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Associations between Inflammatory Marker Profiles and Neurocognitive Functioning in Persons with Schizophrenia and Non-Psychiatric Comparison Subjects

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Introduction

Cognitive deficits in schizophrenia are the strongest predictor of functional disability and subsequent costs, yet the underlying biology remains unclear and effective treatments are lacking (Cloutier et al., 2016). Although inflammation has been implicated in the pathogenesis of schizophrenia, its role in cognitive decline is not fully established.

Persons with schizophrenia (PwS) are often in a persistent inflammatory state, with abnormalities in blood-based biomarkers reflective of acute phase and chronic responses. A meta-analysis determined that C-reactive protein (CRP) is elevated in PwS, regardless of antipsychotic use (Fernandes et al., 2016). Consistent with this finding, our group found increases in high sensitivity CRP (hs-CRP) (Joseph et al., 2015), F2-isoprostanes (a marker of oxidative stress) (Lee et al., 2016), and inflammatory cytokines (TNF-α and IL-6) (Lee et al., 2017). Another meta-analysis reported elevation of IL-6 with psychosis and subsequent normalization with antipsychotics, while TNF-α remained chronically elevated (Miller et al., 2011). We also reported elevations in various chemokines (MCP-1, MIP-1b, Eotaxin-1, TARC, MDC) (Hong et al., 2017) and vascular endothelial biomarkers (ICAM-1 and VCAM-1) (Nguyen et al., 2018), utilizing composite measures.

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In addition to persistent inflammation, PwS have significant and broad neurocognitive deficits spanning episodic memory, processing speed, working memory, and executive function, with relative sparing of crystallized verbal knowledge and visuospatial skills (Palmer et al., 2009). Premorbid cognitive deficits often appear by first grade, reaching a standard deviation below the mean by the end of high school. Further cognitive decline occurs at the first psychotic break, most significantly impacting verbal memory and executive function (Aas et al., 2014). Thereafter, cognitive functioning appears to stabilize, though there are age-related declines in certain domains, like executive functioning (Fucetola et al., 2000). No consensus exists regarding the etiology for these cognitive deficits, although it is thought that inflammation may contribute. One study reported that elevations in CRP during psychotic episodes were inversely associated with cognition, though these relationships did not persist with the resolution of psychotic symptoms (Johnsen et al., 2016). Furthermore, anti-inflammatory treatment trials have not shown global cognitive improvements among PwS (Buchanan et al., 2020).

Sex differences in plasma levels of several inflammatory biomarkers have been noted (O'Connor and Irwin, 2010; Slavich and Irwin, 2014), suggesting sex-specific molecular profiles in PwS (Joseph et al., 2015; Ramsey et al., 2013). These sex differences in cognitive deficits among PwS have been partly attributed to hormonal changes, with low estrogen levels linked to lower verbal and executive function in women of reproductive age (Ko et al., 2006b). In postmenopausal PwS, administration of a selective estrogen receptor modulator (SERM) had positive effects on verbal memory and executive function (Huerta-Ramos et al., 2014). However, the literature linking sex-specific differences in inflammatory markers with cognitive dysfunction in PwS remains lacking.

The present study sought to expand on previous work regarding the association between inflammation in neurocognitive dysfunction in PwS, with exploration of sex differences. Nine inflammatory biomarkers were evaluated representing different sources of inflammation: acute phase reactants (hs-CRP, SAA), chemoattractants (MCP-1, IL-8, IP-10), pro-inflammatory (ICAM-1, IL-6), and anti-inflammatory (BDNF, Fractalkine) biomarkers. We investigated three neurocognitive domains: executive functioning, processing speed, and visuospatial performance. We then examined the intersecting role of diagnostic group on the associations between inflammation and cognition. Based on our previous work, we hypothesized that 1) PwS would show more severe cognitive deficits and greater inflammation compared to NCs, and 2) inflammation would be associated with cognitive deficits differentially based on the cognitive domain examined. We further explored sex differences in the relationship between inflammation and cognitive measures by diagnostic group.

Materials and methods

Participants

Study methodology has been previously described (Lee et al., 2016). Briefly, 282 participants were recruited from the greater San Diego area and provided written informed consent. A diagnosis of schizophrenia was based on the Structured Clinical Interview for the DSM-IV-TR (SCID) (First, 2002). DSM-5 (American Psychiatric Association, 2013)

was not yet available at the time the first study participants were recruited, but the subjects recruited since its availability have met criteria for a diagnosis of schizophrenia under both definitions. Non-psychiatric comparison participants (NCs) were recruited from an ongoing survey study of successful aging in healthy adults and were excluded from the study if they had a past or present diagnosis of a major neuropsychiatric disorder based on the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Exclusion criteria were: 1) other current DSM-IV-TR Axis I diagnoses; 2) alcohol or other non-tobacco substance abuse or dependence within 3 prior months; 3) diagnosis of dementia, intellectual disability disorder, or a major neurological disorder; 4) medical disability affecting a subject's ability to complete study procedures. The University of California San Diego (UCSD) Office of IRB Administration reviewed and approved the study protocol. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, the study design was reviewed by an appropriate ethical committee, and informed consent of the participants was obtained after the nature of the procedures had been fully explained.

Sociodemographic and clinical characteristics

Sociodemographic characteristics (sex, age, ethnicity/race, and education), as well as health behavior (smoking status) and schizophrenia-related variables (age of onset, duration of illness, daily dose of antipsychotics) that could affect levels of inflammatory biomarkers were obtained through participant interviews and review of records. Body mass index (BMI) was determined from participant's measured height and weight. Subjects completed standardized assessments for mental health (Short Form Health Survey - Mental), psychopathology (Patient Health Questionnaire-9 for depression, Calgary Depression Scale for schizophrenia, Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS), physical health (Short Form Health Survey - Physical), and medical co-morbidity (Cumulative Illness Rating Scale - Geriatric) (Addington et al., 1994; Andreasen and Olsen, 1982; Kroenke et al., 2001; Linn et al., 1968; Ware and Sherbourne, 1992).

Neurocognitive assessments

As executive functioning may be especially vulnerable to cognitive decline in PwS (Fucetola et al., 2000), we included three subtests from the Delis-Kaplan Executive Function System (Delis et al., 2001): Trail Making (letter-number sequencing task), Color Word Inhibition (switching condition), and the Letter Fluency task (total F, A, and S trials). T-scores coded such that higher scores represent better performance and were then averaged into an executive functioning composite score. Processing speed was included given a meta-analysis identified it as a central feature in the cognitive deficit of PwS (Dickinson et al., 2007), and was derived from the time taken to complete executive functioning tests. Visuospatial skill was added as a relatively spared domain in PwS to check for specificity of findings in the other two domains, and was assessed with the Judgment of Line Orientation test (JOLO) (Benton et al., 1994). In secondary analyses to compare PwS with cognitive deficits to those without, we used a Deficit Score (DS) approach, converting T-scores for the executive function subtests and processing speed measures into DS. Global DS was calculated as the mean DS of the individual subscores and was used to classify subjects as impaired (global DS >= 0.50) or non-impaired (global DS <0.50) (Carey et al., 2004).

Biomarker Assays

Participants had a fasting blood draw, where 65 mL of blood was collected in ethylenediaminetetraacetic acid (EDTA)-treated vacutainers between 7:00 am and 12:00 pm for testing various biomarkers. Samples were centrifuged at 3000 rpm, and plasma was stored at −80°C until assays were performed. Plasma biomarker levels were quantified using Meso Scale Discovery (MSD) MULTI-SPOT® Assay System and analyzed on a SECTOR Imager 2400 instrument (Rockville, MD, USA). Using MSD Discovery Workbench® analysis software, standard curves were formed by fitting ECL signal from calibrators to a 4-parameter logistic model with a 1/y2 weighting. Samples were run in duplicates, using V-PLEX Human Biomarker panels (Catalog # K151A0H-2) to measure the biomarkers. Human fractalkine/CX3CL1 kit (Catalog # K151MKD-2) was used to assay fractalkine levels. V-PLEX kits are fully validated according to fit-for-purpose principles and the FDA's analytical validation guidelines according to the manufacturer (MSD). The laboratory technician performing the assays was "blind" to the subject's diagnosis. Intra-and inter-assay variability was <10% for all assays, except the inter-assay variation for MCP-1 (16.5%). Plasma hs-CRP levels were measured with a commercially available (MSD, Rockville, MD) enzyme-linked immunosorbent assay (ELISA) at the UCSD Clinical & Translational Research Institute (CTRI). Intra- and inter-assay coefficients were <5%. The lowest detected levels for specific biomarkers were as follows: 0.11 pg/mL (IL-6), 40.95 pg/mL (MCP-1), 0.96 pg/mL (IL-8), 82.93 pg/mL (IP-10), 36.20 ng/mL (ICAM-1) and 2040.14 pg/mL (fractalkine), 0.10 pg/mL (hs-CRP), 142.03 ng/mL (SAA), and 17.51 pg/mL (BDNF). No sample showed levels below the detection limits.

Statistical Analysis

Biomarker levels were log-transformed for all analyses to reduce heteroscedasticity and improve inference efficiency. Sociodemographic, biomarker and clinical outcome variables were summarized, and their differences were compared using independent sample t-tests, chi-square tests, ANOVAs, or linear regression.

We used partial least squares (PLS) regression to determine associations of biomarkers with each of the cognitive outcomes (Garthwaite, 1994). Unlike standard multiple linear regression, PLS constructs a series of ordered composite variables from a linear combination of biomarkers so that the first composite variable has the highest correlation with a cognitive outcome, followed by the second, third, and so on. Relationships between cognitive outcomes and biomarkers were examined through these composite variables. Another popular approach for creating composite variables is principal component analysis (PCA). Like PCA, PLS composite variables are also ordered. But, unlike PCA, PLS composite variables are ordered by their correlations with the response in the regression model (Garthwaite, 1994). As our interest here is to find a small set of composite variables of the biomarkers to explain the most variability in the cognitive outcome, we opted for PLS.

We determined the number of composite variables in each analysis by changes in adjusted R squares and p-values. We examined potential moderation effects by group and sex by including their interactions with the selected composite variables, centering them at their respective means to reduce multicollinearity. We also used the least absolute shrinkage and

selection operator (LASSO) for variable selection from a list of covariates (age, education, BMI, smoking status) to create final parsimonious models. To control for potential effects of impairment status and diagnostic group, we performed sensitivity analyses. Notably, we included these two variables and their 2- and 3-way interactions as well as their interactions with sex, while controlling for covariates when performing PLS. For executive function, none of the interactions were significant, therefore, we recomputed PLS while controlling for main effects of impairment status, diagnostic group, and covariates. For processing speed, some of the 3-way interactions could not be fit because of limited impairment in NCs compared to PwS. We removed such interactions and refit PLS accordingly. We then performed linear regression analyses for both outcomes using the extracted composite variables.

We imputed missing data for some biomarkers (0–28% of values, depending on the group and biomarker) using their relationships with each other to maximize all observed biomarker data in the analyses. We performed analyses for both the original and imputed data and obtained similar results. For consistency, we report results based on the imputed data. Statistical significance was set at $p < 0.05$ (two-tailed), adjusted for false discovery rate (Benjamini and Hochberg, 1995).

Results

Demographics and sex characteristics

PwS and NCs were similar in age, race, and sex distribution, thus observed group differences in biomarkers can be interpreted as independent of any biomarker relationships with those demographics (Table 1). NCs had more years of education, lower BMI, and fewer active smokers. When further split by sex, female PwS had higher BMI than male PwS (both groups had higher BMIs than NCs). Other sociodemographic variables were similar by sex. PwS had higher depressive symptoms, lower mental and physical well-being, and higher medical comorbidity (as measured by the Cumulative Illness Rating Scale) than NCs. PwS had worse executive functioning than NCs with no sex difference. Female PwS had worse processing speed than the other groups (female PwS < male PwS < female NCs = male NCs). Female PwS had worse visuospatial skills than the other groups (female PwS < males PwS = female NCs < male NCs).

Inflammatory biomarker differences, PLS & Canonical Correlation Analysis

PwS had higher hs-CRP ($t(277) = -3.749$, $p < 0.001$), SAA ($t(244) = -2.256$, $p = 0.025$), and ICAM-1 ($t(244) = -2.967$, $p = 0.003$) compared to NCs. When stratified by sex and diagnosis, these 3 biomarkers with the addition of fractalkine had a main effect of group (Table 1). There was no main effect of group for IL-8, MCP-1, BDNF, IP-10, and IL-6, though the latter two showed a trend towards significance ($F(3,246) = [2.528]$, $p=.058$ and $F(3,245) = [2.571]$, $p=.055$, respectively). Post hoc comparisons determined that elevation of plasma SAA was specific to male PwS ($p = 0.021$, 95% CI = [1994.0, 34420.9]), and for IL-6 was specific to female PwS ($p = 0.037$, 95% CI = [0.02, 1.15]).

Using PLS regression, we obtained an inflammatory biomarker composite that reflected the highest correlation with results on cognitive functioning tests while controlling for covariates (Supplemental Table 1). For executive functioning, the linear regression with this composite variable showed a significant three-way biomarker composite by diagnostic group by sex interaction after variable selection using LASSO, with education remaining as a covariate (Table 2A). Wald tests for the effects of each subgroup demonstrated a significant effect for male NCs in driving the interaction (Z=10.64, p=.001), with subgroup comparisons showing a significant difference between male NCs and female NCs (Z=4.77, p=.03), as well as between male NCs and male PwS (Z=6.79, p=.009). Male NCs had better executive function than female NCs and male PwS.

Applying the same approach for processing speed, we identified a significant three-way biomarker composite by diagnosis by sex interaction after variable selection using LASSO, with education remaining as a covariate (Table 2B). Wald tests for the effects of each subgroup demonstrated a significant effect for female PwS in driving the interaction (Z=4.36, p=.04), with subgroup comparisons showing a significant difference between female and male PwS (Z=5.23, p=.02). Female PwS had worse processing speed than male PwS.

For visuospatial functioning, in contrast to executive function and processing speed, the final model showed no significant three-way interaction after variable selection by LASSO, with education and BMI remaining as covariates (Table 2C). The trimmed model showed that higher inflammation was associated with worse visuospatial functioning.

The results of sensitivity analyses controlling for impairment status and diagnostic group demonstrated that PLS biomarker composites still yielded results similar to our original analysis, justifying the inclusion of all PwS regardless of cognitive impairment when deriving biomarker composites. The final models for executive functioning and processing showed a significant 3-way interaction between the inflammation composite, diagnosis, and sex. Considering impairment status as a covariate, the revised final models show the same 3-way interactions remaining significant (see Table 2A and 2B). Furthermore, the biomarkers that made up the inflammatory composite remained the same, with only slight differences in the loadings (see Supplemental Table 1).

Discussion

We identified sex-specific associations between inflammation and two cognitive domains (processing speed and executive functioning) but not visuospatial processing. Increased inflammation was associated with worse processing speed only in female PwS. To the best of our knowledge, this is the first report linking sex-specific differences in inflammatory markers with cognitive dysfunction in PwS.

We did not detect a sex-specific relationship between inflammation and executive function in PwS; increased inflammation was associated with worse executive function only in male NCs. A meta-analysis by Bora reported a modest relationship between CRP levels and planning/problem-solving abilities in three studies of PwS (r=−.10, CI 0 to −.19,

p=.04), though the studies did not specifically examine sex differences and all three study cohorts were predominantly male (Boozalis et al., 2017; Bora, 2019; Bulzacka et al., 2016; Dickerson et al., 2012). The same meta-analysis also reported a significant relationship between CRP levels and speed-based executive functioning (r=−.10, CI −.03 to −.18, p =.009) in five studies of PwS. Like our current findings, the meta-regression did not find any significant effect of sex on the CRP-executive functioning relationship. These findings may reflect the complexity of chronic schizophrenia, where many other factors (smoking, obesity, medication exposures, comorbid medical illnesses) may be contributing to executive functioning deficits, despite our best efforts to mitigate their effects by including them as covariates in our analyses.

The current study's association between processing speed and inflammation is consistent with previously published studies (Bora, 2019; Bulzacka et al., 2016). One meta-analysis reported higher CRP levels were associated with lower processing speed scores (r =−.11, CI −.04 to −.19, p=.004), though the effect size was small and sex differences were not specifically examined in these six studies (Bora, 2019). Female PwS were previously shown to have better processing speed (Leger and Neill, 2016; Torniainen et al., 2011; Tsai et al., 2012). The sex-specific differences in the current study were consistent with a large study of older non-demented community-dwelling older adults that found a significant association between increased IL-12 levels and processing speed deficits only in women (Trollor et al., 2012). These observed sex differences may reflect sex hormone-mediated cognitive aging (Alwerdt et al., 2019; Hogervorst et al., 2004; Kilpi et al., 2020) and could contribute to higher prevalence of non-amnestic MCI and all-type dementia in women (Au et al., 2017; Cao et al., 2020).

The current study found higher inflammation was associated with worse visuospatial functioning, which was consistent with prior studies. One study of 905 PwS found the −1031T/C polymorphism of the tumor necrosis factor gene was associated with worse visuospatial functioning (Xiu et al., 2018). Another study of 27 PwS showed that percentage of IL-17 producing NK cells was associated with visuospatial functioning (Borovcanin et al., 2020). In contrast to executive function and processing speed, we did not detect sex-specific associations between inflammation and visuospatial functioning, consistent with other studies of PwS (Bozikas et al., 2010; Han et al., 2012).

Interestingly, the acute phase proteins hs-CRP and SAA made the greatest contribution to the inflammatory composite variables for all three cognitive domains. Inflammatory stimuli activate the release of peripheral cytokines such as IL-6, which then activates the release of hs-CRP and SAA from the liver resulting in a systemic inflammatory response (Sack, 2020). SAA's role may be similar to hs-CRP, as both are regulated by IL-6 activity within the liver (Gur et al., 2017; Schultz and Arnold, 1990). SAA was the only biomarker examined with elevation specific to male PwS (as opposed to the more pronounced elevation of hs-CRP and IL-6 in female PwS). These sex-specific biomarker discrepancies may partly explain the worse overall cognitive performance in female PwS compared to male PwS, with the important caveat that these findings of sex differences were part of exploratory analyses meant to generate rather than test specific hypotheses. IL-6, ICAM-1 and BDNF contributed less to the inflammatory composite variable, but their potential role in cognitive

deficits could still be significant. For example, the results from one study suggested that IL-6 may play a role in processing speed deficits in PwS (Frydecka et al., 2015). ICAM-1, an endothelial protein that binds to integrins found on the leukocyte surface to regulate immune cell trafficking into the brain, is elevated in plasma and contributes to processing speed deficits in PwS (Cai et al., 2020; Weickert et al., 2018). Finally, an association between lower BDNF and cognitive deficits including processing speed in PwS was reported in a meta-analysis (Bora, 2019).

Cognitive deficits have been resistant to treatment with current antipsychotic drugs (Carpenter and Koenig, 2008; Fusar-Poli et al., 2015). The association of processing speed with inflammation in female PwS suggests that anti-inflammatory treatment may be a useful approach to enhancing processing speed in this selected population. Overall, the evidence for anti-inflammatory or hormone treatments improving cognition in PwS remains lacking (Buchanan et al., 2020). However, there have been some reports that anti-inflammatories have improved cognitive deficits. For example, hormone replacement therapy (HRT), which includes the anti-inflammatory estrogen, improved processing speed in female PwS (Ko et al., 2006a). A meta-analysis that found minocycline and pregnenolone augmentation therapy improved visual learning/memory, attention, and executive function in PwS is illustrative of inconsistencies in this area, with no reported improvement in processing speed (Cho et al., 2019). These limited and disparate findings regarding anti-inflammatory treatments in PwS underscore the need for better mechanistic understanding of the link between inflammation and cognitive deficits in PwS. Further studies will be required to help stratify which subpopulations may benefit the most from anti-inflammatory treatment approaches.

Limitations

Inflammatory biomarkers were assayed in plasma as a surrogate for measuring levels directly in cerebrospinal fluid and levels of peripheral biomarkers may not reflect levels of these biomarkers in the central nervous system (CNS). In support of using periperal biomarker levels, one study reported that CNS changes in immune/inflammatory mRNA expression are reflected in similar mRNA expression changes in lymphocytes (Gatta et al., 2021). Selection of specific biomarkers and cognitive tests were based on available literature, and we may have overlooked additional important inflammatory biomarkers as well as cognitive domains. Given this study population consisted of stable outpatients on medication, the generalizability of our findings to other groups of PwS such as acutely psychotic patients, chronically hospitalized patients, or medication-free patients is quite limited. Furthermore, the cross-sectional nature of the present study does not address the question whether the relationships described between inflammation, sex, and cognition remain stable over time.

Summary

The “inflammatory profile” utilized in this study could help identify pathways affecting processing speed in female PwS. This cognitive domain would be an important priority to address given its central role in the cognitive deficits of PwS and that many other cognitive operations are dependent on speed. Interventions aimed at reducing levels of biomarkers like

hs-CRP and/or SAA may prove effective at mitigating deficits in processing speed in female PwS, though timing of these interventions remains unclear. It will be important to investigate the association between the inflammatory composite variable from this study and processing speed in future longitudinal studies to determine if the association between inflammation and processing speed in female PwS evolves over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Diagnosis and sex differences across Demographic and Clinical features, Neurocognitive tests, and Inflammatory Biomarkers

	Schizophrenia female			Schizophrenia male			Non-psych comparison female			Non-psych comparison male			ANOVA/Chi square test/t-test			Post hoc paired comparisons
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	F/X^2/t	Df	Sig.	
Sociodemographic																
Age at visit	64	48.6	10.26	79	47.8	10.05	74	48.3	11.63	65	49.1	10.76	0.40	280	0.693	
Race (%)	64			79			74			65			14.10	15	0.518	
Caucasian	27	42.2		37	46.8		40	54.1		40	61.5					
African American	13	20.3		13	16.5		9	12.2		8	12.3					
Hispanic/Latinx	22	34.4		22	27.8		20	27		14	21.5					
Other	2	3.1		7	8.9		5	6.8		3	4.6					
Current Smoker (%)	64	43.8		79	58.2		74	5.4		65	9.2		70.87	3	<.001	Sf = Sm > Nf = Nm
Education - Total Years	64	12.8	2.01	79	12.1	2.30	74	14.6	1.94	65	14.4	2.40	8.31	280	<.001	Sf = Sm < Nf = Nm
Mental																
Calgary Depression Scale Total Score	63	3.6	3.74	79	3.3	3.91	73	0.8	1.52	65	0.5	1.37	−7.91	278	<.001	Sf = Sm > Nf = Nm
PHQ9 Severity Score (Depression)	61	7.9	6.34	75	7.5	6.69	67	1.9	2.35	62	2.1	3.27	−9.18	263	<.001	Sf = Sm > Nf = Nm
SF-36 Mental Component	63	43.0	11.28	76	42.9	11.31	67	54.8	5.02	63	54.5	6.66	10.63	267	<.001	Sf = Sm < Nf = Nm
Physical																
CIRS - Total Score	64	7.2	5.01	79	6.0	4.16	73	2.9	3.10	64	2.9	3.41	−7.66	278	<.001	Sf = Sm > Nf = Nm
SF-36 Physical Component	63	41.3	10.16	76	44.6	9.99	67	51.3	8.37	63	51.3	10.02	6.99	267	<.001	Sf = Sm < Nf = Nm
Body Mass Index	62	34.1	8.35	78	30.7	6.09	73	27.7	7.59	65	27.6	5.49	−5.37	276	<.001	Sf > Sm > Nf = Nm
Neurocognitive																
Executive functioning	63	38.1	11.50	77	37.8	29.50	74	55.1	6.98	65	53.3	8.09	7.93	277	<.001	Sf = Sm < Nf = Nm
Processing speed	63	40.0	10.10	78	42.0	9.08	74	55.2	5.39	65	53.6	6.10	14.10	278	<.001	Sf < Sm < Nf = Nm
Visuospatial functioning	39	17.8	5.15	61	22.8	5.68	54	23.3	4.09	42	26.8	3.02	5.37	194	<.001	Sf < Sm = Nf < Nm
Illness-specific characteristics																
Age of Onset	63	22.7	8.12	77	23.2	7.30							−0.41	138	0.685	

	Schizophrenia female			Schizophrenia male			Non-psych comparison female			Non-psych comparison male			ANOVA/Chi square test/t-test			Post hoc paired comparisons
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	F/X²/t	Df	Sig.	
Duration of Illness	63	26.0	11.45	77	24.3	10.62							0.86	138	0.389	
Antipsychotics dose *	64	1.7	1.65	79	2.0	1.49							−0.92	141	0.360	
Positive symptoms (SAPS)	64	6.5	3.94	79	6.6	4.43							−0.07	141	0.943	
Negative symptoms (SANS)	64	7.2	4.28	79	7.2	4.48							−0.003	141	0.997	
Biomarkers																
IP-10 (Interferon gamma-induced Protein-10)	60	487.3	406.6	74	332.0	355.8	64	443.9	464.7	49	345.2	187.0	2.528	246	0.058	
MCP-1; CCL2 (Monocyte Chemotactic Protein-1)	60	100.9	42.0	74	95.3	32.0	64	95.0	67.6	49	81.9	35.9	1.556	246	0.201	
IL-6 (Interleukin-6)	59	1.3	1.3	74	0.9	0.5	64	0.7	0.4	49	1.1	2.2	2.571	245	0.055	Sf > Nf
IL-8 (Interleukin-8)	59	4.2	2.5	74	4.2	4.4	64	4.6	6.8	49	3.6	2.8	0.377	245	0.77	
Hs-CRP (High sensitivity C-reactive protein)	64	6.3	6.7	79	4.2	10.0	73	2.5	4.2	63	1.8	2.4	6.000	278	0.001	Sf > Nf = Nm
SAA (Serum Amyloid A)	59	8382.3	12817	74	20523.2	58518	64	7509.3	17841	49	2315.8	3731	3.325	245	0.02	Sm > Nm
ICAM-1/CD54 (Intercellular Adhesion Molecule-1)	59	482.4	239.2	74	501.9	323.9	64	399.7	172.5	49	405.2	159.2	2.990	245	0.032	
BDNF (Brain Derived Neurotrophic Factor)	60	641.6	676.5	72	580.2	729.0	61	833.3	1296.0	47	839.4	1516.8	0.930	239	0.427	
Fractalkine	60	6797.8	2620.1	73	5267.4	1685.1	64	6166.0	1852.9	49	6185.0	2071.2	6.256	245	<.001	Sf > Sm

SD = Standard Deviation

PHQ-9 = Patient Health Questionnaire

SF-36 = Short Form health survey

CIRS = Cumulative Illness Rating Scale

JOLO = Judgment of Line Orientation

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SAPS = Scale for the Assessment of Positive Symptoms

SANS = Scale for the Assessment of Negative Symptoms

Sf = Schizophrenia female

Sm = Schizophrenia male

Nf = Non-psychiatric female

Nm = Non-psychiatric male

* World Health Organization defined daily dose

Table 2.

Results from partial least squares for association of composite biomarker variable with neurocognitive functioning: A) Executive functioning, B) Processing speed, and C) Visuospatial functioning.

2A.

Factors for Processing speed	**Estimate**	**SE**	***t*-value**	***p*-adjusted**	η_p^2
Diagnosis (ref: Non-psychiatric comparison)	−12.62	1.48	−8.51	<0.001***	0.30
Sex (ref: Female)	−2.11	1.42	−1.49	0.20	0.001
Education	0.76	0.22	3.48	0.002**	0.04
Inflammation Composite	0.13	0.56	0.23	0.27	0.002
Diagnosis × Sex	3.33	2.02	1.64	0.18	0.008
Inflammation Composite × Diagnosis	−1.46	0.84	−1.74	0.18	0.0002
Inflammation Composite × Sex	−1.16	0.97	−1.20	0.27	0.004
Inflammation Composite × Diagnosis × Sex	2.97	1.29	2.30	0.05*	0.02

2B.

Factors for visuospatial functioning	**Estimate**	**SE**	***t*-value**	***p*-adjusted**	η_p^2
Diagnosis (ref: Non-psychiatric comparison)	−3.43	0.75	−4.59	<0.001***	0.10
Sex (ref: Female)	4.30	0.67	6.40	<0.001***	0.18
Education	0.27	0.16	1.70	0.12	0.02
Inflammation Composite	−0.72	0.30	−2.41	0.03*	0.02
Body Mass Index	−0.05	0.05	−1.10	0.23	0.01
Inflammation Composite × Sex	0.66	0.40	1.65	0.12	0.01

2C.

Factors for Executive Functioning	**Estimate**	**SE**	***t*-value**	***p*-adjusted**	η_p^2
Diagnosis (ref: Non-psychiatric comparison)	−13.35	1.64	−8.13	<0.001***	0.24
Sex (ref: Female)	−3.27	1.58	−2.07	0.11	0.002
Education	1.44	0.24	5.95	<0.001***	0.11
Inflammation Composite	−0.15	0.61	−0.25	0.23	0.01
Diagnosis × Sex	6.15	2.25	2.73	0.02*	0.02
Inflammation Composite × Diagnosis	−0.80	0.92	−0.87	0.43	0.01
Inflammation Composite × Sex	−2.69	1.06	−2.54	0.31	0.001
Inflammation Composite × Diagnosis × Sex	3.72	1.41	2.65	0.03*	0.02

* $0.01 < p < 0.05$

** $0.001 < p < 0.01$

*** $p < 0.001$

Residual degrees of freedom: 269

* $0.01 < p < 0.05$

** 0.001 < p < 0.01

*** p < 0.001

Residual degrees of freedom: 271

* 0.01< *p* < 0.05

** 0.001 < p < 0.01

*** p < 0.001

Residual degrees of freedom: 189