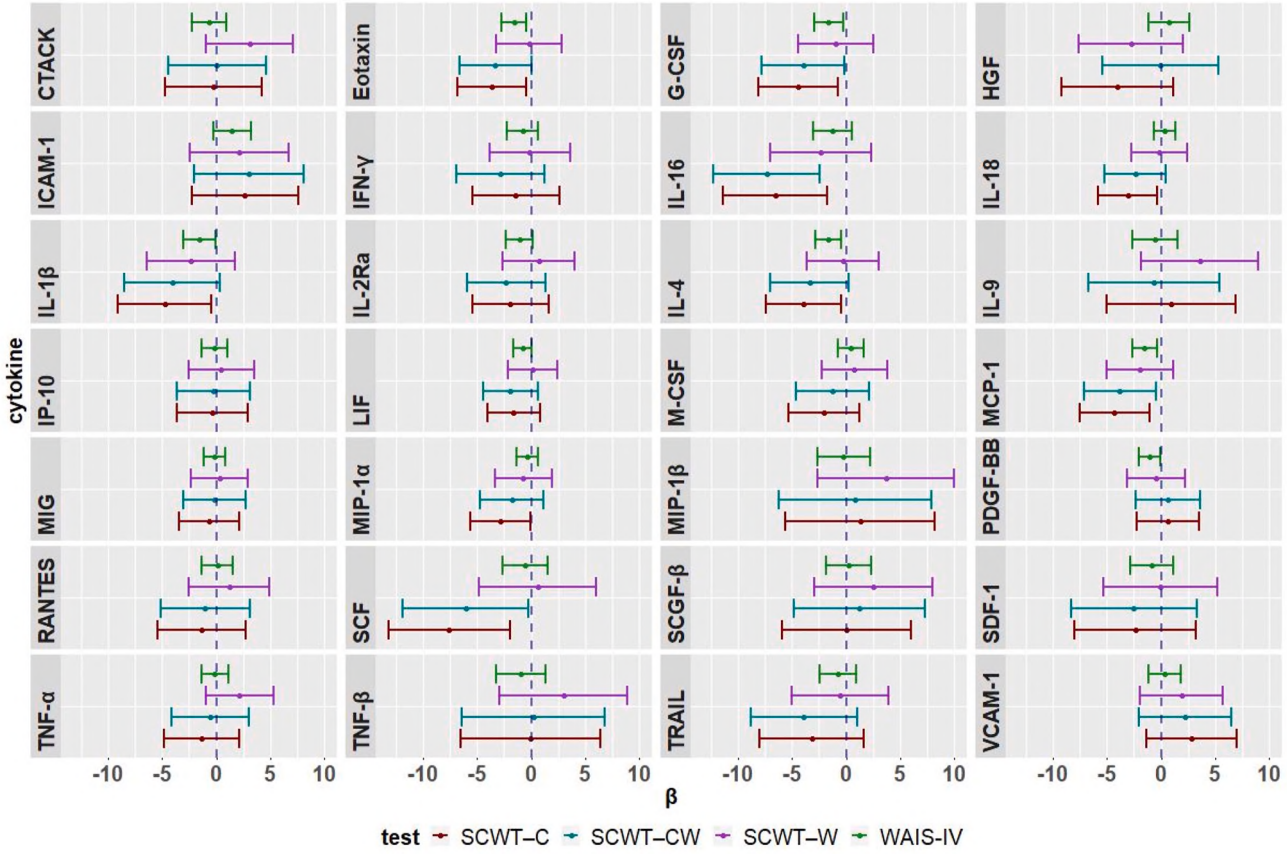

Fig. 1. Forest plot of the multiple linear regression models fitted for the 28 cytokines for the four cognitive tests. The β-estimate and confidence interval for each model is displayed; SCWT: Stroop Color and Word Test - word (W), color (C), color – words (CW), WAIS-IV: Wechsler Adult Intelligence Scale.

CSF (β: 3.99, 95% CI: 7.78 to −0.19, p-value: 0.0396) were significantly associated with poorer performances in the SCWT-CW cognitive test.

However, none of these associations remained significant after adjusting for multiple testing.

4. Discussion

The present study examined the cognitive performance and the levels of peripheral serum cytokines in 100 consecutively hospitalized adult patients with severe depression. The largest limitations in the patients' cognitive performance were recorded with respect to the patients' WM (impairment: 11.0%, mild/borderline negative alteration: 23.0%). A smaller number of patients showed negative changes in their IC depending on the subtest (impairment: 1.0%–3.1%, mild/borderline negative alteration: 4.1%–12.4%). Higher levels of the cytokines eotaxin, IL-1β, IL-4, MCP-1, G-CSF, and PGF-BB were associated with a poorer performance in the patients' WM. In addition, higher levels of the cytokines eotaxin, IL-1β, IL-4, IL-16, IL-18, MCP-1, G-CSF, SCF, and MIP-1α were associated with poorer performance in the patients' IC. However, none of the associations remained statistically significant after adjustment for multiple testing.

MCP-1 is a chemokine that may play a major role in major depression due to its association with key cytokines, neurotransmitters, and neuropeptides. In the present study, elevated levels of MCP-1 were associated with poorer performance in the patients' WM and IC. MCP-1 was already shown to be associated with the pathogenesis of different mental and neurodegenerative disorders including MDD (Pae, 2014; Perry et al., 2021; Lee et al., 2018). Three meta-analyses found elevated MCP-1 levels in patients with depression (Eyre et al., 2016; Köhler et al., 2017; Leighton et al., 2018). In terms of its potential association with cognitive function, MCP-1 levels were associated with longitudinal declines in cognitive performance in older adults (Sanchez-Sanchez et al., 2022). In patients with MDD, Goldsmith et al. (2016) found an association of higher MCP-1 levels and worse performance of psychomotor speed, whereas Wang et al. (2023) found no correlation of MCP-1 with subjective cognitive function. MCP-1 plays an important role in the modulation of other cytokines such as IL-4, IL-6 and IL-8 (Pae, 2014). There are assumptions about its pathophysiological involvement in neurodegeneration and its association with cognitive decline which consider changes in the hippocampus structure and amyloid plaques (Sanchez-Sanchez et al., 2022), however, the specific mechanism how it may affect cognitive function in patients with MDD needs further investigation.

Another cytokine capable of inducing IL-4 is IL-18, which also showed a negative association with the patients' IC in the present study. A meta-analysis of 107 studies confirmed higher levels of IL-18 in patients with depression compared to healthy controls (Osimo et al., 2020). The association of IL-18 with cognitive function was mainly investigated in neurodegenerative disorders (Salani et al., 2013; Zhang et al., 2013; Bossù et al., 2008; Wu et al., 2016). However, Tian et al. (2021) reported an association between an increase of IL-18 and memory deficits in patients with MDD after modified electroconvulsive therapy. Findings from other studies suggest that the interaction of three cytokines, namely IL-18, NLRP3 and NF-κB may affect depression-related memory regulation (Kaufmann et al., 2017; Koo et al., 2010; Su et al., 2017).

Similar with the findings regarding MCP-1 and IL-18, increased levels of IL-4 were found to be associated with poorer performance of WM and IC in the present study. A meta-analysis of 82 studies found no differences between IL-4 levels in patients with depression compared with healthy controls (Köhler et al., 2017) whereas another meta-analysis of 107 studies reported significant lower IL-4 levels in patients with depression compared with controls (Osimo et al., 2020). In contrast to the findings from the present study, beneficial effects of T cell–derived IL-4 on cognitive function in mice have been reported (Derecki et al., 2010). The role of IL-4 in cognitive functioning in depressive patients has not been examined so far. However, the ability of IL-4 to induce eotaxin may contribute to a possible explanation for the results of the present study (Sirivichayakul et al., 2019).

Similar with MCP-1, IL-18, and IL-4, elevated eotaxin levels were associated with a poorer performance in both the WM and IC tests in the present study. Eotaxin is a chemokine that may be induced by Th-2 cytokines including IL-4 and be able to cross the blood-brain barrier. Eotaxin can promote the migration and activation of microglia which in turn leads to a production of reactive oxygen species that enhance glutamate-induced neuronal death (Parajuli et al., 2015; Teixeira et al., 2018). In several studies, elevated eotaxin levels were observed in patients with MDD (Simon et al., 2008; Grassi-Oliveira et al., 2012). Nevertheless, a meta-analysis failed to identify significant differences between eotaxin levels in persons with and without depression (Leighton et al., 2018). The fact that this meta-analysis also included studies with subjects with other medical comorbidities and milder depression levels may have contributed to these results. In terms of cognitive function, studies suggested that eotaxin affects cognitive decline in healthy, older individuals as well as executive, memory and attention functions in patients with schizophrenia (Sirivichayakul et al., 2019). Consistent with the present study, Smagula et al. (2017) found elevated eotaxin levels being associated with impaired executive functions in patients with MDD, however their sample consisted of older patients, and therefore further results from studies with younger MDD patients are needed.

IL-1β is a pro-inflammatory cytokine suggested to be related with depressive disorders (Jin et al., 2020; Das et al., 2021). Increased levels of IL-1β were confirmed by a meta-analysis in older patients with depression (Ng et al., 2018). In contrast, other meta-analyses found no significant association between depression and elevated IL-1β (Köhler et al., 2017; Haapakoski et al., 2015; Dowlati et al., 2010). In the present study IL-1β showed a negative association with WM and IC. These findings are in line with the results from Jin et al. (2020) showing a negative correlation of IL-1β levels with overall cognitive function in patients with MDD. In addition, Wang et al. (2023) showed that patient with MDD who reported subjective cognitive decline had higher plasma level of IL-1β than patients without cognitive decline. Moreover, Tateishi et al. (2020) demonstrated by administering repetitive transcranial magnetic stimulation (rTMS) to patients with treatment-resistant depression, that lowered peripheral IL-1β levels were associated with an improvement of the patient's cognitive performance (Tateishi et al., 2020). In the literature, IL-1β is described as a double-edged sword regulating synaptic processes and memory abilities in physiological conditions. However, when IL-1β is over-expressed, it inhibits hippocampus-mediated memory (Na et al., 2014; Marciniak et al., 2015). IL-1β has also been reported to be able to induce MIP-1α (Menten et al., 2002).

In line with these findings, increased levels of MIP-1α were also associated with a poorer WM and IC in the present study. Elevated levels of MIP-1α were already suggested to be involved in the pathogenesis of depression (Merendino et al., 2004). Marciniak et al. (2015) also proposed a neuromodulatory function of MIP-1α. Their data supported that MIP-1α impairs basal synaptic transmission (Marciniak et al., 2015). Findings on the impact of increased MIP-1α level on cognition in patients with MDD are lacking so far.

In the present study, higher levels of IL-16 were associated with poorer IC. So far, IL-16 has been little described in the literature in the context of mental illness. Elevated IL-16 levels were, however, suggested to be associated with slowing attention-executive, learning and memory, and psychomotor speed among HIV-infected adults (Okafor et al., 2017). Beggiato et al. (2020) also showed that by inhibiting the overexpression of IL-16 cognitive deficits in animal models could be reversed (Beggiato et al., 2020).

Furthermore, PDGF-BB was negatively associated with the patients' WM in the present study. PDGF-BB has been reported to protect the neurons from oxidative insults and energy deprivation (Chen et al.,

2021). However, binding of PDGF-BB to its receptor PDGFRβ may contribute to a breakdown of the blood-brain barrier, which was regarded as an early marker of human cognitive dysfunction (Nation et al., 2019; Kapoor and Nation, 2022). Also, an elevation of PDGRFβ in individuals with cognitive dysfunction has been observed (Miners et al., 2019; Nation et al., 2019).

We found that higher levels of SCF were associated with a poorer performance in the patient's IC. So far, SCF was shown to have a neuroprotective effect in the brain. SCF can down regulate microglial expression of pro-inflammatory cytokines and enhance microglial expression of the mRNAs of nerve growth factor (NGF) and BDNF (Wang et al., 2023). Supporting those findings, Ping et al. (2019) reported that the cognitive function can be improved in animal models by administering SCF (Ping et al., 2019). SCF has also been reported to be involved in the process of remission and recovery from depression (Benedetti et al., 2016). Recently, Wang et al. (2023) also found a positive correlation of SCF levels with subjective cognitive impairment in patients with MDD but a negative correlation of PDGF-BB levels. A model including SCF, PDGF-BB and baseline cognitive impairment demonstrated a good prediction of residual subjective cognitive impairment in MDD.

Finally, we found that higher levels of G-CSF were associated with a poorer performance in the tests for WM and IC. G-CSF was shown to have an anti-inflammatory effect and to enhance neurogenesis in animal models of neurodegenerative diseases, such as amyotrophic lateral sclerosis (Tsai et al., 2017). Jim et al. (2012) reported an improvement of cognitive impairment in cancer patients after the administration of G-CSF (Jim et al., 2012). Thus, the results of the present study are contrary to prior research, the role of G-CSF in cognitive impairment associated with MDD remains unclear and requires further investigation.

Overall, the results of the present study showed that besides pro-inflammatory cytokines, chemokines and growth factors may play an important role for cognitive impairment in patients with MDD. Prior investigations often had a focus on neurodegenerative effects and diseases. Thus, further investigations are needed to confirm the findings of the present study, particularly in younger patients, to better understand the involvement and the interplay of these biomarkers in the cognitive impairment in MDD. At best, future studies will identify cytokines which are relevant prognostic factors or may be potential targets for new treatment approaches.

Our study has several limitations that should be considered. Firstly, none of the p-values remained significant after adjusting for multiple testing. Secondly, only patients with a severe major depression were included, which limits the transferability of the result to patients with milder depression. Two specific tests were chosen to test cognitive performance. Other tests for WM and IC might produce different results. No information on physical activity was available, which was shown to affect cytokine levels in prior studies (Ma et al., 2022). A large number of patients suffered from diseases of the musculoskeletal system, but the proportion of inflammatory or immune diseases is unknown. Furthermore, information on other immune diseases, inflammatory diseases and intake of immunomodulatory or anti-inflammatory medication was not available. A strength of this study was the relatively large number of cytokines measured in comparison to previously published work and the adjustment of the regression models for a variety of relevant confounders. Another strength is the homogeneous and comprehensively described study population.

In conclusion, the study identified higher levels of eotaxin, IL-1β, IL-4, IL-16, IL-18, MCP-1, G-CSF, SCF, PGF-BB and MIP-1α as being associated with poorer cognitive performance in patients with severe depression. Further research is needed to understand the interplay between these cytokines, chemokines and growth factors in MDD and their pathophysiological mechanisms of affecting cognitive function, and to identify candidate cytokines with prognostic or therapeutic relevance.

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Contributors

Study conception and design: CM, JL, JB, MS, IK;
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All authors reviewed and approved the final version of the manuscript.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2023.09.009.

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