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Supplementary Material S1 Task implementation

1. Models, estimates, and analysis parameters

In the following sections, we will discuss the models we used in the study, detailing the choices, validations, parameters, and justifications for specific preferences based on the logic of the analysis. Since all of the data will be presented, the choices we made can be discussed, albeit in another location and from a different perspective, which we hope will increase the study's contribution.

2. Overview of the assumptions for analysis

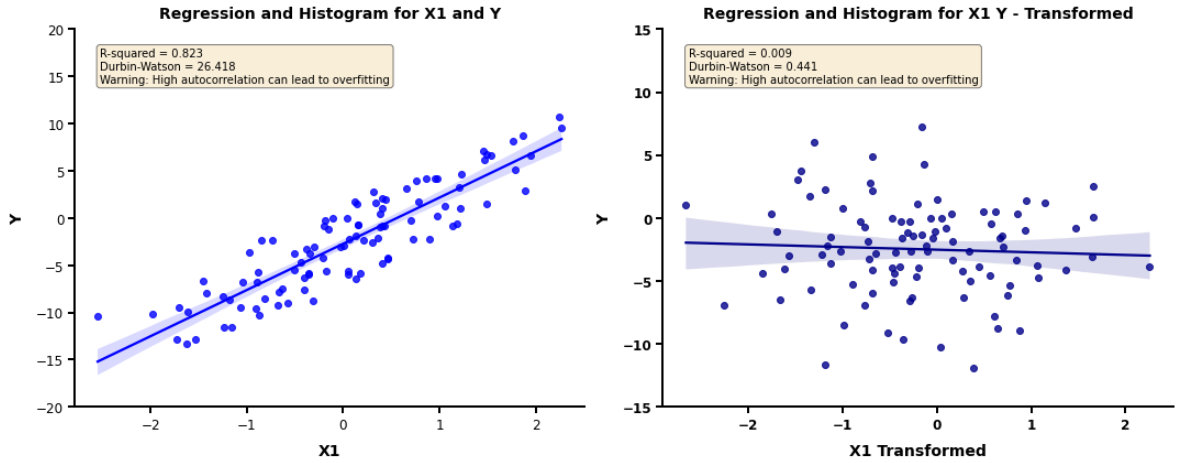
Population-based studies meticulously analyze an extensive array of demographic and clinical variables, ranging from straightforward measures like age and sex to more intricate factors such as socioeconomic status and pre-existing health conditions. However, despite a thorough examination of these variables, the predictive power of certain demographic factors is often inconsistent across studies. For instance, a meta-analysis by Griffiths et al.[1] found that variables like occupational status and geographic location frequently lack consistent predictive value across different studies. This discrepancy underscores the complexity inherent in modeling disease and treatment outcomes. It emphasizes the critical need for caution when interpreting study findings and the need to account for a diverse range of potential confounding factors. By considering the interplay between various demographic and clinical variables, researchers can develop more robust models and gain deeper insights into factors that influence health outcomes.

When evaluating the reliability of reported effects, it is fundamental to consider the width of CIs. For example, an effect size of 0.48 with a CI ranging from 0.27 to 0.76 suggests a moderate degree of uncertainty about the estimate. However, CIs that cross zero, such as from -0.72 to 0.14, indicate significant uncertainty and may challenge the credibility of the findings. Properly understanding and interpreting these intervals is essential in the scientific process, particularly for assessing the reliability and variability of estimates. Reports often overlook crucial statistical considerations, such as autocorrelation, multicollinearity, and the risk of overfitting.[2]

Autocorrelation occurs when residuals from one observation are correlated with residuals from another, violating the assumption of independence typically required in regression analyses. This can lead to inflated models and misleading significance tests. Multicollinearity involves high correlations among predictor variables, which can make it difficult to discern the individual effects of predictors on the outcome, often resulting in unstable coefficient estimates.[3] Overfitting happens when a model is excessively complex, capturing the noise along with the signal in the dataset, which reduces its ability to generalize to new data.[4]

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Supplementary Figure S1 Linear vs transformed associations between X1 and Y: implications for model fit and autocorrelation



Scatterplots illustrating the relationship between X1 and Y before (left) and after transformation (right). In the original scale, X1 shows a strong positive linear association with Y ($R^2 = 0.82$), but with evidence of autocorrelation (Durbin-Watson = 0.46), suggesting potential overfitting or violation of independence assumptions. After transformation, the association is attenuated ($R^2 = 0.09$), with improved residual independence (Durbin-Watson = 0.44), indicating that the initial relationship may have been driven by scale-dependent structure or non-stationarity. The shaded bands represent 95% confidence intervals around the fitted regression lines.

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

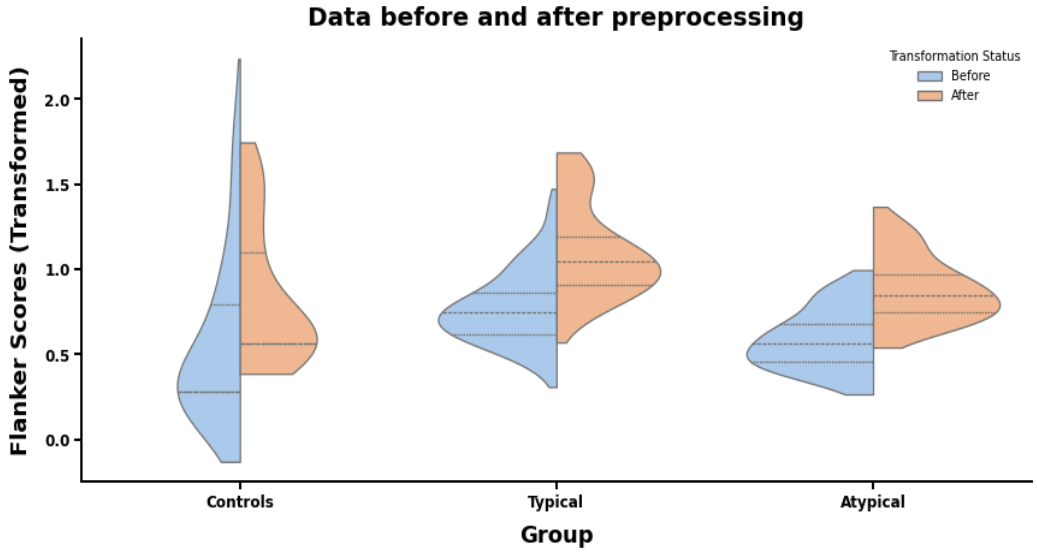
Addressing these issues is fundamental to ensuring the accuracy of model predictions and maintaining the integrity of the data. Before exploring the detailed methodology of our model, it is important to outline the strategies we employed to enhance the reliability and validity of our findings.[5] By systematically addressing these issues, our analysis aims to provide a more accurate and reliable interpretation of the data, ensuring that our findings can be confidently applied to real-world contexts. This rigorous approach to data analysis underscores and enhances the credibility of the outcomes. These strategies are designed to mitigate the above mentioned statistical challenges and ensure rigorous analysis.[6]

3. Data preprocessing and model building

Initially, we examined the data for missing or extreme values. We assessed the distributional properties of the variables by examining their kurtosis and skewness. Outliers

were identified using Z-scores and quartiles, with data points exceeding ± 2 SDs from the mean within the quartile range flagged as potential outliers. For categorical variables, after mapping, we refactored them for improved representation and analysis.[6] To illustrate the preprocessing steps, we present data from our pilot study using the Flanker task. Nevertheless, we meticulously examined all variables to determine whether or not transformation was necessary.

Supplementary Figure S2 Visualization of data normalization using Box-Cox transformation



These violin plots illustrate the distribution of Flanker reaction times (RTs) (transformed) before and after applying the Box-Cox transformation with a power parameter. To optimize the skewness reduction, the lambda parameter for the Box-Cox transformation was determined using maximum likelihood estimation. The analysis tested lambda values ranging from -2.0 to 2.0 at 0.1 intervals, finding that a lambda of 0.5 maximized the log-likelihood function, indicating the most favorable transformation for normalizing the data.[7]

Initially, the data showed a considerable right skewness and visible outliers, particularly noticeable in the left violins, with long tails extending from the median. Following the transformation, the graphs' distribution was notably more compact and symmetric: the tail lengths were reduced, and the data points were more tightly clustered around the median. This indicates a reduction in skewness and a uniform spread, which are preferable for many statistical procedures. The transformation efficiently minimized the influence of outliers and brought the distribution closer to normality. After comparing the data before and after transformation, we observed no significant differences. This ensures that the original data integrity remains intact while improving its suitability for further analysis.[8]

4. Model selection

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

establish a foundational model. Following variable selection, we quantitatively assessed the initial model using established criteria. This included measures such as Akaike's information criterion and Bayesian information criterion to assess model fit. We also used leave-P-out cross-validation to ensure the robustness of our model. After initial assessment, we observed skewness and kurtosis values of 1.142 and 1.882, respectively. However, following application of the Box-Cox transformation, these values improved significantly to 0.589 and -0.675. This transformation proved more effective than alternative methods like bootstrapping resampling, and stabilizing the data distribution, thus enhancing the reliability of our model.

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

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

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Supplementary Material S2 Procedures

1. Stimuli and apparatus

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

2. Procedures

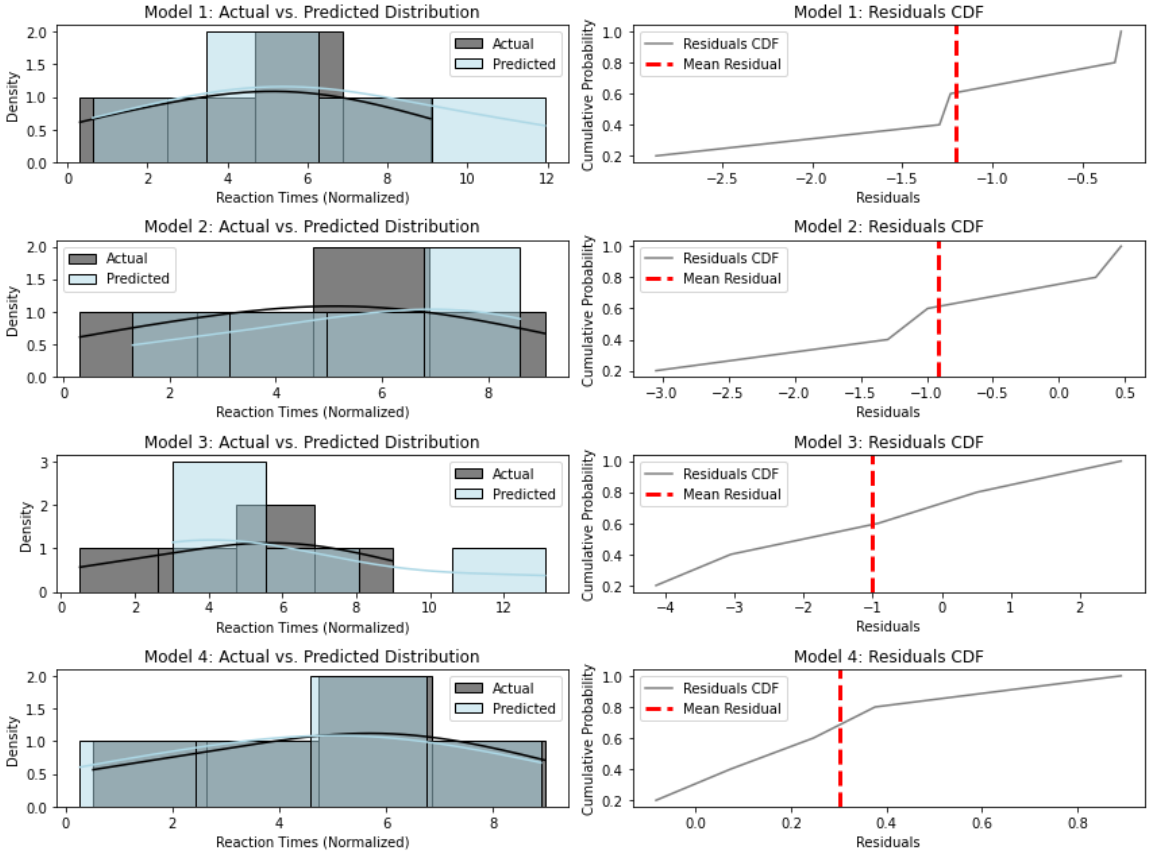
Our testing protocol mitigated potential confounders, such as individual differences in psychomotor velocity, to ensure that our measurements accurately reflect cognitive performance. Participants underwent a baseline RT assessment that consisted of four blocks, each designed with task variations like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

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

Model 4 demonstrated better fit and precision, as evidenced by enhanced performance in posterior predictive checks. The robustness of the model was confirmed through metrics, such as lower Watanabe-Akaike Information Criterion scores (Model 1 = 267, Model 2 = 290, Model 3 = 270, Model 4 = 212) and higher explained sum of squares values, indicating that it effectively captured true cognitive effects, free from psychomotor variability.

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Supplementary Figure S3 Model-wise comparison of observed vs predicted distributions and residual behavior

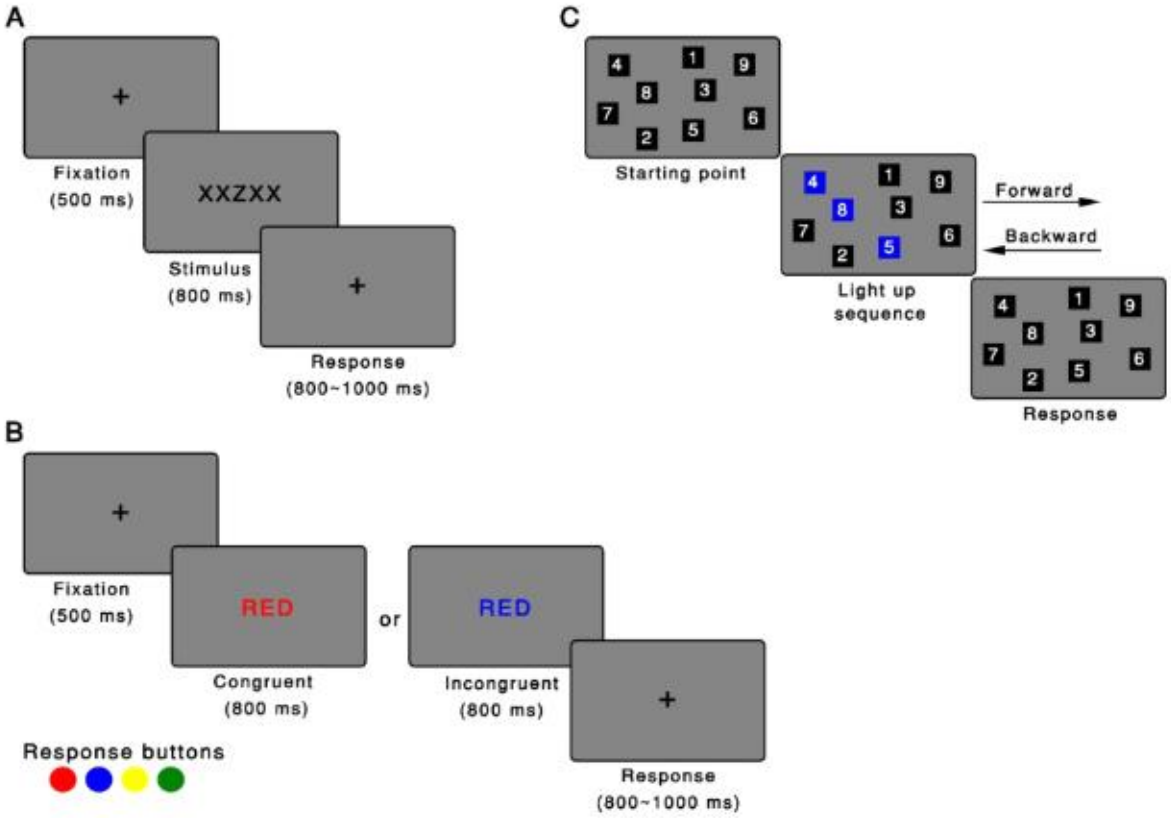


Distributions of observed and predicted values (left panels) and corresponding residual cumulative distribution functions (right panels) are shown for Models 1-4. The models varied in how well the predicted values captured the spread and center of the observed data, with some showing wider dispersion or small shifts. The residual CDFs provided a complementary view of fit, with the dashed red line marking the mean residual. Departures from symmetry and shifts away from zero indicate bias or uneven error structure across models. CDF = cumulative distribution function.

The graphs show four distinct models in a Bayesian hierarchical framework. On the left are histograms comparing the actual and predicted values. A closer overlap between these histograms (in which actual values are dark grey and predicted values are light blue) demonstrates a better fit, indicating that the model more accurately predicted the observed data. On the right, the graphs show the cumulative distribution function for the residuals, which are the differences between the predicted and actual values. This setup allowed us to visually gauge the accuracy and reliability of each prediction, emphasizing the importance of alignment between predicted and actual values, as well as a balanced distribution of residuals for robust model performance in a Bayesian context.

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Supplementary Figure S4 Schematic representation of the cognitive tests. A) Flanker task, B) Stroop test, and C) Corsi test.

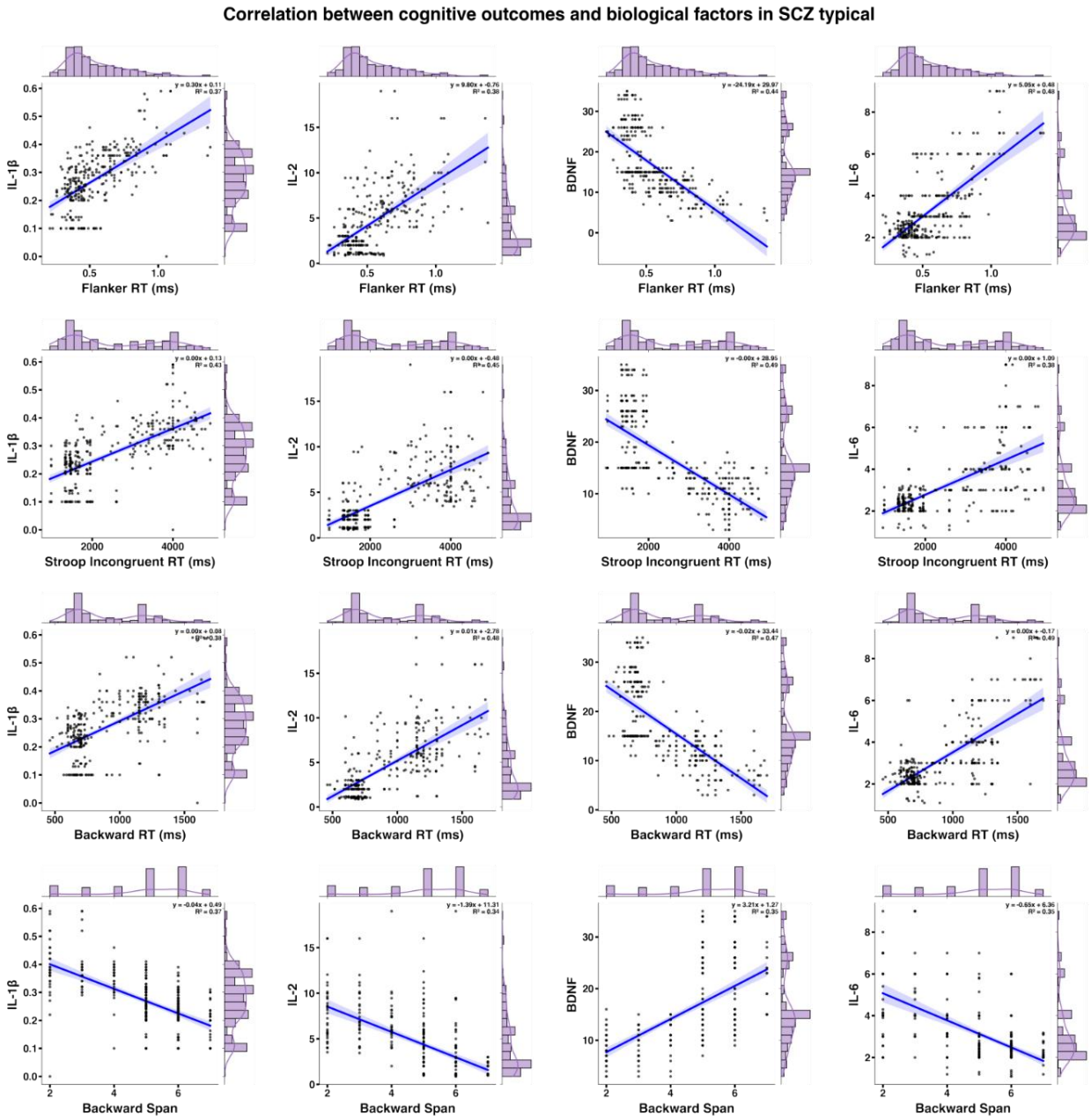


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Supplementary Material S3 Additional analyses

1. Correlation analyses between the cognitive outcomes and biomarkers

Supplementary Figure S5 Interrelated data examination using scatter plots for schizophrenia typical patients



Each column represents ILs and neurotrophic factors as predictor variables, while each row indicates cognitive task outcome variables. On the diagonal, histograms represent the distribution of each variable, with vertical lines marking the mean and standard deviation, providing insight into the central tendency and variability. Best-fit regression lines in the scatter plots illustrate the degree of linear relationship between the variables. IL = interleukin; RT = reaction time; SCZ = schizophrenia.

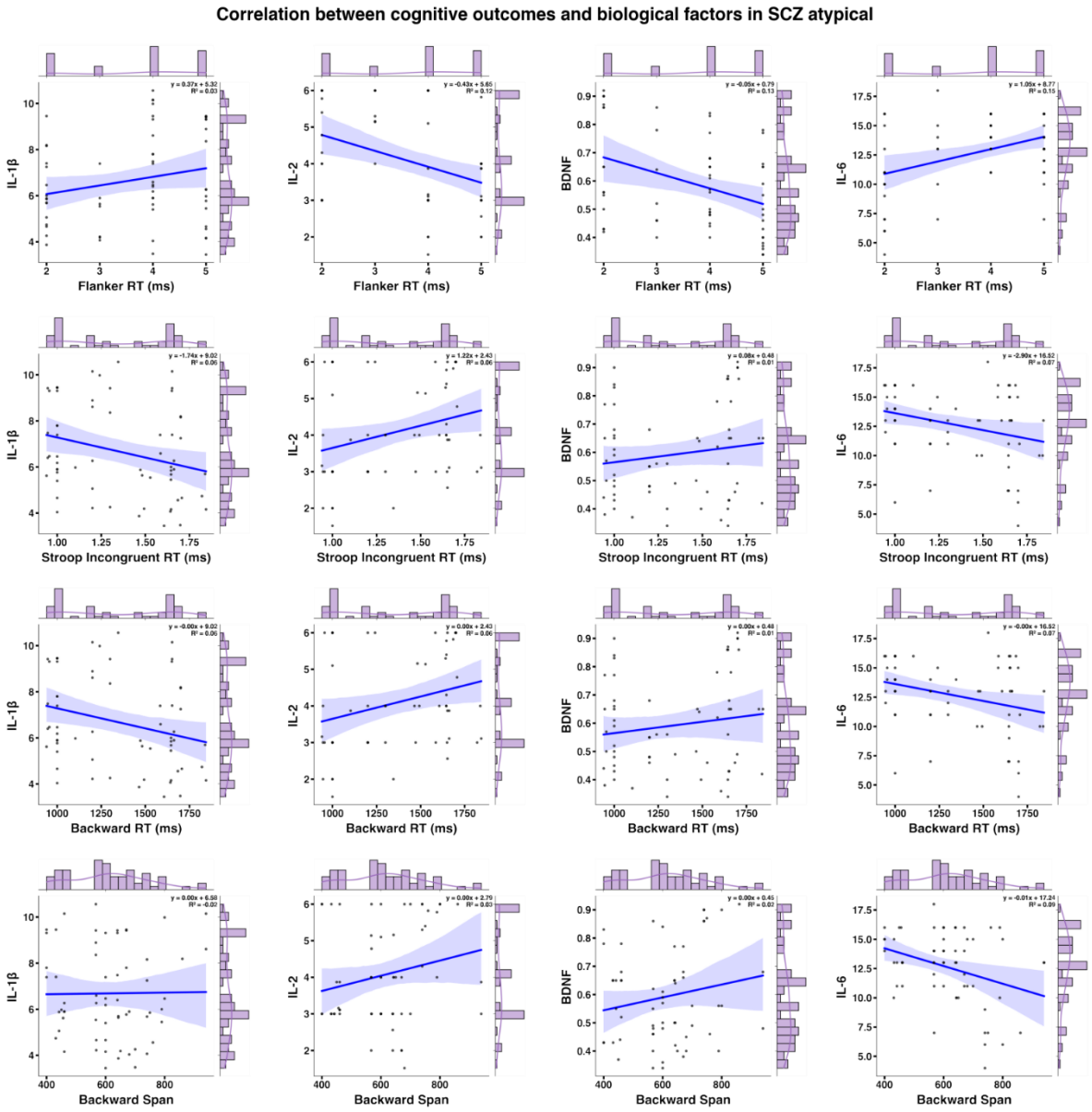
Overall interpretation

In examining cognitive task outcomes and biomarkers, we observed variable RTs across the Flanker, Stroop, and Corsi Backward RT, and Backward Span tasks. The moderate correlation coefficients between these tasks not only indicate a degree of predictability but also highlight the complex nature of cognitive mechanisms. The moderate adjusted R^2 values indicate the potential for investigation into other contributing factors, which could enrich our understanding of cognitive dynamics. The skewness noted in RT distributions, while commonly seen in cognitive testing, offers a realistic observation into the variability of human processing speeds and emphasizes the need for continuous investigation that can accommodate such complexities.[9,10]

Furthermore, the relationship between working memory capacity and biomarkers like ILs and BDNF, though subtle, opens new avenues for exploring how cognitive functions might be intertwined with biological states. These findings, aligned with the other analyses, encourage further investigation into the biological underpinnings of cognitive processes.

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Supplementary Figure S6 Interrelated data examination using scatter plots for schizophrenia patients on atypical medications



Each column represents ILs and neurotrophic factors as predictor variables, while each row indicates cognitive task outcome variables. On the diagonal, histograms represent the distribution of each variable, with vertical lines marking the mean and standard deviation, providing insight into the central tendency and variability. Best-fit regression lines in the scatter plots illustrate the degree of linear relationship between the variables. IL = interleukin; RT = reaction time; SCZ = schizophrenia.

Overall interpretation

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

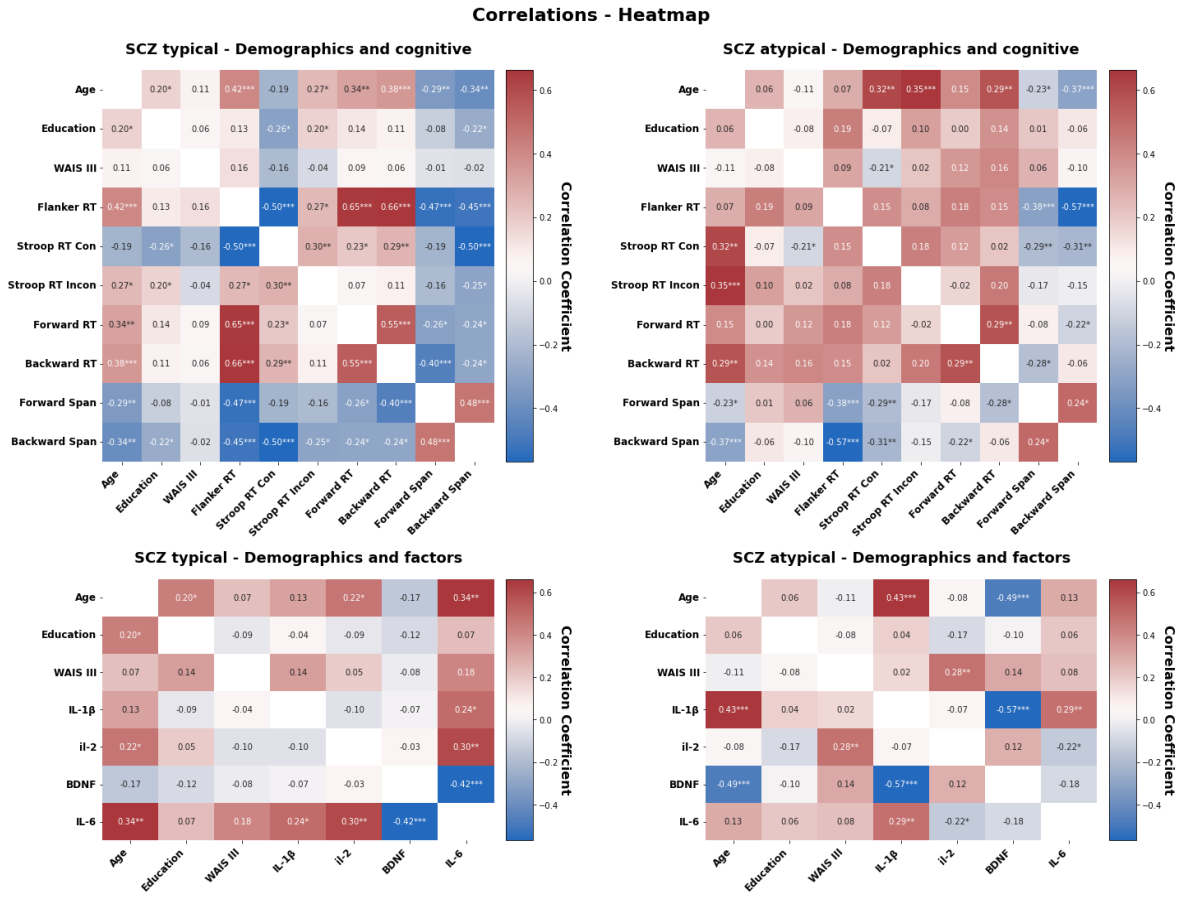
Furthermore, the skewness in the data, while notable, didn't undermine the validity of the findings. It highlights the need for methods that can manage complex data, a typical

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requirement in RT studies. Despite this skewness, the lack of extreme outliers maintains the reliability of the cognitive assessments used in this study. In summary, these graphs offer insight into the relationships between different cognitive tasks. The observed correlations indicate the presence of shared cognitive processes that affect performance across these tasks, although they do not suggest that a single cognitive ability dictates performance across all tasks. This highlights the diverse nature of cognitive functioning, involving multiple cognitive skills across various tasks.[11]

It is difficult to capture the full complexity of such data with certain models, such as regression analysis. While these models are undoubtedly useful, they may not sufficiently address the complex understanding of conditions like schizophrenia. This suggests the need for a broader, more detailed approach involving advanced methods and deeper analyses to better understand and address the complexities of schizophrenia. Such approaches lay the foundation for more comprehensive examinations of the neurocognitive aspects of schizophrenia, leading to personalized interpretations and interventions.

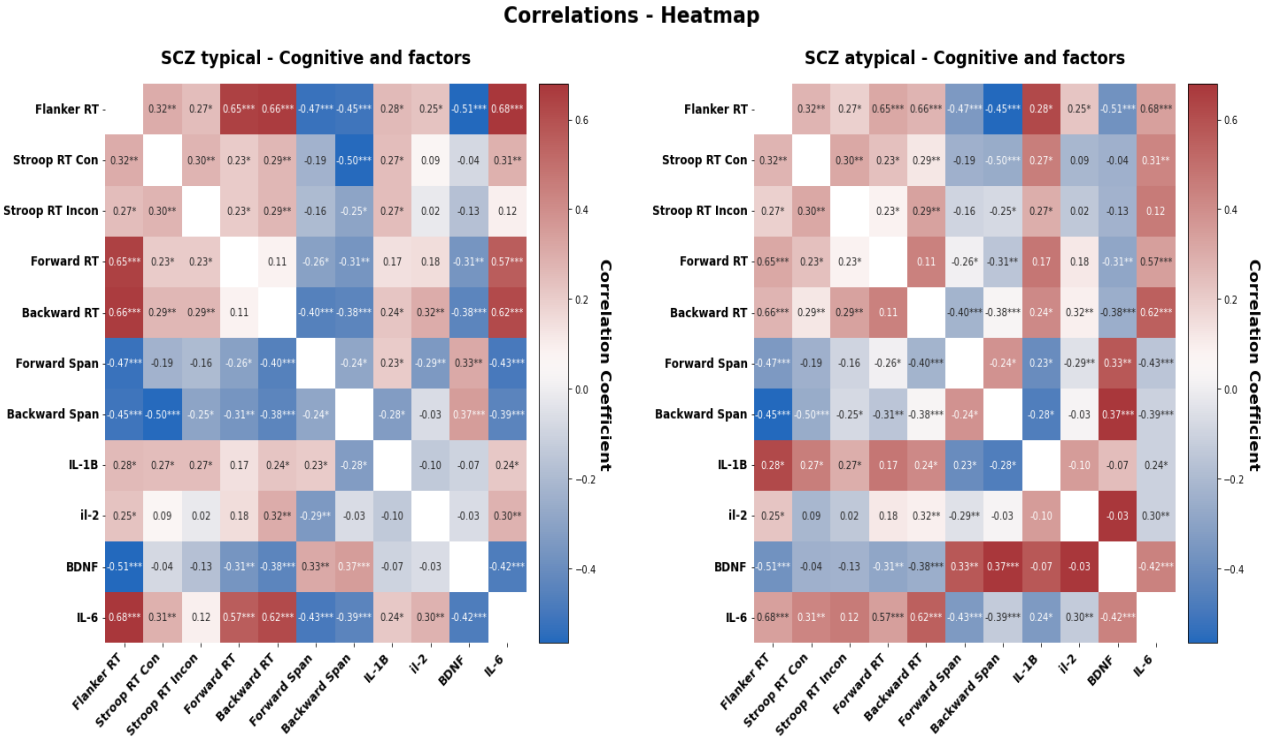
Supplementary Figure S7 Correlation matrix overview



The upper matrix displays correlations between demographic characteristics and cognitive outcomes, while the lower matrix examines the correlations between demographic factors and biomarkers for both schizophrenia groups. The strength of the correlation is indicated by the intensity of the color, with deeper shades representing stronger associations. BDNF = brain-derived neurotrophic factor; IL = interleukin; RT = reaction time; SCZ = schizophrenia; WAIS III = Wechsler Adult Intelligence Scale – Third Edition.
*** p < 0.001, ** p < 0.01.

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Supplementary Figure S8 Correlation heatmap in schizophrenia patients



The matrix on the left maps the correlation coefficients between cognitive functions and biomarkers for schizophrenia patients on typical medication. The corresponding matrix on the right presents the analysis for those on atypical medication. The strength of color reflects the degree of correlation, with more intense colors indicating stronger relationships. BDNF = brain-derived neurotrophic factor; IL = interleukin; RT = reaction time; SCZ = schizophrenia.
*** p < 0.001, ** p < 0.01.

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

1. Flanker task

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

Notably, medication dosage was robustly and positively associated with task performance (β = 0.44, SE = 0.003, p < 0.001; 95%CI 0.438 to 0.442), as well as with illness duration (β = 0.50, SE = 0.056, p < 0.001; 95%CI 0.444 to 0.556). Among biomarkers, elevated levels of IL-1β (β = 0.36, SE = 0.019, p < 0.001; 95%CI 0.332 to 0.388), IL-6 (β = 0.58, SE = 0.009, p < 0.001; 95%CI 0.561 to 0.599), and IL-2 (β = 0.32, SE = 0.015, p = 0.009; 95%CI 0.305 to 0.335) aligned with the hypothesis, suggesting that systemic inflammation influences cognitive function. Lower BDNF levels were also associated with decreased performance (β = -0.20, SE = 0.006, p < 0.001; 95%CI -0.212 to

-0.188), further supporting the hypothesis that systemic inflammation affects cognitive function.

2. Stroop incongruent

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

The analysis revealed that higher IL levels were associated with increased RT, suggesting a decline in cognitive performance. Similarly, lower BDNF levels correlate with poorer outcomes. There was a significant positive correlation between medication dosage and reduced performance, with a substantial regression coefficient ($\beta = 0.0034$, SE = 0.000, $p < 0.001$; 95%CI 0.002 to 0.004). Illness duration also correlated positively with worsened performance ($\beta = 0.1171$, SE = 0.019, $p < 0.0001$; 95%CI 0.080 to 0.154).

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

3. Corsi backward RT

The multiple regression model of Corsi Backward RT was highly significant ($p < 0.001$), explaining 56.7% of the variance in performance outcomes (adjusted $R^2 = 0.567$; $\omega^2 = 0.586$). The model fit statistics, including a RMSE of 0.27 and a mean absolute error of 0.30, confirmed that the regression model adequately captured the relationship between the predictors and performance outcomes.

The analysis indicated that higher IL levels are associated with increased RT, implying a decline in performance. Conversely, lower BDNF levels are linked to worse outcomes. There was a significant positive correlation between medication dosage and reduced performance, evidenced by a notable regression coefficient ($\beta = 0.176$, SE = 0.092, $p = 0.008$; 95%CI 0.050 to 0.328). Interestingly, illness duration did not significantly correlate with worse performance ($\beta = 4.176$, SE = 2.102, $p = 0.088$; 95%CI 0.720 to 8.986).

Among biomarkers, elevated levels of IL-1β ($\beta = 0.053$, SE = 0.003, $p < 0.001$; 95%CI 0.026 to 0.080), IL-2 ($\beta = 0.162$, SE = 0.090, $p = 0.048$; 95%CI 0.004 to 0.324), and IL-6 ($\beta = 0.040$, SE = 0.028, $p = 0.014$; 95%CI 0.009 to 0.072) were observed. These findings align with the hypothesis, suggesting that systemic inflammation may influence cognitive function. Additionally, BDNF levels were negatively associated with performance ($\beta = -0.014$, SE = 0.030, $p < 0.001$; 95%CI -0.253 to -0.021), which aligns with the hypothesis, suggesting that systemic inflammation may influence cognitive function.

4. Corsi backward span

The multiple regression model analyzing Corsi Backward Span was highly significant ($p < 0.001$), explaining 41.4% of the variance in performance outcomes (adjusted $R^2 = 0.414$; $\omega^2 = 0.382$). Model fit indicators, including a RMSE of 0.27 and a mean absolute

error of 0.30, confirmed that the regression model effectively captures the relationship between the predictors and performance outcomes.

The analysis revealed that higher IL levels were associated with increased RT, indicating a decline in performance. Conversely, lower BDNF levels were linked to worse outcomes. There was a significant positive correlation between medication dosage and reduced performance, evidenced by a notable regression coefficient (β = 0.102, SE = 0.018, p < 0.001; 95%CI 0.067 to 0.140); illness duration was also strongly correlated with worse performance (β = 0.129, SE = 0.019, p < 0.001; 95%CI 0.092 to 0.166).

Among biomarkers, elevated levels of IL-1β (β = 0.074, SE = 0.037, p = 0.049; 95%CI 0.016 to 0.189), IL-2 (β = 0.126, SE = 0.030, p = 0.020; 95%CI 0.067 to 0.184), and IL-6 (β = 0.122, SE = 0.012, p < 0.001; 95%CI 0.099 to 0.146) were observed. These findings align with the hypothesis that systemic inflammation could influence cognitive function. Additionally, BDNF levels were negatively associated with performance (β = -0.168, SE = 0.040, p = 0.004; 95%CI -0.246 to -0.090), aligning with the hypothesis that systemic inflammation plays a role in reduced cognitive function.

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

1. Flanker task

The multiple regression model demonstrated significant results (p < 0.001), explaining 26.4% of the variance in performance outcomes (adjusted R^2 = 0.264; ω^2 = 0.255). The model's adequacy is further supported by a RMSE of 9.219 and a mean absolute error of 7.290. The analysis revealed that higher IL levels or lower BDNF levels correlate with increased flanker scores, indicating reduced cognitive performance.

The analysis highlighted a substantial negative correlation between medication dosage and task performance (β = -2.805, SE = 0.804, p < 0.001; 95%CI -4.438 to -1.229), suggesting that higher medication dosage was associated with worse outcomes. Similarly, longer illness duration also negatively affected performance (β = 0.322, SE = 0.102, p = 0.004; 95%CI 0.122 to 0.522).

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

2. Stroop incongruent

The multiple regression model demonstrated significant results (p < 0.001), explaining 40% of the variance in performance outcomes (adjusted R^2 = 0.379; ω^2 = 0.380). The model is further supported by an RMSE of 0.724 and a mean absolute error of 0.799. The analysis identified that higher IL-6 levels were associated with increased RT, suggesting a decline in cognitive performance.

The results indicated a strong negative correlation between chlorpromazine equivalent dosage and task performance (β = -3.120, SE = 0.801, p < 0.001; 95%CI -4.794 to -1.588), indicating that higher dosage is linked with poorer outcomes. IL-6 was also found

to negatively influence performance (β = 0.1235, SE = 0.044, p = 0.007; 95%CI 0.035 to 0.212), aligning with the hypothesis that systemic inflammation can have complex effects on cognitive function.

However, illness duration, IL-1β, IL-2, and BDNF showed no significant effects in this model. This suggests that their influence on cognitive performance might be mediated by more complex interactions or latent variables not captured in the current analysis. This indicates that linear regression may not adequately model the relationships and underlying mechanisms that affect cognitive function. Consequently, exploring these relationships through structural equation modeling could provide deeper insights, as structural equation modeling allows for the analysis of multiple dependent relationships simultaneously and can account for latent constructs that might influence the observed outcomes.

3. Corsi backward RT

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

The analysis showed that higher biomarker levels are linked to greater RT, indicating reduced cognitive performance. Specifically, IL-1β was associated with significantly reduced performance (β = 4.297, SE = 1.190, p = 0.022; 95%CI 1.965 to 6.629), and IL-2 also led to increased backward time (β = 5.162, SE = 2.074, p = 0.046; 95%CI 1.096 to 9.227), suggesting an adverse impact on cognition. IL-6 followed a similar pattern (β = 8.397, SE = 3.613, p = 0.044; 95%CI 1.316 to 15.478), reinforcing the negative influence of these higher cytokine levels on cognitive performance.

The analysis also revealed a strong negative correlation between chlorpromazine dosage and task performance (β = -3.210, SE = 0.801, p < 0.001; 95%CI -4.780 to -1.640), indicating that higher dosage was associated with poorer cognitive outcomes. However, illness duration, IL-1β, IL-2, and BDNF did not show significant effects in this model, indicating that their influence may be less direct or obscured by other interacting factors in this study. This suggests that structural equation modeling may better capture the complex interactions and latent variables that could influence these outcomes.

4. Corsi backward span

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

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

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Additionally, lower BDNF levels were linked with decreased performance (β = -2.920, SE = 1.206, p < 0.001; 95%CI -5.320 to -0.501). The analysis also highlighted a substantial negative correlation between chlorpromazine dosage and task performance (β = -2.067, SE = 0.700, p = 0.008; 95%CI -3.400 to -0.463), suggesting that higher chlorpromazine dosage is associated with reduced cognitive outcomes.

These findings underscore the significant influence of systemic inflammation and biological changes on cognitive function, as evidenced by the relationships between cytokine levels, BDNF levels, dosage, and cognitive performance. This suggests that interventions aimed at modulating these biomarkers could potentially improve cognitive outcomes in individuals affected by these changes.[12,13]

Supplementary Table S1 Model metrics for classifier groups

Category	Group	Precision	Specificity	LR+	LR-	Accuracy
Class scores						
	HCs	0.86	0.90	6.72	0.10	0.90
	SCZ typical	0.80	0.84	5.44	0.12	0.87
	SCZ atypical	0.76	0.78	3.32	0.21	0.67
Accuracy – Overall						0.86

HCs = healthy controls; LR = likelihood ratio; SCZ = schizophrenia.

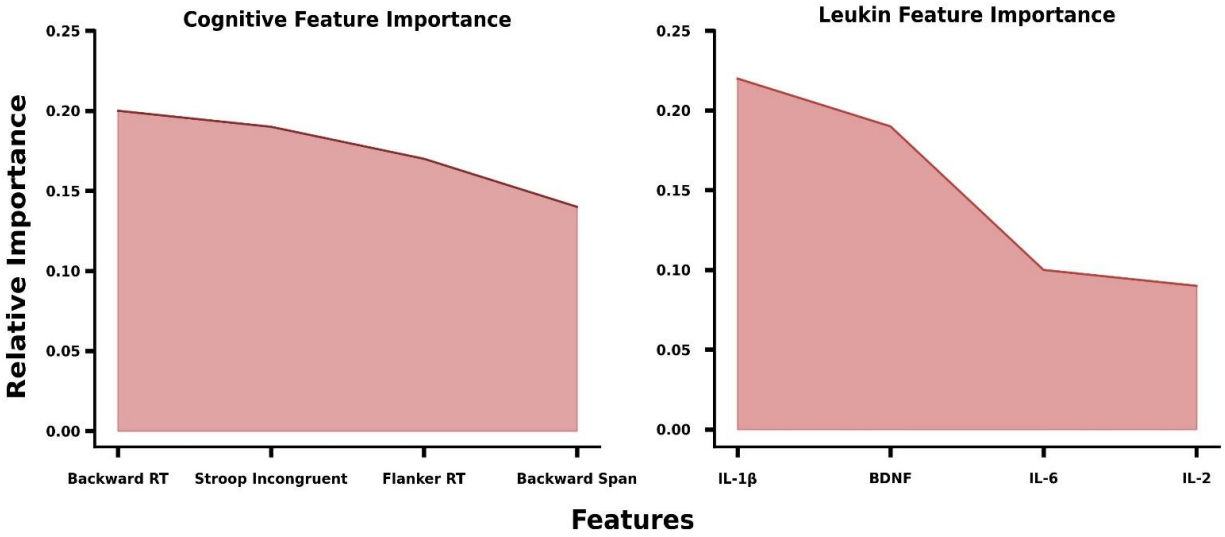
Supplementary Table S2 Model features and their relative importance

Feature	Relative importance
IL-1β	0.22
IL-2	0.09
BDNF	0.19
IL-6	0.10
Flanker (RT)	0.17
Corsi forward (Span)	0.02
Corsi backward (Span)	0.14
Corsi forward (RT)	0.06
Corsi backward (RT)	0.20
Stroop congruent (RT)	0.03
Stroop incongruent (RT)	0.19

BDNF = brain-derived neurotrophic factor; IL = interleukin; RT = reaction time.

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Supplementary Figure S9 Relative importance of features in predictive models



Cognitive features are shown on the left, with attentional control measures such as Flanker RT being the most prominent, while the right focuses on interleukin features, with IL-1β being the most influential biomarker. IL = interleukin; RT = reaction time.

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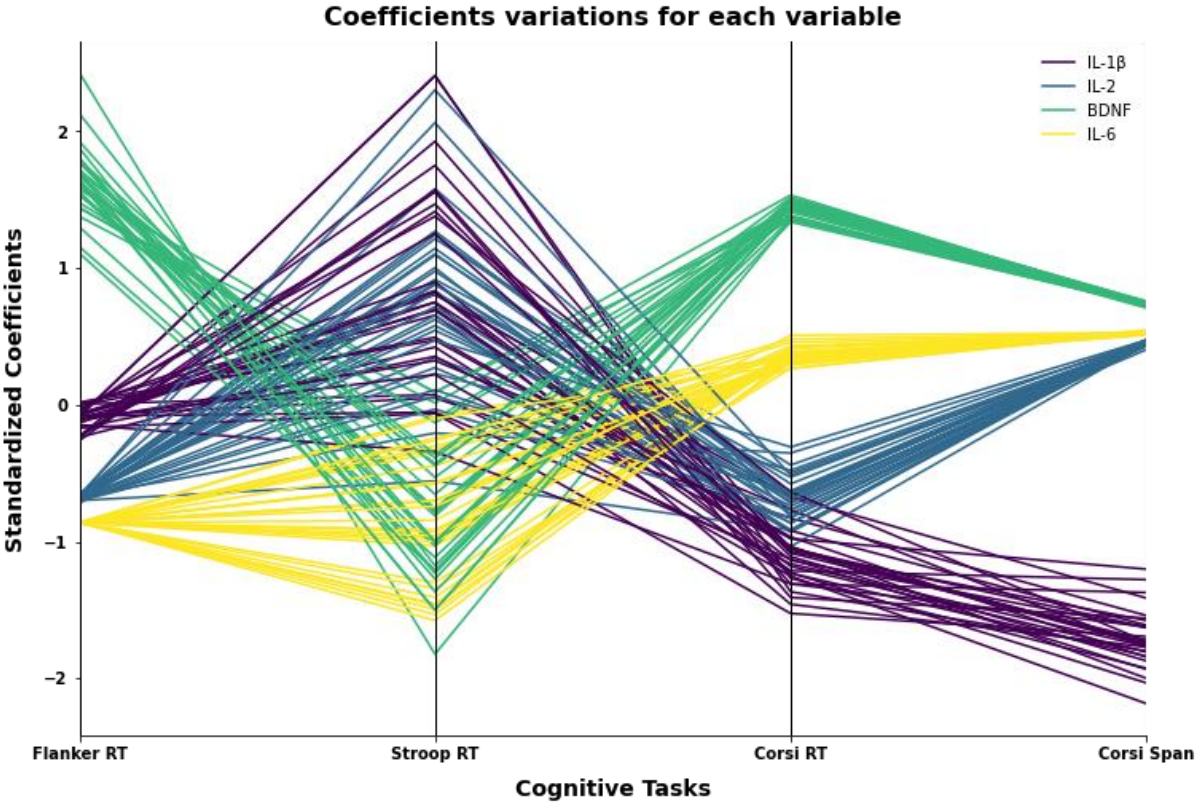
Supplementary Table S3 Interaction effects of moderators on predictors and outcomes relationships

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

BDNF = brain-derived neurotrophic factor; IL = interleukin; PANSS = Positive and Negative Syndrome Scale; RT = reaction time.

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Supplementary Figure S10 Variation of coefficients across variables in cognitive tasks



Each line in the parallel plot represents coefficient variation across four cognitive tasks (Flanker RT, Stroop Incongruent RT, Corsi Backward RT and Corsi Backward Span) for interleukins IL-1β, IL-2, BDNF, and IL-6. BDNF = brain-derived neurotrophic factor; IL = interleukin; RT = reaction time.

References

1. Griffiths K, Millgate E, Egerton A, MacCabe JH. Demographic and clinical variables associated with response to clozapine in schizophrenia: a systematic review and meta-analysis. Psychol Med. 2021;51:376-86.
2. Hespanhol L, Vallio CS, Costa LM, Saragiotto BT. Understanding and interpreting confidence and credible intervals around effect estimates. Braz J Phys Ther. 2019;23:290-301.
3. Dormann CF, Elith J, Bacher S, Buchmann C, Carl G, Carré G, et al. Collinearity: a review of methods to deal with it and a simulation study evaluating their performance. Ecography. 2013;36:27-46.
4. Subramanian J, Simon R. Overfitting in prediction models - is it a problem only in high dimensions? Contemp Clin Trials. 2013;36:636-41.
5. Efthimiou O, Seo M, Chalkou K, Debray T, Egger M, Salanti G. Developing clinical prediction models: a step-by-step guide. BMJ. 2024;386:e078276.
6. Lee DK. Data transformation: a focus on the interpretation. Korean J Anesthesiol. 2020;73:503-8.
7. Riani M, Atkinson AC, Corbellini A. Automatic robust Box–Cox and extended Yeo–Johnson transformations in regression. Stat Methods Appl. 2023;32:75-102.
8. Leys C, Delacre M, Mora YL, Lakens D, Ley C. How to Classify, Detect, and Manage Univariate and Multivariate Outliers, With Emphasis on Pre-Registration. Int Rev Soc Psychol. 2019;32:5.
9. 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.
10. McAfoose J, Baune BT. Evidence for a cytokine model of cognitive function. Neurosci Biobehav Rev. 2009;33:355-66.
11. Joyce EM, Roiser JP. Cognitive heterogeneity in schizophrenia. Curr Opin Psychiatry. 2007;20:268-72.
12. Baek S-H, Kim H, Kim J-W, Ryu S, Lee J-Y, Kim J-M, et al. Association between peripheral inflammatory cytokines and cognitive function in patients with first-episode schizophrenia. J Pers Med. 2022;12:1137.
13. Momtazmanesh S, Zare-Shahabadi A, Rezaei N. Cytokine alterations in schizophrenia: an updated review. Front Psychiatry. 2019;10:892.