

## Stage-specific computational mechanisms of working memory deficits in first-episode and chronic schizophrenia

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### ARTICLE INFO

**Keywords:**

Computational modeling  
Bayesian hierarchical drift-diffusion modeling  
Working memory impairment  
First-episode and chronic schizophrenia

### ABSTRACT

**Background:** Cognitive dysfunction, particularly working memory (WM) impairment, constitutes a core feature of schizophrenia and is largely unresponsive to available antipsychotic treatments. The computational mechanisms underlying WM deficits at different illness stages and their associations with clinical symptom dimensions remain poorly understood.

**Methods:** We applied hierarchical drift diffusion modeling (HDDM) to dissect latent cognitive processes underlying WM performance in a *two-back* task among patients with first-episode schizophrenia (FES,  $N = 103$ , illness duration  $\leq 2$  years), chronic schizophrenia (ChSz,  $N = 108$ , illness duration  $\geq 5$  years), and healthy controls (HCs,  $N = 85$ ). Multiple regression and mediation analyses were conducted to examine associations between HDDM parameters, clinical symptoms, and conventional metrics.

**Results:** Both patient groups exhibited significant WM deficits compared to HCs, with ChSz patients demonstrating more pronounced impairments than FES patients. HDDM analysis revealed that patients showed significantly reduced drift rate and prolonged non-decision time compared to HCs. Notably, while non-decision time remained comparable between FES and ChSz groups, drift rate was significantly lower in ChSz patients, mediated the relationship between illness stage and WM performance, and negatively correlated with negative symptoms and general psychopathology.

**Conclusions:** This study reveals distinct computational profiles of WM deficits across different stages of schizophrenia. While non-decision time impairments emerge early and persist, reduced drift rate progressively deteriorates with illness duration and is closely linked to specific clinical symptoms. These findings enhance our understanding of WM dysfunction across illness stages and support the development of targeted cognitive interventions tailored to illness stage and symptom severity.

### 1. Introduction

Cognitive deficits, a hallmark feature of schizophrenia that significantly contributes to functional disability, remain largely unresponsive to existing antipsychotic medications (McCutcheon et al., 2023). Among the affected cognitive domains, working memory, the ability to temporarily maintain and manipulate information for complex cognitive processes, is of particular interest due to its central role in higher-order cognition (Barch and Smith, 2008) and its documented associations with clinical symptoms in schizophrenia (Park and Gooding, 2014). Despite widespread working memory dysfunction documented in schizophrenia (Forbes et al., 2009), the stage-dependent profiles of these impairments

and their relationship to symptom dimensions remain poorly understood.

Schizophrenia is a highly heterogeneous disorder that typically progresses through distinct stages, including high genetic risk (HR), ultra-high risk for psychosis (UHR), first-episode schizophrenia (FES), and chronic schizophrenia (ChSz) (McCutcheon et al., 2020). These stages are characterized by various abnormalities linked to genetic, prenatal, and environmental factors (C. Zhao et al., 2018). These alterations may differ across the specific stages of the disorder and be more pronounced during certain phases (Pantelis et al., 2005). FES represents the initial clinical manifestation of schizophrenia and is thought to arise from neurodevelopmental abnormalities (Kahn and Sommer, 2015). In

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contrast, ChSz reflects the cumulative effects of disease progression, treatment, and reductions in cortical volume (Pasternak et al., 2015). Elucidating the stage-dependent trajectory of working memory dysfunction may reveal phase-specific mechanisms underlying cognitive deficits in schizophrenia and identify targeted interventional opportunities (Ellison-Wright et al., 2008).

Behavioral studies have consistently documented working memory deficits in patients with FES and ChSz compared to healthy controls. These studies typically use traditional measures of task accuracy and reaction times (Gotra et al., 2022; Zanello et al., 2009). However, these metrics alone provide limited insight into underlying neurocognitive mechanisms, as they represent the final output of multiple cognitive processes rather than elucidating the specific components that may be impaired. To address this limitation, computational modeling approaches, particularly the Hierarchical Drift Diffusion Model (HDDM), have emerged as powerful tools for decomposing the subcomponents of cognitive processing and decision-making (Wilson and Collins, 2019). Unlike conventional behavioral analyses that treat accuracy and reaction times as separate measures, drift-diffusion models integrate both metrics into a unified framework while accounting for trial-by-trial variability in performance. These models conceptualize decision-making as a process of noisy evidence accumulation toward a response threshold.

The *N*-back paradigm, a widely validated behavioral measure of working memory, engages multiple cognitive processes, including rapid encoding, active maintenance, continuous updating, and information retrieval (Murphy et al., 2020). Its two-alternative forced-choice structure makes it particularly well-suited for HDDM analysis, which can effectively disentangle these cognitive sub-processes during task performance (Li et al., 2024; Pedersen et al., 2023). HDDM decomposes task performance into the following parameters that reflect distinct cognitive processes: drift rate ( $v$ ), representing the efficiency of evidence accumulation; boundary separation ( $a$ ), indicating the amount of evidence required for a decision; non-decision time ( $t$ ), indexing perceptual and motor latencies; and starting point bias ( $z$ ), capturing decision biases (Wiecki et al., 2013). Through this computational approach, we can examine whether working memory deficits in schizophrenia arise from impairments in specific cognitive mechanisms, such as slower evidence accumulation, altered decision thresholds, or increased processing variability.

The dorsolateral prefrontal cortex (DLPFC) plays a central role in evidence accumulation by integrating information from multiple sources and guiding decision-making, particularly in the action domain (Lin et al., 2020). Previous studies have demonstrated that longer illness duration is associated with reduced prefrontal cortex (PFC) activation (Elsabagh et al., 2009), and patients with ChSz exhibit smaller prefrontal cortical gray matter volumes compared to patients with FES (Molina et al., 2004; Premkumar et al., 2006). Consequently, the drift rate in patients with ChSz may be lower than that observed in those with FES, reflecting potential impairments in evidence accumulation during decision-making tasks. Applying HDDM to schizophrenia research allows for a fine-grained characterization of these processes and the identification of stage-specific computational abnormalities in working memory. For instance, deficits in drift rate may indicate inefficient evidence accumulation, while reductions in boundary separation may reflect impulsivity or lowered decision thresholds (Pedersen et al., 2023).

Therefore, this study aimed to leverage HDDM to investigate the computational mechanisms underlying working memory impairments across illness stages of schizophrenia compared to healthy controls (HCs). We hypothesize that FES and ChSz patients exhibit distinct patterns of abnormalities in HDDM parameters relative to HCs, and ChSz patients may demonstrate more pronounced impairments than FES patients. We further hypothesize that these differences are primarily driven by alterations in the drift rate parameter ( $v$ )—which reflects evidence accumulation efficiency—and that these drift rate deficits are

associated with progressive deterioration in working memory function as the illness advances, as well as with worsening psychopathological symptoms.

## 2. Methods

### 2.1. Data collection

#### 2.1.1. Participant recruitment

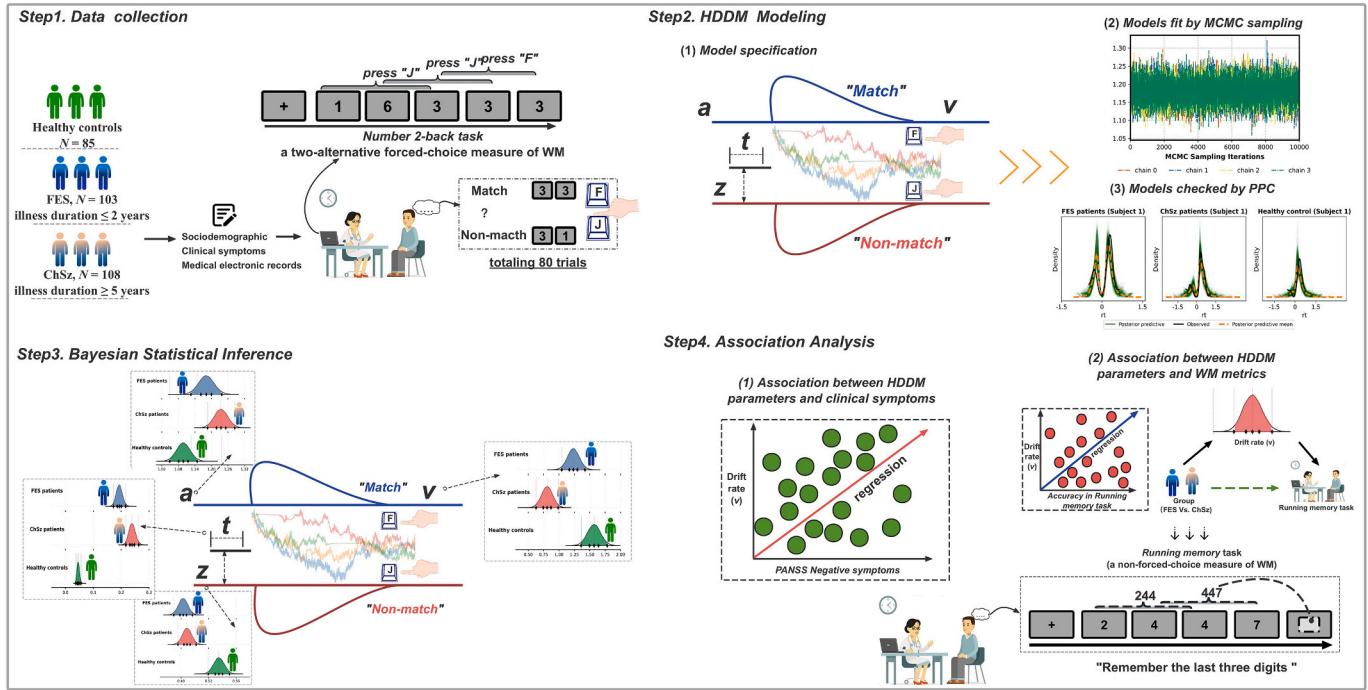
The study was conducted from March to August 2022. The participants were 211 individuals who had been diagnosed with schizophrenia, including 103 patients with FES and 108 patients with ChSz (Fig. 1, Table 1). Patients with FES and ChSz were defined according to the patient edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV). The duration of the disease was  $\leq 2$  years for patients with FES and  $\geq 5$  years for patients with ChSz (Fig. 2A) (Zhao et al., 2018). Symptom severity in each patient with schizophrenia was evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Detailed clinical information, such as duration of illness and types and dosages of antipsychotic drugs, was obtained from the patients' electronic medical records. Additionally, we recruited 85 HCs matched for age, gender, and education level through both offline promotions and online advertisements. HCs participants were physically healthy individuals with no history of psychiatric illness or brain injury (Table 1).

All participants in the FES and ChSz groups had received inpatient treatment at the Third People's Hospital in Lanzhou City within the past two years. Diagnoses were made by two resident psychiatrists using the ICD-10 diagnostic criteria for schizophrenia (F20.900). Participants were further screened by two resident psychiatrists using the Structured Clinical Interview for DSM-IV Axis I Disorders. All patients were in stable condition and received consistent treatment, with no changes in medications expected during the study. The inclusion criteria were age 18–65 years and the ability to communicate effectively, complete experimental tasks, and voluntarily sign the informed consent form. Individuals with severe physical diseases, visual abnormalities, or adverse drug reactions were excluded from the study (detailed inclusion and exclusion criteria are listed in Supplementary Table S1).

#### 2.1.2. Assessments

**2.1.2.1. Working memory behavioral tasks.** We employed two behavioral tasks to assess working memory. The first was a two-alternative forced-choice *number two-back* paradigm, which measured working memory performance (X. Zhao et al., 2023) and explored the computational mechanisms underlying working memory deficits across illness stages using the HDDM. In each trial, a digit (1–9) was presented in the center of the screen for 500 ms, followed by a 2500-ms interstimulus interval. Participants indicated whether each digit matched the one presented two trials prior by pressing “*F*” for a match and “*J*” for a nonmatch. After a practice block, the test block consisted of 84 trials (42 match, 42 nonmatch). The primary outcome measures were *d*-prime scores, calculated as the standardized hit rate minus the standardized false alarm rate ( $d$ -prime scores =  $Z$  (hit rate) -  $Z$  (false alarm rate)), and reaction times (Haavet et al., 2010) (details in the Supplementary Materials).

To validate findings from the *number two-back* paradigm, a second non-forced-choice task, the *running memory updating* (RM) task, was administered (X. Zhao et al., 2023). Two versions of this task were employed, varying the digit presentation duration (1750 ms vs. 750 ms). Participants were required to continuously update their memory to maintain the last three digits presented in a sequence of varying length. The key outcome measure was the proportion of items correctly recalled in the correct serial position (see Supplementary Material for details). The RM task complements the *number two-back* task in assessing working



**Fig. 1.** Schematic diagram of the study design and analysis pipelines

Note: Step 1: Data Collection. Working memory performance was assessed using a *two-back* task in 103 first-episode schizophrenia (FES; illness duration  $\leq 2$  years) patients, 108 chronic schizophrenia (ChSz; illness duration  $\geq 5$  years) patients, and 85 healthy controls. Clinical symptoms were evaluated using the PANSS. Electronic medical records and sociodemographic information were also collected.

Step 2: HDDM modeling. Responses from the *two-back* task were modeled using HDDM. HDDM parameters, including drift rate ( $v$ ), boundary separation ( $\alpha$ ), non-decision time ( $t$ ), and starting point bias ( $z$ ), were estimated using Markov Chain Monte Carlo (MCMC) sampling. Posterior predictive checks (PPC) were performed to validate the HDDM models.

Step 3: Bayesian Statistical Inference. HDDM parameters were compared between the FES and ChSz groups using Bayesian hypothesis testing.

Step 4: Association analysis. Relationships between HDDM parameters and clinical measures (e.g., PANSS negative symptoms) and WM task metrics (e.g., accuracy in RM task) were investigated using correlation and regression analyses. Mediation analyses, controlling for age of onset, gender, and education level, examined the potential mediating effects of *two-back* task computational parameters on the relationships between illness duration (FES vs. ChSz patients), clinical symptoms, and working memory reaction times.

Abbreviations: FES, first-episode schizophrenia; ChSz, chronic schizophrenia.

memory, with the former targeting recollection-based retrieval processes and the latter primarily assessing recognition-based and familiarity-based processes (Wang et al., 2025). Hence, the relationship between behavioral performance metrics in the RM task and computational parameters derived from the *two-back* task will be examined to identify shared underlying working memory processes across schizophrenia illness stages and HCs (Fig. 1). This approach aimed to provide convergent evidence for the cognitive mechanisms underlying working memory deficits in schizophrenia, as captured by the HDDM analysis of the two-alternative forced-choice task.

**2.1.2.2. Behavioral task and clinical scale analyses.** One-way analyses of covariance (ANCOVAs) were conducted to examine group differences among FES, ChSz, and HCs in each working memory measure, controlling for sociodemographic variables (i.e., age, gender, and educational level). Post-hoc pairwise comparisons were performed using Bonferroni correction to identify specific group differences. A Benjamini-Hochberg (BH) false discovery rate (FDR) correction was applied to account for multiple comparisons (Benjamini et al., 2001). Partial correlation analyses, controlling for age of onset, gender, and educational level as covariates, were used to examine the relationships among illness duration, working memory performance, and PANSS scores within the FES and ChSz groups, with FDR correction for multiple comparisons.

**2.1.2.3. HDDM analysis.** Trial-by-trial choice and response time data from the *two-back* task were analyzed across the groups (FES, ChSz, and

HCs) using the HDDM package (v1.0.1) (Wiecki et al., 2013). Input data consisted of four columns: subject ID, trial number, response type (0 = "non-match", indicating that the currently presented number does not match the number presented two positions earlier; 1 = "match", indicating that the currently presented number matches the number presented two positions earlier), and reaction time in seconds (Supplementary Fig. S1).

### 2.1.3. Model specification and fitting

We defined three models to investigate differences in *number two-back* task processing among patients with FES, those with ChSz, and HCs (Supplementary Table S2). i) Baseline Model (M0): We set a baseline model (M0), incorporating the decision boundary ( $\alpha$ ), drift rate ( $v$ ), and non-decision time ( $t$ ). This model assumed no decision bias (i.e.,  $z$  was fixed at 0.5, the default setting in the HDDM package). It also included trial-by-trial variability in drift rate ( $s_v$ ), starting point ( $s_z$ ), and non-decision time ( $s_t$ ), allowing participant-specific parameters to vary across trials rather than remaining fixed (Ratcliff and McKoon, 2008). This model provided a common baseline for all three groups (FES, ChSz, and HCs). ii) Hierarchical Model (M1): To examine group differences, we constructed a hierarchical model (M1) with group-dependent parameters. This model allowed the decision boundary ( $\alpha$ ), drift rate ( $v$ ), non-decision time ( $t$ ), and decision bias ( $z$ ) to vary among the FES, ChSz, and HCs groups. This helped us understand the specific parameter estimates for each group. iii) Mixed-Effects Regression Model (M2): As the primary analysis, we modeled data from the three groups together in a mixed-effects regression model (M2) to estimate group differences while

**Table 1**  
Participant demographics and clinical characteristics.

Variable	FES patients (N = 103)	ChSz patients (N = 108)	Healthy controls (N = 85)	Statistic	Corrected p-value
Current age (years)	31.66 ± 9.60	31.40 ± 9.56	34.74 ± 11.13	F = 3.119	0.069
Gender, n (%)					
Male	66 (64.08 %)	55 (50.93 %)	42 (49.41 %)	$\chi^2 = 5.227$	0.073
Female	37 (35.92 %)	53 (49.07 %)	43 (50.59 %)		
Education level, n (%)				$\chi^2 = 20.202$	0.069
Primary School	21 (20.39 %)	17 (15.74 %)	9 (10.59 %)		
Middle School	31 (30.10 %)	40 (37.04 %)	22 (25.88 %)		
High School	18 (17.48 %)	22 (20.37 %)	24 (28.24 %)		
Diploma	12 (11.65 %)	11 (10.19 %)	5 (5.88 %)		
Bachelor's Degree	19 (18.45 %)	17 (15.74 %)	17 (20.00 %)		
Master's Degree	2 (1.94 %)	1 (0.93 %)	8 (9.41 %)		
PANSS Scale					
PANSS Negative	17.48 ± 5.60	23.67 ± 6.83	N/A	t = -7.182	< 0.001
PANSS Positive	17.87 ± 4.84	16.66 ± 4.31	N/A	t = 1.928	0.083
PANSS General Psychopathology	34.98 ± 4.37	37.42 ± 5.71	N/A	t = -3.469	0.001
PANSS Total	70.33 ± 10.77	77.74 ± 12.22	N/A	t = -4.664	< 0.001
Age of onset (years)	29.65 ± 9.65	22.59 ± 8.24	N/A	t = 5.721	< 0.001
Illness duration (years)	0.54 ± 0.43	9.35 ± 3.54	N/A	t = -25.099	< 0.001
OZP equivalent dosage (mg/day)	11.41 ± 5.03	15.95 ± 5.88	N/A	t = -6.015	< 0.001

Note: Corrected p-value refers to the significance level after FDR BH correction.

Abbreviations: N/A, Not Applicable; FES, first-episode schizophrenia; ChSz, chronic schizophrenia; PANSS, Positive and Negative Syndrome Scale; OZP, Olanzapine Equivalent Dosage.

accounting for individual variability (Pedersen et al., 2023). In this model, group contrast was used by default for the categorical variable in the regression. We considered two classes of group differences: 1) FES and ChSz relative to HCs: The group variable was coded as “1” for FES, “2” for ChSz, and “3” for HCs. The intercept ( $v_{\text{intercept}}$ ) represented the estimation of drift rate ( $v$ ) for the FES and ChSz groups, while the slope ( $v_C$  (Group, Treatment ('3')) [T, HCs]) represented the difference in drift rate for the HCs group compared to the FES and ChSz groups. 2) FES relative to ChSz: In a separate analysis including only FES and ChSz groups, the group variable was coded as “1” for FES and “2” for ChSz. The intercept ( $v_{\text{intercept}}$ ) represented the estimation of drift rate ( $v$ ) for the ChSz group, while the slope ( $v_C$  (Group, Treatment ('1')) [T, FES]) represented the difference in drift rate for the FES group compared to the ChSz group. We also included decision boundary ( $a$ ), non-decision time ( $t$ ), and decision bias ( $z$ ) parameters in this model.

Regarding priors, we used default values from the HDDM package, which are informed by a wide range of empirical studies yet remain sufficiently conservative to allow for deviations in mean parameters based on the data (Cataldo et al., 2023; Saleh et al., 2023; Wiecki et al.,

2013). Models were fit using hierarchical Bayesian methods with Markov chain Monte Carlo (MCMC) sampling to estimate posterior parameter distributions. For each model, four MCMC chains were run with 15,000 samples per chain, discarding the first 5000 as burn-in. The resulting posterior samples and inference data were then used for further analysis and interpretation (Dillon et al., 2022).

## 2.2. Model diagnostics, comparison, and posterior predictive checks

The Python library ArviZ was used for model diagnostics: (1) visualizing MCMC traces to assess convergence and mixing; and (2) calculating the Gelman-Rubin statistic ( $R$ ), confirming  $R < 1.01$  (Vehtari et al., 2017). Model comparison was performed using the deviance information criterion (DIC), with smaller values indicating better fit (Spiegelhalter et al., 2002). After validating reasonably good model fits, posterior predictive checks were performed using the *post\_pred\_gen* function in HDDM to run 500 simulations drawing from the posterior distributions (Peters and D'Esposito, 2020). Simulated data were compared to observed data patterns (including group-level and individual-level) to assess model adequacy.

## 2.3. Statistical inference and association analysis

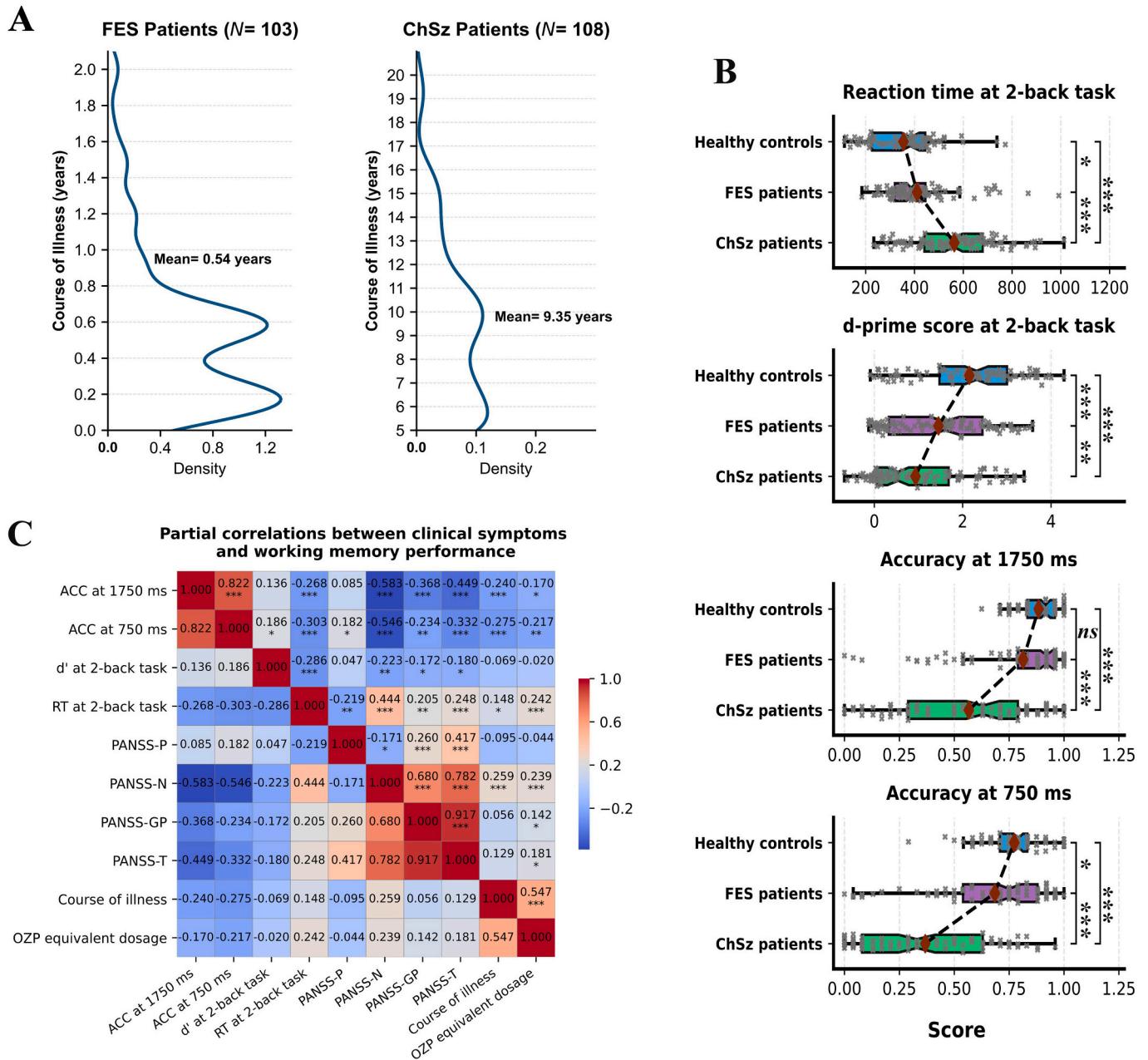
Group differences between the FES and ChSz groups were examined by plotting the posterior distribution for each parameter and quantified using Bayesian ANOVA. The strength of evidence was evaluated using Bayes factors ( $BF_{10}$ ), which can support either the alternative ( $BF_{10} > 1$ ) or null ( $BF_{10} < 1$ ) hypothesis (Lee & Wagenmakers, 2014). The 95 % highest density interval (HDI) of the difference distribution among patients with FES, those with ChSz, and HCs was calculated. Following Kruschke and Liddell (2018) strategy, regions of practical equivalence (ROPE) were tailored to the specific paradigm and research question (Pan et al., 2025) and defined for each parameter (e.g., for the  $v$  parameter, ROPE was the interval [-0.2, 0.2]) around the null value. Conclusions were drawn based on the relationship between the 95 % HDI and ROPE. If the 95 % HDI partially overlapped with the ROPE, the Bayesian probability value ( $P_{\text{P|D}}$ ), indicating the proportion of the 95 % HDI within the ROPE and the probability of practical parameter equivalence between conditions, was calculated (see Supplementary Material for details).

Multiple regression analyses were performed to examine the relationships between each HDDM parameter and clinical measures (PANSS scales, illness duration, and Olanzapine Equivalent Dosage), as well as behavioral performance on the *two-back* task (Saleh et al., 2023). Age of onset, gender, and education level were included as covariates where applicable to control for potential confounding effects, and FDR corrections were applied to account for multiple comparisons. Additionally, mediation analyses, controlled for age of onset, gender, and education level, were conducted using bootstrap confidence intervals with 3000 samples to investigate the potential mediating effects of computational parameters derived from the *two-back* task on the relationships between illness duration (comparing FES vs. ChSz patients) and working memory conventional metrics (e.g., *d*-prime scores) (L. Liu et al., 2022).

## 3. Results

### 3.1. Working memory impairment profiles and clinical correlates in patients with FES and ChSz

An ANCOVA, controlling for age, gender, and education level, revealed significant group differences in reaction times and *d*-prime scores during the *two-back* task (all  $p_{\text{FDR}} < 0.001$ ). Post-hoc analyses revealed that both FES and ChSz patients performed significantly worse than healthy controls across all working memory measures (all  $p_{\text{FDR}} < 0.05$ ) (Fig. 2B), except for accuracy at the 1750 ms stimulus presentation

**Fig. 2.** Behavioral task and clinical scale analyses

Note: A) Distribution of illness duration (years) for patients with FES and those with ChSz. B) Comparison of working memory performance among FES patients, ChSz patients, and healthy controls, controlling for sociodemographic factors (age, gender, and education level) (FDR corrected). C) Partial correlations between working memory performance, PANSS scores, illness duration, and Olanzapine Equivalent Dosage in patients with schizophrenia, controlling for sociodemographic factors (age, gender, education level, and age of onset) (FDR corrected).

Abbreviations: ACC, accuracy; RT, reaction time; PANSS-P, PANSS – Positive Subscale; PANSS-N, PANSS – Negative Subscale; PANSS-GP, PANSS – General Psychopathology Subscale; PANSS-T, PANSS – Total Score; FES, first-episode schizophrenia; ChSz, chronic schizophrenia; OZP, Olanzapine Equivalent Dosage. Asterisks denote significance levels: \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .

speed, where the difference between FES patients and controls did not reach statistical significance ( $p_{FDR} = 0.087$ ). Notably, FES patients exhibited significantly shorter reaction times, and higher  $d'$ -prime scores compared to ChSz patients (all  $p_{FDR} < 0.05$ ). Similar patterns were observed in the RM task, with significant group differences observed in accuracy at both presentation speeds (1750 ms and 750 ms per digit; all  $p_{FDR} < 0.001$ ). FES patients demonstrated better performance than ChSz patients (all  $p_{FDR} < 0.05$ , Fig. 2B). These performance differences between FES and ChSz groups remained significant even after adjusting for age of onset (Supplementary Table S3, Fig. S2).

Partial correlation analyses, controlling for age of onset, gender, and education level, revealed significant relationships between working memory performance and psychopathological symptoms. In the two-back task, reaction times positively correlated with PANSS negative symptom scores ( $r = 0.444$ ,  $p_{FDR} < 0.001$ ), and general psychopathology scores ( $r = 0.205$ ,  $p_{FDR} < 0.01$ ), while showing a negative correlation with PANSS positive symptom scores ( $r = -0.219$ ,  $p_{FDR} < 0.01$ ) (Fig. 2C). Furthermore,  $d'$ -prime scores exhibited negative correlations with both PANSS negative symptom scores ( $r = -0.223$ ,  $p_{FDR} < 0.01$ ) and general psychopathology scores ( $r = -0.172$ ,  $p_{FDR} < 0.05$ ). Illness

duration was positively correlated with reaction times on the *two-back* task ( $r = 0.148, p_{FDR} < 0.05$ ), yet showed no significant association with *d*-prime scores ( $r = -0.069, p_{FDR} > 0.05$ ). Notably, antipsychotic medication dosage (olanzapine equivalent) demonstrated a significant positive correlation with *two-back* reaction times ( $r = 0.242, p_{FDR} < 0.001$ ), while having no significant association with *d*-prime scores ( $r = -0.020, p_{FDR} > 0.05$ ). Further analyses identified significant negative associations between illness duration and *RM* task performance at both presentation speeds (1750 ms:  $r = -0.240, p_{FDR} < 0.001$ ; 750 ms:  $r = -0.275, p_{FDR} < 0.001$ ). *RM* task accuracy at both stimulus speeds negatively correlated with PANSS negative symptom scores (1750 ms:  $r = -0.583, p_{FDR} < 0.001$ ; 750 ms:  $r = -0.546, p_{FDR} < 0.001$ ) and general psychopathology scores (1750 ms:  $r = -0.368, p_{FDR} < 0.001$ ; 750 ms:  $r = -0.234, p_{FDR} < 0.01$ ). Interestingly, PANSS positive symptom scores showed a significant positive correlation with *RM* task accuracy at 750 ms ( $r = 0.182, p_{FDR} < 0.05$ ), but not at 1750 ms ( $r = 0.085, p_{FDR} > 0.05$ ). Medication dosage also negatively correlated with *RM* task accuracy (1750 ms:  $r = -0.170, p_{FDR} < 0.05$ ; 750 ms:  $r = -0.217, p_{FDR} < 0.01$ ).

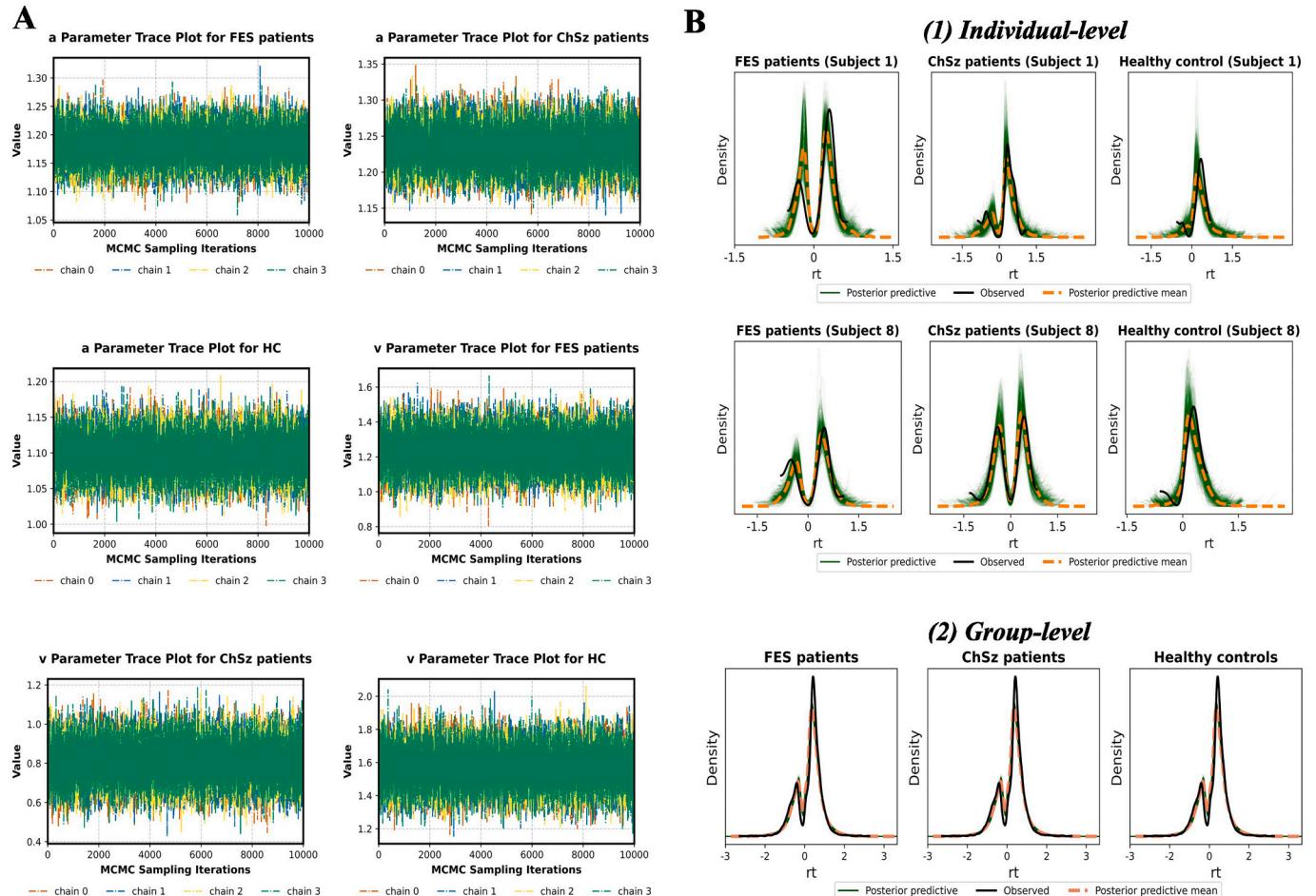
### 3.2. Computational mechanisms of working memory deficits in schizophrenia and associations with clinical and behavioral measures

#### 3.2.1. Robust fit of HDDM to the *two-back* task

The HDDM provided a robust fit to the *two-back* task, as evidenced by MCMC trace plots and R' (Fig. 3A, Supplementary Fig. S2). The R' values were below the recommended threshold of 1.01 (Supplementary Table S4), indicating satisfactory convergence (Brooks & Gelman, 1998). Predictive checks, conducted by simulating data using posterior estimates of model parameters, showed strong agreement with the observed data at both the individual and group levels, confirming the validity of the model fit (Fig. 3B). Model comparison revealed that drift rate ( $v$ ) was the key parameter differentiating between patient groups and healthy controls (Supplementary Table S5), with the drift rate regression model (Model 2v) demonstrating substantially better fit than all alternative models (details in Supplementary materials).

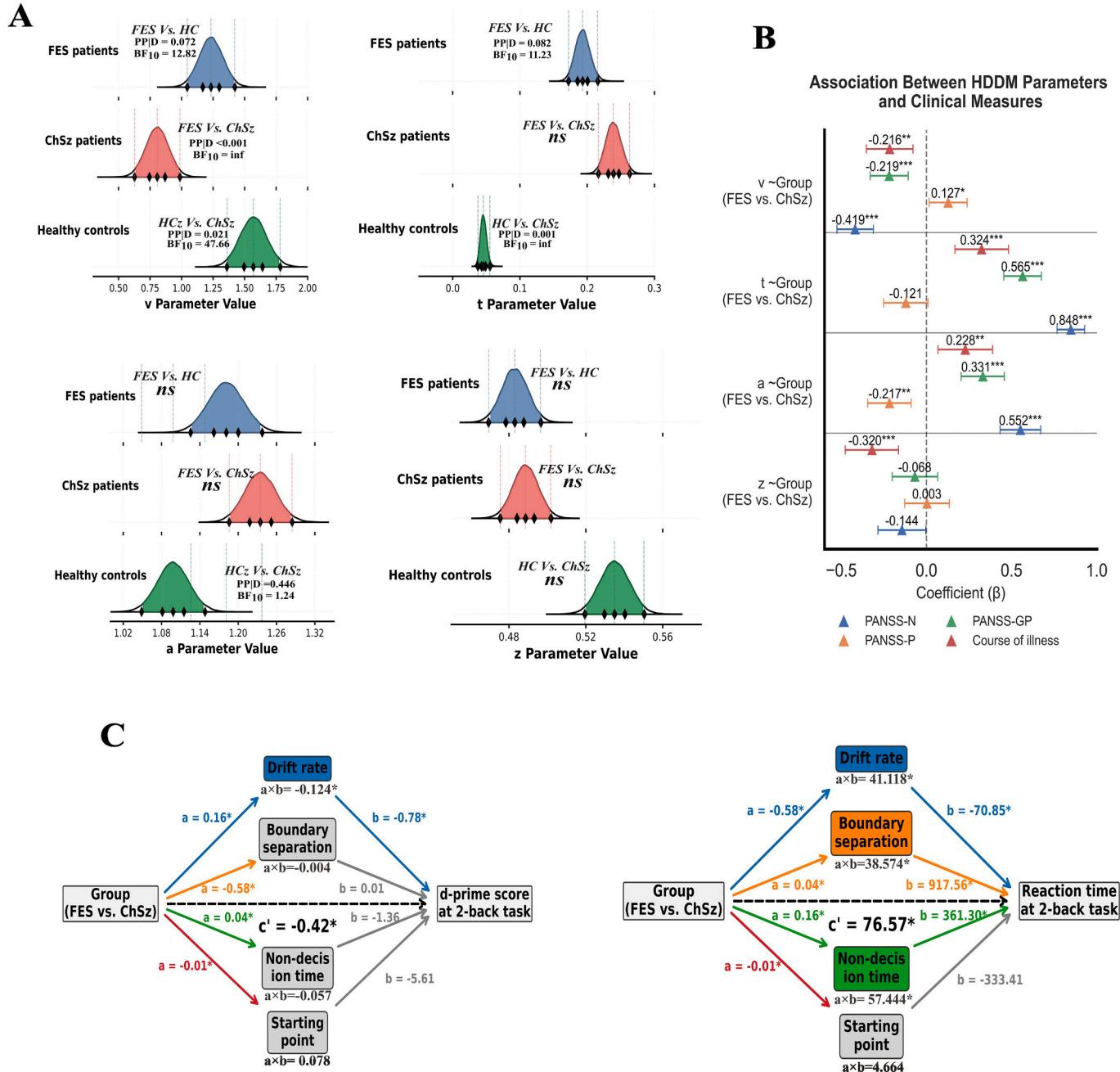
#### 3.2.2. Distinct patterns of impairment in HDDM parameters across patient groups

Bayesian ANOVA revealed significant differences in drift rate ( $v$ ) among the three groups, with healthy controls showing the highest  $v$ , followed by FES patients, and ChSz patients exhibiting the lowest  $v$



**Fig. 3.** Model diagnosis and posterior predictive checks

Note: A) MCMC sampling trace plots for patients with first-episode schizophrenia (FES), those with Chronic Schizophrenia (ChSz), and Healthy controls. The convergence and reliability of MCMC chains are demonstrated by their stable oscillation around constant values with overlapping trajectories across different chains, creating a characteristic “caterpillar” pattern. B) Posterior predictive check plots comparing observed and model-predicted reaction time (RT) distributions at both individual and group levels. The observed RT distributions are represented by solid black lines. Green lines indicate individual posterior predictive samples, with each line representing a predicted RT distribution derived from a single posterior sample. The orange dashed lines show the mean predicted RT distribution averaged across all posterior predictive samples. Abbreviations: FES, first-episode schizophrenia; ChSz, chronic schizophrenia; RT, reaction time (second). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



**Fig. 4.** HDDM statistical inference and association analysis with clinical and behavioral measures

Note: A) Ridgeplot of parameter posteriors for the FES and ChSz groups and statistical inference on parameters. B) Multiple regression analyses examine the relationships between each HDDM parameter and clinical measures (PANSS scales and illness duration), adjusting for age of onset, gender, educational level, and OZP equivalent, with FDR correction applied. C) Mediation analyses, controlled for age of onset, gender, and education level, using bootstrap confidence intervals (3000 samples) to assess the potential mediating effects of computational parameters derived from the two-back task on the relationships between illness duration (comparing FES vs. ChSz patients) and working memory behavioral metrics. Asterisks denote significance levels: \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ . Abbreviations: FES, first-episode schizophrenia; ChSz, chronic schizophrenia; drift rate ( $v$ ): representing the efficiency of evidence accumulation; boundary separation ( $a$ ): indicating the amount of evidence required for a decision; non-decision time ( $t$ ): reflecting perceptual and motor latencies; starting point bias ( $z$ ): capturing decision biases.

(Fig. 4A). Compared to healthy controls, FES patients had a significantly lower  $v$  (Mean Difference =  $-0.402$ ; 95 % highest density interval [HDI]:  $-0.686$  to  $-0.136$ ; posterior probability given data [PP|D] =  $0.072$ ; Bayes factor [ $BF_{10}$ ] =  $12.82$ ), and this difference was even more pronounced between ChSz patients and healthy controls (Mean Difference =  $-0.842$ ; 95 % HDI:  $-1.077$  to  $-0.583$ ; PP|D <  $0.001$ ; BF<sub>10</sub> = infinite [inf]) (Supplementary Fig. S3). When directly comparing patient groups, ChSz patients showed a significantly lower  $v$  than FES patients

(Mean Difference =  $0.494$ ; 95 % HDI:  $0.224$  to  $0.783$ ; PP|D =  $0.021$ ; BF<sub>10</sub> =  $47.66$ ). Non-decision time ( $t$ ) was significantly prolonged in FES patients compared to healthy controls (Mean Difference =  $0.162$ ; 95 % HDI:  $0.145$  to  $0.179$ ; PP|D =  $0.0817$ ; BF<sub>10</sub> =  $11.23$ ) and even longer in ChSz patients (Mean Difference =  $0.219$ ; 95 % HDI:  $0.197$  to  $0.243$ ; PP|D <  $0.001$ ; BF<sub>10</sub> = inf). However, no significant difference in  $t$  was observed between FES and ChSz patients (PP|D =  $1.00$ ). Although ChSz patients showed a significantly lower boundary separation ( $a$ ) compared

to healthy controls (Mean Difference = 0.159; 95 % HDI: 0.090 to 0.231; PP|D = 0.446;  $BF_{10} = 1.24$ ), the evidential strength for this difference was relatively weak. No significant differences in  $a$  were found between FES and ChSz patients or between FES patients and healthy controls. Starting point ( $z$ ) did not differ significantly among the three groups (all PP|D = 1.00).

### 3.3. Associations between HDDM parameters and clinical and behavioral measures

Multiple linear regression analyses, controlling for age of onset, gender, education level, and olanzapine-equivalent dosage, revealed significant associations between HDDM parameters and clinical measures. Drift rate ( $v$ ) exhibited negative correlations with negative symptoms ( $\beta = -0.419, p < 0.001, R^2 = 0.491$ ), general psychopathology ( $\beta = -0.219, p < 0.001, R^2 = 0.387$ ), and illness duration ( $\beta = -0.216, p = 0.003, R^2 = 0.372$ ), but demonstrated a positive correlation with positive symptoms ( $\beta = 0.127, p = 0.033, R^2 = 0.359$ ) (Fig. 4B). Conversely, boundary separation ( $a$ ) was positively associated with negative symptoms ( $\beta = 0.552, p < 0.001, R^2 = 0.366$ ), general psychopathology ( $\beta = 0.331, p < 0.001, R^2 = 0.211$ ), and illness duration ( $\beta = 0.228, p = 0.007, R^2 = 0.143$ ), yet negatively correlated with positive symptoms ( $\beta = -0.217, p = 0.002, R^2 = 0.156$ ). Furthermore, non-decision time ( $t$ ) strongly correlated with negative symptoms ( $\beta = 0.848, p < 0.001, R^2 = 0.708$ ), general psychopathology ( $\beta = 0.565, p < 0.001, R^2 = 0.400$ ), and illness duration ( $\beta = 0.324, p < 0.001, R^2 = 0.170$ ). Starting point ( $z$ ) showed a significant negative correlation with illness duration ( $\beta = -0.320, p < 0.001, R^2 = 0.175$ ).

Mediation analyses were conducted to explore whether HDDM parameters mediated differences in cognitive task performance between patient groups (FES vs. ChSz). Drift rate ( $v$ ) significantly mediated group differences in sensitivity ( $d$ -prime scores) during the *two-back* task ( $p = 0.002$ ) (Fig. 4C). Regarding reaction times on the same task, non-decision time ( $t$ ) was identified as the strongest mediator, accounting for 42.86 % of the total effect ( $p < 0.001$ ). Significant mediation effects were also observed for drift rate (30.68 %,  $p < 0.001$ ) and boundary separation (28.78 %,  $p = 0.002$ ), while starting point ( $z$ ) did not show significant mediation effects.

To provide convergent evidence for the cognitive mechanisms underlying working memory deficits in schizophrenia as captured by the HDDM parameters, we further examined associations between computational parameters derived from the *two-back* task and behavioral performance on the RM task. Results indicated that drift rate ( $v$ ) significantly mediated diagnostic group differences in RM performance at both the 1750 ms interval ( $p = 0.004$ , mediation proportion = 13.52 %) and the 750 ms interval ( $p = 0.011$ , mediation proportion = 11.07 %) (Supplementary Fig. 4 A). Similarly, non-decision time ( $t$ ) was a significant mediator at both retention intervals (1750 ms:  $p = 0.026$ , mediation proportion = 9.49 %; 750 ms:  $p = 0.002$ , mediation proportion = 10.48 %). However, neither boundary separation ( $a$ ) nor starting point ( $z$ ) significantly mediated group differences on the RM task.

### 3.4. Complementary analysis for age of onset

Our study included FES and ChSz groups with similar chronological age but different ages of onset, which is consistent with previous reports (Y. Liu et al., 2019; Yang et al., 2019) (Table 1, Supplementary Fig. S5A). However, the mathematical relationship—Chronological age  $\approx$  Age of Onset + Illness Duration—inevitably introduces multicollinearity (Supplementary Fig. S5B, S5C). To minimize the potential confounding effects of age of onset, we conducted the following complementary analyses: First, we used propensity score matching (PSM) to balance potential confounders between groups (Chan et al., 2021; Stroup et al., 2016). Logistic regression was applied using four key clinical covariates (age of onset, gender, education level, and medication dosage), and 1:1 nearest neighbor matching was performed with a caliper width of 0.2

standard deviations of the logit of the propensity score (Austin, 2011). This resulted in 54 successfully matched pairs (ChSz and FES,  $N = 54$  each), with age of onset, gender, education, and olanzapine dose effectively matched (all  $p > 0.05$ , Standardized Mean Difference  $< 0.25$ ) (Supplementary Table S6, Fig. S6A,6B). Subsequent correlation analysis found no significant association between illness duration and age of onset in the matched sample ( $r = -0.118, p = 0.224$ ) (Supplementary Fig. 6C). Moreover, we further stratified the FES and ChSz groups using a well-validated neurodevelopmental threshold of 25 years (Fathalli et al., 2008; Huang and Lee, 2006), forming early-onset (< 25 years) and late-onset ( $\geq 25$  years) subgroups (Supplementary Table S7). This stratification allowed for validation of results across these distinct subgroups. As expected, both PSM and subgroup analyses validated the main findings on WM performance (Supplementary Fig. S7) and HDDM analysis (Supplementary Fig. S8).

## 4. Discussion

Our study revealed that patients with FES (illness duration  $\leq 2$  years) and ChSz (illness duration  $\geq 5$  years) performed significantly worse than healthy controls on working memory tasks, as assessed by two-alternative forced-choice and non-forced-choice paradigms. Notably, the ChSz group exhibited more severe working memory impairments, which were closely associated with more pronounced negative symptoms. By leveraging the HDDM to analyze performance on the *two-back* task, we observed that abnormalities in both the drift rate and non-decision time parameters contributed to the behavioral deficits observed in schizophrenia patients relative to healthy controls. While non-decision time showed no significant difference between the FES and ChSz groups—which suggests this computational process may remain relatively stable over the course of the illness—the drift rate was not only significantly reduced in the ChSz group compared to the FES group but also significantly modulated the group differences in working memory task performance (e.g.,  $d$ -prime scores) and showed significant negative correlations with illness duration and negative symptoms, but a positive correlation with positive symptoms.

Our findings align with prior research demonstrating that working memory impairment is a core neuropsychological deficit in individuals with schizophrenia (Melle, 2019) and that cognitive impairments, including working memory deficits, vary in severity between FES and ChSz patients (Sponheim et al., 2010; Wu et al., 2016). Moreover, our results support previous studies showing that longer illness duration is associated with worse working memory performance (Piskulic et al., 2007; Sponheim et al., 2010), potentially reflecting underlying changes in brain function and structure. Evidence suggests that longer illness duration is linked to impaired activation of the prefrontal cortex (PFC) during working memory tasks (Elsabagh et al., 2009) and reduced prefrontal cortical gray matter volumes in ChSz patients compared to FES patients (Molina et al., 2004; Premkumar et al., 2006), likely contributing to the observed differences in working memory performance between these groups. Despite the evidence supporting more pronounced WM deficits in ChSz patients compared to FES patients, it is important to acknowledge that some studies have not found significant differences between these groups (O’Ceallaigh et al., 2000; Zanello et al., 2009), which may be attributed to several factors. One important factor is the lack of standardized criteria for classifying FES and ChSz patients (Ellison-Wright et al., 2008), with studies using various cutoffs ranging from 6 months (Zanello et al., 2009) to 3 years (Friedman et al., 2008) or even 5 years (Chang et al., 2021). Shorter illness duration differences may not be sufficient to lead to changes in WM (Zanello et al., 2009). Moreover, differences in age of onset between the included FES and ChSz patients can also influence the results (Lyu et al., 2023). Another potential reason for the inconsistency is the inclusion of different covariates across studies. Rek-Owodziń et al. (2022) found that after adding clinical variables like number of hospitalizations and other symptom dimensions as covariates, the original WM differences between

FES and ChSz became non-significant, highlighting the impact of covariate selection on study outcomes. To reduce heterogeneity, future research should establish and adopt more consistent standards for grouping patients and selecting covariates.

In addition to pathological factors, some studies suggest that pharmacological treatment may also be an important factor associated with the observed more severe working memory impairment in ChSz patients (MacKenzie et al., 2018), as chronic patients often receive antipsychotic medication for longer durations and at higher doses (Supplementary Fig. S9), which may in turn lead to the development of secondary negative symptoms (Kirschner et al., 2017) and metabolic abnormalities (Bora et al., 2017), potentially negatively influencing working memory. However, the impact of antipsychotics on working memory may be confounded by clinical symptoms, as more severe symptoms may require higher doses. In our study, we found that the effect of medication on working memory performance was significantly partially mediated by the severity of clinical symptoms, but a direct effect remained significant (Supplementary Fig. S4C). This suggests that while clinical symptoms play an important role in the relationship between medication and working memory, antipsychotic use may still have a significant effect on working memory performance. It is crucial to acknowledge that the current study design cannot fully disentangle the independent effects of medication use and disease progression on working memory. Prospective follow-up studies and rigorously controlled clinical trials are needed to further elucidate this complex relationship and establish causal links.

Our further analysis demonstrated that working memory impairments appeared to be associated with clinical symptom severity, particularly negative symptoms and general psychopathology. Patients with severe negative symptoms, such as low motivation, may lack sufficient drive and ability to focus, potentially affecting their information processing and storage capacities and contributing to working memory impairments (De Pieri et al., 2024). Those with more pronounced general psychopathological symptoms, including anxiety, tension, and depression, could experience depleted cognitive resources, impaired attentional regulation, and heightened emotional fluctuations, which may be associated with poorer working memory task performance. Nonetheless, it is important to acknowledge that the relationship between clinical symptoms and working memory was not found in other studies (Bagger et al., 2003; Y. Liu et al., 2021). These discrepancies might partially stem from methodological variations, such as differences in sample sizes and working memory assessment tools. Moreover, our mediation analyses suggest that certain behavioral computational parameters (e.g., drift rate) could play a role in moderating the relationship between clinical symptoms and working memory behavioral performance (Supplementary Fig. S4B). Interestingly, these parameters appear to be influenced by factors like illness duration (Shen et al., 2024), which might partially explain some of the variability observed in the relationship between working memory impairments and clinical symptom severity. Future work could further investigate whether the heterogeneity in the underlying computational processes of working memory modulates the relationship between clinical symptoms and working memory behavioral performance (e.g., reaction times) in patients with schizophrenia.

As expected, our HDDM analysis revealed that the observed behavioral impairments in schizophrenia corresponded to abnormalities in drift rate and non-decision time parameters compared to healthy controls. Both FES and ChSz showed significantly prolonged non-decision times relative to controls, with no significant difference between patient groups. This pattern suggests that non-decisional processing deficits emerge early in the illness course and remain relatively stable over time. The prolonged non-decision times, likely reflecting slowed sensorimotor and encoding/response execution processes, likely contribute to the working memory deficits observed on the *number two-back* task in both patient groups. This finding is consistent with previous HDDM studies identifying increased non-decision time as a

characteristic feature of schizophrenia (Fish et al., 2018) and aligns with recent meta-analytic evidence showing comparable processing speed deficits across illness stages in schizophrenia (Cai et al., 2024).

Interestingly, we found that the drift rate may worsen with illness progression, while non-decision time remains relatively stable. Specifically, we observed a clear gradient change in drift rate (healthy controls > FES > ChSz), consistent with the results for the *d*-prime scores (see Supplementary Table S8), as ChSz patients exhibited a higher false alarm rate and lower hit rate. Mediation analysis results also supported this, indicating that group (FES vs. ChSz) affected working memory task performance by significantly influencing the drift rate, suggesting that the drift rate may be a key factor driving the differences in working memory task performance between FES and ChSz patients. The decrease in information processing efficiency may be a core marker of disease progression. The drift rate represents the efficiency of evidence accumulation during decision-making tasks (Ratcliff and McKoon, 2008). The dorsolateral prefrontal cortex (DLPFC) plays a key role in integrating evidence from various sources and translating it into appropriate action decisions (Lin et al., 2020). The slower drift rate observed in the ChSz group suggests that these patients require more time to accumulate sufficient evidence to make a decision, potentially leading to increased errors and longer response times in working memory tasks. Furthermore, we observed that the drift rate in patients showed negative associations with negative symptoms and general psychopathology but positive associations with positive symptoms. The motivational deficits intrinsic to negative symptoms may impair patients' ability to sustain attention and engagement during tasks, hindering the effective integration of sensory inputs and task-relevant information, ultimately resulting in reduced drift rates (Saleh et al., 2023). Moreover, general psychopathology features, such as anxiety and depression, have also been linked to lower drift rates, potentially reflecting a generalized cognitive or affective burden that impedes efficient information processing (Lawlor et al., 2020). In contrast, positive symptoms, including delusions and hallucinations, have been associated with elevated drift rates (Scaramozzino et al., 2024), possibly due to aberrant salience attribution to task-irrelevant stimuli.

This study has some limitations. First, the stage-specific computational profiles of working memory deficits in patients with schizophrenia were derived from cross-sectional rather than longitudinal data. Consequently, the computational profiles of working memory observed in chronic patients may reflect a combination of illness severity, treatment resistance, and selection factors rather than solely representing disease progression. Selection biases likely exist, as patients with more favorable outcomes are typically underrepresented in chronic samples due to attrition from clinical services (Conus et al., 2010). This potential sampling bias may skew the chronic group toward cases with greater treatment resistance. Additionally, our study utilized patient education level as a covariate in the regression model instead of parental education level due to data constraints. We recognize that a patient's education level may be influenced by the disease itself, potentially introducing reverse causality (Gage et al., 2022). Although our supplementary analyses comparing models with and without patient education level as a covariate (Supplementary Tables S3, S8, and Fig. S10) did not change our main findings, we acknowledge this limitation. Future research should employ longitudinal designs and enhance the recording of family background information, including parental education levels, to elucidate the mechanisms underlying the progression of working memory deficits from first-episode to chronic stages of schizophrenia and to address potential confounding factors. Second, like previous reports, our study included FES and ChSz groups with similar chronological ages but different ages of onset (Y. Liu et al., 2019; Yang et al., 2019). Although we conducted sensitivity analyses, including subgroup analyses and propensity score matching to control for age of onset, the complete separation of these factors remains challenging in cross-sectional designs, as group classification (FES vs. ChSz) partially encompasses this information. Future prospective longitudinal studies tracking

individuals from illness onset will be necessary to conclusively validate the independent effects of these factors. Third, although we converted antipsychotic medication doses to olanzapine equivalents and controlled for medication effects in our analyses (Supplementary Fig. S1) (Gardner et al., 2010; Leucht et al., 2015), the potential impact of different pharmacological agents on working memory performance cannot be entirely ruled out. Future studies should aim to recruit medication-naïve patients or those on a more homogeneous treatment regimen to minimize confounding effects and facilitate more precise interpretations of the observed cognitive deficits. Fourth, our study did not incorporate neuroimaging techniques to connect the drift diffusion model results to the neural basis of cognitive deficits in schizophrenia. Previous research has explored the neural underpinnings of information processing in working memory tasks (Borgan et al., 2021). Combining neuroimaging methods with computational modeling approaches could provide deeper insights into the neural mechanisms underlying the observed differences in drift rate between patients with FES and those with ChSz.

In conclusion, our study provides novel insights into the nature and extent of working memory impairments across different stages of schizophrenia. By employing the HDDM, we identified that the observed impairments in conventional metrics among patients were related to abnormalities in drift rate and non-decision time parameters compared to HCs. While deficits in non-decision time may emerge early and persist throughout the illness, reduced drift rate—reflecting diminished efficiency of evidence accumulation during decision-making—progressively deteriorates with longer illness duration and is closely associated with more severe negative symptoms and general psychopathology. These findings highlight a targeted area for future research and may inform the development of more targeted cognitive remediation approaches for patients with chronic schizophrenia.

#### Code availability statement

Scripts to run the main analyses have been made publicly available and can be accessed at <https://github.com/Two-back-task-HDDM>.

#### CRediT authorship contribution statement

**Tongyi Zhang:** Visualization, Software, Formal analysis, Data curation, Conceptualization, Writing – review & editing, Writing – original draft. **Xiaolong Yang:** Funding acquisition, Conceptualization. **Pei Mu:** Data curation, Writing – review & editing. **Xiaoning Huo:** Resources, Conceptualization, Writing – review & editing. **Xin Zhao:** Supervision, Resources, Funding acquisition, Conceptualization, Writing – review & editing.

#### Ethical standards

This study was conducted in full compliance with the ethical guidelines and approved protocols of the Ethics Committee at the Third People's Hospital of Lanzhou City and Northwest Normal University (Lanzhou, China). Prior to participation, all participants were provided with comprehensive information regarding the study's aims, procedures, potential risks, and benefits. The study adhered to the principles outlined in the *Declaration of Helsinki*, and written informed consent was obtained from all participants.

#### Role of the funding source

This work was supported by the National Natural Science Foundation of China (No. 32260207 [to Xin Zhao]) and the Lanzhou City Science and Technology Program Project (No. 2022-3-56 [to Xiaolong Yang]).

#### Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2025.06.012>.

#### Data availability

The raw data used in this study are protected and are not publicly available due to data privacy. These data can be accessed upon reasonable request to the corresponding author (X.Z.). Derived data supporting the findings of this study are available from the corresponding author (X.Z.) upon request.

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