



## Research Paper

# Network analysis of cognitive deficit in patients with schizophrenia spectrum disorders

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## ABSTRACT

**Background:** Cognitive impairments are found in 80% of patients with schizophrenia. The severity of these impairments significantly affects the recovery of patients in terms of social functioning.

Network analysis is the most suitable approach for studying complex relationships among cognitive functions. **Aim:** To build a network model of neurocognitive functions for identifying both the severity of impairments in individual functions and the vertices central to the whole model.

**Methods:** The study included 115 patients with schizophrenia and schizophrenia spectrum disorders and a comparison group, comprising 99 healthy subjects. The severity of clinical symptoms was assessed using the PANSS, CDSS and YMRS, and the SAS and BARS for extrapyramidal symptoms and akathisia. Subjects from the comparison group completed screening questionnaires QIDS-SR and PQ-16. Neurocognitive functions were assessed using the BACS.

**Results:** The patients performed worse than the healthy subjects on all tests. In the cognitive network models of healthy subjects, fewer connections were revealed and the central place was occupied by working memory, the functioning of which depends upon everyday functioning in the community. In the cognitive models of patients there was a greater connectedness of neurocognitive functions. Furthermore, the central place of the networks in patients is occupied by the processing speed, evaluated primarily using the Symbol Coding test, which reflects the dependence of patient activity on lower-order functions.

**Conclusion:** The processing speed deficit is key to schizophrenia and it may be considered a potential endophenotype of the disease.

## 1. Introduction

Cognitive impairments are found in 80% of patients with schizophrenia, including patients experiencing their first psychotic episode, who have not previously received treatment with psychotropic drugs (Keefe and Fenton, 2007; Fatouros-Bergman et al., 2014).

Differences in cognitive structure have been reported in a number of factor analysis studies (McCleery et al., 2015; Nuechterlein et al., 2004). Several domains were identified, including speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory and reasoning/problem solving, which were considered specific for schizophrenia (Nuechterlein et al., 2008). In some studies, the structure of cognitive deficit was represented as associated but separate cognitive domains (for example, McCleery et al., 2015). Other authors reported the presence of a single factor that reflected the generalized deficit which may have systemic biological

underpinnings (Dickinson and Harvey, 2008). The number of factors in multifactor models may also differ: six-, seven- and three-factor models of cognitive deficit have all been obtained in studies (Lo et al., 2016; McCleery et al., 2015; Schretlen et al., 2013). This diversity of results is to some extent explained by the use of different methods in evaluating and analyzing the results. However, it is also necessary to take into account that cognitive functions are not isolated from each other, and the impairment of one of them can negatively affect the work of the entire cognitive system, which makes it imperative to study not only individual cognitive domains, but also the connections between these domains.

A tool for evaluating these relationships can be, for example, methods of network analysis based on “graph theory” (see Fried et al., 2017; van den Heuvel et al., 2010), which has already become widespread in medicine (Farahani et al., 2019; Gysi and Nowick, 2020; Lee et al., 2019; Rubinov and Sporns, 2010 and others). Network analysis does not rely on an a priori model of cause-effect relationships among

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variables and produces spatially ordered networks in which key variables are located at the center of the network and variables with fewer connections at the periphery. For example, applying network analysis to data collected on psychopathologic variables, neurocognition, functional capacity, personal resources, and functioning in individuals with schizophrenia revealed the high centrality of functional capacity and everyday life skills (Galderisi et al., 2018). A study of the neurocognitive network model revealed that the connection structure of cognitive functions in patients experiencing their first psychotic episode could be distinguished from that of patients with depression and from that of healthy subjects (Liang et al., 2018).

Another factor affecting the structure of cognitive deficit may be the transdiagnostic nature of these impairments. Within the framework of the Research Domain Criteria (RDoC) project, it was proposed that psychotic spectrum disorders be considered rather than individual diagnostic categories (Insel et al., 2010). Studies of cognitive impairment in schizophrenia and schizoaffective disorder have shown significant similarity in these disorders (Madre et al., 2016), which has enabled the consideration of both of these disorders as schizophrenia spectrum disorders. Schizotypal disorder is less often included in this spectrum, but there is evidence for an association between the severity of schizotypal traits and schizophrenia (Ettinger et al., 2014). Evidence of genetic overlap between schizophrenia and schizotypy comes from family studies, which show that first-degree relatives of schizophrenia patients have increased levels of schizotypy. In addition to increased mean levels of schizotypy in the relatives of schizophrenia patients in comparison to control subjects without a first-degree relative with schizophrenia, there are also reports of associations between the profile and severity of clinical symptoms in the patients and the dimensions of schizotypy in their relatives (Ettinger et al., 2014). Several studies showed that individuals with high levels of schizotypal traits exhibit alterations in neurocognitive task performance and underlying brain function which are similar to the deficits seen in patients with schizophrenia (Nelson et al., 2013). In addition, studies of oculomotor deficits and neurological soft signs showed some biological similarity between people who score highly on measures of schizotypy and people with schizophrenia (Nelson et al., 2013). Schizotypal disorder is included in the category “Schizophrenia, schizotypal and delusional disorders (F20-F29)” (International Classification of Diseases and Related Health Problems 10th Revision. <https://icd.who.int/browse10/2010/en>. Visit date 2 Aug, 2021) and characterized by such symptoms as cold or inappropriate affect, anhedonia, odd or eccentric behavior, a tendency to social withdrawal, paranoid or bizarre ideas not amounting to true delusions, obsessive ruminations, thought disorders and perceptual disturbances, occasional transient quasi-psychotic episodes with intense illusions, auditory or other hallucinations, and delusion-like ideas, usually occurring without external provocation. These data made it possible to include schizotypal disorder in schizophrenia spectrum disorders along with schizophrenia and schizoaffective disorder.

The network model of the interactions between cognitive variables can provide new insights into understanding brain functions in the context of schizophrenia spectrum disorders.

## 2. Methods

### 2.1. Sample

The study included 115 inpatients with schizophrenia and schizophrenia spectrum disorders (F20, F21, F25, according to ICD-10), aged between 18 and 55 years, whose native language was Russian. Patients with acute polymorphic psychotic disorder with symptoms of schizophrenia and acute schizophrenia-like psychotic disorder (F23.01 and F23.02 according to ICD-10) were also included. These patients had symptoms of schizophrenia but these symptoms had lasted for less than approximately one month. If the schizophrenic symptoms persist the diagnosis should be changed to schizophrenia.

The study did not include patients with more than four scores on P2 (Conceptual disorganization), P4 (Excitement), P7 (Hostility), G10 (Disorientation) and G14 (Poor impulse control) PANSS items as these symptoms could influence the understanding of instructions and the execution of tasks. Those with a comorbid dependence on psychoactive substances and those with a history of traumatic brain injuries with loss of consciousness for at least 10 min or other organic brain lesions were also excluded from the study.

The study also included a comparison group, comprising 99 healthy subjects. The inclusion criteria were individuals between the age of 18 and 55 years, the absence of a history of mental disorders or organic brain damage, as well as results on screening scales of less than six points.

Prior to the research procedures, each participant signed an informed consent. The study was approved by the local ethics committee and was in accordance with the Declaration of Helsinki.

### 2.2. Clinical assessment

The psychiatrist conducted a clinical interview with the patients and collected anamnestic data to clarify the diagnosis. The severity of clinical symptoms was assessed using the Structured Clinical Interview for the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989), the CDSS (Addington et al., 1990), YMRS (Young et al., 1978) and the SAS (Simpson and Angus, 1970) and BARS (Barnes, 2003).

Subjects from the comparison group were also interviewed by a specialist and completed screening questionnaires to identify symptoms of depression and a high risk of psychosis: Quick Inventory of Depressive Symptomatology – Self-Reported Version (QIDS-SR) (Rush et al., 2003) and Prodromal Questionnaire (PQ-16) (Loewy et al., 2005).

### 2.3. Neurocognitive assessment

The neurocognitive functions of the subjects were assessed using the battery Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2006). The battery consists of six subtests, which enable the evaluation of verbal and working memory, motor skills, verbal fluency, processing speed, attention and executive functions.

### 2.4. Statistical analysis

Statistical analysis and data visualization were performed in the R 4.0.3 environment, using the RStudio V 1.3.1093 software. For the analysis of data with a normal distribution, the *t*-test and the Pearson correlation were used; for the analysis of data with a distribution other than normal, the Mann-Whitney criterion and the Spearman correlation were used. Analysis of covariance (ANCOVA) was used to examine the between-group cognitive differences, taking PANSS scores into account.

Cognitive variables were depicted as nodes in the network, but the mean values of these variables were not used this study as the aim was the analysis of relations between these variables. Their correlations were used as edges. Thicker edges represent stronger correlations.

Two types of network were created. The first type, named “correlations” or “paired correlations”, represented the association network with zero-order correlations and provided a first general representation of the pairwise associations among variables. The second type was built on partial correlations, where the association between each pair of nodes is controlled for the influence of all the other variables. These correlations control for the shared variance between nodes and express the strength of the unique links connecting pairs of variables. The network display was based on the algorithm of Fruchterman and Reingold, which places strongly associated nodes at the center of the graph and weakly associated ones at the periphery.

### 3. Results

The study included 214 participants, including 115 patients with schizophrenia and schizophrenia spectrum disorders and 99 healthy subjects. The demographic characteristics of the sample are shown in Table 1. Despite the fact that there were more men in the sample of patients in the group, there were no statistically significant differences on this basis. There were also no age differences between the groups. Patients were primarily diagnosed with schizophrenia (46% of the sample), their psychopathological symptoms did not interfere with the assimilation of instructions and the performance of tasks.

Patients performed worse than the healthy subjects on all tests. The results are shown in Table 2. However, covariate analysis showed that differences in verbal fluency became insignificant when taking into account negative symptoms. Differences in the Tower of London test became insignificant when taking into account positive symptoms.

To construct a model of neurocognitive impairments, paired correlations between the variables were firstly analyzed. Table 3 shows the paired correlations among patients and among the healthy subjects. Differences in structure between the groups were observed both in terms of strength and number of significant correlations. With regard to the healthy subjects, their number was less than that of the patients, and the strongest was found between working memory function (evaluated by the Digit Sequencing test) and verbal fluency, while in absolute values this remained weak ( $r = 0.39$ ). Among the patients, almost all functions were related to one other. In addition, these connections were more powerful.

Since the cognitive functions themselves are not isolated, it was necessary to take into account their potential, indirect influence on one other, through connections with the third function. To eliminate such indirect influences, partial correlations were calculated (Table 4). The analysis took into account the relationships identified at the trend level, should a significant pair correlation be detected between these variables.

There was an expected decrease in the number of significant relationships in both groups. The patient group approached the control group in terms of the number of significant connections and their strength.

Clinical symptoms can also affect test results, therefore, with regard to the patient group, partial correlations were also calculated, taking into account not only the influence of other cognitive functions, but also the severity of clinical symptoms (Table 5). The total PANSS score was

**Table 1**  
Demographic characteristics of the sample.

	Patients	Control group
Total	115	99
Men (%)	50 (43%)	34 (34%)
Mean age ± SD	29.23 ± 8.1	30.36 ± 7.6
Education		
Higher degree	49 (43%)	78 (79%)
Specialized secondary (including incomplete higher education)	45 (39%)	6 (6%)
Secondary education	21 (18%)	15 (15%)
Clinical characteristics		
F20 (Schizophrenia)	53 (46%)	–
F21 (Schizotypal disorder)	15 (13%)	–
F23 (Acute and transient psychotic disorders)	19 (17%)	–
F25 (Schizoaffective disorder)	28 (24%)	–
Age of subclinical symptoms appearance	20.57 ± 6.8	–
Age of onset	23.85 ± 6.6	–
Duration of subclinical stage	3.28 ± 4.6	–
Duration of illness	5.13 ± 6.9	–
PANSS, Positive symptoms	18.02 ± 2.9	–
PANSS, Negative symptoms	20.90 ± 3.8	–
PANSS, General symptoms	38.91 ± 6.2	–
PANSS total	77.83 ± 12.9	–

**Table 2**  
Performance in neurocognitive tests.

	Patients	Control group
Verbal Memory (VM)	43.63 ± 11.6**	50.03 ± 6.9
Digit Sequencing (DS)	19.18 ± 3.9**	21.56 ± 3.4
Token Motor Task (TMT)	63.04 ± 13.4**	72.99 ± 11.1
Verbal Fluency (VF)	51.23 ± 13.6**	58.33 ± 13.8
Symbol Coding (SC)	49.3 ± 13.8**	63.31 ± 8.4
Tower of London (TL)	16.95 ± 3.7*	18.46 ± 2.4

\*  $p < 0.01$ .

\*\*  $p < 0.001$ .

**Table 3**  
Paired correlations of the test results of healthy subjects and patients.

	VM	DS	TMT	VF	SC	TL
Healthy subjects						
VM						
DS	0.36***					
TMT	0.17	0.25*				
VF	0.14	0.39***	–0.02			
SC	0.27**	0.21*	0.13	0.17		
TL	0.17	0.25*	0.21*	0.04	0.26*	
Patients						
DS	0.57***					
TMT	0.27**	0.31***				
VF	0.42***	0.45***	0.37***			
SC	0.53***	0.63***	0.45***	0.49***		
TL	0.23*	0.38***	0.15	0.41***	0.30**	

Note: for abbreviations see Table 2.

\*  $p < 0.05$ .

\*\*  $p < 0.01$ .

\*\*\*  $p < 0.001$ .

**Table 4**  
Partial correlations of the test results of healthy subjects and patients.

	VM	DS	TMT	VF	SC	TL
Healthy subjects						
VM						
DS	0.27**					
TMT	0.06	0.2*				
VF	–0.002	0.39**	–0.12			
SC	0.19	0.01	0.06	0.13		
TL	0.06	0.21*	0.1	–0.12	0.22*	
Patients						
DS	0.33***					
TMT	–0.001	0.005				
VF	0.16	0.09	0.18			
SC	0.21*	0.35***	0.27**	0.12		
TL	–0.04	0.14	–0.02	0.26**	0.22*	

Note: for abbreviations see Table 2.

^  $p < 0.1$ .

\*  $p < 0.05$ .

\*\*  $p < 0.001$ .

\*\*\*  $p < 0.001$ .

considered.

Based on the obtained data, a network model of neurocognitive functions was constructed for both patients and healthy subjects (Fig. 1). It was observed that the network, based on the paired correlations in patients, was more saturated with connections. In this model, all cognitive functions were approximately equal, and no single central function was identified. However, among the healthy subjects, the central position in the network (the node with the largest number of connections) was occupied by working memory (DS test).

When controlling the indirect influence of cognitive functions on one other, the structure of the model among the healthy subjects does not change a great deal (Fig. 1, Partial correlations). Working memory

**Table 5**

Partial correlations of the test results of patients, taking into account the severity of clinical symptoms, according to the total PANSS score.

	VM	DS	TMT	VF	SC	TL
VM						
DS	0.33***					
TMT	0.04	0.01				
VF	0.11	0.11	0.22*			
SC	0.18*	0.34***	0.26**	0.11		
TL	-0.02	0.15	-0.06	0.27**	0.22*	

Note: for abbreviations see Table 2.

\* p < 0.05.

\*\* p < 0.01.

\*\*\* p < 0.001.

remains the central function of the network, losing its connection with the results of the SC test and the TMT; VF also remains on the periphery. Among the patients, the network structure changes greatly: it becomes significantly poorer. The central component of the network also changes; it becomes the processing speed, estimated using the SC test.

**4. Discussion**

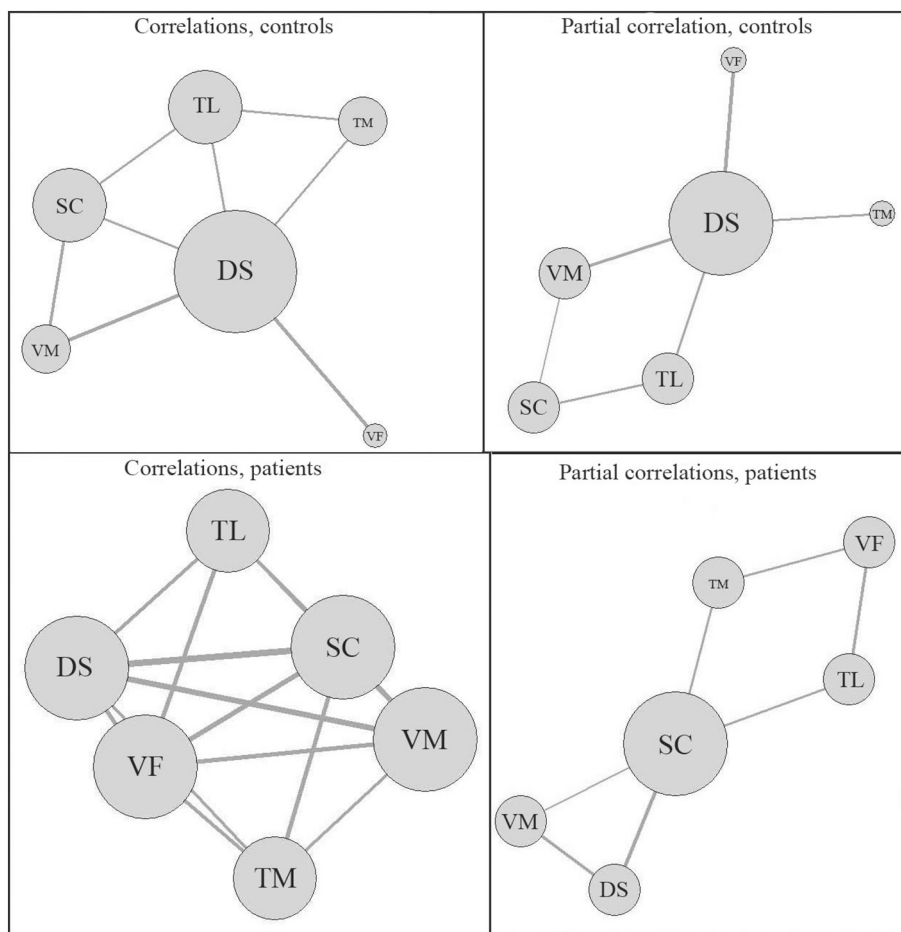
The entire sample of patients was considered as a continuum of disorders of the same spectrum, which made it possible for the results to not have to be limited to one diagnostic category. The results confirm the data that patients with schizophrenia and schizophrenia spectrum disorders have a pronounced cognitive deficit (Fioravanti et al., 2012;

Fatouros-Bergman et al., 2014; Mesholam-Gately et al., 2009). At the same time, the data confirm that the work of individual cognitive functions is connected to the functioning of other cognitive functions, forming a coherent functional system, among both healthy participants and patients. A number of differences in the structures of cognitive functioning in patients and healthy subjects were revealed.

In the cognitive network model of healthy subjects, fewer connections were revealed and the central place was occupied by working memory, the functioning of which depends upon everyday functioning in the community. On the periphery were the results of TMT, VF and SC tests. All of these tests have a time limit, which may indicate that the processing speed for healthy subjects is in a subordinate position in relation to higher-order functions, such as working memory.

The model of the cognitive functions among patients was the reverse of the model built from the data of the control group. There was a greater connectedness of neurocognitive functions, which may reflect the presence of certain factors, affecting the overall, cognitive decline of the disease. Clinical symptoms may be such a factor that affects the high coherence of the network. Furthermore, the central place of the patient network is occupied by the processing speed, evaluated primarily using the Symbol Coding test, which reflects the dependence of patient activity on lower-order functions.

These results are consistent with evidence that the processing speed deficit is key to schizophrenia and is considered a potential endophenotype of the disease (Dickinson et al., 2007; Sánchez et al., 2009). The results of the studies show that of all the cognitive impairments, the decrease of the processing speed is most closely associated with a



**Fig. 1.** Network model of cognitive functions.

Note: VM – test for verbal memory; DS – Digit Sequencing test, which evaluates working memory; TMT - test for motor skills; VF - test for verbal fluency; SC – Symbol Coding test, which evaluates the processing speed; TL - Tower of London test, which evaluates executive functions.

decrease in the brain white matter volume, especially in the corpus callosum, frontal regions, cingular region, anterior radiat crown (Karbasforoushan et al., 2015). It was also observed that the degree to which the processing speed decreases, primarily depends on the severity of white matter deficit. These data suggest that the decrease in processing speed may reflect a mental activity disorder, behind which there is a mismatch in the functioning of various parts of the brain, manifested by psychotic symptoms.

Based on the obtained results, further research is needed regarding the influence of various parameters affecting these changes: the period of the onset of the disease, the level of premorbid functioning and others. In addition, a further study is required to assess the possibilities of influencing the various components of the network, so as to correct the entire system.

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### CRediT authorship contribution statement

M.K. conducted the neurocognitive assessment, the statistical and network analyses and drafting of the article; A.S. contributed to the study design, analysis of the results and took part in drafting of the article. All authors have approved the final article.

### Declaration of competing interest

The authors declare no conflict of interest.

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