Brazilian Journal of Psychiatry
bjp
Revista Brasileira de Psiquiatria

Braz J Psychiatry. 2026;48:e20254669
doi:10.47626/1516-4446-2025-4669
Brazilian Psychiatric Association

CC BY

ORIGINAL ARTICLE

Interconnected cognitive and neuroimmune impairments in schizophrenia: the modulating effects of antipsychotic type, illness duration, and symptom severity

Thiago P. **Fernandes**,[1] Zeke **Degraff**,[2] Fatima M. **Felisberti**,[3] Alisa Viktorovna **Karlova**,[4] Givago S. **Souza**,[5] Irina I. **Shoshina**,[4] Milena E.C. **Oliveira**,[6] Linnea N. **Dahlgren**,[7] Natanael A. **Santos**[1,8]

[1]*Psychology, Neuroscience, and Behaviour, Departamento de Psicologia, Universidade Federal da Paraíba (UFPB), João Pessoa, PB, Brazil.* [2]*Svenskagier Neurologie, Stockholm, Sweden.* [3]*Psychology Department, Kingston University London, London, UK.* [4]*St. Petersburg State University, Saint Petersburg, Russia.* [5]*Núcleo de Medicina Tropical, Universidade Federal do Pará, Belém, PA, Brazil.* [6]*Departamento de Psicologia, Centro Universitário Tabosa de Almeida, Caruaru, PE, Brazil.* [7]*Institute of Neurology, Brussels, Belgium.* [8]*UFPB, João Pessoa, PB, Brazil.*

Objective: Cognitive impairment in schizophrenia (SCZ) is associated with neuroinflammation and neurotrophic dysregulation. The role of pro-inflammatory interleukins (IL) and brain-derived neurotrophic factor (BDNF) in these alterations remains unclear. This study investigated the associations between IL-1β, IL-2, IL-6, BDNF, and cognitive function in patients with SCZ receiving typical or atypical antipsychotics.
Methods: The sample 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 patients receiving atypical antipsychotics (34.0±4.0 years). Cognitive performance was assessed using a battery of attentional, executive, and visuospatial working memory tasks. Data were analyzed using machine-learning algorithms, multivariate statistics, and structural equation modeling.
Results: Patients with SCZ showed pronounced cognitive deficits, reduced BDNF concentrations, and elevated IL levels compared with healthy controls, with the largest alterations observed among those receiving typical antipsychotics. 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 further amplifies inflammatory activity. These observations highlight the need to broaden current assessment approaches and systematically examine biomarkers together with clinical features.

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

Introduction

Schizophrenia (SCZ), a complex psychiatric disorder affecting approximately 1% of the global population, 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 are one of the strongest predictors of functional outcome.[1] These impairments, which include alterations 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, thereby 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]

Correspondence: Thiago P. Fernandes, Departamento de Psicologia, Centro de Ciências Humanas, Letras e Artes, Universidade Federal da Paraíba, Bloco Humanístico, Campus I – Castelo Branco I, CEP 58051-900, João Pessoa, PB, Brazil.
E-mail: thiagompfernandes@gmail.com
Submitted Oct 25 2025, accepted Jan 20 2026.

How to cite this article: Fernandes TP, Degraff Z, Felisberti FM, Karlova AV, Souza GS, Shoshina II, et al. Interconnected cognitive and neuroimmune impairments in schizophrenia: the modulating effects of antipsychotic type, illness duration, and symptom severity. Braz J Psychiatry. 2026;48:e20254669. Epub 2026 Feb 13. http://doi.org/10.47626/1516-4446-2025-4669

Beyond receptor-level effects, cytokine-related mechanisms also contribute 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] Essential for neuronal maintenance and learning, BDNF is typically reduced in SCZ and is associated with cognitive decline.[10] Although proposed as a biomarker, its interaction with immune pathways is still unclear, and its stability in serum vs plasma remains a methodological consideration.[5]

Typical antipsychotics, such as haloperidol, may heighten cytokine activity and worsen cognition. Atypical antipsychotics, acting on dopamine and serotonin systems, appear to be more effective in balancing cytokine levels and enhancing BDNF expression, potentially improving cognitive function.[12] However, findings remain inconsistent due to methodological variability and sample heterogeneity. In particular, differences in treatment duration, medication switching, and comorbid factors may moderate immune and cognitive outcomes, complicating interpretation and contributing to inconsistent findings. These inconsistencies highlight the complexity of cytokine modulation by antipsychotic medications and its link to neuroimmune and cognitive processes in SCZ, which has implications for clinical translation.[5] The directionality of these effects remains debatable. For instance, it is unclear whether elevated cytokines drive cognitive impairment or reflect compensatory activities due to the use of antipsychotics.

This study investigates how cytokines and neurotrophic factors influence 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. Advancing understanding in this field may open avenues for targeted therapies or interventions aimed at improving quality of life and functional outcomes in patients with SCZ.

Methods

Participants

The sample consisted of 162 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). The participants, aged 20 to 50 years, reported no retinal or eye impairments in prior exams.

The patients, who met the DSM-5 criteria for SCZ, were outpatients receiving maintenance antipsychotic therapy. Symptom severity and clinical characteristics were assessed using standardized instruments, including the Positive and Negative Syndrome Scale,[13] the Brief Psychiatric Rating Scale,[14] and the Montgomery-Åsberg Depression Rating Scale.[15] In alignment with our hypotheses, these scales were used to examine variance in symptom severity, symptom manifestation, and clinical features between patient groups. Trained examiners, blinded to the other parts of the study, administered the rating scales. The chlorpromazine equivalent was calculated using the Andreasen method.[16]

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), which are known to influence neurocognitive performance and inflammatory biomarkers in psychiatric populations.[17-19] For healthy controls (HCs), exclusion criteria also included the use of medications known to affect cognitive processing (e.g., benzodiazepines) and any lifetime neuropsychiatric disorder, as assessed by a structured clinical interview. All patients were clinically stable outpatients with no recent substance abuse and had maintained their current antipsychotic therapy regimen for at least 6 months prior to assessment, as confirmed by medical records. Patients were expected to have stable social support, adhere to their medication, and have no 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 ($\geqslant$ 20/20, binocular), verified using a Snellen chart, ensuring adequate visual sensitivity and minimizing individual differences that may influence performance in visually demanding tasks.[20-22] The final sample was drawn from a larger dataset to ensure representative distribution of demographic and clinical characteristics. Recruitment and assessment procedures were standardized across sites through shared protocols, centralized training, and ongoing quality control, contributing to consistent assessment across centers.[20,23]

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 (R&D Systems, Inc., Minneapolis, MN, USA). This ensured the reliability of the serum and the accuracy of cytokine measurement. Blood samples were taken under uniform procedures, such as in the early morning (to control for diurnal variation), by trained professionals using sterile techniques in a clinical environment. According to standard guidelines, the samples were centrifuged at 1,600 $\times$ g for 25 minutes. Participants were instructed to avoid heavy meals to prevent interference or metabolite variability. The use of high-quality reagents and adherence to validated protocols allowed for low intra- and inter-assay variability (coefficients below 9%).[24]

Cognitive tasks

This section describes the cognitive tasks used in the study. Brief descriptions are provided below, with additional methodological details available in Supplementary Materials S1 and S2, Supplementary Figures S1-S4.

These procedures were selected for their sensitivity to cognitive deficits commonly observed in SCZ[10,25] All assessments were administered by trained researchers following standardized protocols to ensure consistency across sessions.

Flanker task

The Flanker task assessed selective attention and attentional control. Participants identified a central target letter while ignoring flanking letters on either side. Reaction time (RT) was the primary outcome measure, with faster RTs indicating better performance.[26] RTs can provide insight into subtle mechanisms not necessarily reflected in error rates, which tend to plateau.

Color-word matching Stroop task

The Stroop task was used to evaluate executive control, particularly inhibitory control and cognitive flexibility. Participants identified the font color of words under congruent (i.e., word meaning matching the font color) and incongruent (word meaning conflicting with the font color) conditions. Faster RTs across conditions indicated better performance.[27]

Corsi block-tapping

The Corsi block-tapping test was administered to assess non-verbal visuospatial working memory and attention span, as well as efficiency and processing speed (i.e., RTs). 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 RTs and higher span values indicated better cognitive performance.[28]

Data analysis

Data distribution was assessed using measures of central tendency and dispersion. Normality was assessed using skewness and kurtosis estimates based on the Monte Carlo methods (cut-off $\pm$ 1.96). Statistical analyses were performed using IBM SPSS Statistics 25 (IBM Corp., Armonk, NY, USA) and MATLAB R2018b (MathWorks, Natick, MA, USA).

Data were normally distributed, allowing the use of parametric tests. Homogeneity of variances was evaluated using Levene's test, and homogeneity of covariance matrices was assessed using Box's M test for multivariate analyses. The χ^2 (3 $\times$ 2) test was used to examine nominal variables, such as sex. Analysis of variance (ANOVA) was used to compare biological and sociodemographic data across groups. A one-way ANOVA was applied specifically to the Flanker test results. Additionally, three separate multivariate ANOVAs were conducted to analyze the test results of the Corsi test (four dependent variables), the Stroop test (two dependent variables), and IL and neurotrophic factor outcomes.

Principal component analysis was used to reduce data dimensionality. Components were retained based on eigenvalues $>$ 1 and inspection of the scree plot. K-means clustering with Euclidean distance was then applied to the retained component scores to identify latent subgroups. The optimal number of clusters was determined using multiple complementary criteria, including the elbow method, silhouette score, Davies-Bouldin index, and Calinski-Harabasz index. Nested cross-validation was implemented to evaluate clustering stability and ensure robustness across resampled datasets.

Random forest models were used to assess feature importance in distinguishing groups. Models were trained using an 80/20 training-testing split and were evaluated using accuracy, precision, and recall metrics. Feature importance scores were normalized to allow direct comparison across predictors. Model stability and performance were evaluated using cross-validation procedures. Sensitivity analyses were conducted to examine the robustness of results across alternative model specifications and potential confounding variables, with additional safeguards implemented to reduce overfitting and improve model reliability.[29]

Structural equation modeling was conducted to evaluate relationships among clinical, biological, and cognitive variables while accounting for potential confounders. Prior to model estimation, the dataset was screened for multicollinearity. Confounders identified in the literature were incorporated as mediators or moderators in the structural equation models. Sensitivity analyses were performed to evaluate the stability of the structural equation modeling results across alternative model specifications.

Ethics statement

This study adhered to Declaration of Helsinki principles for research involving human participants and received ethical approval from the ethics committee of the Universidade Federal da Paraíba (certificate: 45774715.9.0000.5188), the institutional review board of the Svenskagier Neurology Institute (protocol SB-2024-04-002), and the Saint Petersburg State University ethics committee. 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.

Results

Sample characteristics

The characteristics of the participants are summarized in Table 1. The groups did not significantly differ in age [F(2, 309) = 2.21, p = 0.160], education level (F[2, 309]) = 1.14, p = 0.064), or sex ($\chi^2_{[2]}$ = 1.88, p = 0.389). Handedness

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

	HC (n=162)	Typical SCZ (n=88)	Atypical SCZ (n=62)	p-value
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, n	72/90	32/56	19/43	0.389
Handedness, n (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

Data presented as mean (SD), unless otherwise specified.
IL = interleukin; BDNF = brain-derived neurotrophic factor; HC = healthy controls; L/R = left/right; PANSS = Positive and Negative Syndrome Scale; SCZ = schizophrenia.
† SCZ group comparisons only.
Sex and handedness were analyzed using χ^2 tests; all other variables were analyzed using appropriate group comparison tests.
Chlorpromazine-equivalent doses are expressed in mg/day. p-values correspond to group analyses.

differed across groups ($\chi^2_{[2]}$ = 4.32, p = 0.036), with approximately 80% of participants being right-handed.

Biomarkers

Group differences in inflammatory and neurotrophic biomarkers are illustrated in Figure 1. Patients with SCZ showed higher IL-1β, IL-2, and IL-6 levels and lower BDNF concentrations compared with HCs, with the largest deviations observed in the typical antipsychotic group.

Interleukin-1β levels

There were significant differences between groups for IL-1β level (F[2, 309] = 56.50, p < 0.001, ω^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 than HCs (all p < 0.001). SCZ typical also had higher IL-1β levels than SCZ atypical patients (p = 0.016; *g* = 0.40 [95%BCa 0.21-0.50]).

Interleukin-2 levels

There were significant differences between groups for IL-2 levels (F[2, 309] = 54.80, p < 0.001; ω^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 than HCs (all p < 0.001). SCZ typical also had higher IL-2 levels than SCZ atypical patients (p = 0.042; *g* = 0.19 [95%BCa 0.06-0.37]).

Brain-derived neurotrophic factor levels

BDNF level differed significantly between groups (F[2, 309] = 50.65, p < 0.001; ω^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 than HCs (all p < 0.001). The SCZ typical group also had lower BDNF levels than the SCZ atypical group (p < 0.001; *g* = 0.52 [95%BCa 0.28-0.70]).

Interleukin-6 levels

There were significant differences between groups for IL-6 levels (F[2, 309] = 60.40, p < 0.001; ω^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 than HCs (all p < 0.001). The SCZ typical group also had higher IL-6 levels than the SCZ atypical group (p = 0.008; *g* = 0.34 [95%BCa 0.21-0.50]).

Cognitive performance

Cognitive task performance across groups is presented in Figure 2. Overall, patients with SCZ showed slower RTs and reduced accuracy across the Flanker, Stroop, and Corsi tasks compared with HCs.

Flanker task

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

Stroop test

Significant group differences were observed in the Stroop test (F[4, 618] = 74.78, p < 0.001, Pillai's trace = 0.76). For congruent stimuli, both the SCZ typical and SCZ atypical groups had higher RTs than HCs (all p < 0.001). Additionally, the SCZ typical group had a higher RT than the SCZ atypical group (p = 0.036, *g* = 0.27; 95%BCa 0.10-0.44). Similarly, for incongruent stimuli, both patient groups had higher RTs than HCs, with the SCZ typical group having a higher RT than the SCZ atypical group (g = 0.48; 95%BCa 0.26-0.60).

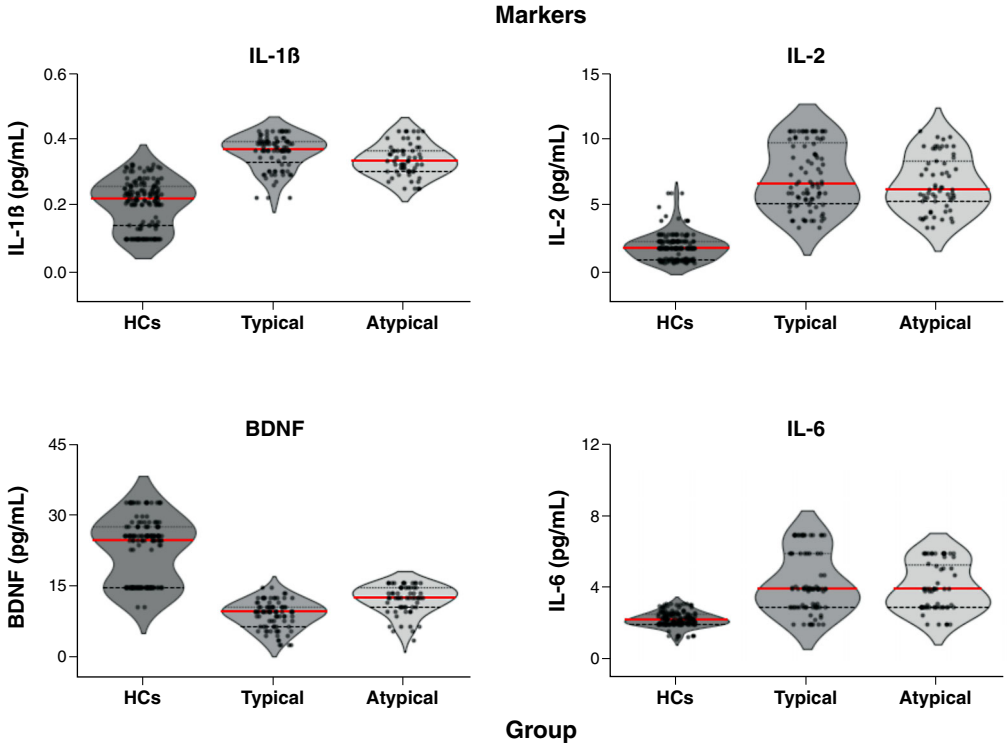


Figure 1 Violin graphs comparing distributions of biomarkers across HCs and schizophrenia groups. Each graph illustrates the median values with solid red lines and the interquartile ranges with dashed black lines, showing the dispersion and central tendency of the data. The width of each violin indicates the density of data points at different levels of each marker. BDNF = brain-derived neurotrophic factor; HCs = healthy controls; IL-1β = interleukin-1β; IL-2 = interleukin-2; IL-6 = interleukin-6.

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 RT: both patient groups had higher RTs than HCs. There was no significant difference between the SCZ typical and SCZ atypical groups ($p = 0.290$).

Corsi backward RT: both patient groups had higher RTs than HCs (all $p < 0.001$), and the SCZ typical group had higher RTs than the SCZ atypical group (Hedges' $g = 0.60$; 95%BCa 0.30-0.89).

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

Corsi backward span: both patient groups had a lower span than HCs (all $p < 0.001$), with lower performance in the SCZ typical group than the SCZ atypical group ($p < 0.001$, $g = 0.61$; 95%BCa 0.33-0.84).

Additional analyses

Correlation and multiple regression analyses

Associations among clinical, cognitive, and biological variables were examined. Detailed results are presented in the Supplementary Material S3, Supplementary Figures S5-S8.

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 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 function: 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 involved pronounced negative correlations between elevated IL-1β and IL-6 levels, and cognitive performance (i.e., Flanker task, 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 had less severe influence (R-values from -0.40 to -0.54, average $p = 0.019$). Additionally, the control cluster, which was characterized by lower levels of IL-1β, IL-2, and IL-6, was positively correlated with

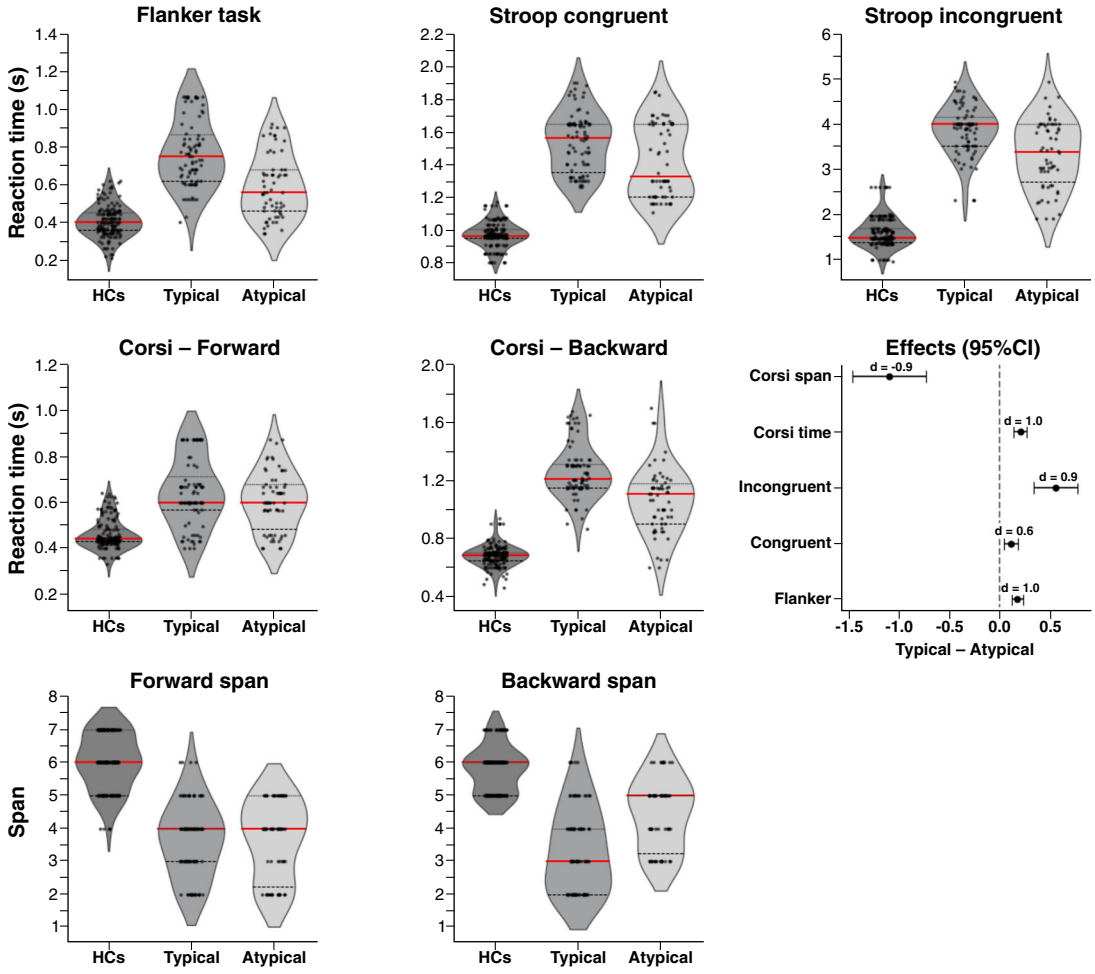


Figure 2 Violin graphs illustrating cognitive task performance in patients with cognitive impairment in schizophrenia and HCs. The graphs detail the results for various tasks. Red solid lines in each violin plot represent median values, while the black dashed lines display the interquartile ranges, illustrating 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 shows the significant differences between the typical and atypical schizophrenia groups, with larger effect sizes and confidence intervals pointing to notably reduced performance in the typical schizophrenia group. HCs = healthy controls.

cognitive outcomes (r = 0.39 to r = 0.60). Negative correlations with BDNF in both the typical (r = -0.51) and atypical (r = -0.43) SCZ clusters further underscored the role of this neurotrophic factor. The SCZ typical group, presenting the highest variance, aligned with expected cognitive variability due to more pronounced pathological manifestations. Conversely, the lower variance among HCs supports the hypothesis of less cognitive disturbance in the absence of pathological conditions.

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 (Supplementary Tables S1 and S2). 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 ILs and BDNF as key predictors, accounting for approximately 40% of the predictive accuracy (Supplementary Table S2). Other significant predictors included Flanker task, Stroop incongruent, and Corsi backward RT results, highlighting the role of biomarkers and cognitive metrics in distinguishing between groups. These findings emphasize the importance of ILs and cognitive metrics in differentiating SCZ subtypes from HCs, affirming the value of integrating biological and cognitive data in clinical and practical contexts (Supplementary Table S2 and Supplementary Figure S9).

Multiple structural equation models

Preliminary analyses showed moderate correlations among key cognitive measures: Flanker RT and Corsi block forward span, Corsi block forward RT, and Stroop

congruent RT had 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 RT correlated strongly with Corsi block forward span, Corsi block forward RT, and Stroop congruent RT, 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 intercorrelations, the Corsi block forward span, Corsi block forward RT, and Stroop congruent RT were excluded from further analyses to avoid redundancy and enhance model precision. Additionally, an autocorrelation assessment among all predictors, including IL levels and BDNF, indicated no significant autocorrelation, allowing for their inclusion in the structural equation models. Before proceeding to group stratification, moderators were rigorously evaluated for their viability within the model. Most variables showed weak associations (e.g., Brief Psychiatric Rating Scale, Positive and Negative Syndrome Scale, age) with coefficients not exceeding the 0.05 threshold and had high residual volumes.

However, exceptions were noted with variables such as illness duration, chlorpromazine equivalent, and total Positive and Negative Syndrome Scale score, which were significantly associated (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 RT, and Stroop incongruent RT, each with $p < 0.01$ and adjusted R^2 = 0.57. Collectively, IL and BDNF levels accounted for between 48.9% and 80% of the variance in outcomes, underscoring their significant predictive power in the model (Supplementary Table S3 and Supplementary Figure S10).

Discussion

In this study, we examined the interactions among biological factors, clinical characteristics, and cognitive performance in patients with SCZ who were receiving typical or atypical antipsychotics. Specifically, we investigated how pro-inflammatory cytokine (IL-1β, IL-2, IL-6) and BDNF levels were related to cognitive outcomes and how these associations interacted 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 had the most pronounced impairments, while those on atypical antipsychotics 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 by modulating neuroinflammatory and neurotrophic pathways. In this model, medication type and illness burden influenced 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 SCZ.[30,31]

Marked dysregulation of inflammatory and neurotrophic pathways was observed in both SCZ groups, with significant differences in IL-1β (ω^2 = 0.39), IL-2 (ω^2 = 0.50), BDNF (ω^2 = 0.41), and IL-6 (ω^2 = 0.35). These changes 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] *In vitro* and preclinical studies have shown that elevated cytokines alter synaptic plasticity, hippocampal neurogenesis, and BDNF-dependent signaling, providing mechanistic support for the observed biomarker-cognition associations.[38,39] Although treatment mitigates some dysregulations, cognitive impairment and biomarker alterations persist over time.[3,40]

Cognitive assessments revealed significant impairments in processing speed, working memory, and executive function in SCZ patients relative to controls (ω^2 = 0.40). Patients receiving typical antipsychotics had 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.[41,42] 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 lower cognitive impairment.[42] 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.[43] Cognitive outcomes were also influenced by illness severity and duration, highlighting the importance of rigorous methodology and control of confounding factors.[44]

Our multivariate approaches further clarified these relationships. Principal component analysis distilled complex data into clusters directly linked to inflammation and cognitive performance, explaining more than 70% of the total variance.[45] Clustering analyses applied to these components revealed distinct biomarker patterns that differentiated SCZ patients, particularly across medication subgroups, from controls based on IL 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, while structural equation modeling analyses further clarified the relationships among biomarkers, clinical variables, medication type, and cognitive outcomes. Emerging analytical tools,

including large language models, may further facilitate the integration and interpretation of complex clinical and biological data.[46] Structural equation modeling identified the most influential predictors and consistently explained a substantial proportion of variance in cognitive performance, providing insight into how inflammatory and neurotrophic changes interact with clinical factors to shape cognitive deficits in SCZ.[9] Furthermore, the analyses showed how these variables were related to and 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 impairment and improving patient outcomes. For instance, studies have shown that, due to their multi-receptor action, atypical antipsychotics result in fewer cognitive deficits than typical antipsychotics.[47] Elevated cytokine levels and reduced BDNF were significant predictors of cognitive impairment, with patients on typical antipsychotics showing more pronounced deficits.[41,44,48] This necessitates different approaches to treatment, focusing on personalized strategies to enhance cognitive outcomes and overall quality of life in SCZ patients.[12,49]

Our study has limitations. The cross-sectional design limits inferences 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 biomarkers and cognitive outcomes. Finally, replication in independent cohorts is required to strengthen the generalizability of the findings, although they may extend to clinically similar populations.

Future research should 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, which could improve clinical outcomes and quality of life for patients.

Acknowledgements

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 study was supported by the Neurology Consortium (NEU, grant no. 2024/002-0012). The Brazilian component was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (grants 305258/2019-2 to NAS and 163780/2020-0 to TPF) and by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (grant 88887.807745/2023-00 to TPF).

The authors would like to thank all of the 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 collaboration possible.

Disclosure

The authors report no conflicts of interest.

Data availability statement

The data analyzed in this study are available from the corresponding author upon reasonable request. Additional methodological details and extended analyses are provided in the Supplementary Materials.

Author contributions

TPF: Conceptualization, Methodology, Writing – original draft, Formal analysis, Data curation, Investigation, Visualization.
ZD: Conceptualization, Methodology, Software, Resources, Data curation, Project supervision.
FMF: Writing – original draft, Data curation.
AVK: Writing – original draft, Data curation.
GSS: Writing – original draft, Data curation.
IIS: Conceptualization, Methodology, Writing – original draft, Investigation, Project supervision.
MECO: Writing – original draft, Data curation.
LND: Conceptualization, Methodology, Writing – original draft, Formal analysis, Data curation, Investigation, Visualization, Project supervision.
NAS: Conceptualization, Methodology, Writing – original draft, Data curation, Investigation, Visualization, Project supervision.
All authors have read and approved of the final version to be published.

Handling Editor: Raffael Massuda

References

1 McCutcheon RA, Keefe RSE, McGuire PK. Cognitive impairment in schizophrenia: aetiology, pathophysiology, and treatment. Mol Psychiatry. 2023;28:1902-18.
2 Fett AKJ, Viechtbauer W, Dominguez MG, Penn DL, van Os J, Krabbendam L. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci Biobehav Rev. 2011;35:573-88.

3 Wang D, Wang Y, Chen Y, Yu L, Wu Z, Liu R, et al. Differences in inflammatory marker profiles and cognitive functioning between deficit and nondeficit schizophrenia. Front Immunol. 2022;13:958972.
4 Zhou X, Tian B, Han HB. Serum interleukin-6 in schizophrenia: a systematic review and meta-analysis. Cytokine. 2021;141:155441.
5 Reale M, Costantini E, Greig NH. Cytokine imbalance in schizophrenia: from research to clinic. Front Psychiatry. 2021;12:536257.
6 Tang G, Chen P, Chen G, Zhong S, Gong J, Zhong H, et al. Inflammation is correlated with abnormal functional connectivity in unmedicated bipolar depression: an independent component analysis study of resting-state fMRI. Psychol Med. 2022;52:3431-41.
7 Almeida NL, Fernandes TP, Lima EH, Sales HF, Santos NA. Combined influence of illness duration and medication type on visual sensitivity in schizophrenia. Braz J Psychiatry. 2020;42:27-32.
8 Shoshina II, Hovis JK, Felisberti FM, Santos NA, Andreeva A, Butler PD, et al. Visual processing and BDNF levels in first-episode schizophrenia. Psychiatry Res. 2021;305:114200.
9 Porter A, Fei S, Damme KSF, Nusslock R, Gratton C, Mittal VA. A meta-analysis and systematic review of single vs multimodal neuroimaging techniques in the classification of psychosis. Mol Psychiatry. 2023;28:3278-92.
10 Nuechterlein KH, Nasrallah H, Velligan D. Measuring cognitive impairments associated with schizophrenia in clinical practice: overview of current challenges and future opportunities. Schizophr Bull. 2024;51:401-21.
11 Ahmad R, Azman KF, Yahaya R, Shafin N, Omar N, Ahmad AH, et al. Brain-derived neurotrophic factor in schizophrenia research: a quantitative review and future directions. AIMS Neurosci. 2023;10:5-32.
12 Chen C-C, Huang T-L. Effects of antipsychotics on the serum BDNF levels in schizophrenia. Psychiatry Res. 2011;189:327-30.
13 Lejeune JA, Northrop A, Kurtz MM. A meta-analysis of cognitive remediation for schizophrenia: efficacy and the role of participant and treatment factors. Schizophr Bull. 2021;47:997-1006.
13 Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale for schizophrenia. Schizophr Bull. 1987;13:261-76.
14 Overall JE, Beller SA. The Brief Psychiatric Rating Scale (BPRS) in geropsychiatric research: I. Factor structure on an inpatient unit. J Gerontol. 1984;39:187-93.
15 Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-9.
16 Andreasen NC, Pressler M, Nopoulos P, Miller D, Ho BC. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol Psychiatry. 2010;67:255-62.
17 Fernandes TP, Felisberti FM, Shoshina II, Almeida NL, Oliveira MEC, Silva GM, et al. Combined influence of medication and symptom severity on visual processing in bipolar disorder. J Psychiatr Res. 2022;147:135-41.
18 Fernandes TP, Santos NA, Dahlgren LN. Prospective study of long COVID-related psychological and biological outcomes in individuals with tobacco use disorder. J Addict Dis. 2026:1-4.
19 Shoshina II, Almeida NL, Oliveira MEC, Trombetta BNT, Silva GM, Fars J, et al. Serum levels of olanzapine are associated with acute cognitive effects in bipolar disorder. Psychiatry Res. 2022;310:114443.
20 Shoshina II, Hovis JK, Felisberti FM, Santos NA, Adreeva A, Butler PD, et al. Visual processing and BDNF levels in first-episode schizophrenia. Psychiatry Res. 2021;305:114200.
21 Fernandes TMP, Silverstein SM, Butler PD, Kéri S, Santos LG, Nogueira RL, et al. Color vision impairments in schizophrenia and the role of antipsychotic medication type. Schizophr Res. 2019;204:162-70.
22 Fernandes TP, Santos NA, Dahlgren LN. Signal-to-noise efficiency explains inter-observer variability in orientation discrimination. Vision (Basel). 2026;10:4.
23 Fernandes TP, Shoshina II, Oliveira MEC, Andreevna VE, Silva GM, Santos NA. Correlates of clinical variables on early-stage visual processing in schizophrenia and bipolar disorder. J Psychiatr Res. 2022;149:323-30.
24 McKay HS, Margolick JB, Martínez-Maza O, Lopez J, Phair J, Rappocciolo G, et al. Multiplex assay reliability and long-term intra-individual variation of serologic inflammatory biomarkers. Cytokine. 2017;90:185-92.
25 Vöhringer PA, Barroilhet SA, Amerio A, Reale ML, Alvear K, Vergne D, et al. Cognitive impairment in bipolar disorder and schizophrenia: a systematic review. Front Psychiatry. 2013;4:87.
26 Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. Percept Psychophys. 1974;16:143-9.
27 Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol. 1935;18:643-62.
28 Kessels RP, van Zandvoort MJ, Postma A, Kappelle LJ, de Haan EH. The Corsi Block-Tapping Task: standardization and normative data. Appl Neuropsychol. 2000;7:252-8.
29 Fernandes TP, Dahlgreen L, Shoshina I, Holm S. Why high-performing psychiatric machine learning models often fail in real-world clinical settings? Psychiatry Clin Neurosci. 2026.
30 Lejeune JA, Northrop A, Kurtz MM. A meta-analysis of cognitive remediation for schizophrenia: efficacy and the role of participant and treatment factors. Schizophr Bull. 2021;47:997-1006.
31 Watson AJ, Harrison L, Preti A, Wykes T, Cella M. Cognitive trajectories following onset of psychosis: a meta-analysis. Br J Psychiatry. 2022;221:714-21.
32 Momtazmanesh S, Zare-Shahabadi A, Rezaei N. Cytokine alterations in schizophrenia: an updated review. Front Psychiatry. 2019;10:892.
33 Jung IEC, Machado AK, da Cruz IB, Barbisan F, Azzolin VF, Duarte T, et al. Haloperidol and risperidone at high concentrations activate an in vitro inflammatory response of RAW 264.7 macrophage cells by induction of apoptosis and modification of cytokine levels. Psychopharmacology (Berl). 2016;233:1715-23.
34 Dombi ZB, Szendi I, Burnet PWJ. Brain derived neurotrophic factor and cognitive dysfunction in the schizophrenia-bipolar spectrum: a systematic review and meta-analysis. Front Psychiatry. 2022;13.
35 Çakici N, Sutterland AL, Penninx BWJH, de Haan L, van Beveren NJM. Changes in peripheral blood compounds following psychopharmacological treatment in drug-naïve first-episode patients with either schizophrenia or major depressive disorder: a meta-analysis. Psychol Med. 2021;51:538-49.
36 Gliwińska A, Czubilińska-Łada J, Więckiewicz G, Świętochowska E, Badeński A, Dworak M, et al. The Role of brain-derived neurotrophic factor (BDNF) in diagnosis and treatment of epilepsy, depression, schizophrenia, anorexia nervosa and Alzheimer's disease as highly drug-resistant diseases: a narrative review. Brain Sci. 2023;13:163.
37 Li Y, Li F, Qin D, Chen H, Wang J, Wang J, et al. The role of brain derived neurotrophic factor in central nervous system. Front Aging Neurosci. 2022;14:986443.
38 Blossom V, Ullal SD, D'Souza MM, Ranade AV, Kumar NA, Rai R. Implicating neuroinflammation in hippocampus, prefrontal cortex and amygdala with cognitive deficit: a narrative review. 3 Biotech. 2025;15:320.
39 Yang G, Xu X, Gao W, Wang X, Zhao Y, Xu Y. Microglia-orchestrated neuroinflammation and synaptic remodeling: roles of pro-inflammatory cytokines and receptors in neurodegeneration. Front Cell Neurosci. 2025;19:1700692.
40 Bora E, Akdede BB, Alptekin K. The relationship between cognitive impairment in schizophrenia and metabolic syndrome: a systematic review and meta-analysis. Psychol Med. 2017;47:1030-40.
41 Haddad C, Salameh P, Sacre H, Clément JP, Calvet B. Effects of antipsychotic and anticholinergic medications on cognition in chronic patients with schizophrenia. BMC Psychiatry. 2023;23:61.
42 Nørbak-Emig H, Ebdrup BH, Fagerlund B, Svarer C, Rasmussen H, Friberg L, et al. Frontal D2/3 receptor availability in schizophrenia patients before and after their first antipsychotic treatment: relation to cognitive functions and psychopathology. Int J Neuropsychopharmacol. 2016;19:pyw006.
43 Rajji TK, Mulsant BH, Nakajima S, Caravaggio F, Suzuki T, Uchida H, et al. Cognition and dopamine d2 receptor availability in the striatum in older patients with schizophrenia. Am J Geriatr Psychiatry. 2017;25:1-10.
44 Green MF, Harvey PD. Cognition in schizophrenia: past, present, and future. Schizophr Res Cogn. 2014;1:e1-9.
45 Lovatti BPO, Nascimento MHC, Neto ÁC, Castro EVR, Filgueiras PR. Use of random forest in the identification of important variables. Microchem J. 2019;145:1129-34.

46 Fernandes TP, Dahlgren L, Santos NA, Degraff Z. Assessing the clinical competence of large language models for tobacco use disorder: A multi-domain expert evaluation. J Addict Dis. 2026:1-10.
47 Si Y, Liu C, Kou Y, Dong Z, Zhang J, Wang J, et al. Antipsychotics-induced improvement of cool executive function in individuals living with schizophrenia. Front Psychiatry. 2023;14:1154011.
48 Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry. 2011;70:663-71.
49 Al-Wandi A, Holmberg C, Landén M, Nordenskjöld A. A systematic review and meta-analysis of maintenance treatment for psychotic depression. Nord J Psychiatry. 2022;76:442-50.