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Research Paper

Correlations between age, biomedical variables, and cognition in patients with schizophrenia

Wei Tang[a,b], Kai-li Fan[b], Shu-zhen Zhao[c], Yao-yao Zhang[b], Yan Li[d], Sheng-min Shao[d], Zheng Wang[e,f], Jiang-qiong Ke[d,*]

[a] Department of Psychiatry, Wenzhou Kangning Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325007, PR China
[b] Wenzhou Medical University, Wenzhou, Zhejiang 325006, PR China
[c] Department of Preventive Medicine, School of Public Health & Management, Wenzhou Medical University, Wenzhou, Zhejiang 325035, PR China
[d] Department of Neurology, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325027, PR China
[e] Department of Psychiatry, the Fist Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 31003, PR China
[f] The Key Laboratory of Mental Disorder Management of Zhejiang Province, #79 Qingchun Road, Hangzhou, Zhejiang Province 31003, PR China

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ABSTRACT

Objective: To illustrate the influence of clinical variables on cognition performance in patients with schizophrenia (SCZ).
Methods: Using the 66nao Brain Training device (a novel measurement tool), the cognitive performance of 99 patients with SCZ was evaluated. Patients were diagnosed by the ICD-10 diagnostic criteria for SCZ, and their age were 16–68 years old. Furthermore, we explored the relationship between age, biomedical variables and specific cognitive domains in patients with SCZ. Patients were divided into two groups: various of cognitive domains impairment group and non-impairment group according to the norm scores. All data were analyzed using RStudio Version 1.0.44 (RStudio, Inc.)
Results: Patients with SCZ had obvious cognitive impairment in total and five subdomains of cognitive function. We found that 1) SCZ patients with impaired cognitive total score experienced significant older age and longer illness duration compared with those with normal cognitive total score. 2) SCZ patients with impaired memory experienced significant older age compared with those with normal memory. 3) SCZ patients with impaired attention showed significant lower serum triglyceride (TG) level compared with those with normal attention. 4) SCZ patients with impaired flexibility performed significant longer illness duration compared with those with normal flexibility. 5) SCZ patients with impaired cognitive agility performed significant older age, longer duration, and higher systolic blood pressure (SBP) compared with those with normal cognitive agility. 6) The age, illness duration and SBP in patients with impaired time perception were marginally different from those of subjects with normal time perception.
Conclusion: There are five dimensions (memory, attention, flexibility, cognitive agility, and time perception) of cognitive dysfunction in SCZ patients. Age, illness duration, TG, and SBP might play vital roles in various subdomains of the cognitive deficits respectively in patients with SCZ.

1. Introduction

Schizophrenia (SCZ) is a chronic debilitating neuropsychiatric illness characterized by cognitive symptom, as well as positive and negative symptoms (Khan et al., 2018). Cognitive impairment is acknowledged to be a core feature and reasonable treatment target for SCZ, and it contributes to social dysfunction and life outcomes of the illness (Ang et al., 2017; Sheffield and Barch, 2016). Patients with SCZ have cognitive disorders in both acute and stable phases (Cao et al., 2017). Cognitive deficits typically are even present before illness onset and persist throughout the course of the disorder (Brewer et al., 2006; Godwin et al., 2017). Moreover, it has been consistently reported that patients with SCZ exhibited cognitive decline, especially in attention, memory and executive functions (Mesholam-Gately et al., 2009; Biagianti et al., 2017). A study also demonstrated the relationship between physical performance and cognition in patients with SCZ (Kim et al., 2019).

SCZ patients have significant memory disorders of impaired self-

* Corresponding author.
E-mail address: kjq@wmu.edu.cn (J.-q. Ke).

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initiation of elaborative encoding strategies (Guimond et al., 2017). Prospective forgetting has been found to be one of the key cognitive impairments in individuals with SCZ (Wang et al., 2018). Autobiographical memories of patients with SCZ are less specific than those of healthy participants (Berna et al., 2017). Recent study has indicated a role for the thalamic reticular nucleus (TRN) perturbation in attention and sleep deficits in SCZ (Young and Wimmer, 2017). The SCZ patients were impaired in most of the attention parameters (Luck et al., 2019). Impaired attention and learning functions are popular in SCZ (Mohn and Torgalsbøen, 2018), and sustained attention impairment is considered as a characteristic of SCZ (Hoonakker et al., 2017). A previous study found that there is a strong association between cholesterol levels and cognition in SCZ and further research on the role of serum lipid metabolism in cognition might suggest new treatments for the core deficit of SCZ (Krakowski and Czobor, 2011). Another study indicated that higher triglyceride (TG) level was associated with lower scores on vigilance/attention (Lindenmayer et al., 2012). Cognitive flexibility is defined as the brain processes underlying the adaptive change in behavior in response to changed contingencies in the external or internal environment (Dhawan et al., 2019). A meta-analysis confirmed that the cognitive flexibility of SCZ patients was impaired. However, their illness duration was not a risk factor (Laere et al., 2018).One study suggested that hypertension severity played a role in the magnitude of cognitive deficits observed in SCZ (Morra and Strauss, 2016). Another study has reported that time perception (judgments of time intervals) and temporal processing are impaired in SCZ (Thoenes and Oberfeld, 2017). A previous study showed that metabolic syndrome was strongly associated with cognitive impairment in SCZ throughout the course of illness (Bora et al., 2017). On the contrary, another study showed that treated hypertension and obesity were associated with worse global cognitive ability in bipolar disorder, with no such relationship observed in SCZ (Depp et al., 2014). However, the relationship between age, biomedical variables and specific cognitive subdomain performance of the patients with SCZ hasn't been clarified thoroughly and systematically in the previous studies even some studies generated controversial results. To fill in this research gap, we examined brain function of 99 patients with SCZ in response to a cognition task using 66nao Brain Training device (Tang et al., 2016; Zhou et al., 2018; Tang et al., 2019) objectively. The 66nao Brain Training device assesses five separate cognitive subdomains, including memory, attention, flexibility, cognitive agility, and time perception. In this study, we speculated the SCZ patients who have specific cognitive deficits. Furthermore, we explored the relationship between age, biomedical variables and specific cognitive subdomains in patients with SCZ.

The current study aimed to further illustrate the effect of biomedical variables on cognitive performance in SCZ. Considering that these factors are modifiable, new intervention may help to improve cognition in patients with SCZ, thereby leading to improvements in cognitive function and prognosis.

2. Methods and materials

2.1. Study participants

Data was obtained from the inpatient clinic at the Psychiatry Department of Wenzhou Kangning Hospital of Wenzhou Medical University. Ninety-nine patients with SCZ were recruited. Inclusion criteria were the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis of SCZ. The exclusion criteria were 1) dual diagnosis of schizophrenia, such as a developmental disability, a neurological disorder, or a substance abuse problem; 2) diagnosis of intellectual disabilities; and 3) a change in psychiatric medication or admission to in-patient psychiatric treatment within the last 30 days. The inclusion and exclusion criteria of the patient group were confirmed by retrieving information from hospital medical records. The patients had a mean age of 46.32 years (standard deviation [SD] D 10.60 years), with illness duration of 20.43 years (standard deviation [SD] D 8.83 years). All participants were right-handed. Patients were classified into two groups: normal and impaired cognition groups according to the norm scores using 66nao Brain Training device. The study was approved by the research ethics committee of Wenzhou Kangning Hospital of Wenzhou Medical University. All subjects signed an informed consent and all information was confidential.

All of the SCZ subjects underwent biomedical examinations including cognition task using 66nao Brain Training device, body mass index (BMI),waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting serum plasma levels of blood glucose (FBG), glycosylated hemoglobin (HbA1c), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC).

2.2. Cognition task

We examined brain function of 99 patients with SCZ in response to a cognition task using the 66nao Brain Training device (www.66nao.com). The 66nao Brain Training device assesses five separate cognitive subdomains, including memory, attention, flexibility, cognitive agility, and time perception. The dependent measures were normed total scores for each cognitive subdomain. We have norm scores of the total score and five dimensions scores (N 152,227, total score: M 40.80, SD 3.90; memory: M 7.48, SD 1.97; attention: M 6.73, SD 1.68; flexibility: M 9.91, SD 0.40; cognitive agility: M 8.44, SD 1.09; time perception: M 8.24, SD 1.97).

2.3. Clinical measurements

Various biomedical variables were measured at enrollment. Detailed medical histories, physical examinations, and various laboratory tests were obtained from medical records. WC: the patients stood with their feet 25 to 30 cm apart, and their weight was evenly distributed, waist circumference through umbilical point. BMI: we measured the patients' weight and height to work out their BMI. Body weight was taken with patients wearing light clothing and no shoes. SBP and DBP: we measured systolic and diastolic blood pressure with sphygmomanometer. Blood samples were being collected and the following tests were being carried out: FBG, HbA1c, TG, HDL-C, LDL-C, and TC.

2.4. Statistical analysis

We analyzed the two participant groups on cognitive performance in the five tasks using 66nao Brain Training device. Subsequently, we compared the scores for each dimension between the two groups (normal and impaired cognition groups, according to the norm scores). The differences in the twelve variables of the biomedical data between normal and impaired cognition groups in various subdomains of the cognitive performance were based on Mann-Whitney *U* tests and student *t*-tests, which were mainly based on their distributions. Locally weighted regression (LOESS) models were also performed to investigate the relationships between impaired cognition and these clinical variables, respectively. Data management and all statistical analyses were performed using RStudio Version 1.0.44 (RStudio, Inc.). Significance level was set to 0.05 ($p < 0.05$) for all analyses.

3. Results

3.1. SCZ patients' total score and memory

As shown in Table 1, the patients with impaired total score would be older ($p = 0.008$) and have longer illness duration ($p = 0.006$) as compared with their counterparts. It suggested that the age and illness

Table 1
Variables associated with total score and memory in SCZ patients.

Variables	Normal	Impaired	*p*-Value
Total score			
Age (years)	38.00 (28.00,48.00)	49.00 (42.00,54.00)	0.008
Duration (years)	14.50 ± 9.20	21.41 ± 8.44	0.006
Memory			
Age (years)	40.50 (35.00,50.00)	49.00 (44.00,54.00)	0.009
Duration (years)	18.07 ± 9.71	21.46 ± 8.30	0.079
TG (mmol/L)	1.51 (1.11,2.27)	1.28 (0.92,1.86)	0.065
TC (mmol/L)	4.07 ± 1.15	3.71 ± 0.87	0.087

Data were presented with mean ± standard deviation (SD) when they met normal or similar normal distribution and student *t*-tests were performed to assess the differences between two groups. Otherwise, they were described as median (1st quartile, 3rd quartile) and Mann-Whitney *U* tests were applied to compare the differences between the two groups.

duration would play vital roles in cognitive control in patients with SCZ. However, we did not observed statistical differences of total score between the normal and impaired cognition patients in WC, BMI, SBP, DBP, FBG, HbA1c, TG, HDL-C, LDL-C and TC. Furthermore, SCZ patients with impaired memory would be significantly older than that of SCZ patients with normal memory, while the differences of illness duration, TG and TC between SCZ patients with or without impaired memory were marginal significant. The WC, BMI, SBP, DBP, FBG, HbA1c, HDL-C and LDL-C of the two categories of patients were quite similar.

3.2. SCZ patients' attention and flexibility

Table 2 indicated that only serum TG of SCZ patients with impaired attention was significantly lower than that of patients with normal attention. No significant differences between the two kinds of SCZ patients were observed in the present study, while SCZ patients with impaired flexibility had significant longer illness duration as compared to those with normal flexibility. Marginal differences of age and TG between normal and impaired flexibility were also detected. Other variables including WC, SBP, DBP, FBG, HbA1c, LDL-C and TC were quite comparable in SCZ patients with or without normal attention as well as flexibility.

3.3. SCZ patients' cognitive agility and time perception

It was detected that SCZ patients with abnormal cognitive agility were likely to be older, and had longer illness duration and higher systolic blood pressure compared with those with normal cognitive agility. Moreover, the age, illness duration and systolic blood pressure in patients with impaired time perception were marginally different

Table 2
Variables associated with attention and flexibility in SCZ patients.

Variables	Normal	Impaired	*p*-Value
Attention			
Age (years)	48.00 (38.00,54.00)	48.50 (42.50,52.50)	0.621
Duration (years)	20.55 ± 8.96	20.14 ± 8.68	0.838
TG (mmol/L)	1.45 (1.06,2.04)	1.03 (0.76,1.41)	0.003
HDL-C (mmol/L)	1.08 (0.93,1.37)	1.17 (0.98,1.39)	0.460
Flexibility			
Age (years)	44.00 (34.00,54.00)	48.00 (41.00,54.00)	0.112
Duration (years)	16.85 ± 8.34	21.71 ± 8.71	0.015
TG (mmol/L)	1.68 (1.18,1.90)	1.28 (0.94,1.83)	0.056

Data were presented with mean ± standard deviation (SD) when they met normal or similar normal distribution and student *t*-tests were performed to assess the differences between two groups. Otherwise, they were described as median (1st quartile, 3rd quartile) and Mann-Whitney *U* tests were applied to compare the differences between the two groups.

Table 3
Variables associated with cognitive agility and time perception in SCZ patients.

Variables	Normal	Impaired	*p*-Value
Cognitive agility			
Age (years)	30.00 (24.50,42.50)	49.00 (42.00,54.00)	0.001
Duration (years)	13.42 ± 8.18	21.42 ± 8.57	0.003
SBP (mm Hg)	114.33 ± 10.65	122.37 ± 12.34	0.034
Time perception			
Age (years)	44.50 (34.00,54.00)	49.00 (41.50,54.00)	0.160
Duration (years)	17.18 ± 8.84	21.38 ± 8.73	0.050
SBP (mm Hg)	125.36 ± 9.64	120.24 ± 12.89	0.087

Data were presented with mean ± standard deviation (SD) when they met normal or similar normal distribution and student *t*-tests were performed to assess the differences between two groups. Otherwise, they were described as median (1st quartile, 3rd quartile) and Mann-Whitney *U* tests were applied to compare the differences between the two groups.

from those with normal time perception. Variables such as WC, BMI, DBP, FBG, HbA1c, TG, HDL-C, LDL-C and TC were all comparable in participants with or without normal agility as well as time perception (Table 3).

3.4. Impaired cognition and the biomedical variables

In this study, we also investigated the relationships between the 5 domains of impaired cognition and some clinical variables including age, disease duration, TG, SBP, DBP as well as TC. First, we observed that elevated age and longer duration were significantly associated with the increased odds of impaired cognition (Supplemental Fig. 1). Meanwhile, the likelihood of impaired cognition was also significantly related to elder people (Supplemental Fig. 2). In addition, the presence of impaired subdomain cognition of memory, attention and flexibility were separately associated with lower TG (Supplemental Figs. 2–4). Furthermore, we also detected that the likelihood of impaired subdomain cognition of cognitive agility was positively associated with higher SBP, elevated age and longer duration (Supplemental Fig. 5). Lastly, the presence of impaired subdomain cognition of time perception was also observed to be obviously associated with longer disease duration (Supplemental Fig. 6).

3.5. Relationships between total score and the 5 domains

As shown in Table 4, the average elevated total score (95% confidence interval, 95% CI) with per standard deviation increase of memory score, attention score, flexibility scores, cognitive agility scores and time perception scores were 15.7 (12.5,19.0), 17.4 (12.8,22.0), 15.5 (11.1,20.0), 18.2 (12.8,23.7) and 10.0 (7.6,12.3), respectively. All the five domains were significantly and positively related to the total score of impaired cognition.

4. Discussion

SCZ is a neurodevelopmental disorder associated with a wide range of cognitive dysfunction, including deficits in attention, learning and memory, speed of processing, executive functioning, and problem solving that are present early in the course of disease and are more enduring than psychotic symptoms (Biagianti et al., 2017). There are total cognition and 5 cognitive subdomains assessed by 66nao Brain Training device in this study: memory, attention, flexibility, cognitive agility, and time perception subdomains. Our study shows that the patents with SCZ have various degrees of cognitive deficits, and age and illness duration play key roles in total cognitive control.

Our findings indicate that SCZ patients have different degree of memory difficulties and the age of impaired memory patients with SCZ was significantly older than those of normal memory. Our findings support that the decline in serum TG concentration is associated with

Table 4
Relationships between the total score and 5 domains.

Domains	Unadjusted			Adjusted		
	β (95% CI)	SE	*p*	β (95% CI)	SE	*p*
Memory score	16.6 (13.4,19.7)	1.6	< 0.001	15.7 (12.5,19.0)	1.6	< 0.001
Attention score	17.8 (12.9,22.7)	2.5	< 0.001	17.4 (12.8,22.0)	2.3	< 0.001
Flexibility score	16.7 (12.3,21.2)	2.2	< 0.001	15.5 (11.1,20.0)	2.2	< 0.001
Cognitive agility score	19.5 (14.4,24.5)	2.5	< 0.001	18.2 (12.8,23.7)	2.7	< 0.001
Time perception score	10.4 (7.9,12.8)	1.2	< 0.001	10.0 (7.6,12.3)	1.2	< 0.001

The relationship between the total score and per standard deviation (SD) increase of the 5 domains were assessed by multivariable generalized linear regression models.
Adjuated for age and duration.

the attention impairment of SCZ. Contrary to the two previous studies (Krakowski and Czobor, 2011; Lindenmayer et al., 2012), our study indicates that the serum TG of SCZ patients with impaired attention is significantly lower than that of patients with normal attention, while serum cholesterol does not differ significantly.

A meta-analysis confirmed SCZ patients' illness duration was not a risk factor of the cognitive flexibility impairment (Laere et al., 2018). However our data suggest that illness duration is significantly associated with flexibility. The previous report has suggested that higher pulse pressure predicted the generalized cognitive deficit in SCZ, which confirms the role of metabolic abnormalities in the generalized cognitive deficit in SCZ, and treatment of hypertension might be a novel adjunctive therapy target for remediating cognitive deficits in SCZ (Morra and Strauss, 2016). Our study indicates that SCZ with impaired cognitive agility performs in significantly older age, longer illness duration, and higher SBP than those with normal cognitive agility.

Clinical evidence associated with biological, psychopathological, and cognitive theories strongly suggests that patients with SCZ have a deficit in time perception (de Montalembert et al., 2015), which positive symptoms of SCZ may be related to (Ueda et al., 2018). We also found that the age, illness duration and systolic blood pressure in patients with impaired time perception are marginally different from those of subjects with normal time perception.

As is known to all, one side effect of the drug of the SCZ is obesity, thereby affects the blood glucose. Previous study has shown that the effect of hyperglycemia on SCZ severity might be relevant, particularly longitudinal studies evaluating negative symptomatology and cognitive function (Perry et al., 2017). However, another study suggested blood glucose and abdominal obesity did not predict cognitive performance (Morra and Strauss, 2016), the other study also suggested that impaired glucose tolerance (IGT) patients showed greater frequency in first-episode, drug-naïve SCZ and minimal association with cognitive impairment during the early course of the disorder (Chen et al., 2016). Our study shows that there is no effect of FBG and HbA1c on the SCZ patients' cognitive performances.

This study has several limitations. First, the sample size is small, that may lead to some bias in the statistical analysis, a larger sample is needed in further study. Second, the patients with various procedure of the SCZ were recruited for this study, therefore the study conclusions may not be generalized to the first-episode SCZ population. Third, we didn't have enough subtypes of SCZ. Finally, the positive and negative syndrome scale (PANSS) hasn't been collected. Such research should be performed in the future.

In conclusion, our study focused on the cognitive functioning impairments. In addition, age, illness duration, TG, and SBP might play vital roles in total and various subdomains of the cognitive deficits respectively in patients with SCZ. Future studies with a larger sample size and subtypes of the SCZ are needed. In summary, we have found that age and biomedical variables could affect the cognitive performance in patients with SCZ.

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CRediT authorship contribution statement

Wei Tang: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Data curation. **Kai-li Fan:** Data curation. **Shu-zhen Zhao:** Formal analysis, Methodology. **Yao-yao Zhang:** Data curation. **Yan Li:** Conceptualization, Data curation. **Sheng-min Shao:** Formal analysis. **Zheng Wang:** Supervision, Methodology. **Jiang-qiong Ke:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Data curation.

Declaration of competing interest

The authors have declared that there are no conflicts of interest in relation to the subject of this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scog.2020.100182.

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