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Predictors of within-individual variability in cognitive performance in schizophrenia in a South African case–control study

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Original Article

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Abstract

Introduction: Cognitive dysfunction in schizophrenia may be assessed by measuring within-individual variability (WIV) in performance across a range of cognitive tests. Previous studies have found increased WIV in people with schizophrenia, but no studies have been conducted in low- to middle-income countries where the different sociocultural context may affect WIV. We sought to address this gap by exploring the relationship between WIV and a range of clinical and demographic variables in a large study of people with schizophrenia and matched controls in South Africa. *Methods:* 544 people with schizophrenia and 861 matched controls completed an adapted version of The University of Pennsylvania Computerized Neurocognitive Battery (PennCNB). Demographic and clinical information was collected using the Structured Clinical Interview for DSM-IV Diagnoses. Across-task WIV for performance speed and accuracy on the PennCNB was calculated. Multivariate linear regression was used to assess the relationship between WIV and a diagnosis of schizophrenia in the whole sample, and WIV and selected demographic and clinical variables in people with schizophrenia. *Results:* Increased WIV of performance speed across cognitive tests was significantly associated with a diagnosis of schizophrenia. In people with schizophrenia, increased speed WIV was associated with older age, a lower level of education and a lower score on the Global Assessment of Functioning scale. Increased accuracy WIV was significantly associated with a younger age in people with schizophrenia. *Conclusions:* Measurements of WIV of performance speed can add to the knowledge gained from studies of cognitive dysfunction in schizophrenia in resource-limited settings.

Significant outcomes

- Increased WIV across speed measures was associated with schizophrenia and poorer functional outcomes in the disorder, while no such effects were observed for WIV in accuracy.
- This finding provides support for the use of measures of speed WIV in future studies exploring the biological basis of cognitive dysfunction in schizophrenia.
- The finding of a negative relationship between speed WIV and educational attainment provides further evidence for the positive association between years of education and cognitive function, whether measured by WIV or another metric.

Limitations

- There were substantially more males than females in this cohort, which made accurate assessment of the relationship between sex and WIV challenging.
- A detailed rating scale was not used to assess symptom severity in schizophrenia which may have limited the analysis of the relationship between symptom severity and WIV.

Introduction

Cognitive dysfunction is characteristic of schizophrenia (Saykin *et al.*, 1991; Vinogradov *et al.*, 1998; Rentrop *et al.*, 2010; Cole *et al.*, 2011; Roalf *et al.*, 2013a). Within-individual variability (WIV) in cognitive functioning reflects the extent of the variation in an individual's performance relative to their mean performance, and it has been suggested that WIV provides additional insight into cognitive function over and above mean-based performance measures (MacDonald *et al.*, 2009; Roalf *et al.*, 2013a). WIV indexes risk of psychosis in the general population and is a predictor of functional outcomes in schizophrenia (Vinogradov *et al.*, 1998; Wexler *et al.*, 2004; Reichenberg *et al.*, 2006; Shin *et al.*, 2013; Wallace and Linscott, 2018). Additionally, elevations in WIV have been observed in individuals with high risk of developing psychosis when mean measures of performance are normal (Shin *et al.*, 2013).

WIV may be operationalised in three ways: 1) across-tasks in the same testing session, 2) across-trials of the same task during the same testing session and 3) across-trials of the same task during different testing sessions (MacDonald *et al.*, 2009; Cole *et al.*, 2011). Across-trials and across-task WIV are positively correlated (Hultsch *et al.*, 2002), and elevations in both measures of WIV have been demonstrated in people with schizophrenia (Reichenberg *et al.*, 2006; Cole *et al.*, 2011; Roalf *et al.*, 2013a; Fassbender *et al.*, 2014). Although it is typical to calculate WIV using measures of performance speed, WIV for performance accuracy may also be used to assess cognitive function (MacDonald *et al.*, 2009; Roalf *et al.*, 2013a; Roalf *et al.*, 2014a). Previous studies have found elevated across-task WIV for performance speed and accuracy in people with schizophrenia, reflecting an inability to maintain performance across tasks assessing different neurocognitive domains (Roalf *et al.*, 2013a; Roalf *et al.*, 2013b). Although the neural correlates of WIV require further research, abnormalities of brain white matter and hypoactivity of the dorsolateral prefrontal cortex have been associated with elevated WIV in schizophrenia (Roalf *et al.*, 2013b; Fassbender *et al.*, 2014; Panagiotaropoulou *et al.*, 2019; Ahn *et al.*, 2019). Increased WIV has also been demonstrated in disorders such as attention-deficit hyperactivity disorder (Leth-Steensen *et al.*, 2000; Lin *et al.*, 2015), traumatic brain injury (Stuss *et al.*, 2003) and dementia (Holtzer *et al.*, 2008; Halliday *et al.*, 2018; Webber *et al.*, 2022), including human immunodeficiency virus (HIV)-associated neurocognitive disorder (Vance *et al.*, 2021). Further, factors such as ageing, male sex and lower level of education have been associated with increased WIV (Hilborn *et al.*, 2009; Cole *et al.*, 2011; Roalf *et al.*, 2014a; De Felice and Holland, 2018).

Despite increasing interest in WIV as a measure of cognitive dysfunction, it has only been studied in a limited number of settings. To our knowledge, no studies of WIV in schizophrenia have been conducted in low- and-middle income countries (LMICs) where differences in educational levels, the prevalence of comorbid conditions (such as HIV) and treatment practices may affect the relationship between WIV and specific disorders. To promote the development of contextually relevant diagnostic and treatment practices, there is a need to assess the generalisability of findings from neuropsychological research on schizophrenia from high-income settings to other contexts. Additionally, the association between symptom severity and WIV in schizophrenia remains unclear as results have been inconsistent with some studies finding a positive association and others finding no relationship (Wexler *et al.*, 2004; Pellizzer and Stephane, 2007; Rentrop *et al.*, 2010; Shin *et al.*, 2013; Roalf *et al.*, 2013b; Akiyama *et al.*, 2016).

Here, we aim to address a gap in current knowledge by examining the relationship between across-task WIV and schizophrenia in a large case–control study from South Africa. Data were originally collected for a genetic study on schizophrenia but includes information on a range of cognitive, demographic and clinical variables. Thus, the study is uniquely placed to explore the relationship between 1) WIV and schizophrenia, 2) WIV and demographic variables (age, sex and level of education), and 3) WIV and clinical variables (HIV status, substance use, symptom severity and functional outcomes) in a LMIC.

Materials and methods

Participants

Patients with schizophrenia and matched controls underwent neuropsychological testing as part of the Genomics of Schizophrenia in the South African Xhosa people (SAX) study (Gulsuner et al., 2020). The SAX study is a case–control study that aimed to identify genetic variants and social exposures contributing to schizophrenia risk in the Xhosa population of South Africa. The Xhosa people are one of the largest black African groups in South Africa and live primarily in the Eastern and Western Cape provinces of the country. The SAX study enrolled 2,849 individuals that self-identified as Xhosa from community healthcare clinics and psychiatric hospitals in the Western and Eastern Cape of South Africa between January 2013 and February 2018. Eligible cases were individuals aged 21–60 years with a diagnosis of schizophrenia or schizoaffective disorder for at least 2 years, with the capacity to provide informed consent for the genomics study. Controls were matched to cases for age, sex and level of education and were individuals presenting to the same community healthcare clinics as cases for non-psychiatric medical conditions.

Instruments and measures

A translated Xhosa language version of the Structured Diagnostic Interview for DSM-IV Axis I Disorders (SCID-I) (First and Gibbon, 2004) was administered to all study participants by trained psychiatric nurses. As previously reported, inter-rater reliability for the Xhosa version of the SCID-I was adequate for the principle psychotic disorder ($\kappa = 0.74$, $p < .001$) (Mall *et al.*, 2020). Where possible, information from medical records, family members and healthcare professionals was incorporated and considered in the diagnostic process. Global functioning was assessed using the Global Assessment of Functioning (GAF) scale (Aas, 2011).

An adapted 10-test version of the Pennsylvania Computerized Neurocognitive Battery (PennCNB) was administered to 544 cases and 861 controls ($n = 1{,}405$) in isiXhosa. The PennCNB is designed to assess cognitive domains related to underlying brain networks through the application of "neurobehavioral probes" that have been validated with functional neuroimaging (Gur *et al.*, 1992; Roalf *et al.*, 2014b). The PennCNB has demonstrated adequate psychometric properties in a number of settings (Gur *et al.*, 2001; Gur *et al.*, 2010; Moore *et al.*, 2015; Service *et al.*, 2020; Scott *et al.*, 2021), and evidence for the validity of the Xhosa version of the CNB is presented in Scott *et al.* (2021). The tests included in the Xhosa version of the battery were designed to measure domains

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Table 1. Neurocognitive domains and tests included in the Xhosa version of the PennCNB

Neurobehavioural functions	Domain	Test
Executive-Control	Abstraction/ flexibility	Penn Conditional Exclusion Test
	Attention	Penn Continuous Performance Test
	Working Memory	Fractal N-Back
Episodic Memory	Face Memory	Penn Face Memory
	Spatial Memory	Visual Object Learning Test
Complex Cognition	Non-verbal Reasoning	Penn Matrix Reasoning Test
	Line Orientation	Penn Line Orientation Test
Social Cognition	Emotion Identification	Penn Emotion Recognition Test
Sensorimotor	Sensorimotor Speed	Motor Praxis Test
	Motor Speed	Computerized Finger Tapping Test

of neurocognition and social cognition that are known to be affected in SZ (Scott *et al.*, 2021). Descriptions of the English versions of the tests have been published. Briefly, the Xhosa version of the battery assesses five neurocognitive domains: 1) executive function, 2) episodic memory, 3) complex cognition, 4) social cognition and 5) sensorimotor speed. Table 1 lists the 10 tests included in the Xhosa version of the battery and the neurocognitive domains that they are designed to assess. Measures of speed and accuracy are calculated for each test except for the Motor Praxis Test and Computerized Finger Tapping Test for which only a measure of speed is obtained.

Ethics

All participants provided signed informed consent. To assess capacity to consent, The University of California, San Diego Brief Assessment of Capacity to Consent Questionnaire (UBACC) was administered to all participants (Jeste *et al.*, 2007; Campbell *et al.*, 2017). The study was approved by the University of Cape Town Human Research Ethics Committee (reference number – 049/2013).

Data analysis

Demographic and clinical characteristics of the cases and controls that completed the PennCNB were compared using *t*-tests and Pearson's chi-square tests for continuous and categorical variables, respectively. An index of across-task WIV was calculated for each participant who completed five or more cognitive tests ($n = 1{,}088$) using methodology described in previous studies (Holtzer *et al.*, 2008; Roalf *et al.*, 2013b). First, speed and accuracy measures for each test were *z*-transformed based on the distribution of the entire sample. Second, across-task WIV for both speed and accuracy was calculated using the following equation:

$$\mathrm{WIV} = \sqrt{\sum_{k=1}^{K} \frac{(Z_{ik} - A_i)^2}{(K-1)}}$$

Table 2. Sample demographic and clinical characteristics ($n = 1{,}405$)

	Controls ($n = 861$)	Cases ($n = 544$)	*P*-value
Age, years (SD)	36.48 (9.10)	35.02 (9.36)	0.004**
Sex, (%)			0.748
Male	780 (90.59)	490 (90.07)	0.085
Years of education (%)			
≤7	248 (28.97)	128 (23.62)	
8–11	449 (52.45)	292 (53.87)	
12	92 (10.79)	66 (12.81)	
>12	67 (7.83)	56 (10.33)	<0.001***
HIV status (%)			
Positive	132 (15.33)	24 (4.41)	<0.001***
History of street drug use (%)			
Yes	159 (18.88)	246 (46.24)	
GAF score (SD)	71.11 (12.53)	59.06 (10.00)	<0.001***
Symptom severity			
No Symptoms	–	29 (5.98)	
Mild	–	71 (14.64)	
Moderate	–	382 (78.76)	
Severe	–	3 (0.62)	

GAF, Global Assessment of Functioning Scale; HIV, human immunodeficiency virus.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

where Z_{ik} is the kth test score for the ith individual and:

$$A_i = \sum_{k=1}^{K} \frac{Z_{ik}}{K}$$

is the individual's mean *z*-transformed test score based on all completed cognitive tests in a battery.

For both speed and accuracy WIV, the data were skewed to the right and heteroscedasticity was present. WIV was log-transformed to an approximately normal distribution, and the natural log of WIV was taken as the dependent variable in further analyses. First, the relationship between a diagnosis of schizophrenia and speed and accuracy WIV was assessed using multivariate linear regression in the whole sample. Age, sex, level of education, case–control status, HIV status and history of substance use were included as covariates in the analysis. Second, multivariate linear regression was conducted using cases only with WIV as a dependent variable and age, sex, level of education, HIV status, history of substance use, GAF score, and symptom severity as independent variables. All statistical analyses were performed using IBM SPSS version 28.0.1.0.

Results

Sample characteristics

Of the cases, 96.5% ($n = 525$) had a principal axis 1 diagnosis of schizophrenia. The term schizophrenia will be used to describe the diagnosis of all cases in the remainder of the text. The demographic and clinical characteristics of the sample are

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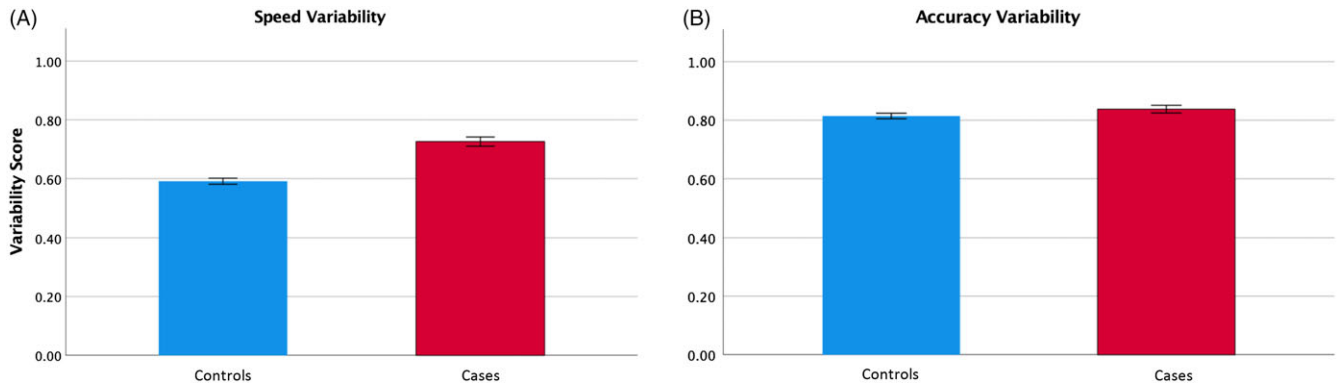

Figure 1. Means (+ standard error of the mean) for across-task within-individual variability for speed and accuracy in matched controls and people with schizophrenia (cases). Higher variability scores are indicative of worse overall performance.

summarised in Table 2. Controls were significantly younger than cases ($p = .004$). Level of education and sex did not differ significantly between the two groups. There was a significantly higher number of controls with a diagnosis of HIV ($p < .001$). Street drug use differed significantly between the two groups with a higher number of cases reporting a history of street drug use ($p < .001$). Scores on the GAF scale were significantly higher amongst controls ($p < .001$).

WIV and schizophrenia

WIV for accuracy and speed measures on the PennCNB is presented in Fig. 1. A multivariate linear regression was used to assess the relationship between WIV for speed and accuracy measures on the PennCNB and a diagnosis of schizophrenia in the entire sample. There was a significant relationship between speed WIV and a diagnosis of schizophrenia ($\beta = 0.255$, $p < .001$), but there was no significant relationship between accuracy WIV and a diagnosis of schizophrenia ($\beta = 0.021$, $p = .51$).

Predictors of WIV in schizophrenia

Amongst cases, speed WIV was significantly associated with age, level of education, and GAF (Table 3). There was a negative association between level of education and speed WIV ($\beta = -0.11$, $p = .035$). A higher GAF score was associated with a lower speed WIV ($\beta = -0.17$, $p = .002$). Symptom severity, substance use, HIV status and sex did not have a significant relationship with speed WIV. Age was positively correlated with WIV for speed ($\beta = 0.22$, $p < .001$) but contrastingly was negatively correlated with WIV for accuracy ($\beta = -0.13$, $p = .022$). Age was the only significant predictor of accuracy WIV in people with schizophrenia (Table 4).

Discussion

In this first study of WIV in cognitive performance in schizophrenia in a LMIC, we provide novel insights into the relationship between WIV and several clinical and demographic variables in this setting. The main findings of this study were as follows: 1) increased speed WIV was significantly associated with a diagnosis of schizophrenia; 2) reduced speed WIV was associated with a higher level of educational attainment and better functional outcomes among people with schizophrenia; and 3) among people with schizophrenia, speed and accuracy WIV were significantly associated with age but with opposite directions of effect, and the magnitude of effect was much larger for speed than accuracy.

The finding of a significant relationship between a diagnosis of schizophrenia and speed WIV in the analysis of the entire sample is in keeping with previous research, which has demonstrated increased WIV in speed measures for cognitive tasks in people with schizophrenia (Roalf *et al.*, 2013a; Roalf *et al.*, 2013b; Fassbender *et al.*, 2014). However, in contrast with previous studies, we did not find a significant relationship between accuracy WIV and schizophrenia (Roalf *et al.*, 2013a; Roalf *et al.*, 2013b). These results may suggest that WIV in speed measures is a more sensitive marker of cognitive dysfunction in schizophrenia in this and possibly other LMIC settings. In the analysis restricted to people with schizophrenia, we found an inverse relationship between speed WIV and global functioning. Converging evidence from multiple studies indicates that reduced WIV in reaction time is a predictor of better functional outcomes in schizophrenia (Vinogradov *et al.*, 1998; Wexler *et al.*, 2004; Rentrop *et al.*, 2010). Although abnormal elevations in WIV have been observed in other neuropsychiatric disorders, measures of speed WIV may be of potential use in clinical practice to identify people with schizophrenia at risk of poor functional outcomes and, thus, inform treatment decisions. Further, the results of this study support the significance of measures of speed WIV in our understanding of schizophrenia. Measures of speed WIV may be used in addition to or as an alternative to mean performance measures in future studies exploring the biological mechanisms contributing to cognitive impairment and functional outcomes in schizophrenia.

Cognitive function is an important determinant of socio-economic attainment (e.g. occupation and income), and physical and mental health outcomes in the general population as well as in people with schizophrenia (Kalechstein *et al.*, 2003; Strenze, 2007; Fioravanti *et al.*, 2012; Batty *et al.*, 2016; Ozawa *et al.*, 2022). Evidence from a recent meta-analysis supports a positive association between educational attainment and cognitive ability (Ritchie and Tucker-Drob, 2018). Schizophrenia is associated with lower educational attainment in both high-income and low- or middle-income countries (Crossley *et al.*, 2022), and therapeutic guidelines recommend interventions to improve educational outcomes in schizophrenia (National Institute for Health and Care Excellence [NICE], 2014; Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016; Norman *et al.*, 2017). This study found that higher educational attainment was associated with lower speed WIV amongst people with schizophrenia. This finding provides further support for the positive impact of educational attainment on cognitive function,

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Table 3. Linear regression analysis of selected predictor variables and WIV speed amongst people with schizophrenia ($n = 353$)

Predictor variables	B	95% CI	β	*p*
Age	0.011	[0.006, 0.016]	0.221	<0.001***
Sex	−0.022	[−0.191, 0.147]	−0.014	0.797
Education	−0.047	[−0.091, −0.003]	−0.111	0.035*
HIV status	−0.005	[−0.233, 0.224]	−0.002	0.969
Substance use	−0.046	[−0.095, 0.004]	−0.098	0.069
Symptom severity	0.067	[−0.011, 0.145]	0.087	0.093
GAF	−0.008	[−0.013, −0.003]	−0.166	0.002**

B, unstandardized regression coefficient; β, standardized regression coefficient; CI, confidence interval; GAF, Global Assessment of Functioning Scale; HIV, human immunodeficiency virus; SE, standard error.
Constant = −0.159, F (7,345) = 6.649, $p < 0.001$***, adj. $R^2 = 0.119$.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Table 4. Linear regression analysis of selected predictor variables and WIV accuracy amongst people with schizophrenia ($n = 353$)

Predictor variables	B	95% CI	β	*p*
Age	−0.005	[−0.008, −0.001]	−0.127	0.022*
Sex	0.015	[−0.113, 0.142]	0.013	0.818
Education	0.002	[−0.031, 0.034]	0.005	0.921
HIV status	0.059	[−0.113, 0.230]	0.036	0.502
Substance use	0.032	[−0.005, 0.070]	0.096	0.088
Symptom severity	0.025	[−0.034, 0.084]	0.045	0.410
GAF	0.000	[−0.004, −0.003]	−0.005	0.922

B, unstandardized regression coefficient; β, standardized regression coefficient; CI, confidence interval; GAF, Global Assessment of Functioning Scale; HIV, human immunodeficiency virus; SE, standard error.
Constant = −0.185, F (7,345) = 1.720, $p = 0.103$, adj. $R^2 = 0.014$.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

whether measured by WIV or another metric. This observation emphasises the relevance of interventions to increase educational attainment, and ultimately improve cognitive function, in people with schizophrenia in LMICs.

In this study, increased age was significantly associated with both greater accuracy and lower speed WIV amongst people with schizophrenia. In studies of WIV across the lifespan in the general population, increasing age after early adulthood is associated with a progressive increase in WIV in cognitive performance (Hultsch *et al.*, 2002; MacDonald *et al.*, 2009; Roalf *et al.*, 2014a). In this study, the finding of a positive relationship between age and speed WIV provides support for a similar relationship between speed WIV and age amongst people with schizophrenia. Contrastingly, age had a negative relationship with accuracy WIV. Although this finding was significant, the model predicting accuracy WIV explained a low amount of variance in accuracy WIV, and age had a small regression coefficient. Thus, the finding should be interpreted with caution and requires replication in other studies. However, that age effects are more pronounced on speed than on accuracy measures on cognitive tests has been established in multiple studies, including those using the PennCNB (Gur *et al.*, 2010; Irani *et al.*, 2012; Moore *et al.*, 2019).

There are certain limitations that need to be considered when interpreting the results of the study. There were substantially more males than females in this cohort, which made accurate assessment of the relationship between sex and WIV challenging. The small number of females may have contributed to the null relationship between sex and WIV in this study when previous research has demonstrated sex differences (Roalf *et al.*, 2014a). Future studies should aim at recruiting more female participants. Similarly, the lack of association between HIV status and WIV must be interpreted with caution as the number of HIV-positive individuals enrolled in the study was limited. Further, additional clinically relevant variables, such as CD4 count and HIV viral load, should be collected in future studies in order to allow for a more nuanced analysis of the relationship between WIV and HIV. While the inclusion of participants with HIV made it possible to assess the relationship between HIV and WIV in persons with schizophrenia, this may have affected the assessment of the relationship between WIV and a diagnosis of schizophrenia. As HIV is associated with cognitive impairment (Keng *et al.*, 2023), future studies aiming to focus on the relationship between WIV and schizophrenia may consider excluding individuals with a diagnosis of HIV. Lastly, the assessment of symptom severity in schizophrenia in this study was limited as it was derived from the SCID and a valid and reliable specific measure, such as the Positive and Negative Syndrome Scale for Schizophrenia (Kay *et al.*, 1987), would be better suited to assess this relationship.

In conclusion, the results of this study extend current knowledge of WIV in cognitive performance in schizophrenia by exploring its relationship with multiple clinical and demographic variables in a resource-limited setting. Generally, increased speed WIV was associated with schizophrenia and poorer functioning in the disorder, while no such effects were observed for WIV in accuracy. This finding suggests that WIV for speed measures might be a more sensitive marker of cognitive impairment in people with schizophrenia who can still maintain performance accuracy across neuropsychological tasks. The finding of an inverse relationship between educational attainment and speed WIV in this setting provided further evidence for the positive association between education and evening out cognitive function. The significant relationship between speed WIV and schizophrenia as well as global functioning in the disorder highlight the potential for future research into WIV to extend our understanding of cognitive impairment in schizophrenia.

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Ethical standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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