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Chemokine MCP1 is associated with cognitive flexibility in schizophrenia: A preliminary analysis

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Abstract

Background: Peripheral levels of pro-inflammatory biomarkers have been shown to be altered in schizophrenia (SZ) and associated with cognitive impairments, but their relevance to specific cognitive domains remains unclear.

Methods: Plasma levels of cytokines, chemokines, and vascular biomarkers were quantified and compared between SZ and healthy comparison (HC) groups. Cognition was assessed using the Delis-Kaplan Executive Function System Trail Making (TM) and Color Word Interference (CWI) tests. Linear regression analyses examined differential relationships of inflammatory biomarkers with executive function between groups.

Results: Plasma levels of TNFα, ICAM1, and MCP1 were higher in individuals with SZ compared to HCs. Higher level of MCP1 was associated with increased CWI Inhibition Switching Errors in SZ but not HCs.

Conclusion: Like other studies, we found evidence for increased peripheral inflammation in SZ. We also showed that SZ with particularly high MCP1 levels had poor cognitive flexibility. Interventions to reduce chemokine elevations might prove beneficial for cognitive performance.

Keywords

serious mental illness; psychosis; cognition; peripheral inflammation; cytokines; executive function

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Data availability: All datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. The data are not publicly available due to them containing information that could compromise research participant privacy.

INTRODUCTION

Schizophrenia (SZ) is a severe chronic illness with a worldwide prevalence of about 1% (Tandon et al., 2009), and contributes to high socioeconomic costs (Insel, 2010). Cognitive dysfunction is among the core symptoms of SZ and deficits negatively impact functional outcome (Galderisi et al., 2013). Further, cognitive impairments do not respond well to current antipsychotic treatments and predict lower rates of symptom remission (Millan et al., 2016). Of the various cognitive domains affected in SZ, executive function, specifically the ability to flexibly shift and adapt one's behavior over time and different circumstances (Barch et al., 2009), is of particular importance to independent living and social functioning (Savla et al., 2011).

An emerging hypothesis posits that deficits in cognitive performance in SZ may be at least partially mediated by systemic inflammation. Individuals with SZ are at increased risk of chronic low-grade peripheral inflammation. The profile of cognitive impairment in SZ strongly overlaps with abilities most vulnerable to changes observed in normal aging (Kirkpatrick et al., 2008). These cognitive deficits may be mediated by the immune system, as evidenced by inflammation-related alterations in the brain (Nguyen et al., 2017b).

Evidence of alterations of specific inflammatory biomarkers in SZ has been mixed (Momtazmanesh et al., 2019). Recent meta-analyses have revealed that general markers of inflammation (e.g., C-reactive protein [CRP] and leukocyte counts), cytokines (e.g., interleukin [IL]-6, IL-8, IL-10, interferon-γ [IFNγ], and tumor necrosis factor-α [TNFα]), and chemokines (e.g., eotaxin-1, macrophage inflammatory protein [MIP]-1α, MIP-1β, and monocyte chemoattractant protein [MCP]1/CCL2) are elevated in SZ, compared to healthy comparison (HC) subjects (Frydecka et al., 2018; Goldsmith et al., 2016; Pillinger et al., 2019). Under an inflammatory condition, a cascade, broadly referred to as the coagulation pathway, induces the release of vascular endothelial markers (Wilson et al., 2003), such as intercellular adhesion molecule (ICAM)1/CD54 and vascular cell adhesion molecule (VCAM)1, which allow the transmigration of leukocytes across the blood-brain barrier (BBB) (Cai et al., 2018). Several studies have found increased blood levels of ICAM1 in SZ (Cai et al., 2018; Nguyen et al., 2017a).

Peripheral inflammation is hypothesized to lead to cognitive impairment via greater active transport of inflammatory mediators across the BBB or stimulation of brain vascular endothelial cells, resulting in neuroinflammation (Lim et al., 2013). Studies in healthy aging populations have shown associations of cognitive decline with neuroinflammation and peripheral inflammation (Lim et al., 2013; Tangestani Fard and Stough, 2019). Support for the role of inflammation in SZ pathology is provided by studies demonstrating improvement of symptoms, including cognitive impairment, with adjunctive treatment with anti-inflammatory agents in addition to regular antipsychotic treatment (Nitta et al., 2013; Rapaport et al., 2005).

The relationship between various peripheral inflammatory biomarkers and cognition in SZ has been previously investigated but with large heterogeneity in results (Bettcher et al.,

2019; Bora, 2019; Misiak et al., 2018). Mixed findings may be partially due to various markers and cognitive domains examined, in addition to differences in clinical characteristics among patients across studies (Goldsmith et al., 2016; Green et al., 2019). Furthermore, the specific relevance of different inflammatory markers and their interplay is not clear yet and neither is their role for specific cognitive domains.

Therefore, the aim of the current study was to investigate the relationship of multiple peripheral biomarkers of inflammation with cognitive deficits in SZ. Considering existing literature, we focused on the cognitive domains of processing speed and executive function. We hypothesized that individuals with SZ would have increased levels of peripheral pro-inflammatory biomarkers compared to HC. Further, we hypothesized that increased levels of peripheral inflammation would be associated with worse cognitive deficits in SZ, but not in HCs, due to low levels and low inter-individual variability of inflammation in the latter group.

METHODS

Participants

This study included 20 outpatients with SZ and 20 non-psychiatric HCs between the ages of 18 and 55 years. For details of recruitment procedures and inclusion criteria, see Supplemental Methods.

Hematology and Inflammatory Biomarkers

Non-fasting blood samples were drawn by a certified phlebotomist into ethylenediaminetetraacetic acid (EDTA)-treated vacutainers. White blood cell counts were assessed by the VA San Diego Clinical Laboratory using standard procedures. Plasma levels of cytokine, chemokine, and vascular biomarkers (CRP, Eotaxin, Fractalkine, IP10, IL6, IL10, ICAM1, IFNγ, MCP1, MIP1β, SAA, TNFα, VEGF, VCAM1) were quantified. For details on analysis procedures see (Hong et al., 2017; Lee et al., 2017). Intra-assay variability was less than 5% for all assays, except IL-10 (intra-assay CV 6%). No sample showed biomarker levels below the detection limits.

Clinical and Neuropsychological Assessment

Positive and negative psychiatric symptoms were evaluated using rater-administered Scales for Assessment of Positive Symptoms (SAPS) and Negative Symptoms (SANS) (Andreasen, 1990). Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CESD) (Radloff, 1977). Cognition, specifically in the domains of processing speed executive function, was assessed using the Delis–Kaplan Executive Function System (D-KEFS) (Delis et al., 2001) Trail Making (TM) Test and Color Word Interference (CWI) Test. Age-corrected scaled scores were examined (see Table 1). All assessments were performed by certified raters.

Statistical Analysis

Statistical analysis was performed using SPSS version 25 (IBM Corp., SPSS Inc., Chicago IL, USA). Statistical tests report two-sided p-values. P-values were then adjusted for

multiple comparisons using the adaptive Benjamini-Hochberg procedure (Benjamini and Hochberg, 2000) to control the false discovery rate (FDR), with $p < 0.10$ considered statistically significant. Adjusted p-values are denoted as q-values. This methodological approach is favored for preliminary analysis to help generate hypotheses. The Kolmogorov Smirnov-Test was used to assess normality of distribution. Values of all biomarkers were log10 transformed due to non-normal distribution.

Group Differences—Demographic, clinical/cognitive, and biomarker variables were compared between groups using independent sample t-tests or Mann Whitney U tests, as appropriate, for continuous variables and Pearson's Chi Square tests for categorical variables.

Correlation and Regression Analyses—We aimed to specifically investigate relationships between inflammation and cognition for those biomarkers that were altered in SZ. Therefore, for biomarkers that were significantly different between groups, we performed Spearman's correlations with cognitive measures of executive function and processing speed within the SZ group. Subsequently, for each significant correlation (after correction for multiple comparisons), linear regression analyses were conducted to examine the differential relationship of group and inflammatory biomarkers on executive function or processing speed, with group, biomarker, and their interaction as independent variables and cognitive measure as the dependent variable.

RESULTS

Sample characteristics

Sociodemographic, psychiatric, and cognitive characteristics for the SZ and HC groups are presented in Table 1. SZ and HC groups did not differ on age, gender or race. As expected, the SZ group had lower levels of education, higher depression levels, and higher positive and negative symptom ratings, compared to HCs.

Group differences between hematologic and inflammatory biomarkers

Plasma levels of leukocytes, CRP, IL-6, TNFα, MCP1 and ICAM1 and VEGF were significantly higher in the SZ group compared to HCs. No group differences were observed for IL-10, IP-10, IFNγ, Eotaxin, MIP1β, Fractalkine, SAA, or VCAM1 (Table 1).

After correction for multiple comparisons, only TNFα ($q = 0.03$), MCP1 ($q = 0.083$), and ICAM1 ($q = 0.083$) remained significantly different between groups (Figure 1).

Relationship between inflammatory biomarkers and executive function measures

Table 2 displays correlations between inflammatory biomarkers that were elevated in SZ (TNFα, MCP1, and ICAM1) and cognitive measures within the SZ group. Relationships that were significant after correction for multiple comparisons were further explored in linear regression analyses to investigate differential relationships of inflammatory biomarkers and cognition between groups.

Differential relationship of inflammatory biomarkers and cognition in SZ and HC

General linear models revealed a main effect of group (standardized β = 6.652, p = 0.006; partial eta-squared = 0.077; overall model fit: R^2 = 0.459) and a group x MCP1 interaction for CWI Inhibition Switching Errors (standardized β = −7.121, p = 0.004; partial eta-squared = 0.231; overall model fit: R^2 = 0.459) (Supplementary Table S1). Follow-up of this interaction revealed that higher levels of MCP1 were associated with worse cognitive flexibility (CWI Inhibition Switching Errors) in the SZ group (β = 0.745, p = 0.005), but there was no relationship in the HC group (β = 0.21, p = 0.453) (Figure 2). There were no significant differential relationships by group between other inflammatory biomarkers (TNFα and ICAM1) and cognitive variables.

DISCUSSION

The current study aimed to investigate how peripheral biomarkers of inflammation are associated with executive function and processing speed in SZ compared to HC. As hypothesized, individuals with SZ demonstrated higher plasma levels of TNFα, ICAM1, and MCP1 compared to HCs, which is consistent with extant literature (Frydecka et al., 2018; Goldsmith et al., 2016; Pillinger et al., 2019). Further in line with our hypothesis, higher levels of MCP1 were associated with worse cognitive flexibility, indicated by worse CWI color naming scores within SZ and more CWI inhibition switching errors in SZ, while there was no relationship of the latter in HC.

MCP1 is a chemokine that recruits immune cells to an inflammation site. MCP1 activity has been associated with neuroinflammation and neurodegeneration in preclinical studies (Stuart and Baune, 2014). Increased blood-levels of MCP1 were associated with memory decline in a longitudinal cohort on healthy aging (Bettcher et al., 2019), and MCP1 has been implicated in mild cognitive impairment and Alzheimer's dementia (Galimberti et al., 2006). MCP1 has also been found to be elevated in SZ as well as in bipolar disorder, depression and mild cognitive impairment (Beumer et al., 2012; Galimberti et al., 2006; Ribeiro-Santos et al., 2014). MCP1 protein expression is constitutive, but its production is also induced by pro-inflammatory cytokines.

Our finding of an inverse relationship of MCP1 blood levels with cognitive flexibility in patients with SZ is partially consistent with the literature. Among studies that specifically investigated associations of MCP1 levels with cognition, Martínez-Cengotitabengoa et al. reported a negative association between MCP1 plasma levels and memory, but not executive function, in patients with first episode SZ; and they did not observe significant differences in levels of MCP1 between SZ and HC participants (Martínez-Cengotitabengoa et al., 2012). Asevedo et al. did not find groups differences in plasma MCP1 levels between SZ and HC participants or any associations of MCP1 with cognitive functions (Asevedo et al., 2013). Orhan et al. observed increased levels of MCP1 in plasma but not in cerebrospinal fluid (CSF) among patients with first-episode SZ (Orhan et al., 2018). Divergent results across studies might be due to the heterogenous roles of MCP1 in the body.

We did not find associations of ICAM1 and TNFα with cognitive impairment after correction for multiple comparison, contrary to previous findings (Cai et al., 2018;

Goldsmith et al., 2020; Nguyen et al., 2017a; Stefanović et al., 2016). A possible explanation might be due to heterogeneity of SZ related to patient and disease characteristics. There may be clinically different subgroups of patients in whom distinct but related mechanisms are differentially involved. As for the dissociation between ICAM1 and MCP1, some studies have examined these biomarkers as measures of cerebrovascular dysfunction in preclinical Alzheimer's disease patients and found gender differences, with males expressing higher levels of both MCP1 and ICAM1 (Janelidze et al., 2018). Although our sample did not differ in sex distribution and we found no differences in TNFα, ICAM1 and MCP1 between sex groups, these effects might be related to more complex underlying processes.

Strengths and limitations

A particular strength of this study is that we examined numerous different variables that assess both timed and process components of executive function (Homack et al., 2005). Further, we investigated a wide range of biomarkers while correcting for multiple testing. Importantly, we screened out individuals with acute inflammatory activity, recent vaccinations, and serious medical illnesses. Several limitations exist. We did not find group differences in biomarkers that have been consistently demonstrated to be increased in SZ. This might be due to the small sample size of our study or high heterogeneity across SZ study samples. Blood draws were not fasting samples but were collected at a consistent time of day across participants. There has been research showing associations of inflammatory biomarkers with lifestyle and health factors (Beumer et al., 2012; Horn et al., 2018); unfortunately, these variables were not available in our sample. Further, we did not have information on psychotropic medications or disease characteristics such as age of onset or duration of illness, which are factors that have shown to be associated with cognition in SZ (MacKenzie et al., 2018; Rajji et al., 2009; Tandon et al., 2009). Psychiatric symptomology such as negative and positive psychotic symptoms and depression can also impact cognitive impairment and functional outcome (Bowie and Harvey, 2006; Leifker et al., 2009; Vöhringer et al., 2013). In our study, measures of psychiatric symptom severity (CESD, SAPS, SANS) were not correlated with measures of cognition. When these measures were included in regression analyses as covariates, findings were no longer significant, which is most likely due to the limited power due to the small sample size in our study. Given the small sample size of our study, we employed an exploratory statistical approach with regards to correcting for multiple comparisons. Our preliminary results will have to be tested in future studies in a hypothesis-driven way, with larger sample sizes to investigate the potential moderating effect of relevant disease characteristics between inflammation and cognition in SZ. Finally, the cross-sectional design of this study limits causal interpretations.

Conclusions and next steps

Overall, our results suggest that cognitive impairments in SZ, specifically cognitive flexibility, is associated with inflammation, specifically increased peripheral levels of the chemokine MCP1. However, MCP1 might only be one marker among others that is related to executive function, given our small sample size and limited power. Nevertheless, if confirmed in larger studies, our findings have important clinical implications for understanding the mechanisms underlying cognitive impairments in SZ and treatments, with

MCP1-related pathways as possible targets. Several directions for future research are envisioned. First, monitoring MCP1 could help understanding why certain patients are resistant to antipsychotic or cognitive treatments. Second, adjunctive anti-inflammatory treatment has been demonstrated to improve SZ symptoms, including cognitive impairment (Müller et al., 2002; Nitta et al., 2013; Rapaport et al., 2005). The development of a more specific treatment target might have fewer side effects and better tolerability for SZ patients. To reach this goal, future studies should examine the associations of up- and down-stream inflammatory mediators of MCP1 with cognition and their relation to neuronal processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

Andreasen NC, 1990. Methods for assessing positive and negative symptoms, in: Schizophrenia: Positive and Negative Symptoms and Syndromes, Modern Problems of Pharmacopsychiatry, Vol. 24. Karger, Basel, Switzerland, pp. 73–88.

Asevedo E, Gadelha A, Noto C, Mansur RB, Zugman A, Belangero SIN, Berberian AA, Scarpato BS, Leclerc E, Teixeira AL, Gama CS, Bressan RA, Brietzke E, 2013. Impact of peripheral levels of chemokines, BDNF and oxidative markers on cognition in individuals with schizophrenia. J. Psychiatr. Res 47, 1376–1382. 10.1016/j.jpsychires.2013.05.032 [PubMed: 23806580]

Barch DM, Braver TS, Carter CS, Poldrack RA, Robbins TW, 2009. CNTRICS Final Task Selection: Executive Control. Schizophr. Bull 35, 115–135. 10.1093/schbul/sbn154 [PubMed: 19011235]

Benjamini Y, Hochberg Y, 2000. On the Adaptive Control of the False Discovery Rate in Multiple Testing With Independent Statistics. J. Educ. Behav. Stat

Bettcher BM, Neuhaus J, Wynn MJ, Elahi FM, Casaletto KB, Saloner R, Fitch R, Karydas A, Kramer JH, 2019. Increases in a Pro-inflammatory Chemokine, MCP-1, Are Related to Decreases in Memory Over Time. Front. Aging Neurosci 11. 10.3389/fnagi.2019.00025

Beumer W, Drexhage RC, De Wit H, Versnel MA, Drexhage HA, Cohen D, 2012. Increased level of serum cytokines, chemokines and adipokines in patients with schizophrenia is associated with disease and metabolic syndrome. Psychoneuroendocrinology 37, 1901–1911. 10.1016/j.psyneuen.2012.04.001 [PubMed: 22541717]

Bora E, 2019. Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: a meta-analysis. Psychol. Med 49, 1971–1979. 10.1017/S0033291719001685 [PubMed: 31284882]

Bowie CR, Harvey PD, 2006. Administration and interpretation of the Trail Making Test. Nat. Protoc 1, 2277–2281. 10.1038/nprot.2006.390 [PubMed: 17406468]

Cai HQ, Catts VS, Webster MJ, Galletly C, Liu D, O'Donnell M, Weickert TW, Weickert CS, 2018. Increased macrophages and changed brain endothelial cell gene expression in the frontal cortex of people with schizophrenia displaying inflammation. Mol. Psychiatry 1–15. 10.1038/s41380-018-0235-x

Delis D, Kaplan E, Kramer J, 2001. Delis-Kaplan Executive Function System (D-KEFS). San Antonio TX Psychol. Corp.

Frydecka D, Krzystek-Korpacka M, Lubeiro A, Stramecki F, Stańczykiewicz B, Beszłej JA, Piotrowski P, Kotowicz K, Szewczuk-Bogusławska M, Pawlak-Adamska E, Misiak B, 2018. Profiling

inflammatory signatures of schizophrenia: A cross-sectional and meta-analysis study. Brain. Behav. Immun 71, 28–36. 10.1016/j.bbi.2018.05.002 [PubMed: 29730395]

Galderisi S, Bucci P, Mucci A, Kirkpatrick B, Pini S, Rossi A, Vita A, Maj M, 2013. Categorical and dimensional approaches to negative symptoms of schizophrenia: Focus on long-term stability and functional outcome. Schizophr. Res 147, 157–162. 10.1016/j.schres.2013.03.020 [PubMed: 23608244]

Galimberti D, Fenoglio C, Lovati C, Venturelli E, Guidi I, Corrà B, Scalabrini D, Clerici F, Mariani C, Bresolin N, Scarpini E, 2006. Serum MCP-1 levels are increased in mild cognitive impairment and mild Alzheimer's disease. Neurobiol. Aging 27, 1763–1768. 10.1016/j.neurobiolaging.2005.10.007 [PubMed: 16307829]

Goldsmith DR, Massa N, Pearce BD, Wommack EC, Alrohaibani A, Goel N, Cuthbert B, Fargotstein M, Felger JC, Haroon E, Miller AH, Duncan E, 2020. Inflammatory markers are associated with psychomotor slowing in patients with schizophrenia compared to healthy controls. NPJ Schizophr. 6. 10.1038/s41537-020-0098-4

Goldsmith DR, Rapaport MH, Miller BJ, 2016. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol. Psychiatry 21, 1696–1709. 10.1038/mp.2016.3 [PubMed: 26903267]

Green MF, Horan WP, Lee J, 2019. Nonsocial and social cognition in schizophrenia: current evidence and future directions. World Psychiatry 18, 146–161. 10.1002/wps.20624 [PubMed: 31059632]

Homack S, Lee D, Riccio CA, 2005. Test Review: Delis-Kaplan Executive Function System. J. Clin. Exp. Neuropsychol 27, 599–609. 10.1080/13803390490918444 [PubMed: 16019636]

Hong S, Lee EE, Martin AS, Soontornniyomkij B, Soontornniyomkij V, Achim CL, Reuter C, Irwin MR, Eyler LT, Jeste DV, 2017. Abnormalities in chemokine levels in schizophrenia and their clinical correlates. Schizophr. Res 181, 63–69. 10.1016/j.schres.2016.09.019 [PubMed: 27650194]

Horn SR, Long MM, Nelson BW, Allen NB, Fisher PA, Byrne ML, 2018. Replication and reproducibility issues in the relationship between C-reactive protein and depression: A systematic review and focused meta-analysis. Brain. Behav. Immun 73, 85–114. 10.1016/j.bbi.2018.06.016 [PubMed: 29928963]

Insel TR, 2010. Rethinking schizophrenia. Nature 468, 187–193. 10.1038/nature09552 [PubMed: 21068826]

Janelidze S, Mattsson N, Stomrud E, Lindberg O, Palmqvist S, Zetterberg H, Blennow K, Hansson O, 2018. CSF biomarkers of neuroinflammation and cerebrovascular dysfunction in early Alzheimer disease. Neurology 91, e867–e877. 10.1212/WNL.0000000000006082 [PubMed: 30054439]

Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E, Bowie CR, 2008. Is Schizophrenia a Syndrome of Accelerated Aging? Schizophr. Bull 34, 1024–1032. 10.1093/schbul/sbm140 [PubMed: 18156637]

Lecrubier Y, Sheehan D, Weiller E, Amorim P, Bonora I, Harnett Sheehan K, Janavs J, Dunbar G, 1997. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. Eur. Psychiatry 12, 224–231. 10.1016/S0924-9338(97)83296-8

Lee EE, Hong S, Martin AS, Eyler LT, Jeste DV, 2017. Inflammation in Schizophrenia: Cytokine Levels and Their Relationships to Demographic and Clinical Variables. Am. J. Geriatr. Psychiatry 25, 50–61. 10.1016/j.jagp.2016.09.009 [PubMed: 27840055]

Leifker FR, Bowie CR, Harvey PD, 2009. Determinants of everyday outcomes in schizophrenia: the influences of cognitive impairment, functional capacity, and symptoms. Schizophr. Res 115, 82–87. 10.1016/j.schres.2009.09.004 [PubMed: 19775869]

Lim A, Lim Alvin, Krajina K, Marsland AL, 2013. Peripheral Inflammation and Cognitive Aging. Inflamm. Psychiatry 28, 175–187. 10.1159/000346362

MacKenzie NE, Kowalchuk C, Agarwal SM, Costa-Dookhan KA, Caravaggio F, Gerretsen P, Chintoh A, Remington GJ, Taylor VH, Müeller DJ, Graff-Guerrero A, Hahn MK, 2018. Antipsychotics, Metabolic Adverse Effects, and Cognitive Function in Schizophrenia. Front. Psychiatry 9. 10.3389/fpsyt.2018.00622

Martínez-Cengotitabengoa M, Mac-Dowell KS, Leza JC, Micó JA, Fernandez M, Echevarría E, Sanjuan J, Elorza J, González-Pinto A, 2012. Cognitive impairment is related to oxidative stress

and chemokine levels in first psychotic episodes. Schizophr. Res 137, 66–72. 10.1016/j.schres.2012.03.004 [PubMed: 22445462]

Millan MJ, Andrieux A, Bartzokis G, Cadenhead K, Dazzan P, Fusar-Poli P, Gallinat J, Giedd J, Grayson DR, Heinrichs M, Kahn R, Krebs M-O, Leboyer M, Lewis D, Marin O, Marin P, Meyer-Lindenberg A, McGorry P, McGuire P, Owen MJ, Patterson P, Sawa A, Spedding M, Uhlhaas P, Vaccarino F, Wahlestedt C, Weinberger D, 2016. Altering the course of schizophrenia: progress and perspectives. Nat. Rev. Drug Discov 15, 485–515. 10.1038/nrd.2016.28 [PubMed: 26939910]

Misiak B, Stańczykiewicz B, Kotowicz K, Rybakowski JK, Samochowiec J, Frydecka D, 2018. Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder: A systematic review. Schizophr. Res 192, 16–29. 10.1016/j.schres.2017.04.015 [PubMed: 28416092]

Momtazmanesh S, Zare-Shahabadi A, Rezaei N, 2019. Cytokine Alterations in Schizophrenia: An Updated Review. Front. Psychiatry 10. 10.3389/fpsyt.2019.00892

Müller N, Riedel M, Scheppach C, Brandstätter B, Sokullu S, Krampe K, Ulmschneider M, Engel RR, Möller H-J, Schwarz MJ, 2002. Beneficial Antipsychotic Effects of Celecoxib Add-On Therapy Compared to Risperidone Alone in Schizophrenia. Am. J. Psychiatry 159, 1029–1034. 10.1176/appi.ajp.159.6.1029 [PubMed: 12042193]

Nguyen TT, Dev SI, Chen G, Liou SC, Martin AS, Irwin MR, Carroll JE, Tu X, Jeste DV, Eyler LT, 2017a. Abnormal levels of vascular endothelial biomarkers in schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci 1–12. 10.1007/s00406-017-0842-6

Nguyen TT, Eyler LT, Jeste DV, 2017b. Systemic Biomarkers of Accelerated Aging in Schizophrenia: A Critical Review and Future Directions. Schizophr. Bull. sbx069 10.1093/schbul/sbx069

Nitta M, Kishimoto T, Müller N, Weiser M, Davidson M, Kane JM, Correll CU, 2013. Adjunctive Use of Nonsteroidal Anti-inflammatory Drugs for Schizophrenia: A Meta-analytic Investigation of Randomized Controlled Trials. Schizophr. Bull 39, 1230–1241. 10.1093/schbul/sbt070 [PubMed: 23720576]

Orhan F, Schwieler L, Fatouros-Bergman H, Malmqvist A, Cervenka S, Collste K, Flyckt L, Farde L, Sellgren CM, Piehl F, Engberg G, Erhardt S, 2018. Increased number of monocytes and plasma levels of MCP-1 and YKL-40 in first-episode psychosis. Acta Psychiatr. Scand 138, 432–440. 10.1111/acps.12944 [PubMed: 30132802]

Pillinger T, Osimo EF, Brugger S, Mondelli V, McCutcheon RA, Howes OD, 2019. A Meta-analysis of Immune Parameters, Variability, and Assessment of Modal Distribution in Psychosis and Test of the Immune Subgroup Hypothesis. Schizophr. Bull 45, 1120–1133. 10.1093/schbul/sby160 [PubMed: 30407606]

Radloff LS, 1977. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Appl. Psychol. Meas 1, 385–401. 10.1177/014662167700100306

Rajji TK, Ismail Z, Mulsant BH, 2009. Age at onset and cognition in schizophrenia: meta-analysis. Br. J. Psychiatry 195, 286–293. 10.1192/bjp.bp.108.060723 [PubMed: 19794194]

Rapaport MH, Delrahim KK, Bresee CJ, Maddux RE, Ahmadpour O, Dolnak D, 2005. Celecoxib augmentation of continuously ill patients with schizophrenia. Biol. Psychiatry 57, 1594–1596. 10.1016/j.biopsych.2005.02.024 [PubMed: 15953498]

Ribeiro-Santos afael, Lucio Teixeira A, Salgado JV, 2014. Evidence for an Immune Role on Cognition in Schizophrenia: A Systematic Review. Curr. Neuropharmacol 12, 273–280. 10.2174/1570159X1203140511160832 [PubMed: 24851091]

Savla GN, Twamley EW, Thompson WK, Delis DC, Jeste DV, Palmer BW, 2011. Evaluation of Specific Executive Functioning Skills and the Processes Underlying Executive Control in Schizophrenia. J. Int. Neuropsychol. Soc. JINS 17, 14–23. 10.1017/S1355617710001177 [PubMed: 21062522]

Spitzer RL, Williams JB, Gibbon M, First MB, 1992. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. Arch. Gen. Psychiatry 49, 624–629. 10.1001/archpsyc.1992.01820080032005 [PubMed: 1637252]

Stefanović MP, Petronijević N, Dunjić-Kostić B, Velimirović M, Nikolić T, Jurišić V, Lačković M, Damjanović A, Totić-Poznanović S, Jovanović AA, Ivković M, 2016. Role of sICAM-1 and

sVCAM-1 as biomarkers in early and late stages of schizophrenia. J. Psychiatr. Res 73, 45–52. 10.1016/j.jpsychires.2015.11.002 [PubMed: 26679764]

Stuart MJ, Baune BT, 2014. Chemokines and chemokine receptors in mood disorders, schizophrenia, and cognitive impairment: A systematic review of biomarker studies. Neurosci. Biobehav. Rev 42, 93–115. 10.1016/j.neubiorev.2014.02.001 [PubMed: 24513303]

Tandon R, Nasrallah HA, Keshavan MS, 2009. Schizophrenia, “just the facts” 4. Clinical features and conceptualization. Schizophr. Res 110, 1–23. 10.1016/j.schres.2009.03.005 [PubMed: 19328655]

Tangestani Fard M, Stough C, 2019. A Review and Hypothesized Model of the Mechanisms That Underpin the Relationship Between Inflammation and Cognition in the Elderly. Front. Aging Neurosci 11. 10.3389/fnagi.2019.00056

Vöhringer PAMS, Barroilhet SPD, Amerio A, Reale ML, Vergne D, Alvear KPD, Ghaemi SNMPH, 2013. Cognitive Impairment in Bipolar Disorder and Schizophrenia: A Systematic Review. Front. Psychiatry 4 10.3389/fpsyt.2013.00087

Wilson CJ, Cohen HJ, Pieper CF, 2003. Cross-Linked Fibrin Degradation Products (D-Dimer), Plasma Cytokines, and Cognitive Decline in Community-Dwelling Elderly Persons: D-Dimer and Plasma Cytokines on Cognitive Decline. J. Am. Geriatr. Soc 51, 1374–1381. 10.1046/j.1532-5415.2003.51454.x [PubMed: 14511156]

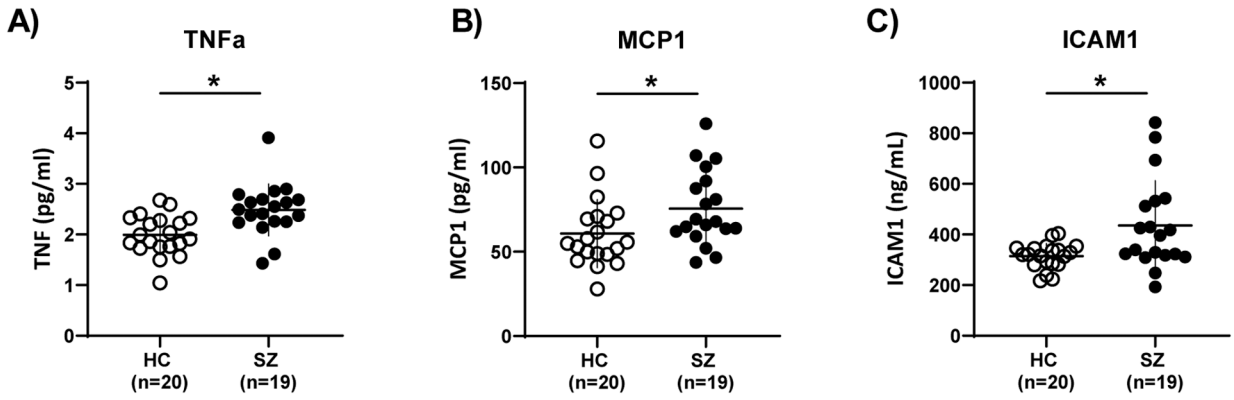

Figure 1:

Group comparison of inflammatory biomarkers

A) Tumor necrosis factor alpha (TNFα) B) Monocyte chemoattractant protein-1 (MCP1), C) Intercellular adhesion molecule 1 (ICAM1).

Mean and standard deviation are depicted. Bars indicate significant results after correction for multiple testing: *q ≤ 0.1. Calculations of inflammatory biomarkers are based on log10-transformed values.

Abbreviations: HC, healthy comparison; SZ, schizophrenia. Units are pg/ml for TNFα and MCP1, and ng/ml for ICAM1.

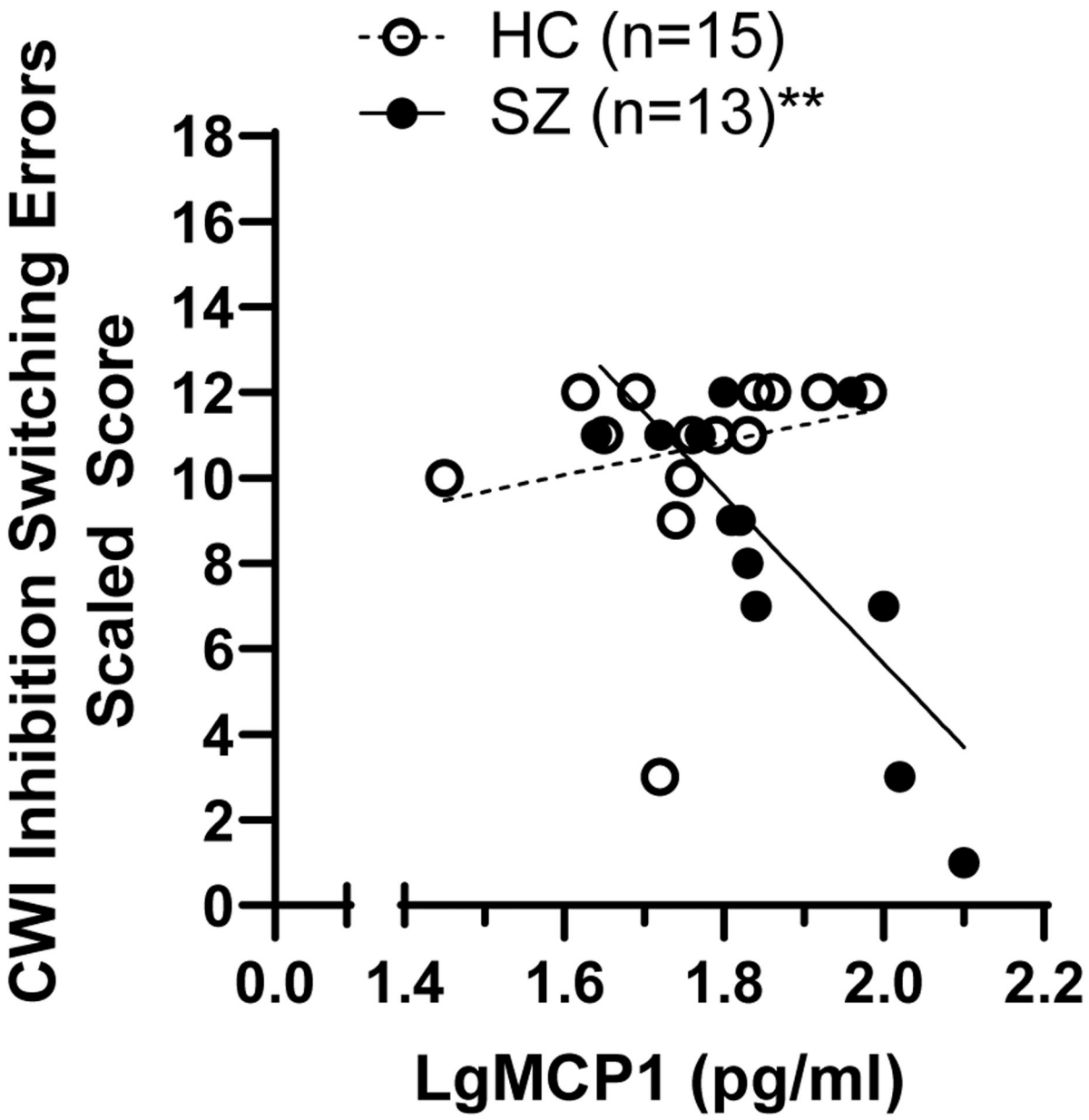

Figure 2:

Differential relationship of the MCP1 with cognition in SZ and HC

Scatterplot demonstrating the interaction of group (SZ versus HC) and MCP1 levels on CWI Inhibition Switching Error Scaled Score. Higher scaled scores indicate better performance.

** $p<0.1$ indicates significant relationship within group.

Abbreviations: CWI, color word interference test; HC, healthy comparison; LgMCP1, Log10 of monocyte chemoattractant protein 1, SZ, schizophrenia.

Table 1:

Group differences in demographic, clinical, and cognitive variables and inflammatory biomarkers between schizophrenia (SZ) and healthy comparison subjects (HC).

	Healthy comparison			Schizophrenia			Test statistics		
	n	Mean	SD	n	Mean	SD		$\chi^2/U/t$	p
Sociodemographic factors									
Age (years)	20	39.95	9.65	20	42.00	7.21	$t=$	−0.761	0.451
Gender (M/F (% M/F))	8/12 (40%/60%)			5/15 (25%/75%)			$\chi^2=$	1.026	0.311
Education (years)	20	15.50	2.31	20	12.15	2.43	$t=$	4.469	**0.000**
Race (n (% Caucasian))	15 (75%)			14 (70%)			$\chi^2=$	8.034	0.154
Symptom Severity									
CESD Total Score	18	2.83	2.90	12	8.17	4.17	$U=$	186.000	**0.001**
SAPS Total Score	7	0.29	0.76	17	5.35	4.05	$U=$	102.500	**0.004**
SANS Total Score	7	0.14	0.38	17	7.06	3.82	$t=$	−7.386	**0.000**
Cognition									
DKEFS - TM Visual Scanning	18	11.72	2.11	17	8.65	3.35	$t=$	3.268	**0.003**
DKEFS - TM Number Sequencing	18	13.00	2.09	17	9.18	3.41	$t=$	4.024	**0.000**
DKEFS - TM Letter Sequencing	18	12.83	1.82	17	8.65	4.72	$U=$	59.000	**0.002**
DKEFS - TM Letter-Number Completion	18	11.61	2.12	17	7.82	3.81	$U=$	65.500	**0.003**
DKEFS - TM Combined Number-Letter Sequencing Comp.	15	13.67	1.95	13	9.54	4.01	$U=$	32.500	**0.002**
DKEFS - CWI Color Naming	18	9.89	3.39	17	7.24	3.19	$t=$	2.379	**0.023**
DKEFS - CWI Inhibition	18	11.72	2.93	17	8.12	4.09	$t=$	3.011	**0.005**
DKEFS - CWI Word Reading	18	10.22	3.19	17	8.82	3.19	$U=$	113.000	0.183
DKEFS - CWI Inhibition Errors	15	10.80	1.86	13	8.00	4.16	$U=$	52.000	**0.028**
DKEFS - CWI Inhibition Switching	18	11.39	2.99	17	8.76	4.16	$U=$	95.000	**0.054**
DKEFS - CWI Inhibition Switching Errors	15	10.67	2.32	13	8.46	3.36	$U=$	49.000	**0.022**
DKEFS - CWI Combined Naming Reading Comp.	15	9.67	3.06	13	7.92	3.25	$U=$	63.000	0.109
Hematology									
Leukocytes (K/μL)	15	6.62	2.07	16	8.22	1.96	$t=$	−2.832	**0.008**
Inflammatory Biomarkers									
CRP (mg/L)	20	1.55	1.67	19	3.47	3.72	$t=$	1.992	**0.054**
IL-6 (pg/mL)	20	1.85	6.06	19	0.98	0.91	$U=$	263	**0.041**
IL-10 (pg/mL)	20	0.22	0.10	19	0.20	0.09	$t=$	0.848	0.402
IP-10 (pg/mL)	20	209.00	98.02	19	332.82	552.64	$U=$	181	0.800
IFNγ (pg/mL)	20	4.83	5.59	19	6.30	9.19	$U=$	198	0.835
TNFα (pg/mL)	20	1.99	0.40	19	2.49	0.51	$t=$	−3.210	**0.003** *
Eotaxin (pg/mL)	20	153.39	125.76	19	164.97	75.40	$t=$	−0.966	0.340
MCP1 (pg/mL)	20	60.77	20.23	19	75.60	22.27	$t=$	−2.330	**0.025** *
MIP1β (pg/mL)	20	67.08	27.69	19	98.93	70.71	$t=$	−1.551	0.129
Fractalkine (pg/mL)	20	10391	2385	19	11037	3032	$t=$	−0.593	0.557
SAA (ng/mL)	20	1964.32	1245	19	3659.49	3942	$t=$	−1.571	0.125

	Healthy comparison			Schizophrenia			Test statistics		
	n	Mean	SD	n	Mean	SD		$\chi^2/U/t$	p
ICAM1 (ng/mL)	20	314.60	50.28	19	435.29	177.44	*U*=	273.000	**0.020** *
VCAM1 (ng/mL)	20	426.81	70.36	19	418.48	65.01	*t*=	0.399	0.692
VEGF (pg/mL)	20	49.88	42.45	19	66.53	43.84	*t*=	−1.700	**0.097**

Mean and standard deviation depicted.

Calculations of inflammatory biomarkers are based on log10-transformed values.

p-values < 0.1 are bolded.

* q<0.1 indicates significance after correction for multiple testing among inflammatory biomarkers, depicting the biomarkers that were considered for correlation analysis.

Abbreviations: CESD, Center for Epidemiologic Studies Depression Scale; Comp., Composite; CRP, high-sensitivity CRP; CWI, color word interference test; D-KEFS, Delis–Kaplan Executive Function; ICAM1, intercellular adhesion molecule 1; IL, interleukin; IP-10, interferon-γ-inducible protein-10; IFNγ, interferon-γ; MCP1, monocyte chemoattractant protein-1; MIP1β, macrophage inflammatory protein 1 beta; SAA, serum amyloid A; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms, TM: trail making test; TNFα, tumor necrosis factor alpha; VCAM1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor.

Table 2:

Correlations between inflammatory biomarkers and cognitive measures within the schizophrenia group

	TNFα			MCP1			ICAM1		
D-KEFS Cognitive measures	**r (s)**	**P**	**n**	**r (s)**	**p**	**n**	**r (s)**	**p**	**n**
TM Visual Scanning Completion	**−0.64**	**0.008** *	16	**−0.5**	**0.049**	16	**−0.55**	**0.026** *	16
TM Number Sequencing	−0.409	0.116	16	−0.102	0.706	16	**−0.453**	**0.078**	16
TM Letter Sequencing	−0.251	0.349	16	−0.216	0.421	16	**−0.57**	**0.020** *	16
TM Letter-Number Switching	**−0.58**	**0.018**	16	−0.341	0.196	16	**−0.484**	**0.057**	16
TM Combined Number-Letter Sequencing Composite	−0.468	0.125	12	−0.497	0.101	12	**−0.67**	**0.018** *	12
CWI Color Naming	−0.402	0.123	16	**−0.7**	**0.003** *	16	−0.150	0.580	16
CWI Word Reading	−0.225	0.402	16	−0.468	0.068	16	−0.141	0.603	16
CWI Inhibition	−0.324	0.220	16	−0.170	0.530	16	−0.274	0.305	16
CWI Inhibition Errors	**−0.568**	**0.054**	12	−0.447	0.145	12	−0.359	0.251	12
CWI Inhibition Switching	−0.229	0.393	16	−0.309	0.244	16	**−0.52**	**0.041** *	16
CWI Inhibition Switching Errors	−0.425	0.169	12	**−0.71**	**0.010** *	12	−0.262	0.411	12
CWI Combined Naming-Reading Composite	−0.199	0.536	12	**−0.59**	**0.044**	12	0.199	0.536	12

Significant correlations with p-values < 0.1 are bolded.

* q<0.1 indicates significance after correction for multiple testing and depicts the pairs that were entered in the next analysis step into regression analysis.

Abbreviations: CWI, color word interference test; D-KEFS, Delis–Kaplan Executive Function System; ICAM1, intercellular adhesion molecule 1; MCP1, monocyte chemoattractant protein-1; TNFα, tumor necrosis factor alpha; TM, trail making test.