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Cognitive functions in schizophrenia: the interplay between blood viscosity, serum osmolarity, and symptom severity

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Abstract

Objective Cognitive impairments—especially in executive function and attention—are core features of schizophrenia and major barriers to functional recovery. Although systemic physiological factors such as blood viscosity and serum osmolarity have been implicated in schizophrenia, their association with cognitive deficits remains largely unexplored. This study aimed to investigate these relationships in male patients with schizophrenia in remission.

Methods A total of 247 male patients diagnosed with schizophrenia in remission were recruited. Cognitive performance was assessed using the Frontal Assessment Battery (FAB), Stroop Test, and Trail Making Test (TMT). Hemorheological parameters, including whole blood viscosity (WBV) at low and high shear rates (LSR and HSR), and serum osmolarity were calculated. Regression analyses were conducted to determine predictors of cognitive outcomes.

Results In the multivariate analysis, higher WBV at HSR ($\beta = 0.122$, $\beta = 0.037$) was positively associated with executive function (FAB scores) and inversely associated with Stroop 5 time ($\beta = -0.134$, $p = 0.025$), TMT-A ($\beta = -0.134$, $p = 0.032$), and TMT-B ($\beta = -0.137$, $p = 0.028$) completion times, reflecting better cognitive performance. While higher serum osmolarity showed a positive correlation with FAB scores in univariate analysis, it did not remain an independent predictor in the multivariate model. The multivariate regression identified WBV at HSR, depressive symptoms, negative symptoms, use of long-acting injectable antipsychotics (LAI), and living arrangements as significant predictors of FAB scores, collectively explaining 16.9% of the variance ($F(8,238) = 7.252$, $p < 0.001$).

Conclusion This study highlights the potential contribution of systemic physiological factors to cognitive function in schizophrenia. Higher WBV, within a physiological range, may support cerebral perfusion and be associated with better executive performance. Although serum osmolarity showed a positive association with executive function in univariate analysis, it was not an independent predictor in multivariate models, and its cognitive relevance remains to be clarified. These findings point to a possible role of physiological parameters in cognitive variability, but further studies are needed before drawing firm clinical implications.

Clinical trial number Not applicable.

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Highlights

- Higher WBV at high shear rates is linked to better executive functioning in schizophrenia.
- Serum osmolarity was associated with executive function in univariate but not multivariate analysis.
- WBV and serum osmolarity may help explain cognitive variability in schizophrenia.

Keywords Schizophrenia, Cognitive performance, Blood viscosity, Serum osmolarity, Executive function

Introduction

Schizophrenia is a chronic, heterogeneous psychiatric disorder affecting approximately 1% of the global population and remains a leading contributor to disability worldwide [1]. The illness is characterized not only by positive symptoms such as delusions and hallucinations but also by persistent cognitive and negative symptoms, which contribute substantially to poor long-term outcomes [2]. Among these, impairments in executive function, attention, working memory, and verbal fluency are particularly prevalent and resistant to treatment, affecting up to 85% of patients even during remission phases [3]. These deficits are now recognized as central features of the disorder and major predictors of social and functional disability [4].

Historically, cognitive dysfunction in schizophrenia was emphasized by pioneers like Kraepelin and Bleuler, and this conceptualization has been supported by modern neuroimaging studies [5, 6]. Functional abnormalities are consistently observed in the prefrontal cortex—particularly the dorsolateral (DLPFC) and orbitofrontal (OFC) regions—which underlie executive function, cognitive flexibility, and inhibitory control [7]. Tasks such as the Stroop Test [8], Trail Making Test (TMT) [9] and Frontal Assessment Battery (FAB) [10] provide robust and reliable means for quantifying these cognitive impairments, offering valuable insights into the neurocognitive underpinnings of Schizophrenia [11, 12].

Despite substantial research into neurocognitive deficits, the physiological mechanisms that may contribute to cognitive heterogeneity in schizophrenia remain poorly defined. In particular, systemic factors such as blood viscosity and serum osmolarity, while clinically relevant in broader medical contexts, have received limited attention in schizophrenia research.

Blood viscosity, reflecting the resistance of blood to flow, plays a crucial role in regulating cerebral perfusion and oxygen delivery. It varies inversely with shear rate, typically being higher during diastole (low shear rate, LSR) and lower during systole (high shear rate, HSR). Elevated blood viscosity, particularly at LSR, has been associated with impaired microvascular perfusion and increased cardiovascular risk [13]. In non-psychiatric populations, altered blood viscosity has been implicated in cognitive decline and small vessel disease [14, 15]. For instance, increased plasma viscosity has been linked to cognitive decline in older adults [14]. Furthermore, a pilot study in Alzheimer's disease patients found significantly elevated whole blood viscosity, which correlated with the severity of microvascular dysfunction, suggesting a potential link between hemorheologic abnormalities and disease pathology [16].

Evidence in schizophrenia is more limited but growing. Notably, Balcıoğlu et al. found reduced WBV in both first-episode psychosis and during acute exacerbations, suggesting a possible phase-dependent alteration in hemorheology [17]. A follow-up study found lower WBV in treatment-resistant patients, along with elevated inflammation [18]. Importantly, remitted patients showed intermediate WBV, indicating dynamic variation across illness phases. These hemorheological changes may relate to symptom severity, inflammatory status, or cardiovascular comorbidity.

Serum osmolarity, a marker of solute concentration influenced by sodium, glucose, and urea, is essential for maintaining fluid balance across compartments [19]. In schizophrenia, abnormalities in osmolar regulation have been observed, including dysregulated vasopressinergic activity, hyponatremia, and polydipsia [20–22]. Disruptions in osmotic homeostasis can influence not only fluid balance but also cerebral blood flow and metabolic function. In healthy older adults, both hypo- and hyperosmolar states have been linked to cognitive decline, especially in memory and executive function [23–25]. However, the relevance of these findings in schizophrenia remains largely unexplored.

The influence of inflammation, metabolic syndrome, and pharmacological treatments on these physiological parameters is also critical to consider. Chronic low-grade inflammation is common in schizophrenia and may contribute to increased blood viscosity and fluid dysregulation [26]. Emerging evidence also suggests that individuals with schizophrenia may be particularly vulnerable to hypoosmolar states due to factors such as psychogenic polydipsia and potential antipsychotic-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH) [21, 27–28]. Metabolic syndrome—affecting up to 40% of patients—is associated with elevated WBV and osmolarity due to dyslipidemia, hyperglycemia, and insulin resistance [29]. Moreover, antipsychotics can significantly impact glucose metabolism, fluid retention, and electrolyte balance, influencing both blood viscosity and osmolarity [27, 30].

Given this background, the relationship between cognitive function and systemic physiological markers like WBV and serum osmolarity in schizophrenia warrants focused investigation. Emerging research from other disease states supports the hypothesis that deviations in these parameters may affect cerebral perfusion and, consequently, cognitive efficiency [31, 32].

This study aims to bridge this gap by examining associations between cognitive performance—particularly executive function, attention, and cognitive flexibility—and systemic physiological parameters in a well-characterized cohort of male schizophrenia patients in remission. By focusing on whole blood viscosity (WBV) at both LSR and HSR and serum osmolarity, we seek to elucidate potential physiological correlates of cognitive variability and identify modifiable factors that may inform future therapeutic strategies.

Methods

Ethics approval

The study protocol was approved by the Ethics Committee of Medipol University (Approval Date: 26.12.2024; Approval Number: 1321). All participants provided verbal and written informed consent after being thoroughly briefed on the study aims and procedures. The study adhered to the principles outlined in the Declaration of Helsinki. This study is not a clinical trial; therefore, a clinical trial number is not applicable.

Data collection and assessment

This cross-sectional study included male patients aged 18–65 years with a diagnosis of schizophrenia, as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), who were receiving care at Community Mental Health Centers (CMHCs) affiliated with Tuzla State Hospital. All diagnoses were confirmed by senior psychiatrists through clinical evaluation in accordance with DSM-5 criteria.

A total of 300 patients in clinical remission were consecutively screened for eligibility. Remission was assessed in accordance with the operationalized criteria proposed by Andreasen et al., which require a score of 3 or lower on each of the following eight items of the Positive and Negative Syndrome Scale (PANSS): P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), N1 (blunted affect), N4 (social withdrawal), N6 (lack of spontaneity), G5 (mannerisms/posturing), and G9 (unusual thought content). For a remission diagnosis, these symptom thresholds had to be sustained for at least six months [33].

Patients were followed in CMHCs and regularly assessed by attending senior psychiatrists. The six-month remission duration was verified retrospectively by reviewing longitudinal clinical documentation, including physician notes, medication stability, and symptom assessments. Patients with no psychotic exacerbations, no need for hospitalization, and no documented functional decline or emergent treatment changes during this period were included.

Relapse was defined based on prior literature as the re-emergence of positive psychotic symptoms, a moderate-to-severe decline in global functioning, or psychiatric hospitalization. Patients exhibiting signs of relapse at the time of assessment were excluded. In addition to PANSS-based remission criteria, participants were required to have a Clinical Global Impression–Severity (CGI-S) score of 4 (moderately ill) or lower. Functional stability and the absence of significant deterioration over the prior six months were verified through detailed review of psychiatric records. Furthermore, all participants had to be willing to provide written informed consent to participate in the study.

Exclusion criteria were strictly applied to ensure the integrity of the study data and to minimize potential confounding variables. Patients were excluded if they exhibited a relapse at the time of blood sampling, evidenced by hospitalization or a marked exacerbation of symptoms. Additional exclusion criteria included the presence of comorbid psychiatric diagnoses, as defined by DSM-5 criteria, or any neurological or physical illnesses that could interfere with the study outcomes.

Patients with Calgary Depression Scale for Schizophrenia (CDSS) scores greater than 11 were also excluded, as the Turkish validation of the CDSS identified a cut-off score of 11/12 for clinically significant depression, ensuring its cultural and clinical relevance [34] This exclusion criterion was applied to create a more homogeneous sample and to avoid confounding effects of clinically significant depressive symptoms on cognitive and physiological parameters.

Patients currently receiving antipsychotic treatment at a total daily dose exceeding the minimum effective dose were excluded from the study. The minimum effective dose was defined as 200 mg/day chlorpromazine equivalent for first-episode patients and 300 mg/day chlorpromazine equivalent for patients with multiple episodes [35, 36]. This exclusion criterion ensures that the impact of cognitive and physiological parameters is not confounded by complex, high-dose, or adjunctive antipsychotic regimens. Patients were also excluded if they had a current or past history of alcohol or substance use disorder, as confirmed by urine toxicology and clinical evaluation, or if they were currently using lithium or carbamazepine. Participants with a current or past history of polydipsia or hyponatremia were excluded, as these conditions could confound the analysis of blood rheology and osmolarity. Moreover, systemic illnesses affecting blood rheology or inflammatory parameters, such

as cardiovascular diseases, diabetes mellitus, hepatic or renal failure, hypertension, acute infections, or chronic inflammatory or immunological conditions, were additional exclusionary factors. Patients who were heavy smokers (defined as smoking more than 20 cigarettes per day), currently or recently taking anti-inflammatory or immunosuppressive medications, or had laboratory abnormalities, including neutropenia, electrolyte imbalances, or evidence of liver or renal dysfunction, were excluded. Nutritional deficiencies, such as anemia or vitamin B12 or folate deficiencies, also disqualified participants. Finally, patients without routine laboratory screening at admission were not eligible for inclusion.

After the inclusion and exclusion criteria were applied, a total of 247 male patients with schizophrenia in clinical remission were enrolled in the study (Fig. 1).

Following informed consent, participants completed a sociodemographic and clinical data form, which included details on age, education, employment, marital status, and treatment history. Clinicians used structured interviews and validated scales to assess remission and symptom severity.

Blood samples were drawn from an arm vein between 8:00 and 9:00 a.m. after at least eight hours of fasting to standardize water and food intake. Routine biochemical assessments— including hemogram, serum lipids, glucose, sodium (Na), blood urea nitrogen (BUN), total protein (TP), and hematocrit (HCT) levels—were conducted in the central laboratory of Tuzla State Hospital.

Serum osmolarity and whole blood viscosity (WBV) were not measured directly, but calculated using validated and widely accepted formulas as follows [37–39]:

$$WBV\ at\ LSR\ (0.5\ s^{-1})\ = \\ (1.89\ \times\ HCT)\ +\ [3.76\ \times\ (TP - 78.42)]$$

$$WBV\ at\ HSR\ (208\ s^{-1})\ = \\ (0.12\ \times\ HCT)\ +\ [0.17\ \times\ (TP\ -\ 2.07)]$$

$$Serum\ osmolarity\ (mOsm/L\ H2O)\ :\ Osmolarity \\ = 2[Na^{+}]\ +\ (Glucose/18)\ +\ (BUN/2.8)$$

Psychometric tools

Positive and negative syndrome scale (PANSS)

The PANSS is a 30-item, semi-structured interview designed to assess the severity of positive, negative, and general psychopathological symptoms in patients with schizophrenia. It includes three subscales: seven items each for positive and negative symptoms, and 16 items for general psychopathology. Each item is rated on a scale from 1 (absent) to 7 (extreme). This tool provides a comprehensive profile of symptom severity and is widely used in research settings. The reliability and validity of the Turkish version were established by Kostakoğlu et al., making it suitable for use in Turkish-speaking populations. The PANSS was administered by trained clinicians to ensure consistent and accurate scoring [40].

Clinical global impression scale (CGI)

The CGI is a widely used tool for evaluating the overall severity of mental illness and the extent of improvement following treatment. It comprises two components: the Severity of Illness scale (CGI-S), ranging from 0 (not ill) to 7 (extremely ill), and the Global Improvement scale (CGI-I), used to assess change over time. In this study, the CGI-S was used to confirm remission, with scores of ≤ 4 indicating a mild or better clinical state. This clinician-rated scale is simple yet robust, providing a subjective assessment based on the evaluator's overall impression of the patient's condition [41].

Calgary depression scale for schizophrenia (CDSS)

The CDSS is a clinician-administered, nine-item scale designed to evaluate depressive symptoms in individuals with schizophrenia. Unlike general depression scales, the CDSS was designed to differentiate genuine depressive symptoms from those that may overlap with negative symptoms or be related to antipsychotic side effects. Each item is rated on a four-point Likert scale. The Turkish validation of the CDSS identified a cut-off score of 11/12 for clinically significant depression, ensuring its cultural and clinical relevance. This scale provides critical insights into the depressive features that may accompany schizophrenia, even in remission [34].

Trail making test (TMT)

The Trail Making Test (TMT) is a widely used neuropsychological tool designed to assess visual search abilities, attention, cognitive flexibility, and motor speed, which are often affected in patients with schizophrenia. This test is divided into two parts, TMT A and TMT B, each targeting distinct cognitive domains. In TMT A, participants are instructed to connect sequentially numbered circles (e.g., 1-2-3) as quickly and accurately as possible. This part primarily measures basic attention and processing speed, providing a foundational understanding of the participant's capacity to focus and respond efficiently. TMT B, on the other hand, involves alternating between numbers and letters in a specific sequence (e.g., 1-A-2-B). This task is more complex, requiring participants to switch between numerical and alphabetical order while maintaining accuracy. It evaluates mental flexibility, task-switching abilities, and overall executive functioning. In both parts of the test, the time taken to complete the task (measured in seconds) and the number of errors made are recorded. Errors are corrected in real time by the evaluator, ensuring that participants continue from

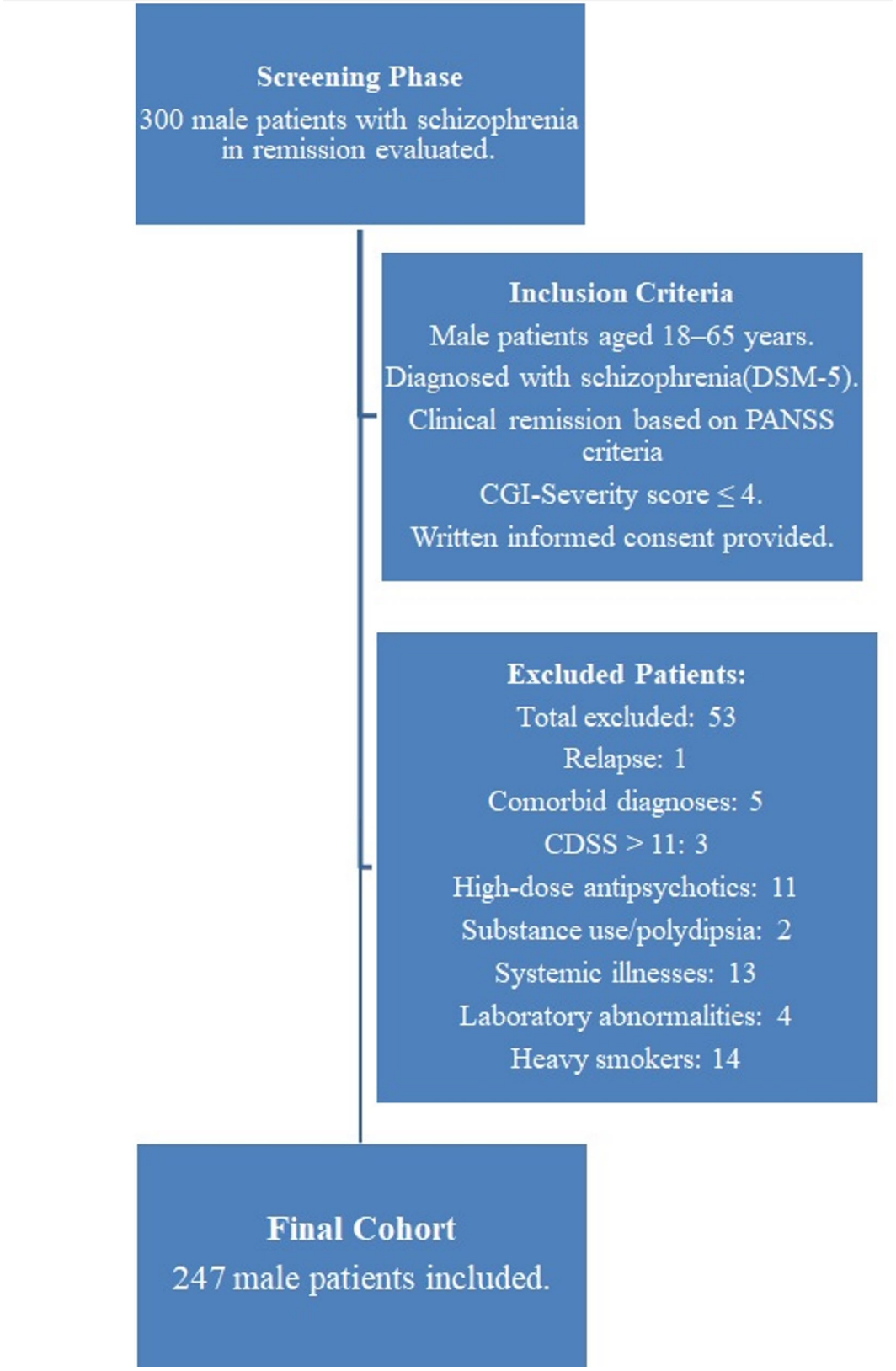

Fig. 1 Flowchart of patient recruitment and eligibility assessment process

the point of the mistake without penalizing their subsequent performance. This approach allows for a clear assessment of their ability to recover and maintain focus. The TMT is particularly useful in studies of schizophrenia, as it offers a detailed evaluation of critical cognitive functions, including attention and executive processing, both of which are often impaired in this population. Its versatility and simplicity make it a valuable component of comprehensive neuropsychological assessments. In this study, TMT-A was utilized to assess attention and working memory, and TMT-B served as an index for the evaluation of executive functions [42].

Stroop test

The Stroop Test is a standardized neuropsychological measure used to assess selective attention, cognitive control, and executive function, particularly involving the anterior cingulate and prefrontal cortex. It requires participants to suppress automatic responses in favor of task-relevant ones, making it a robust measure of inhibitory control and mental flexibility.

In this study, five Stroop conditions were administered using the validated Turkish version included in the TBAG neuropsychological test battery:

Stroop 1 (Reading): Participants read color names printed in black ink to assess basic reading ability and processing speed.

Stroop 2 (Color Naming): Participants named the colors of colored rectangles, evaluating simple attention and perceptual speed.

Stroop 3 (Interference): Participants named the ink color of incongruently colored color names (e.g., the word "red" printed in blue), measuring cognitive inhibition and interference control.

Stroop 4 (Neutral Words): Participants named the ink color of neutral words, serving as a non-conflict baseline for executive processing.

Stroop 5 (Color Interference): A higher-interference condition where participants named the ink color of incongruently printed color names within a mixed-word context, further challenging executive function.

For each condition, completion time, number of errors, and false corrections were recorded and included in the data analysis to provide a comprehensive profile of attentional and executive performance [43].

Frontal assessment battery (FAB)

The Frontal Assessment Battery (FAB) is a brief, clinician-administered tool designed to assess key aspects of frontal lobe functioning, which are commonly impaired in individuals with schizophrenia. It consists of six subtests, each targeting a specific domain of executive function:

1. Conceptualization: Evaluates abstract reasoning and the ability to identify similarities between objects—skills essential for high-level thinking.
2. Mental Flexibility: Assesses verbal fluency and the ability to shift between cognitive sets, reflecting adaptability in thought processes.
3. Motor Programming: Measures the capacity to plan and execute a sequence of motor actions, providing insight into action organization.
4. Interference Sensitivity: Tests the ability to suppress competing or irrelevant stimuli, indicating cognitive control and sustained attention.
5. Inhibitory Control: Assesses resistance to automatic responses in favor of appropriate, context-specific behavior.
6. Environmental Autonomy: Evaluates the degree of dependence on external cues, reflecting behavioral self-regulation.

Each subtest is scored from 0 to 3, yielding a total score between 0 and 18, with higher scores indicating better frontal lobe function. The FAB is widely used in clinical and research settings due to its brevity and strong psychometric properties. The Turkish version, validated by Tunçay et al., has demonstrated good reliability and cultural applicability. In this study, the FAB was used to capture a multidimensional profile of executive function, offering insight into the cognitive performance of schizophrenia patients in remission [44].

Statistical analysis

The Kolmogorov–Smirnov test was used to assess the normality of distribution for all continuous variables. Descriptive statistics were used to summarize demographic, clinical, biochemical, and cognitive data. Normally distributed variables were presented as mean ± standard deviation (SD), and non-normally distributed variables were reported as median (minimum–maximum). Categorical variables were summarized using frequencies and percentages (n, %).

To explore bivariate associations among key study variables, Pearson's correlation coefficients were calculated between cognitive test scores (FAB, Stroop Test, TMT-A, and TMT-B) and clinical, biochemical, and hemorheological markers, including WBV at LSR and HSR), serum osmolarity, PANSS-P, PANSS-N, PANSS-G subscales and the CDS. Variables with statistically significant correlations ($p < 0.05$) were then entered into univariate linear regression models to further evaluate their individual predictive power for each cognitive task. Significant predictors from univariate analyses were subsequently entered into multiple linear regression models to identify independent predictors. Predictor inclusion in multivariate models was guided both by theoretical relevance

and statistical significance in univariate tests. To address potential multicollinearity, variance inflation factor (VIF) values were calculated, and any variable with a VIF > 2.5 was excluded from the model. Notably, since WBV at LSR and HSR rates were highly correlated, only one of these (typically WBV at HSR, which showed stronger associations) was included in the main models to reduce redundancy and avoid collinearity bias. To assess the isolated impact of WBV at LSR, alternative models excluding HSR were constructed and reported separately in the supplementary materials. Multivariate regression analyses were conducted separately for each cognitive measure. For interpretability, both unstandardized (B) and standardized (β) coefficients, along with 95% confidence intervals and p-values, were reported. The final regression models were evaluated using adjusted R^2 and F-statistics to assess model fit.

All statistical tests were two-tailed, and a p-value of < 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics (Version 22.0; IBM Corp., Armonk, NY, USA).

Results

Table 1 provides a comprehensive overview of the sociodemographic and clinical characteristics of the 247 male patients with schizophrenia in remission included in this study, highlighting key variables such as age, marital and educational status, living arrangements, smoking habits, treatment history, and clinical parameters.

The biochemical and hemorheological parameters of the study participants are summarized as follows: The mean glucose level was 101.71 ± 8.02 mg/dL, while the mean sodium (Na) concentration was 139.42 ± 1.35 mmol/L. Blood urea nitrogen (BUN) levels averaged 26.65 ± 4.72 mg/dL, and serum osmolarity was 294.01 ± 2.94 mOsm/L. The median serum osmolarity was 294.77 mOsm/L, with values ranging from 276.82 to 298.18 mOsm/L. Notably, 58 patients exhibited osmolarity levels above 295 mOsm/L.Total protein concentration had a mean value of 6.99 ± 0.40 g/dL.

Hematological parameters revealed a mean hematocrit (Hct) value of 42.80 ± 3.22%. WBV was calculated at both LSR and HSR, with a mean WBV at LSR of 48.87 ± 16.36 and a mean WBV at HSR of 16.67 ± 0.79. These findings provide a detailed profile of the biochemical and hemorheological characteristics of schizophrenia patients in remission.

Table 1 Sociodemographic and clinical characteristics of schizophrenia patients

		Mean ± SD Median (Min-Max) *n* (%)
Age		40.53 ± 9.48
Gender	Male	247 (100.0)
Marital status	Single / Divorced / Widow	212 (85.8)
	Married	35 (14.2)
Educational Level	Primary/ Secondary school	129 (52.2)
	High school	81 (32.8)
	College / PhD	37 (15.0)
Employment Status	Student	3 (1.2)
	Employed	68 (27.5)
	Unemployed	76 (30.8)
	Retired	100 (40.5)
Living Arrangement	Living Alone	12 (4.9)
	Social Service Housing	26 (10.5)
	Living with Family	209 (84.6)
Family History of Psychiatric Illness	No	136 (55.1)
	Yes	111 (44.9)
Smoking Status	Non-smoker	107 (43.3)
	Smoker	140 (56.7)
Long-Acting Injectable Antipsychotics (LAI)	No	138 (55.9)
	Yes	109 (44.1)
History of Suicidality	No	221 (89.5)
	Yes	26 (10.5)
Duration of illness (years)		12.56 ± 6.24
Age at onset		27.97 ± 7.09
Number of Hospitalisations		3 (0–17)

Table 2 Performance metrics across frontal assessment battery, Stroop test, and trail making test (TMT) in schizophrenia patients

		Mean ± SD	Median (Min–Max)
Frontal Assessment Battery (FAB)		12.92 ± 2.52	13 (6–16)
Stroop 1 (Reading)	Completion Time (seconds)	32.99 ± 3.12	32.84 (25.06–40.07)
Stroop 1 (Reading)	Number of Errors	0	0
Stroop 1 (Reading)	False Corrections	0.64 ± 0.48	0–1 (1)
Stroop 2 (Color Naming)	Completion Time (seconds)	24.97 ± 2.25	24.99 (19.47–30.87)
Stroop 2 (Color Naming)	Number of Errors	0.03 ± 0.18	0–1 (0)
Stroop 2 (Color Naming)	False Corrections	0.03 ± 0.18	0–1 (0)
Stroop 3 (Interference)	Completion Time (seconds)	36.44 ± 5.15	36.34 (23.10–50.57)
Stroop 3 (Interference)	Number of Errors	0.09 ± 0.29	0–1 (0)
Stroop 3 (Interference)	False Corrections	0.72 ± 0.45	0–1 (1)
Stroop 4 (Neutral Words)	Completion Time (seconds)	38.35 ± 5.17	37.83 (25.21–55.51)
Stroop 4 (Neutral Words)	Number of Errors	0.19 ± 0.39	0–1 (0)
Stroop 4 (Neutral Words)	False Corrections	1.00 ± 0.24	0–2 (1)
Stroop 5 (Color Interference)	Completion Time (seconds)	43.90 ± 5.45	43.51 (31.70–60.48)
Stroop 5 (Color Interference)	Number of Errors	1.30 ± 0.64	0–3 (1)
Stroop 5 (Color Interference)	False Corrections	2.25 ± 0.65	0–4 (2)
TMT-A	Completion Time (seconds)	69.45 ± 16.74	69.50 (27.67-106.55)
	Number of Errors	0.68 ± 1.59	0 (0–13)
TMT-B	Completion Time (seconds)	96.66 ± 19.95	96.90 (43.54–144.75)
	Number of Errors	1.07 ± 2.36	0 (0–17)

Table 3 Correlation matrix of whole blood viscosity, serum osmolarity, Calgary depression scale, PANSS subscales, and cognitive test performances (Stroop test, FAB, TMT)

	Stroop 1	Stroop 2	Stroop 3	Stroop 4	Stroop 5	FAB	TMT A	TMT B
WBV at LSR	-0.019	0.008	0.066	-0.028	-0.138*	0.134*	-0.123	-0.124
WBV at HSR	-0.019	0.010	0.060	-0.025	-0.141*	0.135*	-0.139*	-0.142*
Serum osmolarity (mOsm/L)	-0.023	0.007	-0.004	-0.061	-0.099	0.165**	-0.015	-0.010
Calgary Depression Scale (CDS)	-0.032	0.059	0.114	0.093	0.130*	-0.222**	0.103	0.111
PANSS Positive Scale (PANSS-P)	-0.040	-0.027	0.049	0.081	0.062	-0.049	0.176**	0.179**
PANSS Negative Scale (PANSS-N)	0.003	-0.026	-0.016	0.111	0.134*	-0.238**	0.145*	0.138*
PANSS General Symptoms Scale (PANSS-G)	0.012	0.078	0.034	0.088	0.204**	-0.138*	-0.016	0.041
Age	-0.054	-0.095	0.066	0.078	0.026	0.068	-0.081	-0.043
Duration of illness	-0.051	-0.102	0.040	0.030	-0.003	0.064	-0.058	-0.039

The table presents Pearson correlation coefficients (r). Statistical significance is indicated as follows: *$p < 0.05$, **$p < 0.01$. CDS, Calgary Depression Scale for assessing depressive symptoms; TMT, Trail Making Test; FAB, Frontal Assessment Battery; PANSS-P, Positive scale of the Positive and Negative Syndrome Scale; PANSS-N, Negative scale of the Positive and Negative Syndrome Scale; PANSS-G, General Symptoms scale of the Positive and Negative Syndrome Scale; WBV at LSR, Whole Blood Viscosity at Low Shear Rate; WBV at HSR, Whole Blood Viscosity at High Shear Rate. Statistical significance set at 0.05

The mean Calgary Depression Scale (CDS) score was 5.04 ± 2.01. The Positive and Negative Syndrome Scale (PANSS) subscales yielded mean scores of 8.28 ± 1.25 for PANSS Positive (PANSS-P), 9.26 ± 1.85 for PANSS Negative (PANSS-N), and 18.82 ± 2.41 for PANSS General Symptoms (PANSS-G). The mean PANSS Total score was 36.36 ± 3.50.

The cognitive performance of patients, assessed through the Frontal Assessment Battery (FAB), Stroop Test, and Trail Making Test (TMT), provided detailed insights into executive functions, attention, and processing speed, as summarized in Table 2.

The results of the correlation analysis are summarized in the Table 3. WBV at LSR was negatively correlated with Stroop 5 time (r = -0.138, $p = 0.030$) and positively correlated with FAB scores ($r = 0.134$, $p = 0.035$). WBV at HSR showed a negative correlation with Stroop 5 time (r = -0.141, $p = 0.026$) and positive correlations with FAB scores ($r = 0.135$, $p = 0.034$), as well as negative correlations with TMT-A (r = -0.139, $p = 0.029$) and TMT-B (r = -0.142, $p = 0.026$) times.

Serum osmolarity was positively correlated with FAB scores ($r = 0.165$, $p = 0.009$), without significant correlations with other variables. The CDS showed a positive correlation with Stroop 5 time ($r = 0.130$, $p = 0.041$) and a negative correlation with FAB scores (r = -0.222, $p < 0.001$).

For PANSS subscales, the PANSS-P was positively correlated with TMT-A ($r = 0.176$, $p = 0.006$) and TMT-B ($r = 0.179$, $p = 0.005$). The PANSS-N showed positive correlations with Stroop 5 time ($r = 0.134$, $p = 0.035$), TMT-A ($r = 0.145$, $p = 0.022$), and TMT-B ($r = 0.138$, $p = 0.031$),

and a negative correlation with FAB scores (r = -0.238, $p < 0.001$). The PANSS-G was positively correlated with Stroop 5 time ($r = 0.204$, $p = 0.001$) and negatively correlated with FAB scores (r = -0.138, $p = 0.030$).

No significant correlations were observed between age, duration of illness, and the assessed cognitive and hemorheological variables.

To explore key predictors of cognitive performance, we applied univariate and multivariate linear regression models for each cognitive domain assessed: executive function (FAB), interference control (Stroop 5), attention (TMT-A), and cognitive flexibility (TMT-B). The FAB, which provides a comprehensive evaluation of executive functioning—including conceptualization, mental flexibility, and inhibitory control—served as the principal outcome in our primary models. Regression results for Stroop 5, TMT-A, and TMT-B are reported in supplementary tables for clarity.

Univariate regression analyses revealed several significant predictors of executive function, as assessed by the FAB. Higher WBV at LSR ($\beta = 0.134$, $p = 0.035$) and HSR ($\beta = 0.135$, $p = 0.034$) were both associated with better FAB scores. Serum osmolarity ($\beta = 0.165$, $p = 0.009$), living with family ($\beta = 0.179$, $p = 0.005$), employment ($\beta = 0.130$, $p = 0.042$), and use of LAI ($\beta = 0.199$, $p = 0.002$) were also positively associated with executive function. In contrast, higher scores on the CDS ($\beta = -0.222$, $p < 0.001$), the PANSS-N ($\beta = -0.238$, $p < 0.001$), and the PANSS-G ($\beta = -0.138$, $p = 0.030$) were significantly associated with poorer FAB performance. Other sociodemographic or clinical variables (age, marital status, education, smoking status, family psychiatric history, and suicidality) did not show significant associations.

Multivariate regression analysis incorporating the most relevant predictors demonstrated that better executive function remained significantly associated with higher WBV at HSR ($\beta = 0.122$, $p = 0.037$), living with family ($\beta = 0.160$, $p = 0.007$), and LAI use ($\beta = 0.139$, $p = 0.020$). Conversely, elevated CDS scores ($\beta = -0.168$, $p = 0.005$) and PANSS-N scores ($\beta = -0.201$, $p = 0.001$) continued to predict poorer FAB performance. Serum osmolarity, PANSS-G scores, employment status, and other covariates did not remain statistically significant in the multivariate model. The final model explained 16.9% of the variance in FAB scores ($F(8,238) = 7.252$, $p < 0.001$) (Table 4).

Figure 2 illustrates the relationship between the observed FAB scores and the values predicted by the model. This scatterplot highlights how several predictors, including WBV at HSR, living arrangement, and the use of LAI antipsychotics, contribute to the variance in observed FAB scores, alongside other factors such as serum osmolarity, CDS, PANSS-N, PANSS-G, and employment status.

An alternative multivariate model was constructed that included WBV at LSR instead of WBV at HSR to mitigate potential multicollinearity. This supplementary model for executive function incorporated WBV at LSR, serum osmolarity, depression severity (CDS), PANSS-Negative and General subscales, employment status, living arrangement, and LAI usage. In this model, WBV at LSR remained a significant predictor of better FAB scores ($\beta = 0.123$, $p = 0.036$), while higher CDS scores ($\beta = -0.167$, $p = 0.005$) and PANSS-N scores ($\beta = -0.201$, $p = 0.001$) were significantly associated with poorer executive performance. Living with family ($\beta = 0.161$, $p = 0.006$) and LAI use ($\beta = 0.137$, $p = 0.022$) also predicted higher FAB scores. Serum osmolarity and other variables showed positive but non-significant trends. The model accounted for 16.9% of the variance in FAB scores ($F(8,238) = 7.259$, $p < 0.001$) (Supplementary Table 1).

Regression analyses were conducted to identify factors associated with Stroop 5 performance, a task that evaluates interference control by measuring participants' ability to suppress automatic responses under cognitively demanding conditions. In the univariate analyses, better Stroop 5 performance—reflected by shorter completion times—was significantly associated with higher WBV at LSR ($\beta = -0.138$, $p = 0.030$) and WBV at HSR ($\beta = -0.141$, $p = 0.026$), living with family ($\beta = -0.241$, $p < 0.001$), current smoking ($\beta = -0.127$, $p = 0.045$), and the use of LAI ($\beta = -0.152$, $p = 0.017$). In contrast, poorer Stroop 5 performance was associated with higher scores on the CDS ($\beta = 0.130$, $p = 0.041$), the PANSS-N ($\beta = 0.134$, $p = 0.035$), and the PANSS-G ($\beta = 0.204$, $p = 0.001$), indicating that greater symptom burden was related to reduced cognitive control.

The multivariate model included variables found to be significant in the univariate analyses. In this model, three predictors remained statistically significant: WBV at HSR ($\beta = -0.134$, $p = 0.025$), PANSS-G scores ($\beta = 0.176$, $p = 0.004$), and living arrangement (with family vs. alone or in social housing; $\beta = -0.233$, $p < 0.001$). CDS ($\beta = 0.103$, $p = 0.086$), PANSS-N ($\beta = 0.094$, $p = 0.120$), smoking status ($\beta = -0.088$, $p = 0.146$), and LAI use ($\beta = -0.096$, $p = 0.113$) did not remain statistically significant in the multivariate model. The final model accounted for 13.8% of the variance in Stroop 5 performance ($F(7,239) = 6.630$, $p < 0.001$). Full regression coefficients and confidence intervals are presented in Supplementary Table 2.

An alternative multivariate model was constructed that included WBV at LSR while excluding WBV at HSR. This model yielded similar findings: WBV at LSR remained a statistically significant predictor of Stroop 5 performance ($\beta = -0.134$, $p = 0.025$), along with the PANSS-G ($\beta = 0.179$, $p = 0.003$) and living arrangement ($\beta = -0.234$, $p < 0.001$). The model explained 13.8% of the variance in

Table 4 Univariate and multivariate regression analyses of clinical, demographic, hemorheological, and biochemical predictors of executive functioning (FAB Scores) in male patients with schizophrenia in remission

	Unstandardized			Standardized		
	B	SE	Lower	Upper	β	*p* value
Univariate regression analysis						
WBV at LSR	0.021	0.010	0.001	0.040	0.134	**0.035**
WBV at HSR	0.429	0.202	0.032	0.826	0.135	**0.034**
Serum osmolarity (mOsm/L)	0.141	0.054	0.035	0.248	0.165	**0.009**
Calgary Depression Scale (CDS)	-0.278	0.078	-0.431	-0.124	-0.222	**< 0.001**
PANSS Positive Scale (PANSS-P)	-0.099	0.129	-0.352	0.155	-0.049	0.445
PANSS Negative Scale (PANSS-N)	-0.324	0.084	-0.490	-0.157	-0.238	**< 0.001**
PANSS General Symptoms Scale (PANSS-G)	-0.144	0.066	-0.274	-0.014	-0.138	**0.030**
age	0.018	0.017	-0.015	0.051	0.068	0.288
duration of illness	0.026	0.026	-0.025	0.076	0.064	0.320
Marital status	-0.156	0.461	-1.063	0.751	-0.022	0.735
Educational Level (> 8 years vs. < 8years)	0.164	0.321	-0.470	0.797	0.032	0.611
Employment Status (employed vs. others)	0.721	0.352	0.027	1.414	0.130	**0.042**
Living Arrangement (with family vs. alone/social home)	1.246	0.438	0.384	2.109	0.179	**0.005**
Smoking	0.342	0.323	-0.295	0.980	0.067	0.291
Family History of Psychiatric Illness	0.500	0.321	-0.133	1.133	0.099	0.121
Long-Acting Injectable Antipsychotics (LAI)	1.008	0.317	0.384	1.632	0.199	**0.002**
History of Suicidality	-0.344	0.523	-1.374	0.686	-0.042	0.511
Multivariate regression analysis						
WBV at HSR	0.390	0.185	0.025	0.755	0.122	**0.037**
Serum osmolarity (mOsm/L)	0.090	0.051	-0.009	0.190	0.106	0.075
Calgary Depression Scale (CDS)	-0.211	0.074	-0.356	-0.066	-0.168	**0.005**
PANSS Negative Scale (PANSS-N)	-0.273	0.080	-0.431	-0.116	-0.201	**0.001**
PANSS General Symptoms Scale (PANSS-G)	-0.086	0.062	-0.208	0.036	-0.083	0.165
Employment Status (employed vs. others)	0.403	0.327	-0.241	1.048	0.073	0.219
Living Arrangement (with family vs. alone/social home)	1.112	0.407	0.310	1.915	0.160	**0.007**
Long-Acting Injectable Antipsychotics (LAI)	0.703	0.301	0.111	1.296	0.139	**0.020**

CDS, Calgary Depression Scale for assessing depressive symptoms; TMT, Trail Making Test; FAB, Frontal Assessment Battery; PANSS-P, Positive scale of the Positive and Negative Syndrome Scale; PANSS-N, Negative scale of the Positive and Negative Syndrome Scale; PANSS-G, General Symptoms scale of the Positive and Negative Syndrome Scale; WBV at LSR, Whole Blood Viscosity at Low Shear Rate; WBV at HSR, Whole Blood Viscosity at High Shear Rate. Statistical significance set at 0.05

Stroop 5 scores ($F(7,239) = 6.630$, $p < 0.001$) (Supplementary Table 3).

To identify factors influencing TMT-A performance—a task measuring visual attention and processing speed—regression analyses were performed. Univariate results indicated that longer completion times, reflecting diminished attentional capacity, were significantly associated with higher scores on both the PANSS-P ($\beta = 0.176$, $p = 0.006$) and PANSS-N ($\beta = 0.145$, $p = 0.022$) subscales. In contrast, better performance (i.e., shorter completion times) was associated with higher WBV at HSR ($\beta = -0.139$, $p = 0.029$). In the multivariate model, three predictors remained statistically significant: WBV at HSR ($\beta = -0.134$, $p = 0.032$), PANSS-P ($\beta = 0.163$, $p = 0.010$), and PANSS-N ($\beta = 0.125$, $p = 0.047$). This model accounted for 5.4% of the variance in TMT-A performance ($F(3,243) = 5.656$, $p = 0.001$). Full regression results are available in Supplementary Table 4.

A supplementary multivariate model was also constructed for TMT-A performance, incorporating WBV at LSR instead of WBV at HSR, alongside the PANSS-P and PANSS-N subscale scores. In this model, all three predictors were statistically significant: WBV at LSR ($\beta = -0.122$, $p = 0.052$), PANSS-P ($\beta = 0.165$, $p = 0.009$), and PANSS-N ($\beta = 0.125$, $p = 0.046$). The model explained 5.1% of the variance in TMT-A performance ($F(3,243) = 5.368$, $p = 0.001$) (Supplementary Table 5).

Regression models were used to examine factors associated with performance on the Trail Making Test-B (TMT-B), a task that evaluates cognitive flexibility and the ability to alternate attention between competing stimuli. In univariate analyses, longer completion times—indicative of poorer cognitive flexibility—were significantly associated with higher PANSS-P ($\beta = 0.179$, $p = 0.005$) and PANSS-N scores ($\beta = 0.138$, $p = 0.031$). Additionally, higher WBV at HSR ($\beta = -0.142$, $p = 0.026$) was associated with shorter completion times, suggesting better cognitive flexibility. In the multivariate model, WBV at HSR ($\beta = -0.137$, $p = 0.028$) and PANSS-P scores ($\beta = 0.166$, $p = 0.008$) remained statistically significant

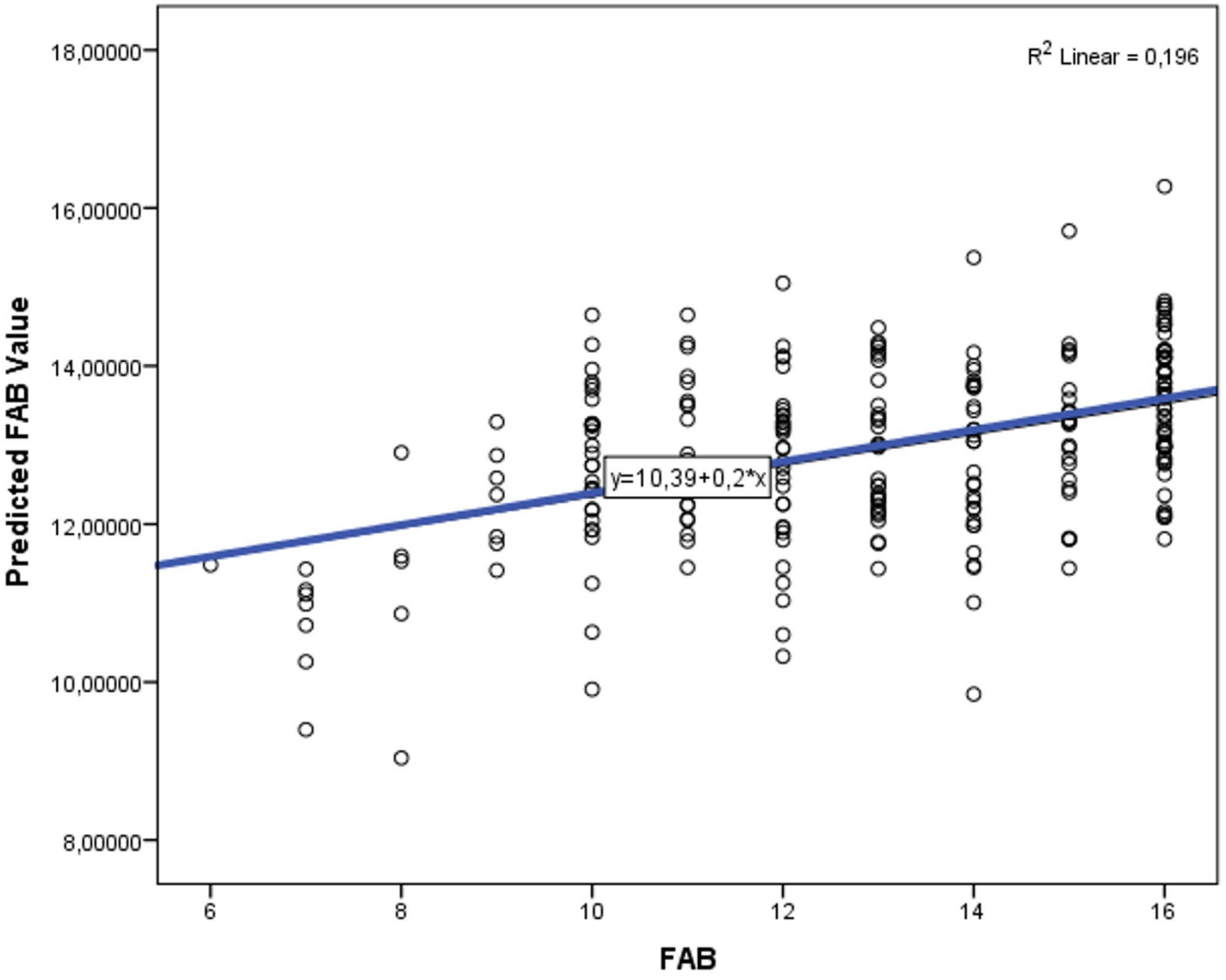

Fig. 2 Multivariate regression model predicting FAB scores based on WBV at HSR, serum osmolarity, PANSS-N, PANSS-G and functional variables (employment, living arrangement, LAI use)

predictors of TMT-B performance. PANSS-N scores ($\beta = 0.116$, $p = 0.063$) did not reach statistical significance. This model accounted for 5.4% of the variance in TMT-B scores ($F(3,243) = 5.647$, $p = 0.001$). Full statistical results are presented in Supplementary Table 6.

Discussion

The present study underscores significant associations between cognitive performance and systemic physiological parameters—specifically hemorheological factors such as WBV at HSR and LSR, as well as biochemical markers like serum osmolarity—in male patients with schizophrenia in remission. Notably, elevated WBV at HSR was positively correlated with enhanced executive functioning, as reflected in higher scores on the FAB and faster completion times on the Stroop 5, TMT-A and TMT-B. Similarly, higher serum osmolarity was associated with better executive performance. Prior research in the general population has identified associations between serum osmolarity, blood viscosity, and cognitive function [23, 31–32], while alterations in these parameters have also been observed in schizophrenia [17–18, 45]. However, the current study extends this body of knowledge by specifically investigating these systemic variables in relation to cognitive performance among remitted schizophrenia patients. To our knowledge, this is among the first studies to examine the interplay between serum osmolarity and blood viscosity (at both LSR and HSR) and neurocognition in this population, providing novel insight into the physiological underpinnings of cognitive dysfunction in schizophrenia. These results align with existing evidence demonstrating that cognitive deficits persist even during clinical remission and are critical determinants of long-term functional outcomes and quality of life [46–47].

These findings are further contextualized when compared with prior research investigating hemorheological parameters in schizophrenia across various clinical

states. In a sample partially composed of patients with schizophrenia, Kalelioğlu et al. reported elevated serum osmolarity in patients experiencing neuroleptic malignant syndrome (NMS) (301.83 ± 20.27 mOsm/L) compared to non-NMS controls (294.20 ± 5.92 mOsm/L), suggesting that osmolarity may reflect systemic stress and fluid imbalance during acute states [45]. Interestingly, our remission-phase patients exhibited a mean serum osmolarity of 294.01 ± 2.94 mOsm/L—nearly identical to Kalelioğlu's control group—supporting the hypothesis that osmolarity stabilizes as clinical symptoms subside. In a separate investigation, Balcıoğlu et al. observed significantly reduced WBV at both LSR (first-episode schizophrenia: 46.48 ± 3.01, schizophrenia with acute exacerbation: 47.51 ± 2.62) and HSR (first-episode schizophrenia: 16.56 ± 0.15, schizophrenia with acute exacerbation: 16.53 ± 0.13) in acute schizophrenia compared to healthy controls (LSR: 57.63 ± 2.86; HSR: 17.22 ± 0.14), which aligns with the broader notion that acute psychotic episodes may impair hemorheological homeostasis [17]. Our remission sample showed WBV values (at LSR: 48.87 ± 16.36; at HSR: 16.67 ± 0.79) that approximate those of stabilized patients, suggesting that osmolar and hemorheological alterations may influence both residual symptoms and cognitive functioning, even during remission. A complementary study by Balcıoğlu et al. focusing on treatment-resistant schizophrenia (TRS) found even lower WBV at HSR (15.54 ± 3.39) and LSR (47.88 ± 19.16) in TRS compared to remitted patients (HSR: 16.76 ± 1.03; LSR: 50.34 ± 21.04) and controls, suggesting a gradient of physiological restoration along the illness continuum [18]. The hemorheological profile of our remission-phase patients closely aligns with that of Balcıoğlu's remitted cohort, further reinforcing the interpretation that systemic parameters such as WBV and osmolarity are sensitive to illness phase and may represent indirect markers of both disease burden and cognitive potential.

The descriptive analysis of our sample revealed a median serum osmolarity of 294.77 mOsm/L, with a narrow range (276.82 to 298.18 mOsm/L), placing the majority of patients within the upper end of the typical physiological range (275–295 mOsm/L) [48]. Notably, a considerable portion of our remitted male patients (58 individuals) exhibited osmolarity levels exceeding 295 mOsm/L, a threshold often associated with mild dehydration or prolonged fasting [24–25]. This finding suggests the presence of subtle, yet potentially relevant, alterations in fluid balance even during a phase of clinical remission in schizophrenia. The subclinical variations in systemic hydration may impact neurovascular coupling and metabolic efficiency, potentially contributing to the persistent cognitive deficits observed in schizophrenia [49]. Therefore, monitoring and potentially addressing even mild deviations in serum osmolarity could be a relevant consideration for optimizing cognitive outcomes in this population. Regarding hemorheology, the WBV at LSR and at HSR appear to be within the spectrum reported in other studies using the De Simone formula [17–18], suggesting that while there might be individual variability, the overall hemorheological profile of our remitted sample is consistent with existing literature.

The relationship between blood viscosity and cognitive function is nuanced and underexplored in schizophrenia, though evidence from other populations has established its significance in systemic and cerebral physiology. Determinants of blood rheology, including WBV, hematocrit (HCT), and plasma viscosity (PV), are critical in maintaining cerebral perfusion, oxygen delivery, and vascular integrity. These factors have traditionally been associated with risks for stroke, coronary events, and cognitive decline, particularly when blood viscosity is excessively elevated, leading to impaired microcirculation [50]. However, our findings challenge this conventional narrative, showing that higher WBV, at both LSR and HSR, correlates with better executive function as measured by FAB scores.

This seemingly paradoxical finding may reflect an optimal rheological balance that supports systemic circulatory stability and may indirectly influence cerebral perfusion. While cerebral blood flow is tightly regulated by autoregulatory mechanisms [51], elevated viscosity at HSR—within a physiological range—may help sustain vascular tone and perfusion pressure, particularly during systemic stress [52]. Furthermore, higher WBV may reflect a systemic milieu with adequate hematocrit and protein levels, essential for oxygen-carrying capacity and vascular integrity [53–54]. These factors could mitigate the risk of hypoperfusion-related cognitive impairments, although the causal contribution of viscosity to neurocognitive outcomes remains speculative and warrants further investigation [53].

In contrast to the detrimental effects of extreme viscosity, which impair microcirculation and promote ischemic events, moderate increases in viscosity may serve a protective role. For example, higher hemoglobin levels, which are closely related to oxygen-carrying capacity and also contribute to whole blood viscosity, have been associated with better cerebral perfusion and cognitive resilience in aging populations [55]. These findings underscore the complexity of the relationship between blood rheology and cognitive function, which is likely context-dependent and modulated by systemic factors such as inflammation, oxidative stress, and endothelial health.

In schizophrenia, where systemic inflammation and vascular dysregulation are prevalent, higher viscosity may indicate a compensatory mechanism that preserves executive functioning by enhancing oxygen and

nutrient delivery to the brain [56]. This interpretation contrasts with the traditional view that lower viscosity is universally beneficial and highlights the need for further research to delineate the optimal rheological conditions for cognitive health in schizophrenia.

While systemic hydration and electrolyte status were not directly measured, serum osmolarity can indirectly reflect underlying fluid balance and solute concentration. Within a physiological range, slightly elevated osmolarity may suggest efficient systemic regulation, supporting optimal neurovascular function and perfusion of key cognitive regions such as the prefrontal cortex. This aligns with the hypothesis that subtle variations in osmolarity—within normal limits—may influence cognitive outcomes by modulating metabolic efficiency and vascular stability in the brain.

Serum osmolarity emerged as a significant biochemical correlate of executive function, with higher osmolarity linked to better FAB scores in this study.

While systemic hydration and electrolyte status were not directly measured in this study, serum osmolarity serves as an indirect biomarker of fluid balance and solute concentration. Within a physiological range, slightly elevated osmolarity may reflect efficient systemic regulation that supports optimal neurovascular coupling and cerebral perfusion—particularly in cognitively critical regions such as the prefrontal cortex. Although previous research in non-psychiatric populations, such as the studies by Nishi et al. [24] and Mantantzis et al. [49], has linked dehydration (typically associated with increased osmolarity) to poorer cognitive performance over time, our findings suggest a more complex relationship. In individuals with schizophrenia in remission, modest elevations in osmolarity within the upper-normal range may represent a regulated, metabolically adaptive state rather than frank dehydration. These findings underscore that the cognitive impact of osmolarity might be context-dependent and modulated by interacting physiological systems—such as neuroendocrine regulation, vascular tone, and glucose transport capacity—rather than a linear function of hydration status alone. Thus, hydration-related physiological markers, including serum osmolarity, may be relevant to cognitive health even in psychiatric populations, though their interpretation requires consideration of broader systemic dynamics.

Conversely, hypo-osmolar states may negatively affect cognitive performance by disrupting neuronal homeostasis and fluid balance. Factors such as antipsychotic-induced fluid retention, chronic inflammation, or metabolic dysregulation common in schizophrenia may lead to lower osmolarity, potentially compounding the cognitive deficits already present in this population [27, 29–30]. Furthermore, individuals with schizophrenia may be particularly vulnerable to developing hypo-osmolar states due to issues like psychogenic polydipsia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) associated with some antipsychotics [21–22, 27]. This interplay underscores the importance of monitoring serum osmolarity as a potential biomarker for both cognitive and systemic health in schizophrenia patients. These findings, supported by longitudinal and prospective studies, highlight the complex relationship between hydration, osmolarity, and cognitive function. Future research should explore whether interventions aimed at optimizing hydration can improve cognitive outcomes, particularly in populations vulnerable to hypo-osmolar states, such as individuals with schizophrenia.

Although not the primary focus of this study, our findings reaffirm the established association between symptom severity and cognitive performance. Specifically, negative symptoms—as measured by the PANSS-N—were linked to poorer executive functioning across Stroop 5, TMT-A/B, and FAB, consistent with previous literature highlighting their impact on cognition in schizophrenia [57–58]. Depressive symptoms, while generally not robustly associated with cognitive deficits in past studies, showed modest correlations with executive functioning in our remission-phase sample. This may reflect subthreshold depressive symptoms that subtly affect cognition through mechanisms such as reduced motivation or psychomotor slowing [59–60]. These findings warrant further investigation, particularly regarding the cognitive impact of mild depressive symptoms during remission.

The interplay between cognitive performance and systemic physiological parameters—particularly WBV and serum osmolarity—reveals a complex and dynamic landscape in schizophrenia. In this study, the observed positive correlation between higher WBV at high shear rate (HSR) and executive functioning in remitted male patients may suggest that optimal hemorheological conditions support cognitive resilience during remission. Notably, Balcıoğlu et al. reported significantly reduced WBV in both first-episode and acutely exacerbated schizophrenia, indicating that lower viscosity may be a feature of acute psychotic states [17]. This reduction has been associated with systemic inflammation and impaired microcirculatory function, factors that likely contribute to neurovascular dysregulation in early or decompensated illness stages. In addition, Gyawali & Richards have demonstrated that altered hemorheology due to systemic inflammation and oxidative stress contributes to impaired tissue perfusion and vascular dysfunction, which are relevant in neuropsychiatric disorders [28].Additionally, in their comparative study of treatment-resistant versus remitted schizophrenia, Balcıoğlu et al. found lower WBV at both LSR and HSR in the treatment-resistant group, potentially reflecting

vascular inefficiency and a hemodynamic profile unfavorable to cognitive functioning [18].

Additionally, Kalelioğlu et al. found elevated serum osmolarity in cases of NMS, a severe antipsychotic-induced condition, likely due to hemoconcentration secondary to dehydration [45]. In contrast, our remitted schizophrenia sample exhibited serum osmolarity values within the normal to upper-normal physiological range, possibly reflecting a more regulated fluid balance during clinical stability.

These phase-dependent variations in hemorheological and biochemical markers highlight the importance of considering illness stage when interpreting physiological correlates of cognition in schizophrenia. While our findings suggest that higher WBV within a normative range may be associated with preserved cognitive performance during remission, they contrast with the reduced WBV seen in acute psychosis and the osmolar abnormalities noted in NMS. This underscores the need for longitudinal and mechanistic investigations to elucidate how systemic physiological dynamics influence cognitive outcomes across different clinical stages of schizophrenia.

Finally, while serum osmolarity showed a positive correlation with executive function (FAB scores) in the univariate analysis, it did not remain an independent predictor in the multivariate model. This suggests that its initial association might be mediated by other factors included in the multivariate model. However, the trend observed in the univariate analysis warrants consideration, as subtle alterations in hydration and electrolyte balance, reflected by serum osmolarity, could still contribute to cognitive efficiency in schizophrenia, even if not as a primary independent driver when accounting for other clinical and physiological variables.

In contrast, the multivariate analysis identified living arrangements (living with family), employment status (being employed), and the use of LAI as independent predictors of better executive function (FAB scores). The association with living with family might reflect increased social support and stability, factors known to positively influence overall well-being and potentially cognitive reserve in individuals with schizophrenia. Similarly, employment often provides structure, social engagement, and a sense of purpose, which could contribute to better cognitive functioning. The positive association with LAI use might be related to improved medication adherence and more stable antipsychotic treatment, potentially leading to better overall symptom management and consequently, enhanced cognitive performance. These findings underscore the complex interplay of social, clinical, and treatment-related factors in shaping cognitive outcomes in schizophrenia, highlighting potential avenues for supportive interventions alongside physiological considerations.

It is noteworthy that our study did not find significant associations between cognitive functioning (as measured by FAB, Stroop, and TMT) and either age or duration of illness within this cohort of male patients in remission. This lack of correlation could suggest that in a relatively stable phase of the illness, the impact of cumulative factors like age and illness chronicity on these specific cognitive domains might be less pronounced, or that other factors, such as the physiological parameters investigated here, symptom severity, and medication effects, may play a more dominant role in shaping cognitive outcomes in remitted patients. Future longitudinal studies with larger and more heterogeneous samples, encompassing various stages of schizophrenia, would be beneficial to further explore the long-term impact of age and illness duration on cognitive function in this population.

Inflammation and altered hemorheology are increasingly recognized as interconnected mechanisms contributing to both the pathophysiology of schizophrenia. In this study, higher WBV was associated with better executive functioning in remitted patients, potentially reflecting more stable vascular dynamics and improved cerebral perfusion. This finding aligns with prior evidence showing reduced WBV during acute psychotic states, which are often characterized by heightened systemic inflammation and compromised microvascular integrity.

These results highlight the relevance of WBV as a potential biomarker bridging systemic physiology and neurocognition in schizophrenia. Future research should explore the mechanistic pathways through which hemorheological and inflammatory profiles influence cognition, with attention to illness phase and treatment response.

Implications for future research and interventions

This study underscores the importance of integrating hemorheological and biochemical parameters into schizophrenia research. Future studies should explore interventions aimed at optimizing blood viscosity and osmolarity, such as hydration protocols, antiplatelet agents, or neuroprotective therapies, to improve cognitive outcomes. Neuroimaging studies could elucidate the mechanisms linking systemic physiology to cognitive function, particularly in the prefrontal cortex.

By advancing our understanding of the interplay between cognitive function, systemic physiology, and disease severity, this research contributes to the growing body of evidence supporting a holistic approach to schizophrenia care. These insights hold potential for improving both cognitive and functional outcomes in this complex and debilitating disorder.

Limitations

This study provides valuable insights into the relationship between cognitive function, hemorheological parameters, and biochemical alterations in male patients with schizophrenia in remission, but several limitations must be acknowledged. The cross-sectional design limits the ability to establish causality, and the exclusive focus on male patients restricts generalizability to females, who may exhibit distinct physiological patterns. By including only patients in clinical remission, the study may not capture the full spectrum of disease severity, particularly during acute phases. Although serum osmolarity and WBV were examined, the study did not assess other relevant biomarkers, such as inflammatory cytokines or oxidative stress markers, which may offer a more comprehensive view of systemic alterations. Lifestyle factors like hydration, diet, and physical activity, as well as the effects of different antipsychotic regimens, were not explicitly controlled, potentially influencing the findings. The single-center design and lack of a healthy control group further limit generalizability and context for interpretation. Additionally, single-time-point measurements of physiological parameters do not account for fluctuations over time, and psychometric tools, while robust, did not cover all cognitive domains, such as verbal memory and social cognition. Future studies should adopt longitudinal designs, include diverse populations, and examine a broader range of biomarkers and cognitive domains to validate and expand these findings.

Conclusion

This study highlights the significant associations between cognitive performance, hemorheological parameters, and biochemical markers in male patients with schizophrenia in remission. Our findings suggest that higher WBV is linked with better executive functioning, indicating that favorable blood flow properties may support cerebral perfusion and contribute to preserved cognitive abilities in stable phases of the illness. Similarly, higher serum osmolarity was associated with improved cognitive outcomes, emphasizing the relevance of systemic hydration and electrolyte regulation in this population.

These results offer new insights into the physiological correlates of cognition in schizophrenia and suggest that measures such as WBV and osmolarity may reflect broader systemic conditions influencing brain function. While causality cannot be inferred, these parameters may serve as accessible clinical markers of cognitive status in remitted patients.

Future research should further explore the mechanistic links between vascular, metabolic, and cognitive domains in schizophrenia, particularly across different illness stages. Longitudinal studies assessing the impact of targeted interventions to optimize fluid balance and blood rheology may help identify novel strategies to enhance cognitive and functional outcomes in affected individuals.

Supplementary Information

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Supplementary Material 1

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Author contributions

Study concept and design: I.Ö.Ü. and T.D.B. Acquisition of data: I.Ö.Ü. Analysis and interpretation of data: I.Ö.Ü, M.P.A, D.A.A, T.D. and T.D.B. Literature research and data preparation: I.Ö.Ü, M.P.A, D.A.A, T.D. and T.D.B. Statistical analysis: I.Ö.Ü, T.D. and T.D.B. Drafting of the manuscript: I.Ö.Ü. Critical revision of the manuscript: all authors. Administrative, technical or material support: all authors.

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Data availability

The data that support the findings of this study are not publicly available due to privacy concerns regarding participant data. However, the data are available from the corresponding author, I.Ö.Ü., upon reasonable request. Please contact I.Ö.Ü. at ipekozonder@gmail.com for further inquiries.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Medipol University (Approval Date: 26.12.2024; Approval Number: 1321). Informed consent was obtained from all participants involved in the study, including consent for the publication of study results, with anonymity maintained throughout participation.

Consent for publication

Consent for publication was obtained from all participants included in the study.

Competing interests

The authors declare no competing interests.

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References

1. Orrico-Sánchez A, López-Lacort M, Muñoz-Quiles C, Sanfélix-Gimeno G, Díez-Domingo J. Epidemiology of schizophrenia and its management over 8-years period using real-world data in Spain. BMC Psychiatry. 2020;20:1–9.

2. Ruiz-Castañeda P, Santiago Molina E, Aguirre Loaiza H, Daza González MT. Positive symptoms of schizophrenia and their relationship with cognitive and emotional executive functions. Cogn Res Princ Implic. 2022;7(1):78. https://doi.org/10.1186/s41235-022-00428-z. PMID: 35960384; PMCID: PMC9374871.
3. Weickert TW, Goldberg TE. First- and second-generation antipsychotic medication and cognitive processing in schizophrenia. Curr Med Group LLC 1. 2005;7:304–10. Current Psychiatry Reports.
4. Nuechterlein KH, Subotnik KL, Green MF, Ventura J, Asarnow RF, Gitlin MJ, Yee CM, Gretchen-Doorly D, Mintz J. Neurocognitive predictors of work outcome in recent-onset schizophrenia. Schizophr Bull. 2011;37(Suppl 2):S33–40. https://doi.org/10.1093/schbul/sbr084. PMID: 21860045; PMCID: PMC3160123.
5. McCutcheon RA, Keefe RSE, McGuire PK. Cognitive impairment in schizophrenia: aetiology, pathophysiology, and treatment. Mol Psychiatry. 2023;28(5):1902–1918. doi: https://doi.org/10.1038/s41380-023-01949-9. Epub 2023 Jan 23. Erratum in: Mol Psychiatry. 2023;28(5):1919. https://doi.org/10.1038/s41380-023-01984-6. PMID: 36690793; PMCID: PMC10575791.
6. Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiatry. 2005;162(12):2233–45. https://doi.org/10.1176/appi.ajp.162.12.2233. PMID: 16330585.).
7. Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch Gen Psychiatry. 2009;66(8):811–22. https://doi.org/10.1001/archgenpsychiatry.2009.91. PMID: 19652121; PMCID: PMC2888482.
8. Scarpina F, Tagini S. The Stroop color and word test. Front Psychol. 2017;8:557. https://doi.org/10.3389/fpsyg.2017.00557. PMID: 28446889; PMCID: PMC5388755.
9. Carone DA, Strauss E, Sherman EMS, Spreen O. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*: A Review of: (3rd ed.), Oxford University Press, New York, 2006. *Applied Neuropsychology*, *14*(1), 62–63. https://doi.org/10.1080/09084280701280502
10. Aiello EN, Esposito A, Gramegna C, Gazzaniga V, Zago S, Difonzo T, Appollonio IM, Bolognini N. The Frontal Assessment Battery (FAB) and its sub-scales: validation and updated normative data in an Italian population sample. Neurol Sci. 2022;43(2):979–984. doi: https://doi.org/10.1007/s10072-021-05392-y. Epub 2021 Jun 29. Erratum in: Neurol Sci. 2022;43(11):6621. https://doi.org/10.1007/s10072-022-06087-8. Erratum in: Neurol Sci. 2023;44(1):425. doi: https://doi.org/10.1007/s10072-022-06295-2. PMID: 34184168; PMCID: PMC8789707.
11. Szöke A, Trandafir A, Dupont ME, Meary A, Schürhoff F, Leboyer M. Longitudinal studies of cognition in schizophrenia: meta-analysis. Br J Psychiatry. 2008;192(4):248–57.
12. Chugunov, D. A., Shmilovich, A. A., Larina, M. R., Goncharenko, S. N., Moiseeva,T. V., Ryauzova, E. S.,… Bukinich, A. A. (2024). Clinical and Psychometric Features of Cognitive and Negative Disorders in Schizophrenia. Neuroscience and Behavioral Physiology, 54(6), 859–865.
13. Devereux RB, Case DB, Alderman MH, Pickering TG, Chien S, Laragh JH. Possible role of increased blood viscosity in the hemodynamics of systemic hypertension. Am J Cardiol. 2000;85(10):1265–8.
14. Rafnsson S, Deary IJ, Whiteman MC, Rumley A, Lowe GDO, Fowkes FGR. Haemorheological predictors of cognitive decline: the Edinburgh artery study. Age Ageing. 2010;39(2):217–22.
15. Elwood PC, Pickering J, Gallacher JEJ. Cognitive function and blood rheology: results from the caerphilly cohort of older men. Age Ageing. 2001;30(2):135–9.
16. Smith CJ, Morris RG, Markus HS. Whole blood viscosity and microvascular abnormalities in Alzheimer's disease. Clin Hemorheol Microcirc. 2009;42(1):3–9.
17. Balcıoğlu YH, Gökçay H, Yeşilkaya ÜH, Namlı MN. Blood viscosity and inflammation in first-episode and acute exacerbations of schizophrenia: A case-control study with healthy controls. Nöro Psikiyatri Arşivi. 2023;60(3):265–70. https://doi.org/10.29399/npa.28394.
18. Balcioglu, et al. Blood viscosity and inflammatory indices in treatment-resistant schizophrenia: A retrospective cross-sectional study. Dusunen Adam J Psychiatr Neurol Sci. 2023;36(2):81–9. https://doi.org/10.14744/DAJPNS.2023.00210.
19. Bourque CW. Central mechanisms of osmosensation and systemic osmoregulation. Nat Rev Neurosci. 2008;9(7):519–31. https://doi.org/10.1038/nrn2400. Epub 2008 May 29. PMID: 18509340.
20. Walsh P, Spelman L, Sharifi N, Thakore JH. Male patients with paranoid schizophrenia have greater ACTH and cortisol secretion in response to metoclopramide-induced AVP release. Psychoneuroendocrinology. 2005;30(5):431–7. Epub 2005 Jan 22. PMID: 15721055.
21. Pires BF, Oliveira JM, Kitayama GV, Tahan VC, Darwin FR, Saraiva LALC, Vilarinho CCT, Dorilêo GB, Amaral JPF, Santana LPB, Farid SP, Albuquerque TVC, Villani AB, Nascimento FS, Pelegrino LDG, Tambelli RA, de Figueiredo ÁT. Primary polydipsia and sIDH type D due to water-electrolytic disturbance in a schizophrenic patient: A case report and systematic review. Open J Psychiatry. 2025;15(1):1–15. https://doi.org/10.4236/ojpsych.2025.151001.
22. Makino, E., Hashimoto, T., Sako, A., Nanasawa, H., Enomoto, T., Hayakawa, T.,… Yanai,H. (2023). Comparison of severe hyponatremia in patients with and without psychiatric diseases: A single-center retrospective study. Psychiatry and Clinical Neurosciences Reports, 2(1), e77.).
23. Lee S, Min J, Kim B, et al. Serum sodium in relation to various domains of cognitive function in the elderly US population. BMC Geriatr. 2021;21:328. https://doi.org/10.1186/s12877-021-02260-4.
24. Nishi SK, Babio N, Paz-Graniel I, et al. Water intake, hydration status and 2-year changes in cognitive performance: a prospective cohort study. BMC Med. 2023;21:82. https://doi.org/10.1186/s12916-023-02771-4.
25. Singer KJ, Davy BM, Davy KP, Katz B. Associations between hydration status and executive function in Middle-Aged and older adults: findings from the nationally representative health and retirement study. J Nutr Gerontol Geriatr. 2024 Jul-Dec;43(3–4):165–83. Epub 2024 Oct 16. PMID: 39413153.
26. Russell A, Ciufolini S, Gardner-Sood P, Bonaccorso S, Gaughran F, Dazzan P, Pariante CM, Mondelli V. Inflammation and metabolic changes in first episode psychosis: preliminary results from a longitudinal study. Brain Behav Immun. 2015;49:25–9. Epub 2015 Jun 19. PMID: 26100489.
27. Bokhari SA, Al-Maktoum D, Alramahi G, Maallah D, Mukhtar MA. (2024). The complexity of managing Antipsychotic-Induced hyponatremia: A case series. Cureus, 16(10), e71038.
28. Gyawali P, Richards RS. Association of altered hemorheology with oxidative stress and inflammation in metabolic syndrome. Redox Rep. 2015;20(3):139–44.
29. Khasanova, A. K., Dobrodeeva, V. S., Shnayder, N. A., Petrova, M. M., Pronina, E.A., Bochanova, E. N.,… Nasyrova, R. F. (2022). Blood and urinary biomarkers of antipsychotic-induced metabolic syndrome. *Metabolites*, *12*(8), 726.
30. Pillinger, T., McCutcheon, R. A., Vano, L., Mizuno, Y., Arumuham, A., Hindley, G.,… Howes, O. D. (2020). Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *The Lancet Psychiatry*, *7*(1), 64–77.
31. Marioni RE, Stewart MC, Murray GD, Deary IJ, Fowkes FG, Lowe GD, Rumley A, Price JF. Peripheral levels of fibrinogen, C-reactive protein, and plasma viscosity predict future cognitive decline in individuals without dementia. Psychosom Med. 2009;71(8):901–6. https://doi.org/10.1097/PSY.0b013e3181b1e538. Epub 2009 Aug 6. PMID: 19661193; PMCID: PMC2762963.
32. Li RY, Cao ZG, Li Y, Wang RT. Increased whole blood viscosity is associated with silent cerebral infarction. Clin Hemorheol Microcirc. 2015;59(4):301-7. https://doi.org/10.3233/CH-131760. PMID: 23988733.
33. Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry. 2005;162:441–9.
34. Aydemir Ö, Esen Danacı A, Deveci A, İçelli İ. Calgary şizofrenide depresyon ölçeği'nin Türkçe Versiyonunun Duyarlılığı ve Özgüllüğü. Nöropsikiyatri Arşivi. 2000;37(3):210–3.
35. Honer WG, Thornton AE, Chen EY, Chan RC, Wong JO, Bergmann A, Falkai P, Pomarol-Clotet E, McKenna PJ, Stip E, Williams R, MacEwan GW, Wasan K, Procyshyn R, Clozapine, Enhancement R, CARE) Study Group. (. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. N Engl J Med. 2006;354(5):472–82. https://doi.org/10.1056/NEJMoa053222. PMID: 16452559.
36. Taylor D, Barnes TRE, Young AH, Marsden J. The Maudsley prescribing guidelines in psychiatry. 13th ed. Wiley Blackwell; 2017.
37. de Simone G, Devereux RB, Chien S, Alderman MH, Atlas SA, Laragh JH. Relation of blood viscosity to demographic and physiologic variables and to cardiovascular risk factors in apparently normal adults. Circulation. 1990;81(1):107– 17. https://doi.org/10.1161/01.cir.81.1.107. PMID: 2297818.
38. Bhagat CI, Garcia-Webb P, Fletcher E, Beilby JP. Calculated vs measured plasma osmolalities revisited. Clin Chem. 1984;30(10):1703–5.
39. Fazekas AS, Funk GC, Klobassa DS, Rüther H, Ziegler I, Zander R, Semmelrock HJ. Evaluation of 36 formulas for calculating plasma osmolality. Intensive Care Med. 2013;39:302–8.
40. Kostakoglu AYŞE, Batur S, Tiryaki A, Gogus A. (1999). Reliability and validity of the Turkish version of the positive and negative syndrome scale (PANSS). Turk Psikoloji Dergisi, *14*(44).

41. Guy W. Clinical global impression scale. The ecdeuassessment manual for Psychopharmacology-Revised. Volume DHEW Publ No ADM. 1976;76(338):218–22.
42. Türkeş N, Can H, Kurt M, Dikeç BE. İz sürme testi'nin 20–49 Yaş Aralığında Türkiye Için norm Belirleme Çalışması. Turk Psikiyatri Derg. 2015;26:189–96.
43. Karakaş S, Irak M, Ersezgin Ö. Wisconsin kart Eşleme testi (WCST) ve Stroop testi TBAG formu Puanlarının test Içi ve testler-arası Ilişkileri. X Ulusal Psikoloji Kongresi Özet Kitabı. 1998;44.
44. Beyazkurk D, Ş Yönetici iş levler, İrkeç C, Yüksel N. Beyin ve Nöropsikoloji. Ankara: Çizgi Tıp Yayınevi; 123–33; 2003.
45. Kalelioglu T, Karamustafalioglu N, Celikel G, Genc A, Emul M. Serum osmolarity and blood viscosity as a potential explanation for the pathophysiology of neuroleptic malignant syndrome. Int J Psychiatry Clin Pract. 2019;23(4):307–10. https://doi.org/10.1080/13651501.2019.1617884.
46. McCutcheon RA, Keefe RS, McGuire PK. Cognitive impairment in schizophrenia: aetiology, pathophysiology, and treatment. Mol Psychiatry. 2023;28(5):1902–18.
47. Luvsannyam E, Jain MS, Pormento MKL, Siddiqui H, Balagtas ARA, Emuze BO, Poprawski T. (2022). Neurobiology of schizophrenia: a comprehensive review. Cureus, *14*(4).
48. Najem O, Shah MM, Zubair M et al. Serum Osmolality. [Updated 2024 Feb 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK567764/
49. Mantantzis K, Drewelies J, Duezel S, Steinhagen-Thiessen E, Demuth I, Wagner GG, Lindenberger U, Gerstorf D. Dehydration predicts longitudinal decline in cognitive functioning and well-being among older adults. Psychol Aging. 2020;35(4):517–28. https://doi.org/10.1037/pag0000471.
50. Snorri Rafnsson IJ, Deary MC, Whiteman A, Rumley GDO, Lowe F, Gerry R, Fowkes. Haemorheological predictors of cognitive decline: the Edinburgh Artery Study, *Age and Ageing*, Volume 39, Issue 2, March 2010, Pages 217–222. https://doi.org/10.1093/ageing/afp227
51. Willie CK, Tzeng YC, Fisher JA, Ainslie PN. Integrative regulation of human brain blood flow. J Physiol. 2014;592(5):841–59.
52. Lowe GDO. 1 Blood rheology in vitro and in vivo. Bailliere's Clin Haematol. 1987;1(3):597–636.
53. Lipowsky HH. Blood rheology aspects of the microcirculation. BIOMEDICAL HEALTH RESEARCH-COMMISSION Eur COMMUNITIES THEN IOS PRESS. 2007;69:307.
54. Lenz C, Rebel A, Waschke KF, Koehler RC, Frietsch T. Blood viscosity modulates tissue perfusion: sometimes and somewhere. Transfus Altern Transfus Med. 2008;9(4):265–72. https://doi.org/10.1111/j.1778-428X.2007.00080.x. PMID: 19122878; PMCID: PMC2519874.
55. Jonassaint CR, Varma VR, Chuang YF, Harris GC, Yasar S, Polinder-Bos H, Carlson MC. Lower hemoglobin is associated with poorer cognitive performance and smaller brain volume in older adults. J Am Geriatr Soc. 2014;62(5):972.
56. Najjar S, Pahlajani S, De Sanctis V, Stern JN, Najjar A, Chong D. Neurovascular unit dysfunction and blood–brain barrier hyperpermeability contribute to schizophrenia neurobiology: a theoretical integration of clinical and experimental evidence. Front Psychiatry. 2017;8:83.
57. Wu Q, Wang X, Wang Y, et al. Developments in biological mechanisms and treatments for negative symptoms and cognitive dysfunction of schizophrenia. Neurosci Bull. 2021;37:1609–24. https://doi.org/10.1007/s12264-021-00740-6.
58. Peng XJ, Hei GR, Yang Y, Liu CC, Xiao JM, Long YJ, Wu RR. The association between cognitive deficits and clinical characteristic in first-episode drug Naive patients with schizophrenia. Front Psychiatry. 2021;12:638773.
59. Chiappelli, J., Kochunov, P., DeRiso, K., Thangavelu, K., Sampath, H., Muellerklein,F.,… Hong, L. E. (2014). Testing trait depression as a potential clinical domain in schizophrenia. Schizophrenia research, 159(1), 243–248.
60. Harvey PD. Mood symptoms, cognition, and everyday functioning: in major depression, bipolar disorder, and schizophrenia. Innov Clin Neurosci. 2011;8(10):14–8. PMID: 22132366; PMCID: PMC3225134.

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