Brazilian Journal of Psychiatry
bjp
Revista Brasileira de Psiquiatria
Brazilian Psychiatric Association
Fully open access
No APCs

BJP PRE-PROOF
(article published as accepted)

Original Article

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http://doi.org/10.47626/1516-4446-2025-4669

Submitted: 25-Oct-2025

Accepted: 20-Jan-2026

Interconnected Cognitive and Neuroimmune Impairments in Schizophrenia: Modulating Effects of Antipsychotic Type, Illness Duration, and Symptom Severity

Running head: Neuroimmune–Cognitive Impairments in Schizophrenia

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Abstract

Objective: Cognitive impairment in schizophrenia (SCZ) is associated with neuroinflammation and neurotrophic dysregulation. The role of pro-inflammatory interleukins and brain-derived neurotrophic factor (BDNF) in cognitive deficits remains unclear. We aimed to examine the associations between IL-1β, IL-2, IL-6, BDNF, and cognitive function in patients with SCZ with typical or atypical antipsychotics.

Methods: Participants included 162 healthy controls (mean age = 33.6 ± 2.0 years), 88 patients with SCZ receiving typical antipsychotics (36.4 ± 6.4 years), and 62 receiving atypical antipsychotics (34.0 ± 4.0 years). Cognitive performance was evaluated using a battery of attentional, executive, and visuospatial working memory tasks. Data were analyzed using machine-learning approaches, multivariate statistics, and structural equation modeling.

Results: SCZ Patients exhibited marked cognitive impairments alongside lower BDNF concentrations and elevated interleukin levels, with the greatest deviations observed among those receiving typical antipsychotic treatment. Higher medication dosages and longer illness duration were associated with greater cognitive decline and stronger neuroimmune dysregulation.

Conclusions: The findings indicate that elevated cytokines and reduced neurotrophic support may contribute to cognitive impairment, whereas persistent cognitive dysfunction can further amplify inflammatory activity. This complexity suggests the need to broaden current assessment approaches and systematically examine biomarkers together with clinical features.

Keywords: Schizophrenia; cognition; interleukins; brain-derived neurotrophic factor; antipsychotics

1. Introduction

Schizophrenia (SCZ) is a complex psychiatric disorder that affects approximately 1% of the global population and imposes a substantial burden on cognitive, emotional, and social functioning. Cognitive deficits, a core feature of SCZ, are present in up to 80% of patients and represent one of the strongest predictors of functional outcome [1]. These impairments, which include deficits in attention, memory, and executive control, significantly compromise daily activities and quality of life and are often considered among the most disabling aspects of the disorder [1,2].

Cognitive dysfunction in SCZ is closely linked to biological abnormalities, particularly neuroinflammation and neurotrophic dysregulation [3,4]. Elevated levels of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-2, and IL-6, play a central role in the disorder's pathophysiology [5]. These cytokines can compromise the blood–brain barrier and activate inflammatory signaling in the central nervous system, exacerbating cognitive decline [6]. In parallel, reductions in brain-derived

neurotrophic factor (BDNF), a key regulator of synaptic plasticity and neuronal survival, have been consistently associated with cognitive impairment and illness severity [7,8]. Understanding how neuroimmune alterations interact with neurotrophic mechanisms is essential for clarifying the biological basis of cognitive dysfunction in SCZ [3,9].

Beyond receptor-level effects, cytokine-related immune activity also contributes to cognitive impairment in SCZ. Elevated IL-1β, IL-2, and IL-6 disrupt synaptic plasticity, neurogenesis, and neurotransmission, worsening attention, memory, and executive performance [10]. Other cytokines, including IL-4, IL-8, and IL-10, amplify neuroinflammation and further affect cognition [8,11]. BDNF, essential for neuronal maintenance and learning, is typically reduced in SCZ and correlates with cognitive decline [10,12]. Although proposed as a biomarker, its interaction with immune pathways is still being elucidated, and its stability across serum versus plasma remains a methodological consideration [5].

Typical antipsychotics such as haloperidol may heighten cytokine activity and worsen cognition [11]. Atypical antipsychotics, acting on dopamine and serotonin systems, appear more effective in balancing cytokine levels and enhancing BDNF expression, potentially improving cognitive function [13]. However, findings remain inconsistent due to methodological variability and sample heterogeneity. In particular, differences in treatment duration, medication switching, and comorbid factors moderate immune and cognitive outcomes, complicating observations and leading to inconsistencies. These inconsistencies highlight the complexity of cytokine modulation by antipsychotic medications and its link to neuroimmune and cognitive processes in SCZ, with implications for clinical translation [5].The directionality of these effects remains debatable. For instance, it is unclear whether elevated cytokines drive cognitive impairments or reflect compensatory activities to the use of antipsychotics.

This study examined how cytokines and neurotrophic factors both influence and relate to cognitive function in SCZ. Consistent with previous studies linking antipsychotic medication, disease progression, and symptom severity, we aimed to clarify interactions among clinical, biological, and cognitive variables. We trust that advancing our understanding in this field will open avenues for targeted therapies or interventions aimed at enhancing the quality of life and functional outcomes in SCZ patients.

2. Methods and Materials

2.1 Participants

One hundred and sixty-two healthy participants (mean age = 33.56 years; *SD* = 2.00), 88 SCZ patients using typical antipsychotics (mean age = 36.40 years; *SD* = 6.40), and 62 SCZ patients using atypical antipsychotics (mean age = 34.01 years; *SD* = 4.00). Participants, aged 20 to 50 years, reported no retinal or eye impairments in self-reports or prior exams.

Patients met DSM-5 criteria for SCZ (American Psychiatric Association, 2013) and were outpatients receiving maintenance antipsychotic treatment. Symptom severity and clinical characteristics were assessed using standardized instruments, including the Positive and Negative Syndrome Scale (PANSS)[14], the Brief Psychiatric Rating Scale (BPRS)[15], and the Montgomery-Åsberg Depression Rating Scale (MADRS) [16]. These scales examined variances in symptom severity, symptom manifestation, and clinical features between patient groups, aligning with the hypotheses. Trained examiners, blinded to other parts of the study, administered the rating scales. The chlorpromazine equivalent was calculated using the Andreasen method [17].

During eligibility screening, 36 participants were excluded due to predefined criteria, including a recent history of neurological disorders (n = 12), cardiovascular disease (n = 3), traumatic brain injury (n = 1), and chronic exposure to neurotoxic substances or substance use disorder (n = 20). For HC, exclusion criteria also included the use of medications known to affect cognitive processing (e.g., benzodiazepines) and any lifetime neuropsychiatric disorder, as assessed by structured clinical interview. All patients were clinically stable outpatients with no recent substance abuse and had maintained their current antipsychotic treatment regimen for at least six months prior to assessment, as confirmed by medical records. Participants were expected to have stable social support and medication adherence and were free of multiple diagnoses or other psychotic disorders. Medication class (typical or atypical antipsychotics) was determined according to routine clinical practice and standard clinical care. All participants had normal or corrected-to-normal visual acuity (≥20/20, binocular), verified using a Snellen chart [18,19]. The final sample was drawn from a larger dataset to ensure a representative distribution of demographic and clinical characteristics. Additional details regarding

eligibility and exclusion criteria are provided in Supplementary Material. (Sup. Material). Recruitment and assessment procedures were standardized across sites through shared protocols, centralized training, and ongoing quality control, contributing to consistent assessment across centers [18,20].

The present study followed the ethical principles of the Declaration of Helsinki and was approved by the Committee of Ethics. Written informed consent was obtained from all of the participants.

2.3 Serum sample collection

Blood samples were collected in triplicate and allowed to clot at room temperature for an hour, easing serum separation for ELISA R&D analysis (Systems, Germany). This ensured serum reliability and cytokine measurement accuracy [21]. Blood samples were taken under uniform procedures, such as in the early morning to control for diurnal variations, by trained professionals using sterile techniques in a clinical environment. According to standard guidelines, the samples were centrifuged at 1600 x g for 25 minutes. Participants were instructed to avoid heavy meals to prevent potential interferences or metabolite variability [22]. The use of high-quality reagents and adherence to validated protocols allowed for maintaining low intra- and inter-assay variability (coefficients below 9%) [23].

2.4 Cognitive Tasks

This section describes the cognitive tasks used in the study. Brief task descriptions are provided below, with additional details available in the Supplementary Material (Sup. Material S1). Tasks were selected for their sensitivity to cognitive deficits commonly observed in SCZ [10,24]. All tasks were administered by trained researchers following standardized procedures to ensure consistency across sessions.

2.4.1 Flanker task. The Flanker task assessed selective attention and attentional control. Participants identified a centrally presented target letter while ignoring flanking letters on either side. Reaction time (RT) was the primary outcome measure, with faster RTs indicating better performance [25]. RTs can provide insights of subtle mechanisms not necessarily reflected in error rates, which tend to plateau.

2.4.2 Stroop color-word interference. The Stroop task evaluated executive control, particularly inhibitory control and cognitive flexibility. Participants identified the font color of words under congruent (word meaning matches the color) and incongruent (word meaning conflicts with the color) conditions. Faster RTs across conditions indicated better performance [26].

2.4.3 Corsi block-tapping. The Corsi Block-Tapping Test was administered to assess non-verbal visuospatial working memory and attention (i.e., span), as well as efficiency and processing speed (i.e., reaction times). Participants were required to reproduce sequences of blocks presented on a computer screen. Blocks were sequentially indicated by a brief visual emphasis, with only one block highlighted at a time. This procedure served exclusively to mark the order of the sequence and did not involve changes in stimulus features. Dependent measures included RT for reproducing forward and backward sequences and the maximum correctly reproduced sequence length (span). Faster reaction times and higher span values indicated better cognitive performance [27].

2.5 Data analysis

For each condition, data distribution was assessed using measures of central tendency and dispersion. To evaluate the normality of distributions, Monte Carlo simulations were used to calculate skewness and kurtosis, with a conventional cut-off value of > 1.96. Statistical analysis was performed using SPSS 25.0 and MATLAB R2018b (mathworks.com).

The groups demonstrated normal distribution, enabling the application of parametric tests. The chi-squared (3 x 2) test was used to examine nominal variables, such as gender. ANOVAs compared biosociodemographic data across groups. An independent ANOVA was applied specifically to the Flanker test results. Additionally, three separate multivariate analyses of variance (MANOVAs) were conducted to analyze the test results of the Corsi test (four dependent variables), the Stroop test (two dependent variables), and interleukin and neurotrophic factor outcomes.

Principal Component Analysis (PCA) reduced the dimensionality of our data. K-means clustering was used for its efficiency in forming distinct clusters. The optimal number of clusters was identified using the elbow method, silhouette score,

Davies-Bouldin index, and Calinski-Harabasz index. Nested cross-validation ensured clustering robustness and reliability.

Random Forest analysis assessed feature importance in distinguishing groups, excelling in both classification and regression tasks. The model was trained on predictor variables (X) and outcome variables (Y) with an 80/20 training/testing split, evaluated using metrics such as accuracy, precision, and recall. Feature importance scores were normalized for direct comparison, with cross-validation confirming model consistency and relevance [28]. Nested cross-validation ensured the model's generalizability across different confounding variables, while sensitivity analyses assessed the robustness of findings under various assumptions.

Multiple multivariate Structural Equation Modeling (SEM) analyses were used to account for variables and confounders, screening the dataset for multicollinearity. Confounders identified through literature were included as mediators or moderators. Sensitivity analyses evaluated the influence of different mitigation strategies on the SEM results [29].

3. Results

3.1 Sample Characteristics

The characteristics of the participants are summarized in Table 1. The groups did not differ in age [F (2, 309) = 2.21, p = .160] or level of education [F (2, 309) = 1.14, p = 0.064]. No significant group differences were observed for gender [χ (2) = 1.88, p = 0.389]. Handedness differed across groups [χ (2) = 4.32, p = 0.036] with approximately 80% of participants being right-handed.

Table 1. Demographic, clinical, and biological characteristics of the sample.

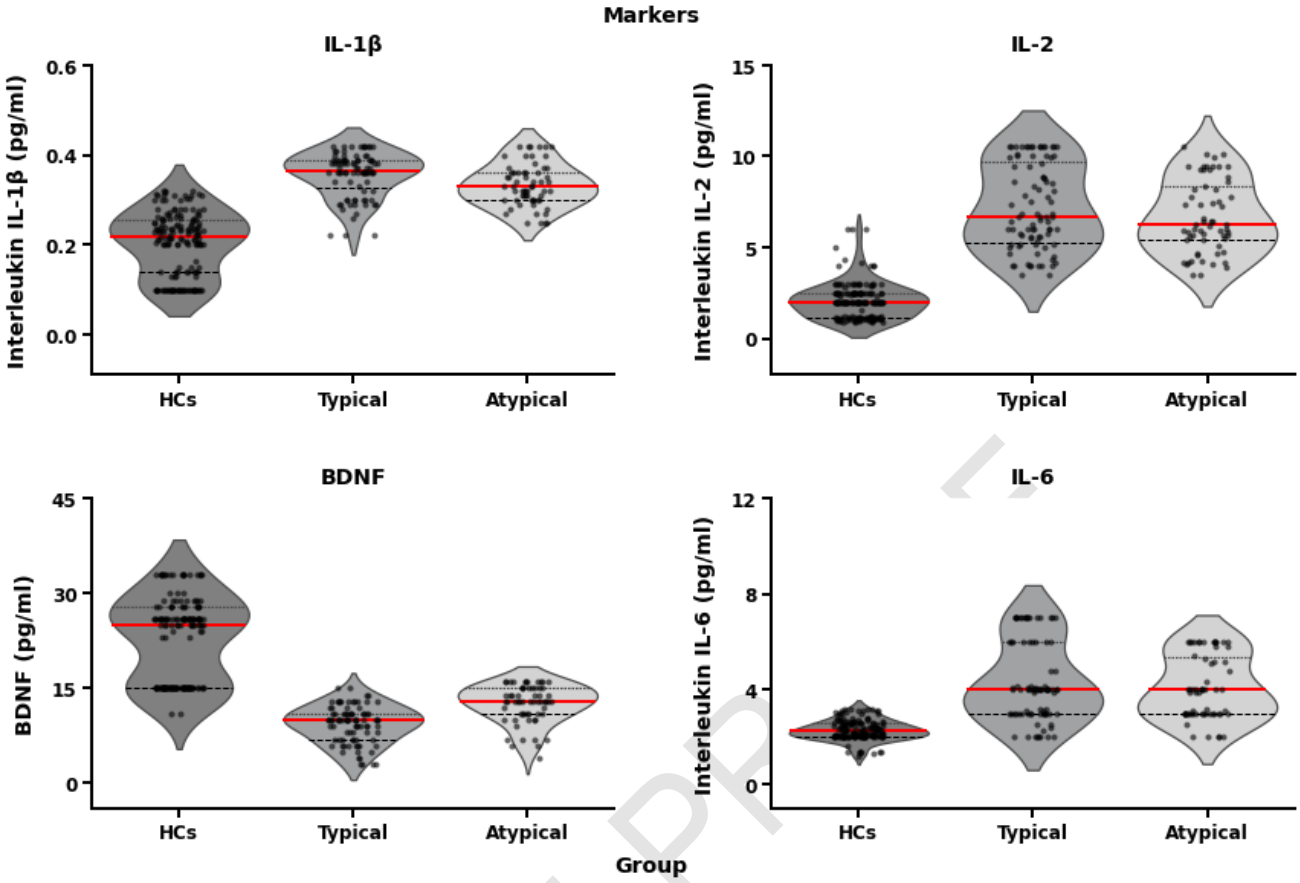
	HC (n = 162)	**Typical SCZ (n = 88)**	**Atypical SCZ (n = 62)**	**p-value**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Age, years	33.56 (2.00)	36.40 (6.40)	34.01 (4.00)	0.160
Education, years	15.72 (5.52)	13.92 (7.60)	14.12 (2.27)	0.064
Male/Female	72/90	32/56	19/43	0.389
Handedness (L/R)	40/122	14/74	6/56	0.036

Duration of the disease, years	0.00	11.59 (4.30)	9.00 (6.10)	0.052
Chlorpromazine-equivalent	0.00	963.96 (341.04)	882.61 (650.87)	0.370*
PANSS Total	0.00	40.16 (19.44)	37.00 (12.06)	0.223*
PANSS Positive	0.00	10.97 (2.50)	9.01 (3.50)	0.001*
PANSS Negative	0.00	10.03 (8.14)	7.50 (4.58)	0.017*
IL-1β (pg/ml)	0.22 (0.15)	0.38 (0.09)	0.34 (0.07)	< 0.001
IL-2 (pg/ml)	2.09 (0.97)	7.80 (3.54)	6.72 (1.99)	< 0.001
BDNF (ng/ml)	22.82 (7.36)	9.34 (2.96)	12.63 (3.04)	< 0.001
IL-6 (pg/ml)	2.00 (0.82)	4.26 (2.59)	3.29 (1.52)	< 0.001

Note: Values are reported as mean (SD) unless otherwise indicated. HC = healthy controls; SCZ = schizophrenia; PANSS = Positive and Negative Syndrome Scale; BDNF = brain-derived neurotrophic factor. p-values correspond to group analyses. * indicates SCZ group comparisons only. Sex and handedness were analyzed using chi-square tests; all other variables were analyzed using appropriate group comparison tests. Chlorpromazine-equivalent doses are expressed in mg/day.

3.2 Biological Markers

Fig. 1 – Violin graphs comparing distributions of biological markers across healthy controls (HCs) and schizophrenia (SCZ) groups. Each graph illustrates the median values with solid red lines and the interquartile ranges with dashed black lines, showing the dispersion and central tendency of the data. The width of each violin indicates the density of data points at different levels of each marker.



3.2.1 IL-1β Levels

There were significant differences between groups for IL-1β levels [F (2, 309) = 56.50, $p < 0.001$, $\omega^2 = 0.35$; 95% BCa: 0.28 – 0.42]. Post-hoc analysis showed that both SCZ typical and SCZ atypical patients had higher IL-1β levels compared to HCs (all p-values < 0.001). SCZ typical also had higher IL-1β levels compared to SCZ atypical patients [p = 0.016; g = 0.40 (95% BCa: 0.21 – 0.50)].

3.2.2 IL-2 Levels

There were significant differences between groups for IL-2 levels [F (2, 309) = 54.80, $p < 0.001$; $\omega^2 = 0.48$; 95% BCa: 0.34 – 0.60]. Post-hoc analysis showed that both SCZ typical and SCZ atypical patients had higher IL-2 levels compared to HCs (all p-values < 0.001). SCZ typical also had higher IL-2 levels compared to SCZ atypical patients [p = 0.042; g = 0.19 (95% BCa: 0.06 – 0.37)].

3.2.3 BDNF Levels

There were significant differences between groups for BDNF levels [F (2, 309) = 50.65, $p < 0.001$; $\omega^2 = 0.39$; 95% BCa: 0.30 – 0.46]. Post-hoc analysis showed that both SCZ typical and SCZ atypical patients had lower BDNF levels compared to HCs (all p-values < 0.001). SCZ typical also had lower BDNF levels compared to SCZ atypical patients [p < 0.001; g = 0.52 (95% BCa: 0.28 – 0.70)].

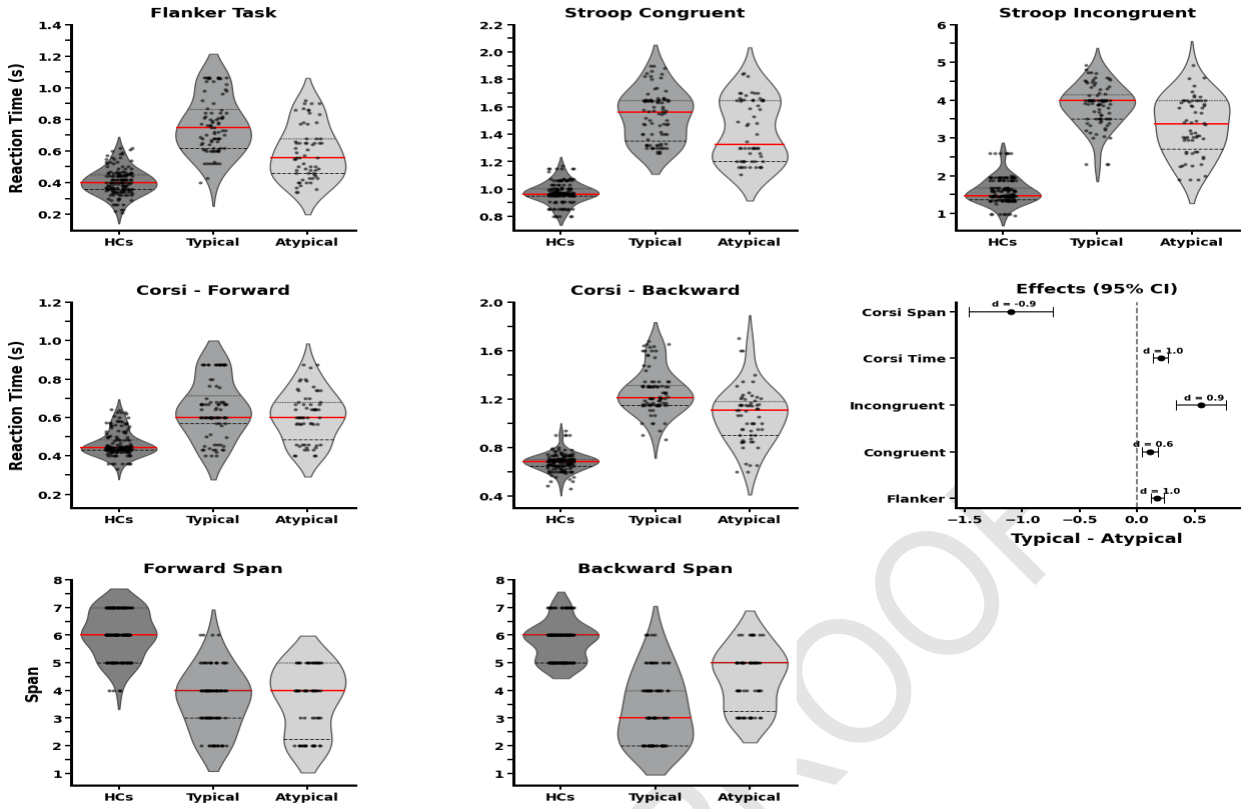
3.2.4 IL-6 Levels

There were significant differences between groups for IL-6 levels [F (2, 309) = 60.40, $p < 0.001$; $\omega^2 = 0.33$; 95% BCa: 0.27 – 0.44]. Post-hoc analysis showed that both SCZ typical and SCZ atypical patients had higher IL-6 levels compared to HCs (all p-values < 0.001). SCZ typical also had higher IL-6 levels compared to SCZ atypical patients [$p = 0.008$; g = 0.34 (95% BCa: 0.21 – 0.50)].

3.3 Cognitive Performance

The results of the tasks are summarized in Fig 2. A Table with descriptive statistics of the tasks is in the Supplementary Material (Sup. Material – Table S1)

Fig. 2 – Violin graphs illustrating cognitive task performance across healthy controls (HCs) and schizophrenia (SCZ) groups. The graphs detail outcomes for various tasks. Red solid lines within each violin plot represent the median values, while the black dashed lines display the interquartile ranges, illustrating data dispersion and central tendency. The width of each violin indicates the density of data points at different values. Adjacent to the plots, an effect size graph underscores significant differences between the typical and atypical SCZ groups, with larger effect sizes and confidence intervals pointing to notably reduced performance in the typical SCZ group.



3.3.1 Flanker task

There were significant differences between groups for the Flanker task [F (2, 309) = 62.80, $p < 0.001$; $\omega^2 = 0.38$ (95% BCa: 0.29 – 0.52)]. Post hoc analysis revealed that both SCZ typical and SCZ atypical patients exhibited higher RTs compared to HCs (all p-values < 0.001), suggesting reduced performance in both patient groups. Additionally, SCZ typical patients had higher RTs than SCZ atypical patients [g = 0.40 (95% BCa: 0.19 – 0.60)].

3.3.2 Stroop test

In the Stroop test, significant group differences were observed [F (4, 618) = 74.78, p < 0.001, Pillai's Trace = 0.76]. For congruent stimuli, both SCZ typical and SCZ atypical patients exhibited higher RTs compared to HCs (all p-values < 0.001). Additionally, SCZ typical patients demonstrated higher RTs than SCZ atypical patients (p = 0.036, g = 0.27; 95% BCa: 0.10 – 0.44). Similarly, for incongruent stimuli, both patient groups showed elevated RTs compared to HCs, with SCZ typical patients presenting higher RTs than SCZ atypical patients (g = 0.48; 95% BCa: 0.26 – 0.60).

3.3.3 Corsi test

Analysis of the Corsi test revealed significant differences between groups [F (8, 614) = 62.32, p < 0.001, Pillai's Trace = 0.78].

Corsi Forward RTs: Both patient groups exhibited higher RTs compared to HCs. There was no significant difference between SCZ typical and SCZ atypical patients (p = 0.290).

Corsi Backward RTs: Both patient groups had higher RTs than HCs (all p-values < 0.001), and SCZ typical patients exhibited higher RTs than SCZ atypical patients, (Hedges' g = 0.60; 95% BCa: 0.30 – 0.89).

Corsi Forward Span: Both patient groups had lower span than HCs (all p-values < 0.001). Lower span refers to a reduced ability to reproduce sequences of information. However, despite these differences, performance between SCZ typical and SCZ atypical patients was comparable (p = 0.873).

Corsi Backward Span: Both patient groups had lower span than HCs (all p-values < 0.001), with SCZ typical patients showing reduced performance compared to SCZ atypical patients (p < 0.001, g = 0.61; 95% BCa: 0.33 – 0.84).

3.4 Additional analyses

3.4.1 Principal component and clustering analyses

The analysis showed a silhouette score of 0.42 and a Calinski-Harabasz index of 201.06, indicating well-defined clusters. Diagnostic tests confirmed model robustness: the Breusch-Pagan test (p = 0.39) found no heteroscedasticity, and the Durbin-Watson statistic (1.06) showed minimal positive autocorrelation. The Akaike Information Criterion (AIC) of 200.49 suggests a reasonable model fit. Validation through K-fold and leave-one-out cross-validation resulted in low mean squared errors (0.02 and 0.001), verifying the model's accuracy and reliability.

These findings reveal significant variations among the clusters regarding the influence of cytokines on cognitive functions: Cluster 1 (SCZ typical), cluster 2 (HCs), and cluster 3 (SCZ atypical) explain 36%, 13% and 20% of the variance, respectively. The SCZ typical cluster exhibits pronounced negative correlations between elevated IL-1β and lL-6 levels, and cognitive performance (i.e., Flanker, Stroop incongruent, Corsi backward span, r values spanning from -0.50 to -0.59, all p < 0.01), suggesting a severe relationship. In contrast, the atypical SCZ cluster

demonstrates a less severe influence, (r values from -0.40 to -0.54, average p = 0.019). Additionally, the Control cluster, characterized by lower levels of IL-1β, IL-2, and IL-6, displays positive correlations with cognitive outcomes (r = 0.39 to r = 0.60). Negative correlations with BDNF in both typical (r = -0.51) and atypical (r = -0.43) SCZ clusters further underscore the role of this neurotrophic factor. The SCZ typical group, presenting the highest variance, aligns with the expected cognitive variability due to more pronounced pathological manifestations. Conversely, the lower variance in HCs supports the hypothesis of less cognitive disturbance in the absence of pathological conditions.

3.5 Feature importance analysis for group differentiation

We used a Random Forest classifier to differentiate SCZ patients from HCs, training it on predictor variables and target labels (see Supplementary Tables S2 and S3). The classifier achieved 80% overall accuracy, with high precision: 86% for HCs, 84% for typical SCZ, and 64% for atypical SCZ. Specificity was robust: 90% for HCs, 84% for typical SCZ, and 78% for atypical SCZ.

Feature importance analysis, normalized to sum to 100%, identified interleukins and BDNF as key predictors, accounting for approximately 40% of the predictive accuracy (see Supplementary Table S3). Other significant predictors included Flanker, Stroop incongruent, and Corsi backward RTs, highlighting the role of biological markers and cognitive metrics in distinguishing between groups. These findings emphasize the importance of interleukins and cognitive metrics in differentiating SCZ subtypes from HCs, affirming the value of integrating biological and cognitive data in clinical and practical contexts (see Supplementary Table S3 and Supplementary Fig S7).

3.6 Multiple Structural Equation Models (SEMs)

Preliminary analyses unveiled moderate correlations among key cognitive measures: Flanker RTs and Corsi Block Forward Span, Corsi Block Forward RTs, and Stroop Congruent RTs displayed correlation coefficients of 0.42, 0.45, and 0.40, respectively. More pronounced correlations were observed between these cognitive tasks and more challenging cognitive measures. Specifically, Stroop Incongruent RTs correlated strongly with Corsi Block Forward Span, Corsi Block Forward RTs, and Stroop Congruent RTs, showing coefficients of 0.70, 0.74, and 0.80,

respectively. Similar strong correlations were noted with Corsi Block Backward Span and Flanker RTs, highlighting the interconnectedness of these cognitive functions.

Based on these inter-correlations, Corsi Block Forward Span, Corsi Block Forward RTs, and Stroop Congruent RTs were excluded from further analyses to avoid redundancy and enhance model precision. Additionally, an autocorrelation assessment among all predictors, including interleukin levels, and BDNF, indicated no significant autocorrelation, allowing for their inclusion in the SEMs. Before proceeding to group stratification, moderators were rigorously evaluated for their viability within the model. Most variables showed weak associations (e.g., BPRS, PANSS, age) with coefficients not exceeding the 0.05 threshold and displaying high residual volumes.

However, exceptions were noted with variables such as duration of disease, chlorpromazine equivalent, and PANSS total, which exhibited significant associations (Adjusted $R^2 = 0.70$, 0.56, and 0.61 respectively; all $p < 0.001$). Similarly, significant relationships were found for Corsi Block Backward Span, Corsi Block Backward RTs, and Stroop Incongruent RTs, each showing p-values < 0.01 and adjusted $R^2 = 0.57$. Collectively, interleukin levels and BDNF accounted for between 48.9% and 80% of the variance in outcomes, underscoring their significant predictive power in the model (see Supplementary Table S4).

4. Discussion

In this study, we examined the interactions among biological factors, clinical characteristics, and cognitive performance in patients with SCZ receiving typical or atypical antipsychotics. Specifically, we investigated how pro-inflammatory cytokines (IL-1β, IL-2, IL-6) and BDNF relate to cognitive outcomes and how these associations interact with symptom severity and illness duration.

The results revealed moderate to large effect sizes (0.56 to 1.12) across the measurements, indicating significant differences between the SCZ groups and controls. Patients on typical antipsychotics exhibited the most pronounced impairments, while those on atypical antipsychotics also showed similar patterns, but to a lesser extent. Higher antipsychotic doses, longer illness duration, and altered cytokine and BDNF levels emerged as key predictors of cognitive deficits. Clinical and treatment-related factors may influence cognition indirectly through modulation

of neuroinflammatory and neurotrophic pathways. In this model, medication type and illness burden influence biomarker expression, which in turn mediates the severity of cognitive dysfunction. These findings support a biologically mediated pathway linking clinical variables and treatment exposure to cognitive outcomes in SC [30,31].

Marked dysregulation of inflammatory and neurotrophic pathways was observed in n SCZ groups, with significant differences in IL-1β ($\omega^2 = 0.39$), IL-2 ($\omega^2 = 0.50$), BDNF ($\omega^2 = 0.41$), and IL-6 ($\omega^2 = 0.35$). These alterations suggest that disease-related changes extend beyond central neural processes to systemic physiology. Both typical and atypical antipsychotics modulate cytokine levels, and meta-analytic evidence shows that typical agents are associated with increased IL-1β, IL-2, and IL-6, alongside functional changes in the prefrontal cortex and hippocampus [32–34]. Likewise, changes in BDNF associated with antipsychotic use are linked to alterations in neuroplasticity and cognitive performance [35,37,38]. In vitro and preclinical studies demonstrate that elevated cytokines alter synaptic plasticity, hippocampal neurogenesis, and BDNF-dependent signalling, providing mechanistic support for the observed biomarker–cognition associations [39,40]. Although treatment mitigates some dysregulations, both cognitive impairments and biomarker alterations persist over time [3,41].

Cognitive assessments revealed significant impairments in processing speed, working memory, and executive functions in SCZ patients relative to controls ($\omega^2 = 0.40$). Patients receiving typical antipsychotics exhibited more pronounced deficits, particularly in response inhibition and cognitive flexibility, than those receiving atypical antipsychotics (Hedges' g = 0.33). These differences align with known pharmacological distinctions between antipsychotic classes [42,43]. Typical antipsychotics primarily block dopamine D2 receptors, which can lead to severe cognitive side effects. In contrast, atypical antipsychotics also target serotonin receptors, which may result in fewer cognitive impairments [43]. However, cognitive outcomes are strongly influenced by illness severity and medication dose. Evidence indicates a dose-dependent relationship, with higher antipsychotic exposure associated with greater cognitive impairment [44]. Cognitive outcomes were also influenced by illness severity and duration, highlighting the importance of rigorous methodology and control of confounding factors [45].

Multivariate approaches further clarified these relationship. PCA distilled complex data into clusters directly linked to inflammation and cognitive performance,

explaining more than 70% of the total variance [46]. Clustering analyses applied to these components revealed distinct biomarker patterns differentiating SCZ patients, particularly across medication subgroups, from controls based on interleukin levels and BDNF. Random Forest modeling achieved high classification accuracy based on biological and clinical variables, suggesting that multivariate machine-learning approaches may aid early identification and monitoring of disease progression in SCZ SEM analyses further clarified the relationships among biological markers, clinical variables, medication type, and cognitive outcomes. SEM identified the most influential predictors and consistently explained a substantial proportion of variance in cognitive performance, providing insight into how inflammatory and neurotrophic alterations interact with clinical factors to shape cognitive deficits in SCZ [9]. Furthermore, the analyses elucidated how these variables related and were influenced by other variables in the model, such as symptom severity and illness duration, supporting a multilevel model in which clinical burden and treatment exposure modulate biological pathways that contribute to cognitive dysfunction.

Together, these results support integrated models that account for biological, clinical, and cognitive factors. They inform future research and therapeutic interventions aimed at mitigating cognitive impairments and improving patient outcomes. For instance, studies demonstrated that atypical antipsychotics, due to their multi-receptor action, might lead to fewer cognitive deficits compared to typical antipsychotics [47]. Elevated cytokine levels and reduced BDNF were significant predictors of cognitive impairments, with patients on typical antipsychotics showing more pronounced deficits [42,45,48]. This necessitates different approaches to treatment, focusing on personalized strategies to enhance cognitive outcomes and overall quality of life in SCZ patients [13,49].

Our study has limitations. The cross-sectional design limits inference about temporal relationships and causal pathways. Although the sample size was sufficient to detect significant effects, it may not fully capture the heterogeneity of SCZ, particularly less common but clinically meaningful subgroups. Despite controlling for multiple confounders, unmeasured factors, including nonrandomized exposure to typical or atypical antipsychotics, never-medicated individuals, medical or psychiatric comorbidities, and other clinical and metabolic factors, may have influenced the findings. Longitudinal studies with baseline and follow-up assessments that account for medication initiation and treatment duration are needed to clarify the directionality

of associations between biological markers and cognitive outcomes. Finally, replication in independent cohorts is required to strengthen generalizability, although the findings may extend to clinically similar populations.

Future research should aim to address these limitations by expanding sample sizes, ensuring greater demographic and clinical diversity, and integrating multimodal approaches such as genomics, proteomics, metabolomics, and neuroimaging to better characterize the biological basis of cognitive deficits in SCZ Together, these advances may support the development and validation of machine-learning models for early diagnosis and personalized treatment strategies, with the potential to improve clinical outcomes and quality of life for patients.

Acknowledgements: We sincerely thank all volunteers for their time, effort, and willingness to participate in this study. We also express our gratitude to the collaborating institutions in Brazil, Sweden, and Russia for their valuable logistical and technical support throughout all phases of data collection and analysis. Special thanks are extended to the research coordinators, laboratory staff, and clinical teams whose commitment made this collaborative work possible.

Disclosure: The authors report no conflicts of interest.

Data statement: The data analyzed during the current study are available from the corresponding author on reasonable request. Additional methodological details and extended analyses are provided in the Supplementary Materials.

Ethical statements: This study adhered to the principles of the Declaration of Helsinki for research involving human participants and received ethical approval from the Ethics Committee of a Brazilian public university (CAAE: 42983821.6.0000.5188), the Institutional Review Board of the Svenskagier Neurology Institute (protocol SB-2024-04-002), and the Ethics Committee of Saint Petersburg State University (SPbU). Participation was voluntary, and all participants provided written informed consent prior to inclusion in the study. The capacity of each participant to provide informed consent was assessed, and all procedures complied with local regulatory and ethical guidelines.

Funding Statement: Research conducted in Russia was supported by St. Petersburg State University (ID 140835307. Neurobiological markers of cognitive impairment in schizophrenia). The Swedish arm of this research was supported by the SRC (2022-0299) and NEU (2024/002-0012). The Brazilian component was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; grants 305258/2019-2 to NS and 163780/2020-0 to TF) and by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES; grant 88887.807745/2023-00 to TF).

CRediT authorship contribution statement: TF: Conceptualization, Methodology, Writing – original draft, Formal analysis, Data curation, Investigation, and Visualization. ZD: Conceptualization, Methodology, Software, Resources, Data curation, and Project supervision. FMF: Writing – original draft and Data curation. AVK: Writing – original draft and Data curation. GSS: Writing – original draft and Data curation. IIS: Conceptualization, Methodology, Writing – original draft, Investigation, and Project supervision. MECO: Writing – original draft and Data curation. LND: Conceptualization, Methodology, Writing – original draft, Formal analysis, Data curation, Investigation, Visualization, and Project supervision. NAS: Conceptualization, Methodology, Writing – original draft, Data curation, Investigation, Visualization, and Project supervision. All authors reviewed and approved the final manuscript.

Edited by: Dr. Raffael Massuda

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Supplementary Material

Section 1 – Task Implementation

1. Models, estimates, and parameters for analyses

In the following sections, we will dissect models that we utilized in the study, detailing the choices, validations, parameters, and justifications for specific preferences, involving the logic of the analysis. All data will be presented transparently. Therefore, we can debate the choices, albeit in another location and from a different perspective. We hope to contribute to this aspect in some way.

2. Overview of the assumptions for analysis

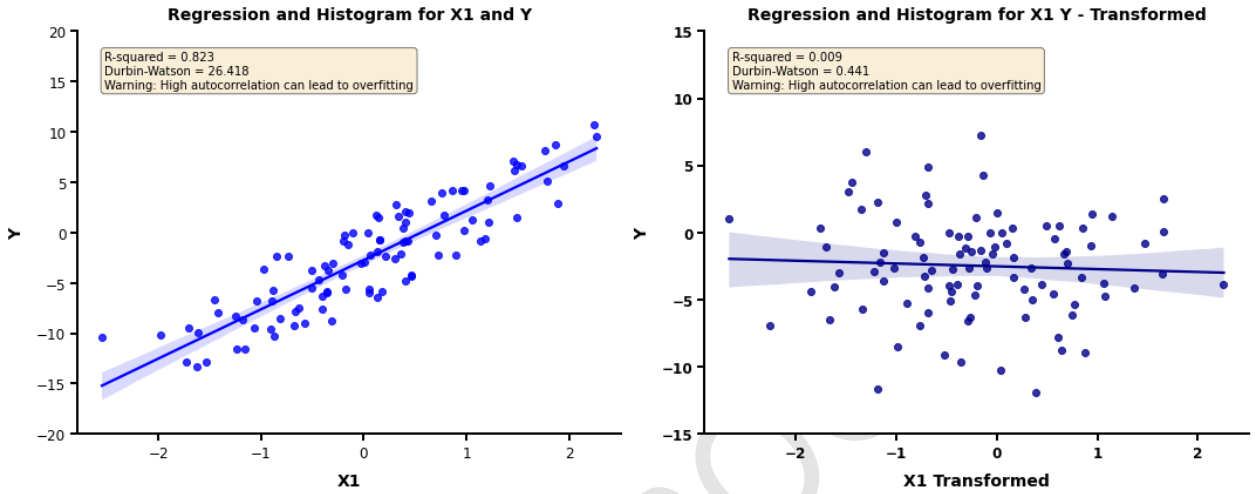
Population-based studies meticulously analyze an extensive array of demographic and clinical variables, ranging from straightforward measures like age and gender to more intricate factors such as socio-economic status and pre-existing health conditions. However, despite the thorough examination of these variables, the predictive power of certain demographic factors often exhibits inconsistency across studies. For instance, Griffiths et al. (2021) conducted a meta-analysis, revealing that variables like occupational status and geographic location frequently lack consistent predictive value across different research endeavors. This discrepancy underscores the complexity inherent in modeling disease and treatment outcomes. It emphasizes the critical need for caution when interpreting study findings and to account for a diverse range of potential confounding factors. By considering the interplay between various demographic and clinical variables, researchers can develop more robust models and gain deeper insights into the factors influencing health outcomes.

Incorporating every demographic variable without discrimination can cause model bloat and may lead to redundant complexity. The process of simplifying models involves excluding variables that fail to provide consistent predictive outcomes. Such a strategy was supported by findings from Griffiths et al. (2021) and Okhuijsen-Pfeifer et al. (2020), who demonstrated that removing these variables could lead to clearer and more interpretable results. Reducing model complexity helps manage data variability and prevent issues like overfitting, thereby enhancing the robustness of the findings. This approach ensures that the analyses are not only more efficient but also more accurate.

When evaluating the reliability of reported effects, it is fundamental to consider the width of confidence intervals (CIs). For example, an effect size of 0.48 with CIs ranging from 0.27 to 0.76 suggests a moderate degree of uncertainty about the estimate. However, confidence intervals that cross zero, such as from -0.72 to 0.14, indicate significant uncertainty and potentially challenge the credibility of the findings. Properly understanding and interpreting these intervals is essential in the scientific process, particularly for assessing the reliability and variability of estimates. Reports often overlook crucial statistical considerations, such as autocorrelation, multicollinearity, and the risk of overfitting.

Autocorrelation occurs when residuals from one observation are correlated with residuals from another, violating the assumption of independence typically required in regression analyses. This can lead to inflated models and misleading significance tests. Multicollinearity involves high correlations among predictor variables, which can make it

difficult to discern the individual effects of predictors on the outcome, often resulting in unstable coefficient estimates. Overfitting happens when a model is excessively complex, capturing the noise along with the signal in the dataset, which reduces its ability to generalize to new data (Subramanian & Simon, 2013).



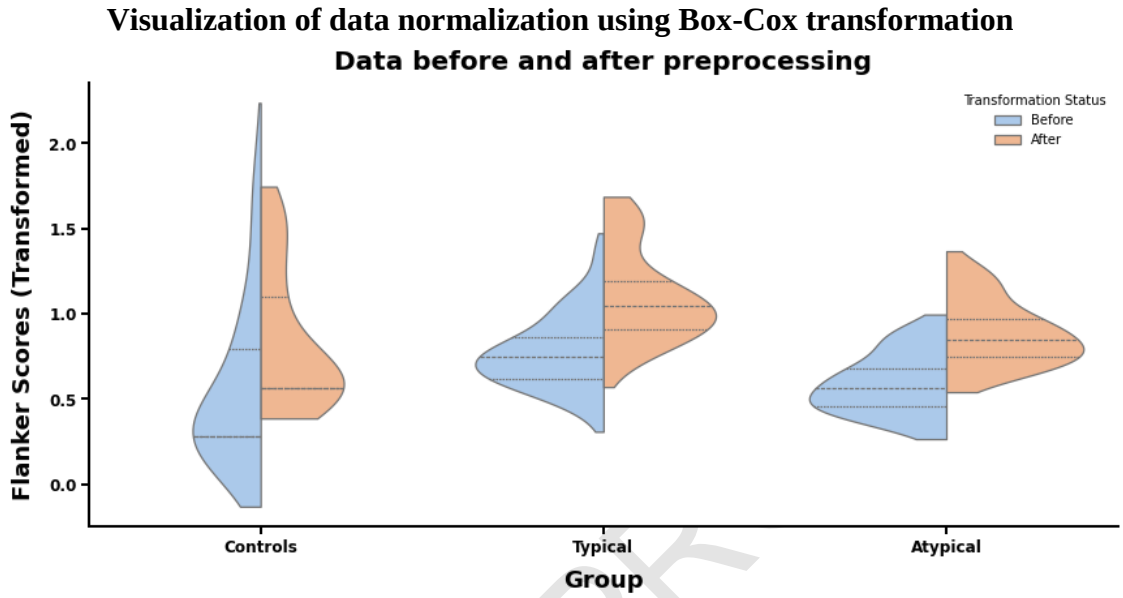
The left graph shows a strong positive relationship between X1 and Y, with about 82% of Y's variability explained by changes in X1. However, the exceedingly high Durbin-Watson statistic of 26 signals a concerning level of autocorrelation in the residuals, implying a strong correlation between the errors of adjacent observations. This violates the assumption of independence and suggests potential issues with the model's reliability and predictive accuracy. Conversely, the right plot displays a weak relationship between X1 and Y, with only about 0.8% of Y's variance explained. While the Durbin-Watson statistic (i.e., 0.442) suggests less autocorrelation, it still poses challenges to model accuracy. Autocorrelation undermines the assumption of independence in regression analysis and can lead to biased parameter estimates and inflated standard errors. Addressing autocorrelation through techniques such as including lagged variables or using autoregressive models is essential for improving the precision and reliability of outcomes.

Addressing these issues is fundamental to ensuring the accuracy of model predictions and maintaining the integrity of the data. Before exploring the detailed methodology of our model, it is important to outline the strategies we employed to enhance the reliability and validity of our findings. By systematically addressing these issues, our analysis aims to provide a more accurate and reliable interpretation of the data, ensuring that our findings can be confidently applied to real-world contexts. This rigorous approach to data analysis underscores and enhances the credibility of the outcomes. These strategies are designed to mitigate the statistical challenges previously mentioned and ensure rigorous analysis (Lee, 2020).

3. Data preprocessing and model build

Initially, we examined the data for missing or extreme values. We assessed the distributional properties of the variables by examining their kurtosis and skewness. Outliers were identified using Z-scores and quartiles, with data points exceeding ±2 standard deviations from the mean within the quartile range flagged as potential outliers. For

categorical variables, after mapping, we refactored them for improved representation and analysis (Lee, 2020). To illustrate the preprocessing steps, we present data from our pilot study using the Flanker task. Nevertheless, we meticulously examined all variables to determine whether transformation was necessary or not.



The provided violin plots illustrate the distribution of Flanker RTs (transformed) before and after applying the Box-Cox transformation with a power parameter. To optimize the skewness reduction, the lambda parameter for the Box-Cox transformation was determined using maximum likelihood estimation (MLE). The analysis tested lambda values ranging from -2 to 2 at 0.1 intervals, finding that a lambda of 0.5 maximized the log-likelihood function, indicating the most favorable transformation for normalizing the data (Riani et al., 2023).

Initially, the data showed a considerable right skewness and visible outliers, particularly noticeable in the left violins, with long tails extending from the median. Following the transformation, the graphs reveal a notably more compact and symmetric distribution. The tail lengths are reduced, and the data points are more tightly clustered around the median. This indicates a reduction in skewness and a uniform spread, which are preferable for many statistical procedures. The transformation efficiently minimized the influence of outliers and brought the distribution closer to normality. After comparing the data before and after transformation, we observed no significant differences. This ensures that the original data integrity remains intact while improving its suitability for further analysis.

4. Model selection

Initial models were selected based on the existing literature identifying key biomarkers, and demographic variables known to influence cognitive functioning. Variables such as age, education level, and levels of certain cytokines were chosen as predictors based on their established associations with cognitive impairment in schizophrenia. In the initial phase of model development, we implemented all available biological markers and cognitive

outcomes to establish a foundational model. Following the selection of variables, we quantitatively assessed the initial model using established criteria. This included measures such as the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) to evaluate model fit. Additionally, we employed Leave-P-Out Cross-Validation (LPOCV) to ensure the robustness of our model. After initial assessment, we observed skewness and kurtosis values of 1.142 and 1.882, respectively. However, following the application of the Box-Cox transformation, these values were significantly improved to 0.589 and -0.675. This transformation proved more effective than alternative methods like bootstrapping resampling, stabilizing the data distribution and enhancing the reliability of our model.

Biomarkers were initially placed in the predictive model, indicating a robust and positive association with worsening cognitive outcomes as evidenced by a coefficient of 10.36. The confidence interval for this estimate, spanning from 4.72 to 27.38, underscores a significant impact, albeit with considerable variability that might stem from individual differences or measurement errors. This initial model suggests that increases in biomarker levels are closely linked with cognitive decline.

After the integration of demographic and clinical variables into the model, the predictive power for worsening cognitive outcomes increased, with the coefficient rising to 12.54. This increase may signify either a heightened influence of biomarkers when considered alongside these additional variables or the added explanatory capacity provided by demographics and clinical history. The narrower confidence interval of 9.72 to 18.02 after including these variables provides a more precise estimate, reinforcing the strength of the association. This enhanced model highlights the intricate interplay between biological markers and broader demographic and clinical contexts, illustrating how these factors collectively drive the prognosis of cognitive outcomes more accurately than when biomarkers are considered in isolation.

Section 2 – Procedures

1. Stimuli and Apparatus

The stimuli were presented on a 21.5" Apple iMac monitor (MHK23BZ/A) with a display resolution of 1920 × 1080 pixels and a refresh rate of 60 Hz. All measurements were performed with binocular vision. The CS-100A Chroma Meter (Konica Minolta, Japan) was used for the gamma-correction. Cognitive measures occurred using MATLAB. Participants were encouraged to take a break whenever they wanted.

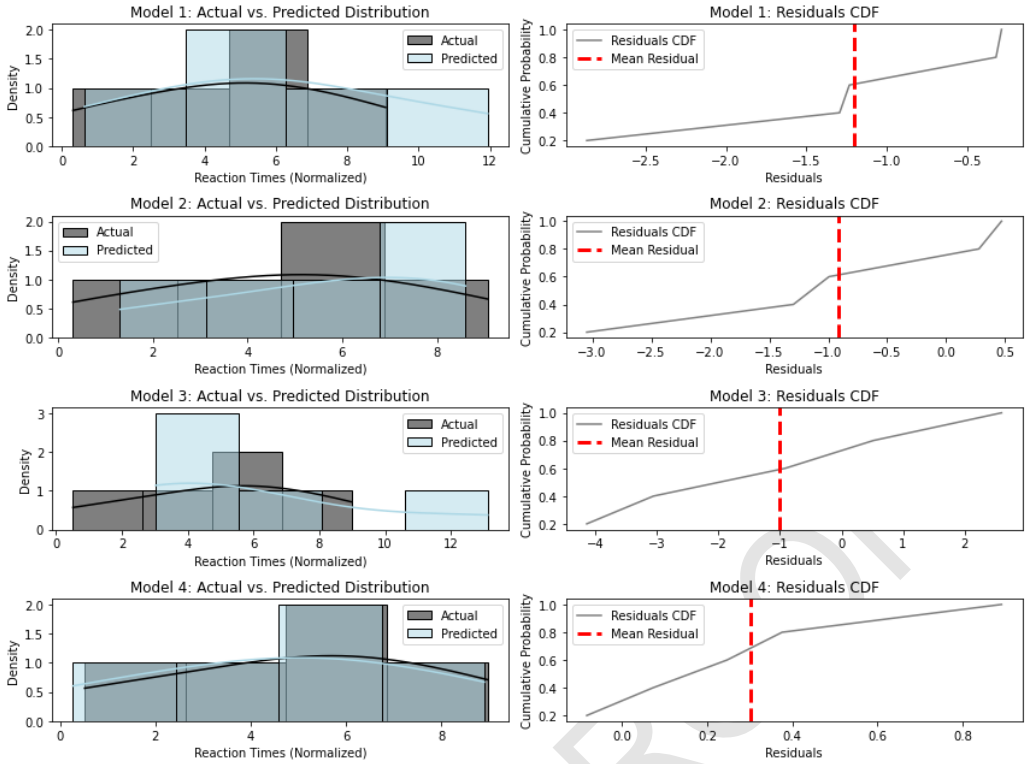
2. Procedures

In our testing protocol, we mitigated potential confounders such as individual differences in psychomotor velocity to ensure that our measurements accurately reflect cognitive performance. Participants underwent a baseline RT assessment composed of four blocks, each designed with task variations like shape matching and target discrimination to prevent anticipatory responses and maintain engagement. We then adjusted these baseline RTs using percentile rankings to normalize for individual differences in psychomotor efficiency.

Subsequent Bayesian hierarchical models progressively incorporated these adjustments: Model 1 provided a basic analysis of unadjusted RTs, serving as a control. Model 2 employed z-score transformations, normalizing RTs against the collected baseline to reduce variability due to individual differences. Model 3 further refined this approach by implementing adjustments based on the baseline data to accommodate for the expected variability in response dynamics—how quickly or slowly participants responded. Model 4 was the culmination of these refinements, employing percentile rankings to capture a holistic view of response agility within the Bayesian framework

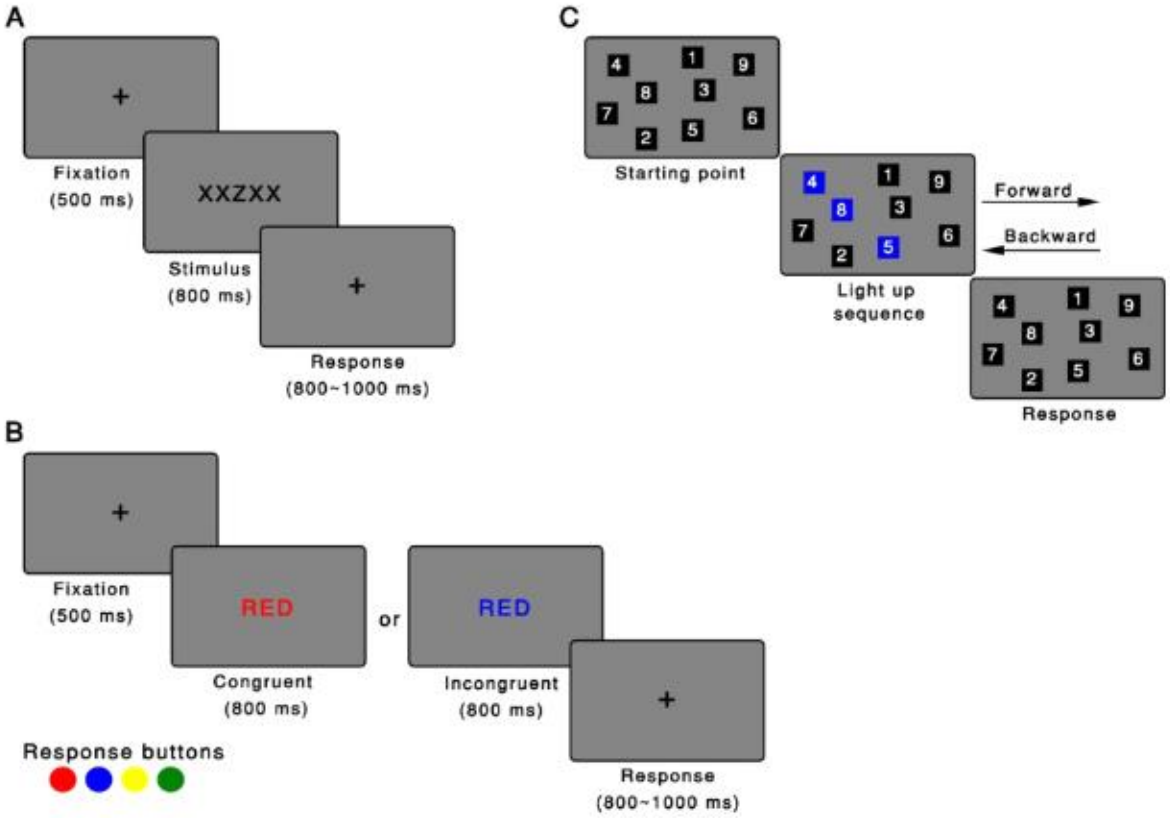
Model 4 demonstrated better fit and precision in our analyses, as evidenced by enhanced performance in posterior predictive checks. The robustness of the model was confirmed through metrics such as lower WAIC scores (Model 1 = 267, Model 2 = 290, Model 3 = 270, Model 4 = 212), higher ESS values, indicating its effectiveness in capturing the true cognitive effects, free from psychomotor variability.

In our testing protocol, we mitigated potential confounders such as individual differences in psychomotor velocity to ensure that our measurements accurately reflect cognitive performance. Participants underwent a baseline RT assessment composed of four blocks, each designed with task variations like shape matching and target discrimination to prevent anticipatory responses and maintain engagement. We then adjusted these baseline RTs using percentile rankings to normalize for individual differences in psychomotor efficiency.



The provided graphs analyze four distinct models within a Bayesian hierarchical framework. On the left, histograms comparing the actual values to the predicted ones. A closer overlap between these histograms—where actual values are depicted in dark shadowed and predicted values in light blue—demonstrates a better fit, indicating that the model has a higher accuracy in predicting the observed data. On the right, the graphs show the cumulative distribution function for the residuals, which are the differences between the predicted and actual values. This setup allows us to visually gauge the accuracy and reliability of each prediction, emphasizing the importance of alignment between predicted and actual values, as well as a balanced distribution of residuals for robust model performance in a Bayesian context.

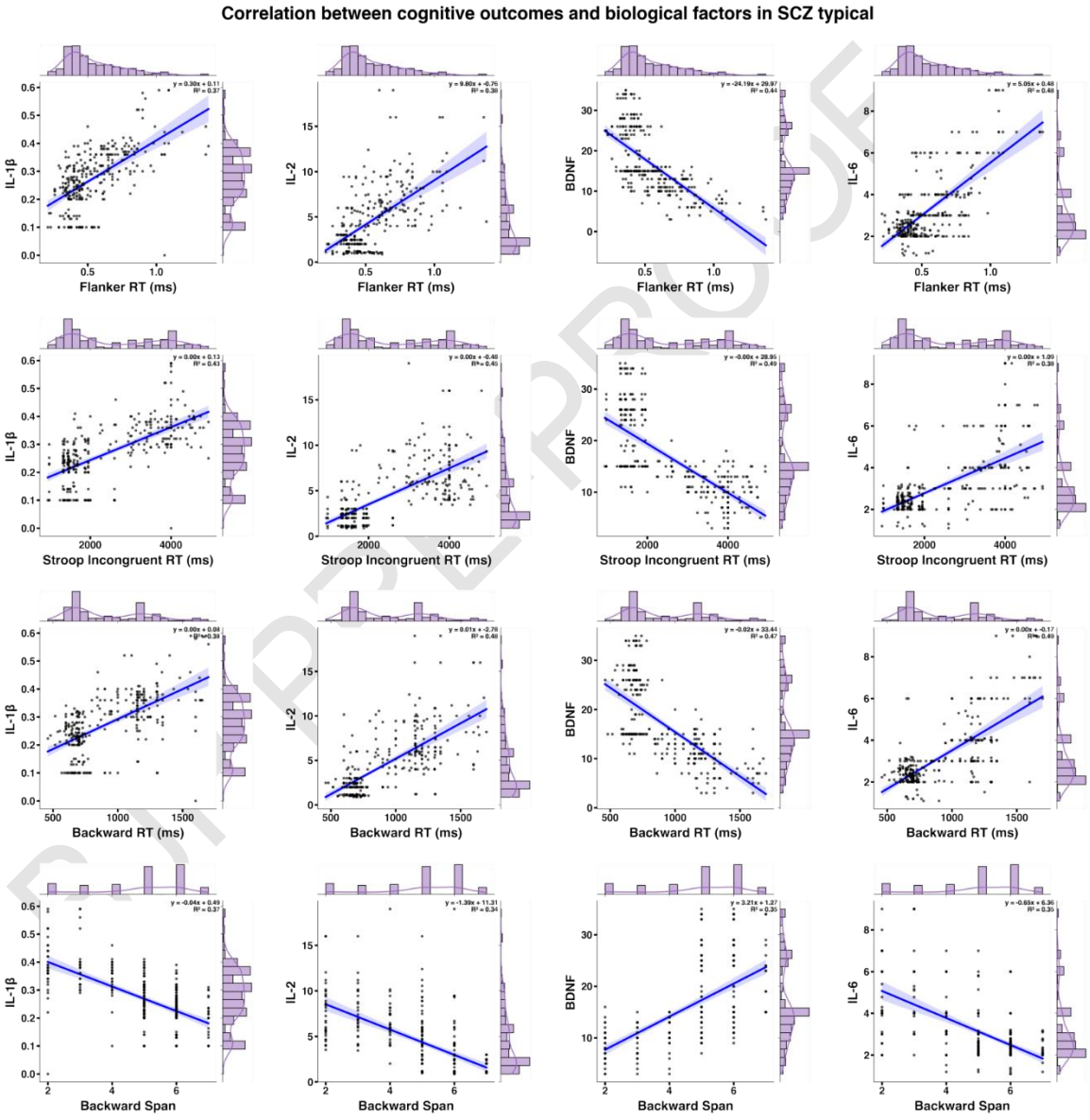
Fig. S1. Schematic representation of the cognitive tests. Flanker task (A), Stroop test (B) and Corsi test (C).



Section 3 – Additional Analyses

1. Correlation analyses between the cognitive outcomes and biomarkers

Fig. S2 – Interrelated data examination using scatter plots for schizophrenia typical patients. Each column represents interleukins and neurotrophic factors as predictor variables, while each row indicates cognitive task outcome variables. On the diagonal, histograms represent the distribution of each variable, with vertical lines marking the mean and standard deviation, providing insight into the central tendency and variability. Best-fit regression lines in the scatter plots illustrate the degree of linear relationship between the variables.



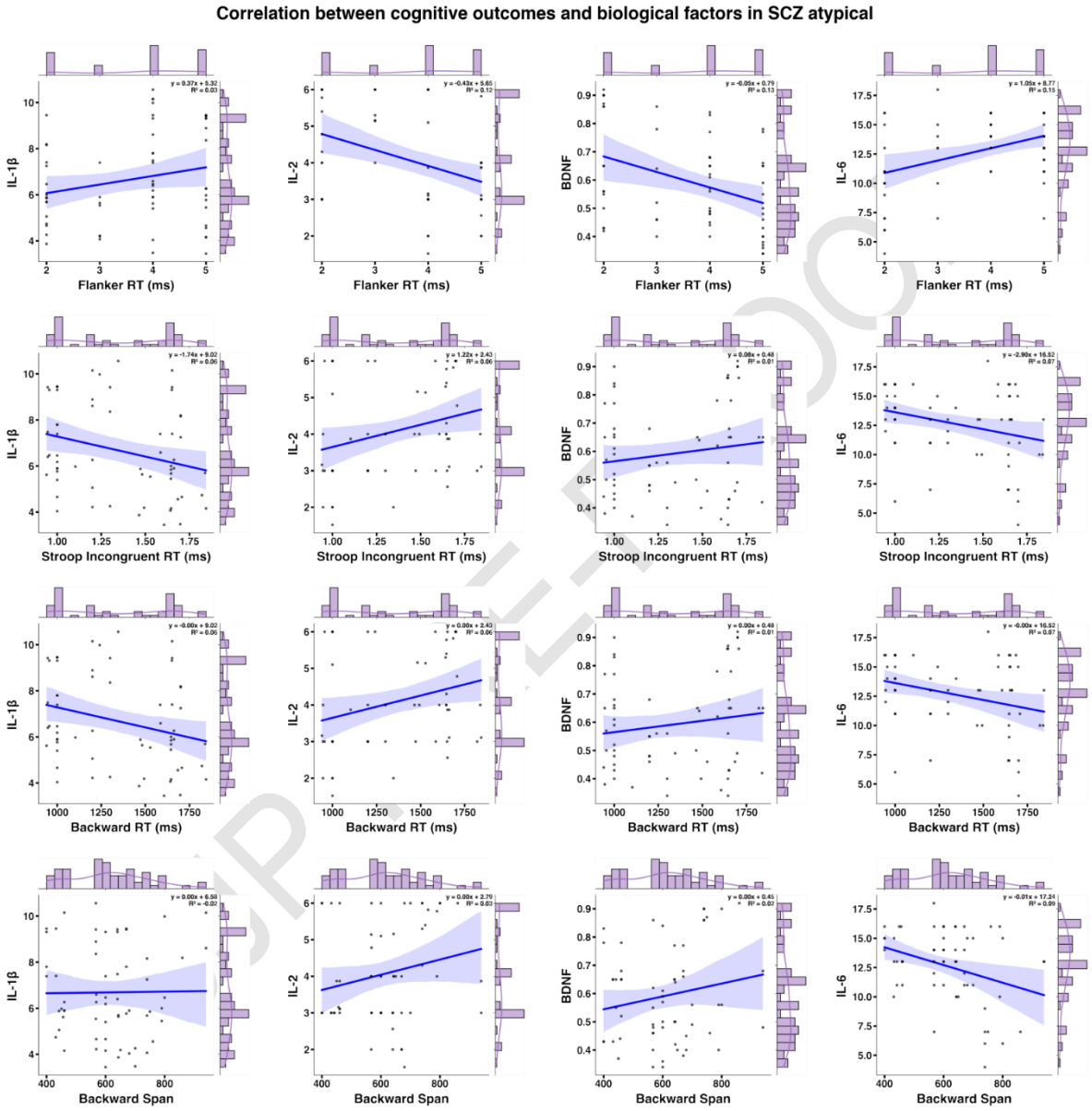
7. Overall interpretation

In examining cognitive task outcomes and biological markers, we observed variable RTs across tasks like the Flanker, Stroop, and Corsi Backward RT and Backward Span. The moderate correlation coefficients between these tasks not only indicate a degree of predictability but also highlight the complex nature of cognitive mechanisms. The moderate

adjusted R^2 values indicates the potential for investigation into other contributing factors, which could enrich our understanding of cognitive dynamics. The skewness noted in RT distributions, while commonly seen in cognitive testing, offers a realistic observation into the variability of human processing speeds and emphasizes the need for continuous investigation that can accommodate such complexities.

Furthermore, the relationship between working memory capacity and biological markers like interleukins and BDNF, though subtle, opens new avenues for exploring how cognitive functions might be intertwined with biological states. These findings – aligned – to the other analyses encourage studies to consider and delve into the biological underpinnings of cognitive processes, potentially leading to breakthroughs in how we understand and enhance cognitive processes.

Fig. S3 – Interrelated data examination using scatter plots for schizophrenia atypical patients. Each column represents interleukins and neurotrophic factors as predictor variables, while each row indicates cognitive task outcome variables. On the diagonal, histograms represent the distribution of each variable, with vertical lines marking the mean and standard deviation, providing insight into the central tendency and variability. Best-fit regression lines in the scatter plots illustrate the degree of linear relationship between the variables.



Overall interpretation

These findings explore the relationships between cognitive performance, specifically RTs in Flanker, Stroop Incongruent, and Corsi Backward tasks, alongside Backward Span. The R^2 values ranged to moderate, indicating various levels of linear association between these variables. Although this variability might seem to limit predictive accuracy, it actually highlights unique patterns in the atypical schizophrenia group.

Furthermore, the presence of skewness in the data, while notable, didn't undermine the validity of the findings. It highlights the need for methods that can manage complex data, a typical requirement in RT studies. Despite this skewness, the lack of extreme outliers maintains the reliability of the cognitive assessments used in this study. In summary, these graphs offer insights into the relationships between different cognitive tasks. The observed correlations indicate the presence of shared cognitive processes that affect performance across these tasks, although they do not suggest a single cognitive ability dictates performance across all tasks. This underscores the diverse nature of cognitive functioning, involving multiple cognitive skills across various tasks.

Employing certain models, such as regression analyses, has its limitations in capturing the full complexity of such data. While these models are undoubtedly useful, they may not sufficiently address the complex understanding of conditions like SCZ. This suggests the need for a broader, more detailed approach that utilizes advanced methods and deeper analyses to better understand and address the complexities of SCZ. Such approaches lay the foundation for more comprehensive examinations of the neurocognitive aspects of SCZ, leading to personalized interpretations and interventions.

Fig. S4 – Correlation matrix overview. The upper matrix displays correlations between demographic characteristics and cognitive outcomes, while the lower matrix examines the correlations between demographic factors and biological markers for both schizophrenia groups. The strength of the correlation is indicated by the intensity of the color, with deeper shades representing stronger associations. *** $p < 0.001$, ** $p < 0.01$

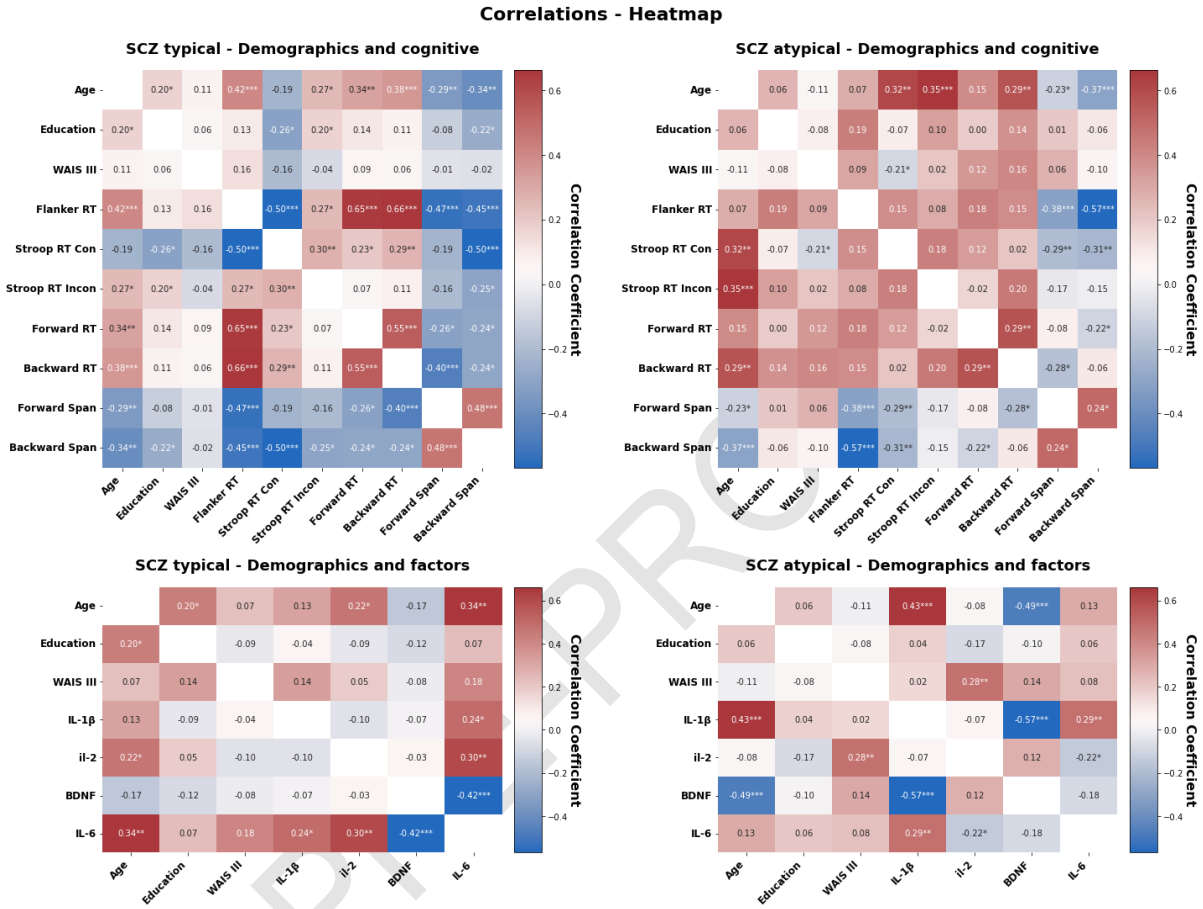
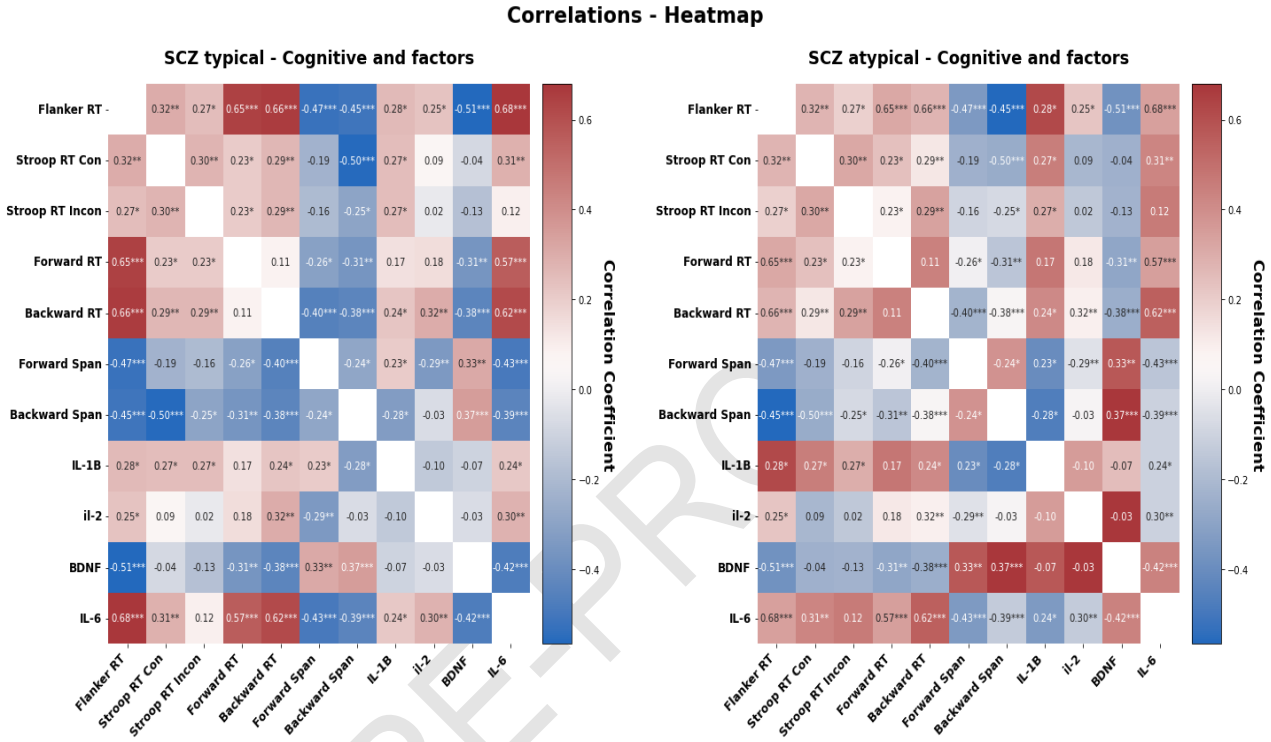


Fig. S5 – Correlation heatmap in schizophrenia patients. The matrix on the left maps the correlation coefficients between cognitive functions and biological markers for schizophrenia patients on typical medication. The corresponding matrix on the right presents the analysis for those on atypical medication. The strength of color reflects the degree of correlation, with more intense colors indicating stronger relationships. *** $p < 0.001$, ** $p < 0.01$



Multiple regression analyses between IL-1β, IL-2, BDNF, IL-6, and the cognitive tasks for schizophrenia typical patients

1. Flanker Task

The multiple regression model was significant ($p < 0.001$), explaining 64% of the variance in performance outcomes (Adjusted $R^2 = 0.64$; $\omega^2 = 0.618$). Additionally, model fit statistics indicate that the regression model adequately captures the relationship between the predictors and performance outcomes, with a root mean square error (RMSE) of 0.12 and a mean absolute error (MAE) of 0.09. It is important to note that positive correlations indicate that higher levels of interleukins, or lower levels of BDNF, are associated either positively or negatively with increased RT, reflecting a reduction in performance.

Notably, medication dosage exhibited a robust positive association with task performance [$\beta = 0.44$, SE = 0.003, $p < 0.001$; 95% CIs (0.438 to 0.442)], as did the duration of the disease [$\beta = 0.50$, SE = 0.056, $p < 0.001$; 95% CIs (0.444 to 0.556)]. Among biological markers, elevated levels of IL-1β [$\beta = 0.36$, SE = 0.019, $p < 0.001$; 95% CIs (0.332 to 0.388)], IL-6 [$\beta = 0.58$, SE = 0.009, $p < 0.001$; 95% CIs (0.561 to 0.599)], and IL-2 [$\beta = 0.32$, SE = 0.015, $p = 0.009$; 95% CIs (0.305 to 0.335)] align with the hypothesis suggesting a potential influence of systemic inflammation on cognitive functions. Additionally, lower BDNF levels were associated with decreased performance [$\beta = -0.20$, SE = 0.006, $p < 0.001$; 95% CIs (-0.212 to -0.188)], further supporting the hypothesis regarding the impact of systemic inflammation on cognitive function.

2. Stroop Incongruent

The multiple regression analysis of the Stroop Incongruent condition was highly significant ($p < 0.001$), explaining 38.2% of the variance in performance outcomes (Adjusted $R^2 = 0.382$; $\omega^2 = 0.367$). Model fit statistics confirm the effectiveness of the regression model in capturing the relationship between predictors and performance outcomes, as indicated by a RMSE of 0.19 and a mean absolute error of 0.27.

The analysis revealed that higher levels of interleukins are associated with increased reaction times, suggesting a decline in cognitive performance. Similarly, lower levels of BDNF correlate with poorer outcomes. The dosage of medication showed a significant positive correlation with reduced performance, with a substantial regression coefficient [$\beta = 0.0034$, SE = 0.000, $p < 0.001$; 95% CIs (0.002 to 0.004)]. The duration of the disease also correlated positively with worsened performance [$\beta = 0.1171$, SE = 0.019, $p < 0.0001$; 95% CIs (0.080 to 0.154)].

Regarding biological markers, elevated levels of IL-1β [$\beta = 0.9626$, SE = 2.201, $p = 0.663$; 95% CIs (-3.414 to 5.339)] and IL-6 [$\beta = 0.1003$, SE = 0.045, $p = 0.029$; 95% CIs (0.010 to 0.190)] were noted. These findings align with the hypothesis that systemic inflammation could impact cognitive functions. Conversely, BDNF levels were negatively associated with performance [$\beta = -0.1369$, SE = 0.058, $p = 0.021$; 95% CIs (-0.253 to -0.021)], further supporting the idea of systemic inflammation's influence on cognitive abilities.

3. Corsi Backward RT

The multiple regression model analyzing the Corsi Backward RT demonstrated high significance ($p < 0.001$), explaining 56.7% of the variance in performance outcomes (Adjusted $R^2 = 0.567$; $\omega^2 = 0.586$). The model fit statistics, including a RMSE of 0.27 and a MA of 0.30, confirm that the regression model adequately captures the relationship between the predictors and performance outcomes.

the analysis indicates that higher levels of interleukins are associated with increased reaction times, implying a decline in performance. Conversely, lower levels of BDNF are linked to worsened outcomes. Medication dosage shows a significant positive correlation with reduced performance, evidenced by a notable regression coefficient [$\beta = 0.176$, SE = 0.092, $p = 0.008$; 95% CIs (0.050 to 0.328)]. Interestingly, the duration of the disease did not correlate significantly with worse performance [$\beta = 4.176$, SE = 2.102, $p = 0.088$; 95% CIs (0.720 to 8.986)].

Among biological markers, elevated levels of IL-1β [$\beta = 0.053$, SE = 0.003, $p < 0.001$; 95% CIs (0.026 to 0.080)], IL-2 [$\beta = 0.162$, SE = 0.090, $p = 0.048$; 95% CIs (0.004 to 0.324)], and IL-6 [$\beta = 0.040$, SE = 0.028, $p = 0.014$; 95% CIs (0.009 to 0.072)] were observed. These findings align with the hypothesis suggesting that systemic inflammation may influence cognitive functions. Additionally, BDNF levels showed a negative association with performance [$\beta = -0.014$, SE = 0.030, $p < 0.001$; 95% CIs (-0.253 to -0.021)], aligning with the hypothesis suggesting a potential influence of systemic inflammation on cognitive functions.

4. Corsi Backward Span

The multiple regression model analyzing the Corsi Backward Span demonstrated high significance ($p < 0.001$), explaining 41.4% of the variance in performance outcomes (Adjusted $R^2 = 0.414$; $\omega^2 = 0.382$). Model fit indicators, including a RMSE of 0.27 and a MA of 0.30, confirm that the regression model effectively captures the relationship between the predictors and performance outcomes.

The analysis revealed that higher levels of interleukins are associated with increased reaction times, indicating a decline in performance. Conversely, lower levels of BDNF are linked to worsened outcomes. Medication dosage demonstrated a significant positive correlation with reduced performance, evidenced by a notable regression coefficient [$\beta = 0.102$, SE = 0.018, $p < 0.001$; 95% CIs (0.067 to 0.140)] and the duration of the disease also showed a strong correlation with worse performance [$\beta = 0.129$, SE = 0.019, $p < 0.001$; 95% CIs (0.092 to 0.166)].

Among biological markers, elevated levels of IL-1β [$\beta = 0.074$, SE = 0.037, $p = 0.049$; 95% CIs (0.016 to 0.189)], IL-2 [$\beta = 0.126$, SE = 0.030, $p = 0.020$; 95% CIs (0.067 to 0.184)], and IL-6 [$\beta = 0.122$, SE = 0.012, $p < 0.001$; 95% CIs (0.099 to 0.146)] were observed. These findings align with the hypothesis suggesting that systemic inflammation may influence cognitive functions. Additionally, BDNF levels were negatively associated with performance [$\beta = -0.168$, SE = 0.040, $p = 0.004$; 95% CIs (-0.246 to -0.090)], aligning with the hypothesis suggesting the potential role of systemic inflammation in cognitive function reduction.

Multiple regression analyses between IL-1β, IL-2, BDNF, IL-6, and the cognitive tasks for schizophrenia atypical patients

1. Flanker Task

The multiple regression model demonstrated significant results ($p < 0.001$), explaining 26.4% of the variance in performance outcomes (Adjusted $R^2 = 0.264$; $\omega^2 = 0.255$). The model's adequacy is further supported by the root mean square error (RMSE) of [RMSE value] and a mean absolute error (MAE) of [MAE value]. Analysis reveals that higher levels of interleukins or lower levels of BDNF correlate with increased flanker scores, indicating a decline in cognitive performance

The analysis highlighted a substantial negative correlation between medication dosage and task performance [$\beta = -2.805$, SE = 0.804, $p < 0.001$; 95% CIs (-4.438 to -1.229)], suggesting that higher medication dosages are associated with poorer outcomes. Similarly, longer disease duration also negatively impacted performance [$\beta = 0.322$, SE = 0.102, $p = 0.004$; 95% CIs (0.122 to 0.522)].

Biological markers showed significant associations as well. IL-1β [$\beta = 0.149$, SE = 0.067, $p = 0.030$; 95% CIs (0.020 to 0.284)], IL-2 [$\beta = 0.200$, SE = 0.092, $p = 0.02$; 95% CIs (0.103 to 0.380)], and IL-6 [$\beta = 0.112$, SE = 0.048, $p = 0.023$; 95% CIs (0.016 to 0.219)] were all positively correlated with increased reaction times, aligning with the hypothesis that systemic inflammation negatively affects cognitive functions. Furthermore, lower BDNF levels were significantly associated with decreased performance [$\beta = -1.311$, SE = 0.413, $p = 0.002$; 95% CIs (-2.137 to -0.500)], reinforcing the idea that systemic inflammation can adversely affect cognitive functions.

2. Stroop Incongruent

The multiple regression model demonstrated significant results ($p < 0.001$), explaining 40% of the variance in performance outcomes (Adjusted $R^2 = 0.379$; $\omega^2 = 0.380$). The model is further supported by an RMSE of 0.724 and a MA of 0.799. The analysis identified that higher levels of IL-6 are associated with increased RTs, suggesting a decline in cognitive performance.

The results indicate a strong negative correlation between CPZ (chlorpromazine equivalent) dosage and task performance [$\beta = -3.120$, SE = 0.801, $p < 0.001$; 95% CIs (-4.794 to -1.588)], indicating that higher dosages of CPZ are linked with poorer outcomes. Furthermore, IL-6 was found to negatively influence performance [$\beta = 0.1235$, SE = 0.044, $p = 0.007$; 95% CIs (0.035 to 0.212)], aligning with the hypothesis that systemic inflammation can have complex effects on cognitive functions.

However, the duration of illness, IL-1β, IL-2, and BDNF did not show significant effects in this model. This suggests that their influence on cognitive performance might be mediated by more complex interactions or latent variables not captured in the current analysis. This indicates a possibility that linear regression may not adequately model the relationships and underlying mechanisms affecting cognitive function. Consequently, exploring these relationships using structural equation modeling (SEM) could provide deeper insights, as SEM allows for the analysis of multiple dependent relationships simultaneously and can account for latent constructs that might be influencing observed outcomes.

3. Corsi Backward RT

The multiple regression model demonstrated significant results ($p < 0.001$), explaining 40% of the variance in performance outcomes (Adjusted $R^2 = 0.28$; $\omega^2 = 0.244$). The model is further supported by an RMSE of 4.922 and a MA of 40.54. These values, typical for cognitive performance measures involving time, suggest that the estimates are reliable for this type of analysis. The analysis shows that elevated levels of biological markers correlate with increased RTs, indicating a decline in cognitive performance.

The analysis shows that higher levels of biological markers are linked to increased RTs, indicating a reduction in cognitive performance. Specifically, IL-1β was associated with significantly reduced performance [$\beta = 4.297$, SE = 1.190, $p = 0.022$; 95% CIs (1.965 to 6.629)], and IL-2 also led to increased backward time [$\beta = 5.162$, SE = 2.074, $p = 0.046$; 95% CIs (1.096 to 9.227)], suggesting an adverse impact on cognition. IL-6 followed a similar pattern [$\beta = 8.397$, SE = 3.613, $p = 0.044$; 95% CIs (1.316 to 15.478)], reinforcing the negative influence of these higher levels of cytokines on cognitive performance.

Furthermore, the analysis revealed a strong negative correlation between CPZ dosage and task performance [$\beta = -3.210$, SE = 0.801, $p < 0.001$; 95% CIs (-4.780 to -1.640)], indicating that higher dosages of CPZ are associated with poorer cognitive outcomes. However, the duration of illness, IL-1β, IL-2, and BDNF did not demonstrate significant effects in this model, indicating that their influence may be less direct or obscured by other interacting factors within the context of this study. This suggests the potential utility of SEM to better capture the complex interactions and latent variables potentially influencing these outcomes.

4. Corsi Backward Span

The multiple regression model demonstrated significant results ($p < 0.01$), explaining 42.3% of the variance in performance outcomes (Adjusted $R^2 = 0.371$; $\omega^2 = 0.244$). The model is further supported by an RMSE of 4.664 and a MA of 3.660, which are consistent with typical values for cognitive performance measures involving time, indicating reliable estimates.

The regression analysis, adjusting for predictors, provided insights into how biochemical markers influence cognitive performance as measured by backward span task. Notably, IL-1β was linked to a significant decrease in performance [$\beta = -5.140$, SE = 0.747, $p < 0.001$; 95% CIs (-7.150 to -3.202)]. Similar adverse impacts were observed for IL-2 [$\beta = -8.034$, SE = 1.647, $p = 0.002$; 95% CIs (-12.030 to -4.030)] and IL-6 [$\beta = -7.180$, SE = 3.122, $p = 0.044$; 95% CIs (-14.200 to -1.020)], which also demonstrated notable reductions in cognitive performance.

Additionally, lower levels of BDNF were linked with a decrease in performance [$\beta = -2.920$, SE = 1.206, $p < 0.001$; 95% CIs (-5.320 to -0.501)]. The analysis also highlighted a substantial negative correlation between chlorpromazine (CPZ) dosage and task performance [$\beta = -2.067$, SE = 0.700, $p = 0.008$; 95% CIs (-3.400 to -0.463)], suggesting that higher dosages of CPZ are associated with reduced cognitive outcomes.

These findings underscore the significant influence of systemic inflammation and biological changes on cognitive functions, as evidenced by the relationships between cytokine levels, BDNF, dosage, and cognitive performance. This suggests that interventions

aimed at modulating these biological markers could potentially improve cognitive outcomes in individuals affected by these changes.

Table S2 – Model metrics for classifier groups

Category	Group	Precision	Specificity	R+	R-	Accuracy
Class Scores						
	HCs	0.86	0.90	.72	.10	0.90
	SCZ typical	0.80	0.84	.44	.12	0.87
	SCZ atypical	0.76	0.78	.32	.21	0.67
Accuracy - Overall						0.86

Table S3 – Feature and relative importances

Feature	Relative Importance
IL-1β	0.22
IL-2	0.09
BDNF	0.19
IL-6	0.10
Flanker (RT)	0.17
Corsi Forward (Span)	0.02
Corsi Backward (Span)	0.14
Corsi Forward (RT)	0.06
Corsi Backward (RT)	0.20
Stroop Congruent (RT)	0.03
Stroop Incongruent (RT)	0.19

Fig S7 – Relative importance of features in predictive models. Cognitive features are shown on the left, with attentional control measures like Flanker RT being the most prominent, while the right focuses on interleukin features, with IL-1β as the most influential biomarker.

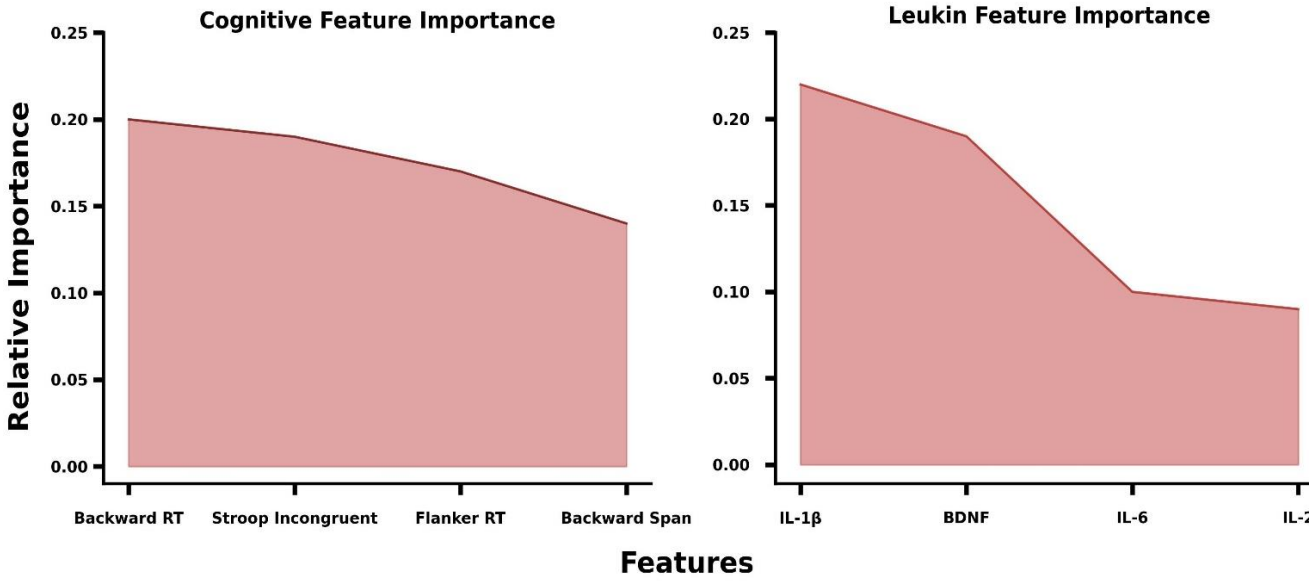


Table S4 –Interaction effects of moderators on predictors and outcomes relationships

Variable	IL-1β	IL-2	BDNF	IL-6
Outcomes				
Flanker (RT)	β = 1.37 (0.08), p < 0.001,	β = 0.34 (0.003), p < 0.001,	β = 4.48 (7.18), p = 0.002	β = 0.03 (0.12), p = 0.001
Corsi Backward (Span)	β = -3.90 (0.65), p < 0.001,	β = -0.27 (0.002), p < 0.001,	β = 0.19 (0.04), p < 0.001	β = -0.15 (0.09), p = 0.03
Corsi Backward (RT)	β = -9.86 (1.26), p < 0.001,	β = -7.74 (3.86), p < 0.001,	β = 2.54 (2.22), p = 0.019	β = -2.56 (2.02), p = 0.006
Stroop Incongruent (RT)	β = 80.12 (4.60), p < 0.001,	β = 76.65 (8.94), p < 0.001,	β = 60.92 (2.86), p = 0.002	β = 59.43 (2.92), p = 0.008
Moderators				
Chlorpromazine	Coefficient = 0.04, p < 0.001,	Coefficient = 0.06, p = 0.004,	Coefficient = 0.09, p < 0.001,	Coefficient = 0.09, p < 0.001,
Duration disease	Coefficient = 0.01, p < 0.001,	Coefficient = -0.40, p < 0.006,	Coefficient = -0.09, p = 0.02,	Coefficient = -0.04, p < 0.001,
PANSS Total	Coefficient = 0.16, p = 0.012,	Coefficient = 0.12, p = 0.006,	Coefficient = 0.26, p = 0.03,	Coefficient = 0.34, p < 0.001,
Diagnostics				
Jarque-Bera	1.06	1.4	1.7	0.96
Durbin-Watson	1.82	1.9	1.96	2.01
Likelihood	220.14	296.9	136.7	160.26

Fig S8 – Variation of coefficients across variables in cognitive tasks. Each line in parallel plot represents coefficient variation across four cognitive tasks (Flanker RT, Stroop Incongruent RT, Corsi Backward RT and Corsi Backward Span) for interleukins IL-1β, IL-2, BDNF, and IL-6.