

Decline in Working Memory in Stable Schizophrenia May Be Related to Attentional Impairment: Mediating Effects of Negative Symptoms, a Cross-Sectional Study

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Background: Schizophrenia (SCZ) is a severe mental illness, Cognitive deficits and negative symptoms (NS) are prevalent in individuals with SCZ and are crucial indicators of functional recovery. It is well known that cognitive symptoms and negative symptoms are interrelated and that negative symptoms can affect the ability to take cognitive tests. However, the specific relationship between attention, working memory (WM), and NS in stable SCZ remains unclear. This study aims to explore these associations and provide valuable insights for the subsequent treatment of SCZ.

Methods: We conducted a comprehensive assessment of 145 patients with stable SCZ using the Chinese Brief Neurocognitive Suite of Tests (C-BCT) and the Positive and Negative Symptom Scale (PANSS).

Results: Patients with abnormal cognition exhibited significantly higher PANSS total scores, cognitive symptom scores, and NS than those with normal cognition ($P < 0.05$). Pearson's correlation analysis revealed significant positive correlations between digital breadth-(DB) and continuous operation(CO) ($r = 0.389$, $P < 0.001$), as well as a significant negative correlation between DB and NS ($r = -0.291$, $P < 0.001$). Moreover, CO showed a negative correlation with NS ($r = -0.173$, $P < 0.05$). However, no significant correlations were found between the digital breadth-antegrade score and CO or NS ($r = 0.148$, $P > 0.05$; $r = -0.068$, $P > 0.05$). Notably, NS were identified as a mediator in the relationship between attention and WM (effect size = 0.024).

Conclusion: Our findings highlight significant associations between WM, attention, and NS in individuals with stable SCZ. Moreover, attention not only directly impacts WM but also indirectly influences it through NS. Addressing cognitive deficits and NS in the treatment of SCZ may lead to improved overall outcomes for affected individuals.

Keywords: stable schizophrenia, working memory, attention, negative symptom, intermediary effect

Introduction

Schizophrenia (SCZ), one of the schizophrenia spectrum disorders, is a severe mental disorder of undetermined etiology and cognitive-emotional dysregulation, with the poorest prognosis of all mental disorders,¹ even affecting the patient's whole life, and the burden of disease for SCZ is one of the highest of all disorders.² Cognitive deficits are prominent and treatment-resistant symptoms of SCZ and serve as prominent indices of patient functioning and treatment outcomes.³ Numerous studies have demonstrated measurable cognitive deficits in individuals with SCZ, including impairments in working memory (WM), attention, information processing speed, and executive functioning.⁴ Notably, in severe mental illness, WM performance has emerged as the most robust predictor of functional outcomes.^{5,6} Moreover, attention and WM are closely intertwined,^{7,8} and individual differences in these abilities are dependent on their interrelated variations.⁹ Lapses in WM performance have been associated with differences in individuals' attention¹⁰, wherein low-ability

individuals exhibit more frequent mind-wandering, particularly during cognitively demanding tasks, and this phenomenon demonstrates synchronized behavior.⁷

The negative symptoms (NS) of SCZ, such as emotional flattening, social withdrawal, lack of pleasure, apathy, and reduced emotional expression, significantly impair social functioning.¹ The underlying mechanisms are complex and may involve reduced gray matter volume in the prefrontal, medial, and superior temporal lobes.¹¹ Dysregulation of multiple neurotransmitters, especially dopamine release, plays a pivotal role in these pathologic changes.¹² Furthermore, these alterations are closely associated with impairments in executive function, attention, and WM.¹³ Previous research has demonstrated that decrement in motor and cognitive speed plays a significant role in both the verbal WM impairment observed in patients and the associations between verbal WM impairment and clinical symptoms and is associated with NS.¹⁴ Another study showed that clinical symptoms, mainly NS, mediate the influence of neurocognition and social cognition on functional outcome of SCZ.¹⁵ Interestingly, we observed that medication showed limited effectiveness in alleviating negative and cognitive symptoms. Thus, it is imperative to investigate the relationship between these factors to better manage symptom progression.

The main objective of this study was to explore the relationship between WM, attention, and NS using a mediation model. We hypothesized that attention influences WM, and that NS may mediate the association between attention and WM. The inclusion of a mediation model will help elucidate the intricate interactions among these cognitive and symptomatic aspects of SCZ, paving the way for more targeted and effective interventions.

Materials and Methods

Subjects

In this study, 145 patients with stable SCZ who were hospitalised at Anhui Mental Health Centre from June 2022 to June 2023 were selected for this study; participants were recruited during their hospitalisation and all participants and guardians gave informed consent.

To be eligible for the study, patients needed to meet the following criteria: Meets DSM-V SCZ diagnostic criteria (schizophrenic patients only); Symptomatic stabilizers: clinically stable for ≥ 3 months, with P1, P2, P3, and P6 items ≤ 3 on the PANSS scale, and taking regular antipsychotic single-agent therapy and remaining stable for ≥ 3 months; be between 18 and 60 years old; Obtain informed consent, agree to take cognitive function tests, be able to understand and read Chinese, understand the test program, be able to understand the voice introduction, and be able to operate a simple iPad.

The size of the study sample was estimated using the G*Power 3.1.9 program. The power analysis was conducted using an alpha of 0.05, a power ($1-\beta$) of 0.80, and a medium effect size of 0.50 for a two-tailed test. The desired total sample size for detecting differences between two groups was 128. A total of 180 inpatients were screened, of whom 35 were excluded for the following reasons: Alcohol or substance dependence in the past six months ($n=7$); Significant clinical neurologic disorders; head trauma (loss of consciousness for more than an hour), Parkinson's disease, dementia ($n=14$); Pregnant or breastfeeding women ($n=6$); Presence of a family history of mental retardation ($n=1$); Combined other mental disorders ($n=2$); Their level of visual or auditory functioning affects the test ($n=5$). (shown in Figure 1). Finally, a total of 145 individuals were included in this study.

We collected general clinical data on the day of admission from SCZ patients who met the inclusion criteria, which included data on gender, age, height, weight, body mass index (BMI), duration of illness, and years of education, and calculated chlorpromazine equivalent.^{16,17} We used a 5-factor model of the PANSS scale to assess clinical symptoms, including cognitive factors (P2, N5, N7, G10, G11), arousal factors (P4, P7, G4, G8, G14), depression factors (G2, G3, G6), negativity factors (N1-N7) and positivity factors (P1-P7). Rated by 2 consistency-trained psychiatric clinicians, the higher the symptom score, the more severe the symptom. Cognitive functions of SCZ patients were assessed using the C-BCT. C-BCT is a localized cognitive assessment tool for SCZ adapted for China.¹⁸ The target patients are those who have cognitive impairment and those who have been treated with medication to observe the effects of the treatment. A total of four tests are included, including the connectivity test, symbol encoding, continuous operation, and digital breadth. The patients were tested for information processing speed, executive function, attention, and WM. Each measure shows its T score, deficit, degree of impairment, and percentile (%) in the Chinese test population as a means of assessing

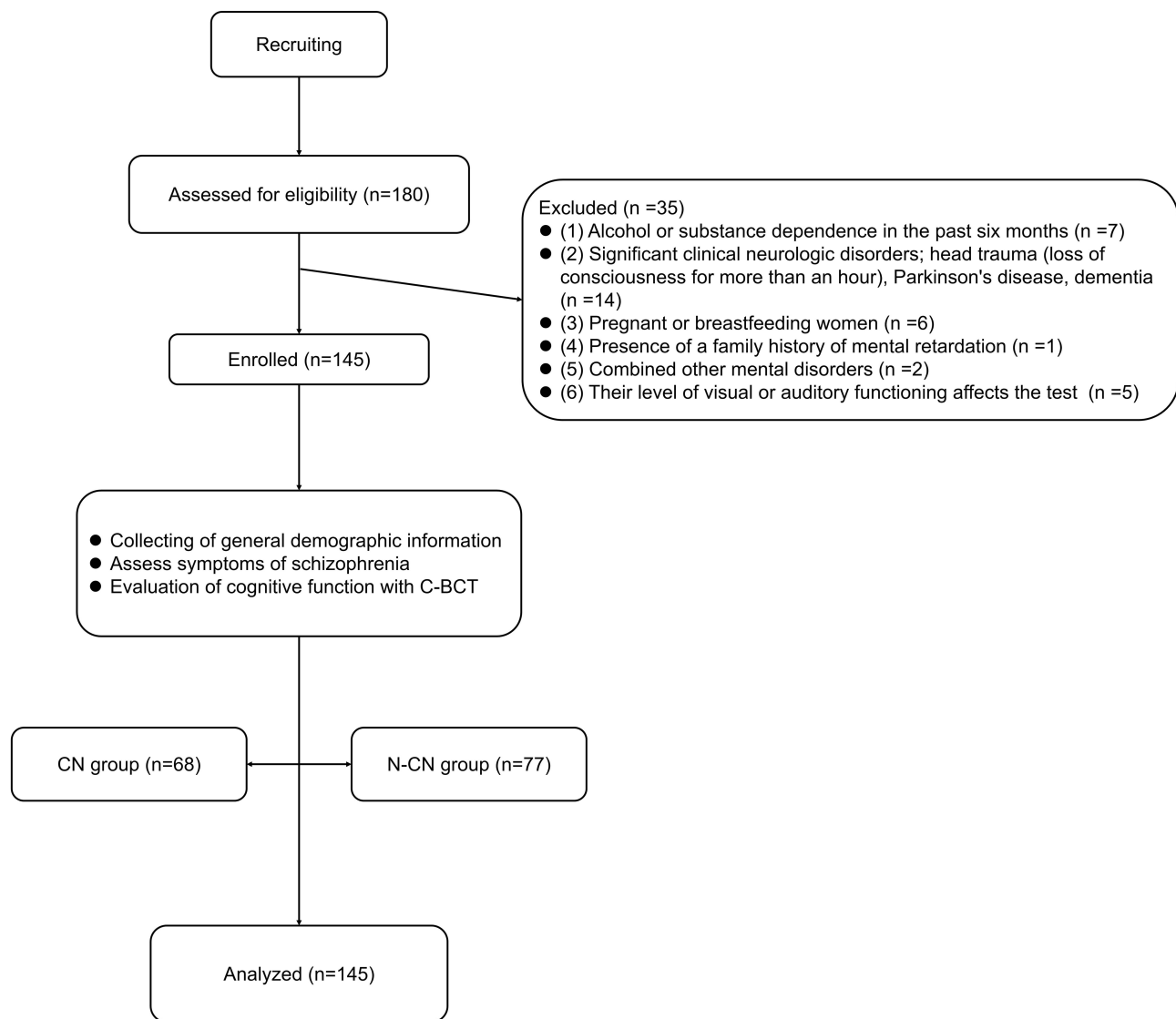


Figure 1 Flow chart.

the patient's cognitive function. In addition to the four tests, there is a total score T-score, deficit, degree of impairment, and percentile (%) in the Chinese test population. This is a composite score of several domains, also including attention and working memory.

We grouped them according to the degree of impairment in the total score, classifying those with relatively normal impairment into the cognitively normal group (not up to the level of the healthy population) and the others into the cognitively abnormal group.

The study was reviewed and approved by the Medical Ethics Committee of the Affiliated Psychological Hospital of Anhui Medical University (Ethics No. HSY-IRB-PJ-JZB-001), and the participants clearly understood the purpose of the study and signed an informed consent form.

Research Design

This study used a cross-sectional design to investigate the relationship between WM and attention in patients with stable SCZ and to analyse their relationship with NS. We categorised them into cognitively normal (CN) and cognitively abnormal (N-CN) groups by the impairment scores in the total score component of the results of the Chinese Brief Neurocognitive Test (C-BCT). We compared whether the two groups differed in general demographic information and

scores on each item of the PANSS scale; analysed whether WM, attention and NS were correlated; and performed mediation analyses.

Data Analysis

Statistical analyses were performed using SPSS 26.0, first checking whether the measured data were characterized by a normal distribution as well as consistency of variance. Normal distribution was represented by $(\bar{x} \pm s)$ and skewed distribution was represented by $M (P_{25}, P_{75})$. General data such as age, height, weight, body mass (BMI), duration of disease, years of education, and chlorpromazine equivalents were analyzed using the independent samples *t*-test, while gender was studied using the chi-square test. Comparisons of 2 groups of measured data that conformed to a normal distribution were performed using 2 independent samples *t*-test; Pearson's correlation analysis was used in this study to explore the correlation between the variables; the difference was considered statistically significant at $P < 0.05$. For the mediation analysis, attention (Continuous Operation, CO) was set as the independent variable and WM (Digital Breadth, DB) as the dependent variable. The mediating effect of the model was explored using the coefficient of variation test.

Results

General Demographic Information and Analysis of Variance

A total of 145 patients with stable SCZ were included in this study. Based on the results of the C-BCT, 68 patients exhibited normal cognition (NC), while 77 patients had abnormal cognition (N-CN). Importantly, there were no significant differences in sex, age, body mass index (BMI), illness duration, years of education, or chlorpromazine equivalents between the two groups ($P > 0.05$). However, the PANSS total score, NS scores, and cognitive symptom scores showed statistically significant differences between the groups ($P < 0.05$). In addition, we compared the cognitive scores and negative symptom scores of men and women separately, and the results showed that there were no significant differences, except for a significant difference in the negative symptom scores ($P < 0.05$). For detailed information, refer to Table 1.

Table 1 Comparison of General Demographic Information and PANSS Scores of CN and N-CN

Index	CN (N=68)	N-CN (N=77)	<i>t</i> / χ^2	<i>P</i>
Age-years	31.37±10.64	32.84±9.96	-0.859	0.392
Gender			-0.608	0.544
Men	29,42.6%	29,37.7%		
Women	39,57.4%	48,62.3%		
BMI (Kg/m ²)	23.28±5.12	24.13±4.84	-1.016	0.311
Years of Education	11.44±3.38	11.45±3.32	-0.024	0.981
Course of a Disease	7.73±6.96	8.39±5.49	-0.627	0.532
Chlorpromazine Equivalent	396.08±204.23	379.44±169.34	0.530	0.597
PANSS Total	79.43±15.72	85.64±19.62	-2.086	0.039*
Positive Symptoms	16.56±3.69	15.86±3.06	1.253	0.212
NS	18.99±8.48	24.61±7.46	-4.251	<0.001**
NS gender			2.388	0.018*
Men	23.98±7.09			
Women	20.63±8.98			
Cognitive Symptoms	11.12±3.23	12.38±3.75	-2.151	0.033*
Depressive Symptoms	6.62±4.70	6.09±3.11	0.805	0.422
Excitatory Symptoms	14.75±4.35	14.75±5.86	-0.004	0.997

Notes: * $p < 0.05$. ** $p < 0.01$.

Abbreviations: NS, negative symptoms; CN, cognitively normal group; N-CN, cognitively abnormal group.

A Study of Relevance

The associations between WM and attention and NS in schizophrenic patients are summarized in Table 2. WM can be represented by DB, digital breadth-retrograde score (DB-RS), digital breadth-antegrade score (DB-AS), and attention can be represented by CO. According to Pearson correlation analysis, DB became significantly positively correlated with CO ($r=0.389$, $p<0.001$) and negatively correlated with NS ($r=-0.291$, $p<0.001$). CO was found to be negatively correlated with NS ($r=-0.173$, $p<0.05$). However, DB-AS were not significantly correlated with CO and NS ($r=0.148$, $p>0.05$; $r=-0.068$, $p>0.05$).

NS Mediate the Relationship Between WM and Attention Associations

Based on the correlation analyses described above, mediating effects were examined using the SPSS macro program PROCESS developed by Hayes.¹⁹ A mediation model based on NS was constructed by creating a structural equation with CO as the independent variable in the model 4 condition (Table 3 and Table 4). In Step 1, regression analyses revealed an estimated effect size of 0.229 ($P < 0.05$) for CO on DB. In Step 2, the regression coefficients were standardized, and the estimated effect size of CO on DB was 0.205 ($P < 0.05$). A difference-in-difference coefficient test indicated that NS mediated the association between CO and DB, with an effect size of 0.024 (Figure 2). Thus, it appears that CO scores not only directly influence DB scores but also have an indirect effect through NS.

Table 2 Correlations Between WM and Attention and NS in Patients with SCZ

	DB-AS	DB-RS	DB	CO
DB-RS	0.413**			
DB	0.743**	0.798**		
CO	0.148	0.402**	0.389**	
NS	-0.068	-0.357**	-0.291**	-0.173*

Notes: * $p<0.05$; ** $p<0.01$.

Abbreviations: SCZ, Schizophrenia; DB-RS, Digital breadth-retrograde score; DB-AS, Digital breadth-antegrade score; DB, Digital breadth; CO, Continuous operation; NS, Negative Symptoms.

Table 3 Mediating Effects of NS on the Relationship Between CO and DB

		R	R ²	SE	β	Estimate	t	p
DB	CO	0.451	0.203	0.045	0.349	0.205	4.593	0.000**
	NS			0.080	-0.230	-0.230	-3.026	0.003*
NS	CO	0.174	0.030	0.046	-0.174	-0.173	-2.106	0.037*

Notes: * $p<0.05$; ** $p<0.01$.

Abbreviations: DB, Digital breadth; CO, Continuous operation; NS, Negative Symptoms.

Table 4 Total, Direct, and Indirect Effects of NS on the Relationship Between CO and DB

	Effect	BootSE	BootLLCI	BootULCI	Relative Effect
Indirect effect	0.024	0.013	0.002	0.052	10.27%
Direct effect	0.205	0.050	0.111	0.307	89.77%
Total effect	0.229	0.051	0.133	0.331	

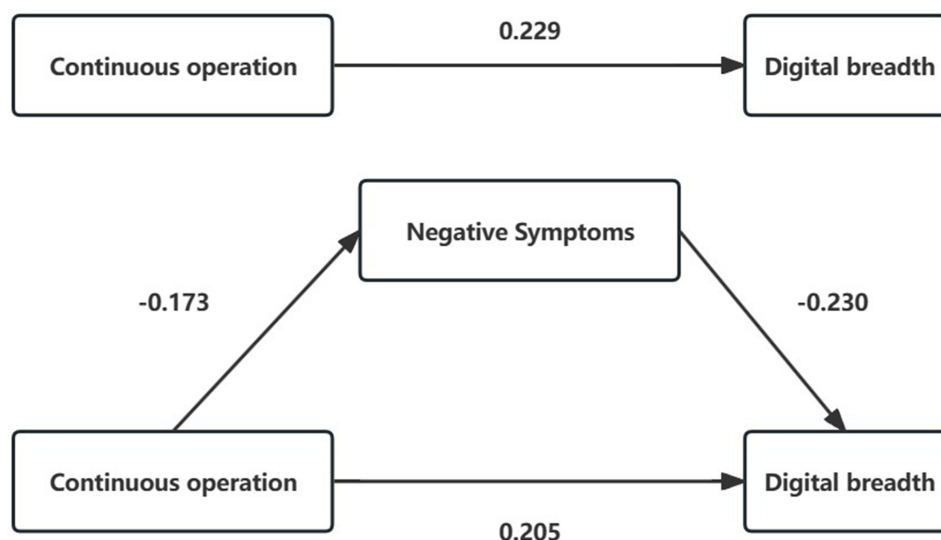


Figure 2 Mediator model of NS in patients with SCZ.

Discussion

The primary objective of this study was to explore the intricate relationship between attention, WM, and NS in stable SCZ. Our findings revealed a strong association between attention, as assessed by the C-BCT, and WM in patients with stable SCZ. Moreover, we observed that NS, as evaluated using the PANSS scale, were also closely related to and mediated the association between attention and WM. This suggests that impaired attention directly or indirectly contributes to a decline in WM through NS. These significant findings offer a valuable theoretical basis for advancing the treatment and prevention of cognitive impairment in SCZ.

Historically, the treatment of SCZ has primarily focused on managing hallucinations and delusions, while negative and cognitive symptoms have proven more challenging to address than positive symptoms.^{20,21} However, numerous previous studies have underscored that negative and cognitive symptoms serve as the most robust predictors of functional outcomes in SCZ.^{22–24} Consequently, targeted improvement of patients' negative symptoms may lead to concurrent enhancements in cognitive impairment symptoms. Our study corroborates these previous findings, as we observed that patients with SCZ exhibiting notable cognitive abnormalities had higher PANSS scale scores and elevated NS scores than those with normal cognition. This finding aligns with previous research, indicating that patients with higher levels of NS exhibit reduced engagement and face greater difficulty in completing cognitive tests. In addition, we briefly compared the cognitive and negative symptoms of men and women due to gender differences in the clinical manifestations of schizophrenia patients, and the results showed that the cognitive and negative symptoms were milder in women compared to men, which may be related to oestrogen,²⁵ and that the cognitive symptoms of women also differed according to the time of month and the reproductive period, which remains to be further investigated.²⁶ Overall, these results further support the association between NS and cognitive impairment in individuals with SCZ.^{27,28}

A significant negative correlation has been reported between NS and prior cognitive functioning, and this correlation has been associated with poorer daily functioning^{29–32}. However, there is limited research exploring how NS specifically impact cognitive functioning subfields.³³ In light of this, our study aimed to examine the relationship between NS, attention, and WM. We found that NS were negatively correlated with attention and WM, while attention and WM showed a positive correlation. These findings suggest that targeting NS may lead to improvements in attention and WM, thereby benefiting overall cognition. Neurobiological evidence further supports the connection between NS and executive/attentional dysfunction in SCZ, involving biochemical, structural, and functional abnormalities in the frontal cortex and related subcortical circuits.^{34–36} Additionally, significant negative correlations were observed between intrinsic hippocampal activity in SCZ, a broad range of cognitive measures, and its association with NS.³⁷ NS and cognitions in schizophrenia have always been a challenge to treat. Considering that medications often show limited effectiveness in

treating NS and cognitive deficits in SCZ, which substantially impact patients' quality of life.³⁸ There are also no pharmacological therapies currently approved specifically for the treatment of negative symptoms,³⁹ and advances in conceptualisation and evaluation have not yet been fully reflected in treatment studies,⁴⁰ many of which have found that cognitive remediation can produce meaningful benefits in terms of cognition and function.^{41,42}

The present study aimed to construct a mediation model using attention (CO) and WM(DB), wherein NS scores play a mediating role. Specifically, we found that attention indirectly or directly influences WM by affecting NS. As argued by Brazo,³⁵ primary and secondary NS may be linked to varying degrees of executive/attentional dysfunction. In our study, we explored this relationship and aimed to contribute to future cognitive improvements by addressing NS. Lam⁴³ suggested that social cognition mediates the relationship between neurocognition and symptoms, and neurocognitive deficits predispose individuals with SCZ to more severe psychiatric symptoms through impairments in social cognition. However, in our study, we focused on subdividing cognitive functioning into attention and WM rather than social cognition. This implies that attention and working memory deficits may adversely affect social cognition and thus social functioning.⁴⁴ Combined neurological and social cognitive treatments may reveal synergistic effects and be integral to creating and sustaining change in the domain of functional outcomes.⁶ To achieve adequate functional outcomes, basic attention and working memory need to be restored first.

Several limitations of the present study are worth noting. Firstly, it is important to emphasise that the mediation analyses of attention, working memory and neurological symptoms were conducted based on cross-sectional data and did not follow up the enrolled patients, thus making it impossible to address the question of which came first. Nevertheless, this study represents a crucial initial step toward longitudinal and more comprehensive research. Second, the present study serves as a preliminary investigation and did not delve into subdivisions of cognitive functions, such as neurocognitive and social cognition, verbal and spatial WM, and even sub-programs of NS. Future studies should explore these aspects in greater depth. In addition, the measurement tool used in this study was the C-BCT, which may have introduced biases in the measurement process, such as subjects' familiarity with the Chinese zodiac sign being variable as the stimulus material was turned into an animal, which is an inherent limitation that should be addressed in future studies. Moreover, cognitive functioning in SCZ is influenced by various complex factors, and in this study, we focused solely on the relationship between attention and WM. To gain a comprehensive understanding of the effects of cognition and symptoms in SCZ, as well as depression and other disorders, further exploration of the mechanisms and influencing factors of cognitive decline and symptom onset is warranted. Such research will provide essential theoretical support for identifying potent drug targets and developing effective behavioral interventions in the future.

Conclusion

Based on our investigation of the relationship between cognitive functioning and NS, we found that both attention deficits and NS significantly contribute to WM decline. In addition, noteworthy studies have shown that in patients with SCZ, attention deficits affect NS, thereby directly or indirectly exacerbating the decline in WM. This suggests that effectively addressing NS could lead to more comprehensive treatment of cognitive deficits. For example, aerobic exercise^{45,46} and cognitive remediation, among others, hold promise for treating both cognitive deficits and NS in SCZ, making them a potentially valuable therapeutic intervention. However, this is based on a cross-sectional study and also lays the groundwork for future longitudinal studies.

Abbreviations

SCZ, Schizophrenia; WM, working memory; NS, negative symptoms; PANSS, the Positive and Negative Symptom Scale; CN, cognitively normal group; N-CN, cognitively abnormal group; C-BCT, the Chinese Brief Neurocognitive Compact Test; DB-AS, Digital breadth-antegrade score; DB-RS, Digital breadth-retrograde score; DB, Digital breadth; CO, Continuous operation.

Data Sharing Statement

The data that support the findings of this study are available from Hefei Fourth People's Hospital but restrictions apply to the availability of those data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Hefei Fourth People's Hospital. To obtain the data in this study, the researchers may be contacted at dn980409@163.com.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of The Anhui Mental Health Centre. Informed consent was obtained from all the subjects. The trial registration number was HSY-IRB-PJ-JZB-001. All procedures carried out in studies conformed to the 1964 Helsinki Declaration and its subsequent amendments or similar ethical standards.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflict of interest.

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