Assessment of cognitive functions and cerebral blood flow in patients with schizophrenia

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Introduction
Although recent efforts have been undertaken to investigate the aspects of short-term cerebral hemodynamics during cognitive challenge in schizophrenia, there are, to the best of our knowledge, no reports on cerebral hemodynamics during prefrontal function.

Objective
This aim of this study was to assess cognitive functions and measure cerebral blood flow (CBF) in patients with schizophrenia.

Patients and methods
Fifty adult inpatients (33 male and 17 female) participated in the study. They were referred from the outpatient clinic of psychiatry at Assiut University Hospital. All patients' guardians provided written consent for their patients to participate in the study after full explanation of the study procedures was provided. All patients met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision, diagnostic criteria for schizophrenia. The control group comprised 25 adults (aged 20–40 years; 14 male and 11 female) who volunteered to participate in the study. They were selected from general population and matched with the patient group for age, sex, and socioeconomic state, and were relatives of other patients in the outpatient clinic in Assiut University Hospital rather than the neuropsychiatric clinic. All patients and controls were subjected to the following after written informed consent was obtained from each first-degree relative for his or her patient: (a) psychiatric interview, (b) Positive and Negative Syndrome Scale, (c) soft neurological sign assessment using Cambridge Neurology Inventory, (d) transcranial Doppler sonography, and (e) Cognitive Ability Screening Instrument.

Results
There was an increased frequency of each of the neurological soft sign scores measured using Cambridge Neurological Inventory part II among schizophrenic patients, especially motor coordination and motor sequencing and their correlation with predominance of negative symptoms. The evaluation of mean velocity of CBF in the middle cerebral artery, anterior cerebral artery, and basilar artery using transcranial Doppler revealed no significant difference between the patient and control groups, except for basilar artery, which had a statistical minimal significance. However, there was a correlation between positive symptoms and increased CBF as well as between negative symptoms and decreased CBF. Cognitive functions that were highly affected in schizophrenic patients were short term memory, orientation, mental manipulation, concentration, abstract thinking, judgment, drawing, and fluency, whereas long term memory and attention were affected to a lesser extent in schizophrenic patients. There was no effect on language function; it was affected by predominance of negative symptoms.

Conclusion
We found that most patients with schizophrenia have moderate-to-marked cognitive dysfunctions. We also found a positive correlation between positive symptoms and increased CBF and between negative symptoms and decreased CBF.

Keywords:
cerebral blood flow, cognitive functions, schizophrenia

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Introduction

Schizophrenia is a mental disease with potentially severe psychopathological and psychosocial outcomes [1]. With respect to this disorder, the prefrontal cortex is the brain region of major interest for researchers in the field. Afferent and efferent connections of this large area of association cortex with other neocortical regions have been extensively described, as well as connections with cingulate cortex, limbic structures, and basal ganglia. From a cognitive viewpoint, the prefrontal cortex participates in the initiation and execution of decision-making, attention, planning, and working memory [2].

Many, if not all, of these functions have been reported to be mildly to strongly dysfunctional in schizophrenic patients [3].

Although recent efforts have been undertaken to investigate aspects of short-term cerebral hemodynamics during cognitive challenge in schizophrenia [4], there are, to the best of our knowledge, no reports on cerebral hemodynamics during prefrontal function. We sought to examine hemodynamic changes during cognitive, prefrontal challenge in schizophrenic using transcranial Doppler (TCD) sonography, which measures cerebral blood flow (CBF) velocity in the basal cerebral arteries [5].

The main advantages of this technique are noninvasiveness, the possibility to measure CBF velocity continuously with a time resolution of 1 s, and a nonrestricting environment for examination. In addition, in comparison with functional MRI, TCD directly measures regional flow changes [6].

A few studies published a detailed report on cerebral hemodynamics under prefrontal challenge in schizophrenic patients in comparison with healthy individuals. The second objective was to determine the neurological soft sign (NSS) frequency in patients with schizophrenia compared with a healthy control, in a recent review of NSS research [7].

Neurological signs occurred in the majority of patients with schizophrenia independent of demographic characteristics and most medication variables, and they were strongly associated with negative symptoms and cognitive impairment. It was also pointed out that there is evidence that the occurrence of these signs is under genetic control and that these signs may represent a trait feature of schizophrenia [8].

The third objective was to assess the cognitive function of schizophrenic patients using Cognitive Ability Screening Instrument (CASI). It was stated that a significant cognitive impairment is common in schizophrenia, affecting up to 75% of patients. It affected a wide range of cognitive functions, particularly memory, attention, motor skills, executive function, and intelligence [9].

Cognitive deficits represent a significant characteristic of schizophrenia. However, the majority of the clinical studies have been conducted in antipsychotic drug-treated patients. Thus, it remains unclear whether significant cognitive impairments exist in the absence of medication. This is the first meta-analysis of cognitive findings in drug-naive patients with schizophrenia. Cognitive impairment is related to social and functional outcome; the evidence is mixed as regards the efficacy of newer atypical antipsychotics in improving cognitive functioning in schizophrenia. It has been claimed that impaired cognitive test performance in patients with schizophrenia may be an epiphenomenon, for example, reflecting lack of motivation or distraction by hallucinations. To convince skeptics that the neuropsychological impairment is important, one would have to demonstrate a clear relationship between cognitive test performance and 'real-life' functional outcome. An important review of this area was published by Green *et al*. [10], who evaluated studies that used cognitive measures as predictors and correlates of functional outcome. The most consistent finding to emerge was that verbal memory functioning was associated with all types of functional outcome. It is notable that verbal memory was the cognitive domain that showed the greatest impairment in the meta-analysis [11].

Patients and methods

Patients

Fifty (33 male and 17 female) adult inpatients participated in the study. They were referred from the outpatient clinic of psychiatry at Assiut University Hospital (AUH). All patients met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision, diagnostic criteria for schizophrenia [12].

Twenty-five (aged 20–40 years; 14 male and 11 female) adults selected from general population and matched with the patient group for age, sex, and socioeconomic status volunteered to participate in the study.

All patients' guardians as well as controls provided written consent to participate in the study after full explanation of the study procedures was provided. Patients between 20 and 40 years of age and patients who did not receive electroconvulsive therapy (ECT) 6 months before the study were included in the study. Patients with a history of major neurological deficits or trauma, those with chronic or serious medical condition that may affect the cognition, those with a history of drug abuse, patients who received ECT 6 months or less before the study, and patients whose relatives refused to provide informed consent were excluded from the study.

Tools for assessment

Patients were interviewed guided by a psychiatric interview sheet of the neurology and psychiatric department in AUSs. It includes a detailed personal history, history of present illness, past personal history, and family history. Patients were diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision. Positive and negative symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), which is a medical scale used for measuring symptom severity of patients with schizophrenia. It was published by Kay *et al.* [13], and Jay *et al*. [14]. It is widely

used in the study of antipsychotic therapy. The name refers to the two types of symptoms in schizophrenia, as defined by the American Psychiatric Association: positive symptoms, which refer to an excess or distortion of normal functions (e.g. hallucinations and delusions), and negative symptoms, which represent a diminution or loss of normal functions [13].

The PANSS is a relatively brief interview, requiring 45–50 min to administer. The interviewer must be trained to a standardized level of reliability [15].

All patients are subjected to this scale individually under the same conditions. To assess a patient using the PANSS, an ~45 min clinical interview is conducted. The patient is rated from 1 to 7 on 30 different symptoms based on the interview as well as reports of family members or primary care hospital workers. All patients and controls were subjected to routine neurological examination and examination of soft neurological signs according to the Cambridge Neurological Inventory [16].

This is a clinical instrument constructed for neurological assessment of psychiatric patients. This instrument is comprehensive, reliable, and easy to administer. It is useful for identifying soft neurological signs and other patterns of neurological impairments – for example, extrapyramidal signs relevant to neurobiological localization and prognosis in psychiatric disorders. Rating was standardized to indicate normal response (0), equivocal response (0.5), abnormal response (1), and grossly abnormal response (2). This full inventory requires 20–40 min to complete. TCD sonography (Vuetax, version 2.0.406; Nicolet Biomedical Inc., USA) was performed for all patients and controls who were subjected to this method individually under the same conditions to assess CBF by measuring mean velocity of main intracranial arteries. It was performed in our neurophysiology unit by the researcher under the supervision of an expert staff member of neuropsychiatry. TCD sonography is a noninvasive technique that uses a 2 MHz, pulsed Doppler transducer to measure the velocity of blood flow within the circle of Willis and the vertebrobasilar system through regions of temporal calvarial thinning (transtemporal) or through the orbits or foramen magnum (suboccipital) [17].

The cognitive functions were assessed using the CASI, which consists of 25 test items and provides quantitative assessment of attention, concentration, orientation, memories for past knowledge and present input, language ability, drawing and writing abilities, list-generating ability, abstract thinking, and judgment. Administration time is ~15–20 min with a maximum total score of 100 [18].

Categorical variables were described using number and percentage, wherein continuous variables were described as mean (SD). The χ^2-test was used to compare categorical variables, whereas the *t*-test was used to compare continuous variables. Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test and *Q–Q* plots. A two tailed *P* value less than 0.05 was considered statistically significant. All analyses were performed with the SPSS 20.0 software (SPSS Inc., Chicago, Illinois).

Results

Demographic and clinical data

Table 1 shows that the patient group consisted of 50 cases 33 (66%) male and 17 (34%) female, whereas the control group consisted of 14 (56%) male and 11 (44%) female. It also shows education and illiteracy in the patient group. It shows that 39 (78%) cases were educated, whereas 11 (22%) cases were illiterates.

As regards marital status in the patient group, 32 (64%) cases were single, 14 (28%) were married, and four were divorced or widowers [8]. As regards family history of psychiatric illnesses among both groups, positive family history was found in 21 (42%) cases, whereas only seven volunteers had a positive family history.

Soft neurological sign assessment

Table 2 shows the frequency of NSS scores measured using Cambridge Neurological Inventory part II among schizophrenic patients and controls.

Soft signs comprised the following: primitive reflexes, sensory integration, motor coordination, and motor sequencing. Our study demonstrated the presence of NSSs among patients with schizophrenia in a high frequency compared with the control group.

Neurosonology study

Table 3 shows the mean value of the mean velocity of CBF (cm/s) in the middle cerebral artery (MCA), anterior cerebral artery (ACA), and basilar artery (BA) measured using TCD sonography in patients compared with the control group. The results show that the mean (SD) value of MCA in the patient group was 54.9 (11.3) but in the control group it was 54.5 (10.9). Moreover, the mean (SD) value of ACA in the patient group was −37.1 (10.4) (direction of flow away), whereas in the control group it was −39.5 (10.4).

However, the mean (SD) value of BA in the patient group was −36.3 (8.0) (direction of flow away) in comparison with −42.6 (9.6) in the control group, and this difference was statistically significant.

PANSS assessment

Table 4 demonstrates the distribution of PANSS score in the patient group.

The mean value for positive subscale was 27.1 ± 3.1.

The mean value for negative subscale was 21.5 ± 4.6.

The mean value for general psychopathology subscale was 42.4 ± 4.3.

The mean value of total PANSS score among patients was 91 ± 7.9, signifying moderately ill schizophrenic patients.

Psychometric tests for cognitive assessment

Table 5 shows the comparison between patients and controls as regards CASI score in its all items, which assess cognitive functions.

Table 1 Demographic data of both groups (cases and controls)

	Cases ($n=50$) [n (%)]	Control ($n=25$) [n (%)]	P value
Sex			
Male	33 (66.0)	14 (56.0)	0.399 (NS)
Female	17 (34.0)	11 (44.0)	
Education			
Educated	39 (78.0)	23 (92.0)	0.131 (NS)
Illiterate	11 (22.0)	2 (8.0)	
Marital state			
Married	14 (28.0)	13 (52.0)	0.067 (NS)
Single	32 (64.0)	12 (48.0)	
Divorced/widow	4 (8.0)	0 (0.0)	

NS, $P>0.05$.
*Significant difference ($P<0.05$).
**Significant difference ($P<0.01$).

Table 2 The comparison between the cases and the control group as regards neurological soft signs

	Cases ($n=50$) [n (%)]	Control ($n=25$) [n (%)]	P value
Primitive reflexes			
Normal	42 (84.0)	25 (100.0)	0.034*
Minimal change	8 (16.0)	0 (0.0)	
Sensory integration			
Normal	6 (12.0)	19 (76.0)	<0.001**
Minimal change	38 (76.0)	6 (24.0)	
Significant change	6 (12.0)	0 (0.0)	
Motor coordination			
Normal	0 (0.0)	15 (60.0)	<0.001**
Minimal change	20 (40.0)	8 (32.0)	
Significant change	30 (60.0)	2 (8.0)	
Motor sequencing			
Normal	1 (2.0)	17 (68.0)	<0.001**
Minimal change	36 (72.0)	8 (32.0)	
Significant change	13 (26.0)	0 (0.0)	

NS, $P>0.05$.
*Significant difference ($P<0.05$).
**Significant difference ($P<0.01$).

Table 3 The mean value of the mean velocity of CBF (cm/s) in the middle cerebral artery (MCA), anterior cerebral artery (ACA), and basilar artery (BA) measured using TCD sonography

	Cases		Controls		
	Mean	SD	Mean	SD	P value
MCA	54.9	11.3	54.5	10.9	0.884 (NS)
ACA	−37.1	10.4	−39.5	10.4	0.346 (NS)
BA	−36.3	8.0	−42.6	9.6	0.003**

ACA, anterior cerebral artery; BA, basilar artery; MCA, middle cerebral artery.
NS, $P>0.05$.
*Significant difference ($P<0.05$).
**Significant difference ($P<0.01$).

Table 4 Demonstrates the distribution of PANSS score in the patient group

	Cases	
	Mean	SD
Positive subscale	27.1	3.1
Negative subscale	21.5	4.6
General psychopathology subscale	42.4	4.3
Total score	91.0	7.9

The difference between the two groups was statistically highly significant at all items, especially short-term memory, mental manipulation and concentration, orientation, fluency of speech, abstract thinking and judgment, and drawing function.

Moreover, total score in comparison with each group was statistically highly significant.

Correlations between positive and negative subscales with mean velocity of cerebral blood flow in the middle cerebral, anterior cerebral, and basilar arteries

Table 6 demonstrates the correlation between positive and negative symptoms of schizophrenia with the mean velocity of CBF in the MCA, ACA, and BA. It was found that there were positive relationships between positive subscale score and the mean velocity of CBF in the MCA and BA; thus, the more prominent the positive symptoms, the higher the velocity of CBF in MCA and BA. However, there was a negative relationship between positive symptoms and mean velocity of CBF in ACA; thus, the more prominent the positive symptoms, the slower the velocity of CBF in ACA.

Moreover, there were negative relationships between negative subscale score and mean velocity of CBF in MCA, ACA and BA; thus, the more prominent the negative symptoms, the slower the velocity of CBF in these arteries.

It also demonstrated a statistically significant correlation between negative symptoms and decrease in CBF in MCA and BA.

Correlation of positive and negative subscales with total score of Cognitive Abilities Screening Instrument

Table 7 shows the correlation between positive and negative subscale scores with the total score of CASI. The results

showed that there was a statistically significant inverse relationship between negative subscale score and total score of CASI; thus, the more prominent the negative symptoms, the greater the deterioration in cognitive functions. However, it was found that, the more prominent the positive symptom, the lesser the deterioration in the cognitive functions, with higher CASI scores (positive correlation).

Correlations of positive and negative subscales with neurological soft sign frequency

Table 8 shows the correlation of positive and negative subscale scores with NSS, including primitive reflexes, sensory integration, motor coordination, and motor sequencing. The results of our study demonstrated that there was a positive correlation between negative subscale score and NSS, which increased with prominence of negative symptoms in patients in contrary to positive symptoms, wherein increase in its score affected negatively on NSS. Moreover, there was a highly statistically significant correlation between negative symptoms and frequency of NSS, especially motor sequencing, primitive reflexes, and sensory integration.

Table 5 Shows the comparison between patients and controls as regards CASI score

	Cases		Control		
	Mean	SD	Mean	SD	*P* value
LTM	9.6	1.0	10.0	0.0	0.046*
STM	10.5	1.3	11.8	0.4	<0.001**
Attention	7.8	0.6	8.0	0.0	0.017*
MM/concentration	8.6	1.3	9.7	0.6	<0.001**
Orientation	16.2	2.3	17.8	0.5	<0.001**
Drawing	8.4	1.7	9.8	0.5	<0.001**
Abstract thinking/judgment	10.0	1.0	11.6	0.7	<0.001**
Fluency	7.7	1.2	9.2	0.8	<0.001**
Language	9.3	1.0	9.5	0.7	0.439 (NS)
Total score	88.1	9.1	97.2	3.1	<0.001**

LTM, long term memory; MM, mental manipulation; STM, short term memory.
NS, $P>0.05$.
*Significant difference ($P<0.05$).
**Significant difference ($P<0.01$).

Table 6 Correlations between positive and negative subscales with a mean velocity of cerebral blood flow of middle cerebral, anterior cerebral, and basilar arteries

	Positive subscale		Negative subscale	
	r value	*P* value	*r* value	*P* value
MCA	0.069	0.316	−0.237	0.0489*
ACA	−0.047	0.374	−0.136	0.172
BA	0.018	0.449	−0.250	0.039*

ACA, anterior cerebral artery; BA, basilar artery; MCA, middle cerebral artery.
*Significant correlation ($P<0.05$).
**Significant correlation ($P<0.01$).

Table 7 Correlation between positive and negative subscales with total score of Cognitive Ability Screening Instrument

	Positive subscale		Negative subscale	
	r value	*P* value	*r* value	*P* value
Total score of CASI	0.25027	0.0398*	−0.51943	0.0001**

CASI, Cognitive Ability Screening Instrument.
*Significant correlation ($P<0.05$).
**Significant correlation ($P<0.01$).

Table 8 Shows the correlation of positive and negative subscale scores with NSS

	Positive subscale		Negative subscale	
	r value	*P* value	*r* value	*P* value
Sensory integration	−0.09211	0.262	0.28420	0.022*
Primitive reflexes	−0.06963	0.315	0.54593	0.000**
Motor coordination	−0.13948	0.167	0.22203	0.060
Motor sequencing	−0.00601	0.483	0.52588	0.000**

*Significant correlation ($P<0.05$).
**Significant correlation ($P<0.01$).

Discussion

Schizophrenia is one of the most serious mental illnesses with about one in 100 people developing the disorder over a lifetime. This illness can begin at any age but commonly manifests itself in the late teens through early to mid 20s [19]. Our study included 50 patients with schizophrenia who were compared with 25 normal volunteers of matched age, sex, and educational level. Patients who were admitted in AUH during the period from 1 January 2014 to 31 October 2014 were included. Patients who had received ECT 6 months or less before the study were excluded for its possible effect on cognitive function.

Neurological soft sign assessment and its correlation with positive and negative subscales

NSS assessment of our schizophrenic patients evaluated using Cambridge Neurological Inventory revealed that soft neurological signs were reported with a significantly higher mean score in all four items of part II score sheet of NSS assessment [16].

Our study demonstrated the presence of NSSs among patients with schizophrenia in a high frequency, which probably indicates the organic nature of the illness. Our results also showed positive correlations between NSS and negative symptoms. These indicate that NSSs are more prominent in patients with negative symptoms than in those with positive symptoms.

This can be explained by structural brain dysfunction in patients with NSS. This was illustrated by Dazzan *et al.* [20], who studied the neuroanatomical basis of NSS in psychotic disorders that may be confounded by the underlying pathogenic process in 77 first-episode psychosis patients evaluated using high-resolution MRI and voxel-based methods of image analysis to investigate brain structure. They showed that higher rates of soft neurological signs (both motor and sensory) were associated with a reduction in the grey matter volume of subcortical structures (putamen, globus pallidus, and thalamus). Signs of sensory integration deficits were additionally associated with volume reduction in the cerebral cortex, including the precentral, superior and middle temporal and lingual gyri. NSSs and their associated brain changes were independent of antipsychotic exposure [20].

Findings of Chan *et al.* [21] are in agreement with ours. In a comprehensive meta-analysis, the difference between schizophrenic patients and healthy controls was determined on the basis of reported statistics. This meta-analytic review of NSS in schizophrenia suggested that the illness expresses itself strongly in these basic motor and sensory deficiencies, with mean effects similar or larger in magnitude than those reported in neurobehavioral and neurobiological literatures, and they found evidence of associations between NSS and both cognitive performance and negative symptoms [21].

Neurosonology assessment and its correlation with positive and negative symptoms

Our results reported a positive correlation between positive symptoms and increased CBF, especially in MCA and BA, whereas prominent negative symptoms caused decreased CBF in our patients. This can be attributed to hypofrontality in patients with negative symptoms, especially in the prefrontal and superior frontal areas, and reduction in size, which indicate chronicity and decreased CBF in these areas [22].

Our results are in agreement with those of Owega *et al.* [23], who studied CBF velocity in acute schizophrenic patients using TCD ultrasonography. A total of 28 acutely psychotic, neuroleptically naive, first-episode schizophrenic patients were assessed using TCD and PANSS twice. After the second examination, they observed psychopathological improvement. Acutely psychotic first-episode schizophrenic patients showed a significant increase in the mean velocity on both sides in the middle, anterior, and posterior cerebral arteries, and hence blood flow showed significant correlations with productive psychotic symptoms [23].

This is in agreement with our study, in which active stage, wherein positive symptoms are more prominent, is associated with increased CBF in areas supplied mainly by MCA, such as the frontotemporal cortex, especially the superior temporal gyrus and Broca's area and primary auditory cortex that produce auditory hallucination. This is considered one of the most frequent and most challenging symptoms in schizophrenia [24].

Our results are also consistent with the findings of Pinkham *et al.* [25], who studied measurement of quantitative CBF in schizophrenia. It included 31 individuals diagnosed with schizophrenia or schizoaffective disorder and 26 healthy controls. The severity of symptoms was assessed using the Scale for Assessment of Negative Symptoms and the Scale for Assessment of Positive Symptoms, and CBF was assessed using arterial spin labeling imaging perfusion MRI. They found relationships between CBF and psychiatric symptoms; greater severity of negative symptoms was associated with reduced CBF in bilateral superior temporal gyrus, cingulate gyrus, and left middle frontal gyrus. Increased severity of positive symptoms was related to both higher CBF in the cingulate gyrus and the superior frontal gyrus and decreased CBF in the precentral gyrus/middle frontal gyrus [25].

Psychometric tests for cognitive assessment

Cognitive deficits are core features of schizophrenia. These deficits are not caused by medication or symptoms, and have a dramatic negative effect on real-world functioning. [26].

Using CASI, we found that schizophrenic patients showed a significant impairment in the following cognitive functions: memory, attention, concentration, abstract thinking, judgment, orientation, mental manipulation, and drawing compared with controls. This probably indicates the anatomical functional brain areas affected by schizophrenia, including the frontotemporal areas, limbic system, and the prefrontal cortex, which are responsible for these cognitive dysfunctions (memory and executive functions). Hence, this impairment is a part of symptoms and not a result of medication or ECT.

Our study showed a negative correlation between severity of negative symptoms and its worsening effect on cognitive function of these patients, whereas positive symptoms did not have a direct influence on the cognitive dysfunction of schizophrenic patients. These findings are in agreement with those of Putnam *et al.* [27], who studied the relation between cognitive impairment and enduring negative symptoms. Symptoms of schizophrenia were evaluated using the PANSS, and cognitive assessment was carried out using the Mini-Mental State Examination, Modified Boston Naming Test, constructional praxis, and Word List Learning and Delayed Recall. The results indicated that there was considerable specificity of cognitive impairment in the Enduring Negative Syndrome even in patients with a chronic course of unremitting illness [27].

Consistent with our results, Hornig *et al.* [28] studied negative symptoms associated with specific memory deficits in schizophrenic patients as a part of cognitive impairment, wherein 20 schizophrenic patients and 32 healthy controls were examined using a neuropsychological test battery for the assessment of temporal (memory) and frontal (executive) faculties. Volumetric measurements of temporal (hippocampus and amygdala) and frontal (orbitofrontal, dorsolateral prefrontal, and anterior cingulate areas) brain areas were performed. Negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms. They found that tests assessing verbal and visuospatial learning and memory functions were worse in schizophrenic patients than in healthy controls, and negative symptoms were significantly correlated with verbal memory functions; thus, negative symptoms in schizophrenia could be more specifically associated with verbal memory deficits compared with executive functions [28].

Recommendations

(1) We recommend future studies to include larger sample size and more concern about subclinical finding in relatives of schizophrenic patients suggest risk for illness development including NSS and TCD.

(2) The effect of antipsychotic drugs and/or ECT on neurological and neurosonology results should be considered in further research studies.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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