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Mediating Effect of Sex-Related Differences in the Relationship Between Cognitive Functioning and Clinical Symptoms in Patients with Schizophrenia

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ABSTRACT

Objective: Sex differences in patients suffering from schizophrenia are well established for clinical symptoms and a number of sociodemographic parameters, but not for cognitive functioning. Data on the relationship between cognition and clinical symptoms are also contradictory. This study was aimed at evaluating cognitive functions, symptomatology, and the relationship between these domains, with consideration of the sex of the patient.

Methods: One hundred and twenty-nine patients (55% males) diagnosed with paranoid schizophrenia in remission according to 10th revision of the International Statistical Classification of Diseases and Related Health Problems completed a broad battery of cognitive tests. Disease severity was measured by the Positive and Negative Syndrome Scale and Clinical Global Impression—Severity. Male and female patients were homogeneous in age, age of illness onset, duration of the disease, and severity of symptomatology.

Results: Patients showed a notable difference in cognitive functioning and in the pattern of links between cognitive functioning and clinical symptoms. Female patients demonstrated higher results in psychomotor speed, while male patients showed higher results in some aspects of executive functioning. The most prominent sex-related difference was that for each of the sexes, those cognitive functions that were more impaired relative to the group trend were associated more closely with the clinical symptomatology of schizophrenia.

Conclusion: Patients' sex is a crucial factor mediating cognitive functioning and the symptomatology of schizophrenia.

Keywords: Clinical symptoms, cognitions, schizophrenia, sex-related differences

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INTRODUCTION

It is well established that many features of schizophrenia are heterogeneous depending on patients' sex: incidence and clinical symptomatology, treatment response and tolerability, concomitant dependencies and social functioning, course of the disease, and long-term outcome. These data led to a proposal to integrate sex-specific aspects into clinical guideline recommendations.[1]

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Clinical symptoms and cognitive impairment, the most salient signs of schizophrenia, have been studied in detail with regard to sex differences.[2-18]

Data on sex differences in manifestations of schizophrenia are relatively strong. Negative symptoms seem to be more severe in male patients,[2,3] while females demonstrate more obvious affective symptomatology and anxiety.[3,4] There are also data indicating that sex differences in schizophrenic symptomatology are only found in chronic patients but not during their first episode of psychosis.[5]

With regard to cognition in schizophrenia, a number of studies have shown that males have a higher level of premorbid cognitive functions,[6] as well as at the first episode,[6,7] and other stages of the disease.[8] Females, unlike males, demonstrate a lack of attention that can contribute to abnormal executive functioning.[9]

On the contrary, several studies have found that male patients performed worse than females on some cognitive measures,[4,10,11] both in adolescents[12] and middle-aged and older persons with schizophrenia.[13] Tsai and co-authors demonstrated that female patients outperformed males in verbal memory, visual recognition, and processing speed.[14] In another study using a broad battery of cognitive tests, the authors showed that cognitive impairment in males affects a larger number of functions than in females.[15] Male patients were significantly impaired across all functions in comparison with normal male subjects and on tests of attention, verbal memory, and executive functions in comparison with female patients.

Some studies failed to detect significant differences between male and female patients with schizophrenia in their level of cognitive functioning,[16] or it was shown that the sex differences found among the patients were typical of a healthy population.[17,18]

The relationship between cognition and clinical manifestations was also studied. The most consistent data on the issue indicates that patients with more prominent negative symptoms also demonstrate more severe cognitive decline,[19] which holds in periods of both acute psychosis and remission.[20] Studies have shown that negative symptoms correlate with impairments of abstract thinking, verbal fluency,[19] working memory,[21] the continuous performance test (CPT), and Wisconsin card sorting test (WCST) performance.[22]

Correlations between cognitive functioning and positive symptoms are rarely found.[23] Servan-Schreiber and coauthors demonstrated that deficits in the processing of context information and signal detection performance correlated with positive symptoms.[24] An improvement in positive, but not negative, symptoms causes improvement in some cognitive domains.[20]

Those works that use 3-dimensional models of psychopathology (positive, negative, and disorganization syndromes) fairly often find relationships between cognition and symptoms of disorganization.[25,26]

It is reasonable that the relationships between clinical symptoms and cognitive functioning depend on the patient's current clinical state. Thus, it was shown that cognitive functions are most closely linked to symptoms of disorganization during an acute episode and with residual positive symptoms at the consolidation of remission.[27]

Hence, the existing data are insufficient to provide a consistent understanding of the relationship between cognition and symptoms of schizophrenia.

We hypothesized that the relationships between clinical symptoms and cognition in patients with schizophrenia could be mediated by the factor of sex. Our study is aimed at clarifying this issue.

MATERIAL AND METHODS

Participants

We enrolled a total of 156 outpatient participants with schizophrenia. The recruitment of patients lasted from September 2013 to March 2015. Twenty-seven patients were excluded because they did not meet the inclusion criteria (mainly age and clinical status) (Figure 1).

The final sample consisted of 129 patients (55% males) who met the following main criteria: Age from 18 to 59 years, diagnosis of paranoid schizophrenia (F20.01 according to 10th revision of the International Statistical Classification of Diseases and Related Health Problems), mild to moderate clinical symptomatology, current antipsychotic therapy in an adequate dosage. The exclusion criteria were defined as the following: other than paranoid forms of schizophrenia (due to clinical homogenization), Positive and Negative Syndrome Scale (PANSS) total score >80, CNS traumas of any genesis in medical history, current or lifetime alcohol and/or drug addiction, and inability to perform cognitive tests.

The patients underwent a single visit with cognitive testing and clinical assessment, performed by trained and certified clinical psychologists and psychiatrists. The assessments were performed independently in order to prevent the influence of some indicators on others, but on the same day.

The majority of patients (more than 85%) completed the whole battery of tests; in some cases, participants were unable to complete a test for various reasons. Missing data were not recovered. Follow-up data were not taken into account in this study.

The groups of males and females did not differ in terms of age of onset or duration of the disease, nor in severity of clinical symptoms (Table 1).

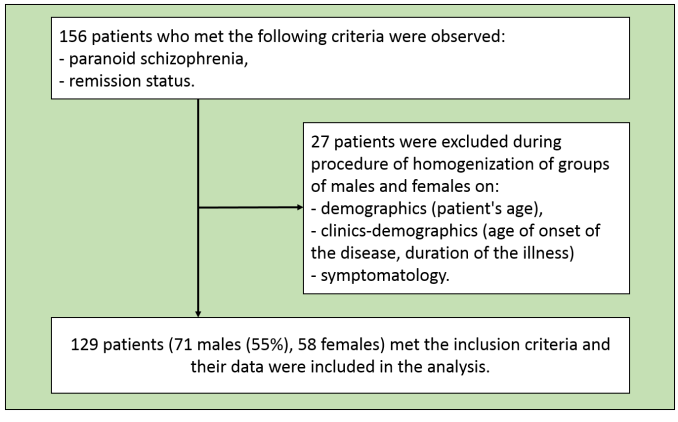

Figure 1. Flowchart for enrollment.

Table 1. Demographic and Clinical Parameters of Male and Female Patients

Parameter	Males Median	Mean (SD)	Females (Median)	Mean (SD)	*P*
Age	37.5	38.97 (11.27)	40.0	40.0 (11.59)	.63
Age of onset of schizophrenia	23.0	24.66 (8.24)	23.0	25.87 (10.64)	.78
Duration of schizophrenia	12.0	13.79 (9.03)	15.0	16.16 (10.47)	.33
PANSS positive score	13.0	13.54 (4.46)	15.0	14.84 (4.48)	.11
PANSS negative score	21.0	22.25 (5.88)	22.0	22.33 (4.43)	.55
PANSS score of general psychopathology	35.0	35.25 (8.67)	37.0	36.36 (6.77)	.32
PANSS total score	69.0	71.04 (15.16)	75.0	73.53 (11.02)	.12
CGI-S	4.0	4.18 (1.07)	4.0	4.29 (1.23)	.82

Mann–Whitney *U*-test for mean.
CGI-S, Clinical Global Impression—Severity; PANSS, Positive and Negative Syndrome Scale.

Measures

The cognitive functions were measured by a battery of tests that included several subtests from the Wechsler adult intelligence scale (WAIS)[28] and Wechsler memory scale (WMS),[29] such as the WAIS subtest VII—symbol coding and WMS subtest VII—paired associates; the Tower of London test (TOL^{DX});[30] the Stroop test;[31] the Schulte tables;[32] the Benton visual retention test (BVRT);[33] the Wisconsin card sorting test (WCST, computer version of CV3 for Windows);[34] the letter cancellation test;[35] and the continuous attention task (CAT).[36] In addition, 4-point Likert scales were used to assess patients' rapport, effort, and cooperation during the testing.

Symbol coding is a widely used neuropsychological test to assess processing speed. The WMS subtest "paired associates" evaluates verbal learning and associative memory. The TOL test is used to assess executive functions and planning. The stroop test is an instrument that is indicative of attention, inhibition, and interference control. Schulte tables is a test used for psychomotor speed and shifting of attention. The Benton test is a test of visual retention. The WCST is used to evaluate cognitive flexibility and abstract thinking. The letter cancellation test lets us assess psychomotor speed, concentration, and stability of attention. The CAT is a computerized test for continuous attention and alertness.

The PANSS with standard and pentagonal scoring models[37] and Marder's factors[38] as well as Clinical Global Impression—Severity (CGI-S)[39] were used as clinical measures. The PANSS uses a semi-structured interview with the patient to assess the severity of the symptoms of schizophrenia. The CGI-S is based on the doctor's assessment of the overall impression of the severity of the patient's illness on the 1-7 scale.

Statistical Analysis

Data were analyzed using the statistical software package STATISTICA for Windows, version 8.0. Nonparametric statistical methods were used. Median, mean, and standard deviation values were used to describe the data. Differences between the groups were tested by the Mann–Whitney *U*-test. The Spearman test was used to determine the significance of the correlations. The results were estimated to be significant at the level of $P < .05$. The number of correlations was also analyzed as an indicator of the intensity of interaction between the clinical and cognitive spheres in groups.

Ethical Approval

The study was approved by the ethical committee of the organization (Number 185 from September 16, 2013). All the patients received full information about the study and provided signed consent to participate.

RESULTS

Patients' cognitive performance (as a whole group) varied from totally intact to significantly impaired. The most obvious deficits, greater than 2 σ, were found in attention productivity, psychomotor speed, and short-term visuospatial memory. The impairment of attention span and stability, working memory (greater than 1.5 σ), and planning and abstract thinking (about 1σ) were less obvious. The interference lay in the normal range.

Comparing males and females' cognitive profiles, we found clear differences between them in certain cognitive domains (Table 2). Female patients had a slightly better result in the psychomotor speed row score ($P = .049$) (symbol coding). There were differences in the Stroop test interference score (.026) and a number of indexes of abstract thinking in the WCST that were in favor of male patients. Females also made errors on the Benton visual retention test more often (.035), mainly of the distortion type (.023).

There were no between-group statistically significant differences for other cognitive measures. However, females demonstrated some advantageous tendencies, not only in psychomotor speed but also in a number of aspects of attention and memory. On the other hand, male patients demonstrated higher results in a number of aspects of executive functioning. The between-group difference was statistically significant for interference and abstract thinking and manifested as a tendency for planning and working memory.

The results of the Benton test (visual retention) also provided evidence that regulatory functions are more intact in male patients. There were more errors in the female group, with no between-group difference in overall level of performance (number of correct reproductions) ($P = .095$). This combination of test indices points out differences not in the functioning of short-term visual memory itself but in the system of error inhibition, i.e., regulation and control of mental activities.

As the second step of the study, we examined the relationships between cognition and clinical symptomatology in groups of males and females. We found notable differences that include both specific cognitive parameters correlated with psychopathology and the number of connections between them.

Table 2. Comparison of Cognitive Performance in Groups of Males and Females

Cognitive function	Advantage		*P*
	Males	Females	
Interference	*		.026
Planning	+		
Abstract thinking	*		.034
Working memory	+		
Attention stability	+		
Visual retention (errors)	*		.023
Semantic memory		+	
Associative memory		+	
Attention concentration		+	
Psychomotor speed		*	.049
Attention productivity		+	

Mann–Whitney *U*-test.
[+]An advantage, but without achieving statistical reliability.
*Significance at $P < .05$.

Among female patients, different parameters of cognitive functioning were more often correlated with negative symptoms, anergia, and emotional–volitional deficit, whereas the male group showed more relationships with the total score of positive symptoms, excitation, and paranoid ideas.

In order to detail the role of the sex factor at the next stage of the study, we analyzed the frequency of correlations in a particular cognitive sphere with symptoms in both groups. We found that the cognitive items that revealed the largest number of correlations with clinical factors were very different in males and females. A chart of frequencies is shown in Figure 2.

In males, the largest quantity of links with clinical factors was found for parameters of effort, cooperativity, and rapport during the testing. The female group showed only a few correlations with these parameters.

In terms of the frequency of correlations with symptomatology in the males, the largest were for simple reaction time (CAT), short-term memory (subtest V of WAIS in direct order/forward row), and attention (Schulte's table and subtest VII of WAIS—symbol coding).

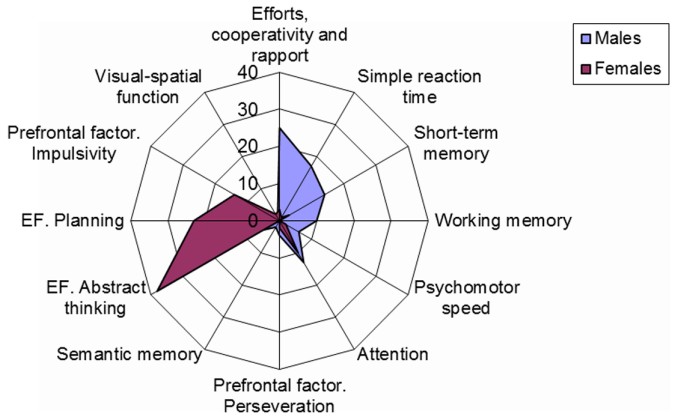

Figure 2. Frequencies of correlations between cognitive domains and clinical symptoms in males and females.

In the females, the most interrelations were found for abstract thinking (from the WCST), followed by planning (the Tower of London test), which is also an aspect of executive functioning. The third most frequent correlation with clinical factors in the group of females was found for impulsivity, also associated with prefrontal activity. This type of error occurred much more rarely in the group of males and was not correlated with any clinical symptoms.

Thus, the cognitive functioning of male patients was characterized at the same time by a higher level of functioning of the most intact aspects of cognition and a lower level of the most impaired functions, whereas females demonstrated a gentler gradient in the level of cognitive performance. Graphically, this difference is represented in Figure 3.

We note that, in a peculiar way, some study results indicate opposing aspects of executive functioning and other cognitive functions. The opposition in trends of executive functioning and functions of attention and memory found in this study concerns both the most intact and the most impaired cognitive parameters, as well as differences between males and females, both in the severity of the impairment and in relation to the intensity (frequencies) of

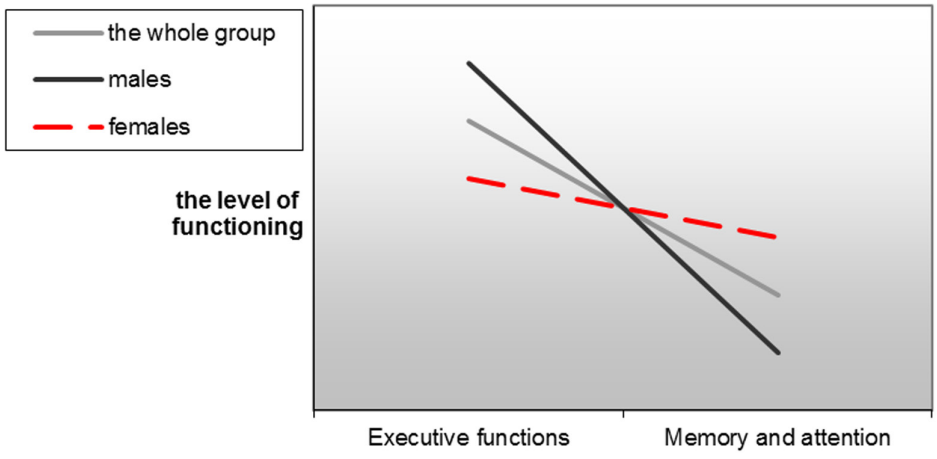

Figure 3. Schematic representation of cognitive profiles in males and females with schizophrenia.

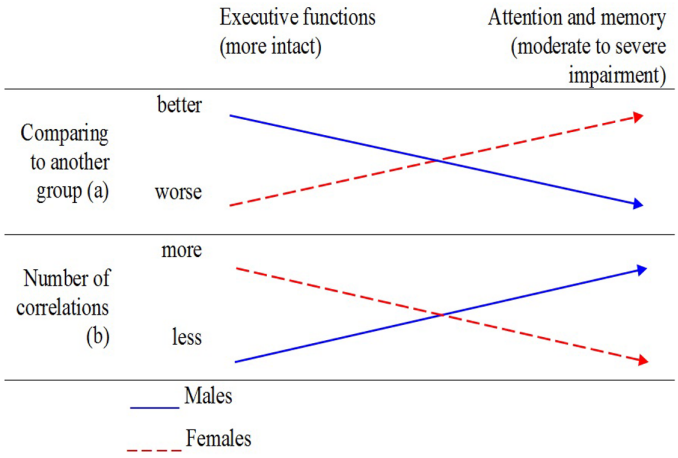

Figure 4. Impairment of executive function and attention (a) and frequency of correlations between cognitive function and clinical factors (b) in groups of male and female patients.

correlations between cognitive items and clinical factors. Figure 4 presents a schematic depiction of these trends in patients of different sexes.

It can be seen that in the group of male patients, a higher level of executive functioning than in females is accompanied by fewer correlations between different measures of executive function and clinical symptoms of schizophrenia, and a lower level of attention is accompanied by more correlations between cognitive items and psychopathology. On the other hand, female patients showed a slightly higher level of attention than did males, and the frequency of correlations between attention and clinical factors was relatively low, while executive functioning (more impaired in the group of females) revealed the most solid associations with psychopathological phenomena.

The observed tendencies can be summarized as follows: In patients of either sex, the cognitive functions that are more impaired relative to the group trend (attention in males and executive functions in females) are more closely interrelated with the psychopathology of schizophrenia.

DISCUSSION

As it can be seen, differences between males and females in cognitive functioning affected the most impaired and the most intact areas of cognition. Even with the homogeneity of the studied groups in terms of clinical symptomatology, males significantly outperformed females in tests that evaluated various aspects of executive functioning, whereas females revealed a tendency to perform better in tests of attention.

According to our results, a female advantage for attention and speed of processing has been found in schizophrenia patients in a systematic review.[40] Male working memory advantage and female advantage for visual memory are also shown in this work but in rodent models for schizophrenia.

We have found that the cognitive functions that are most closely related to clinical symptomatology are those that are more impaired relative to the average group indices (attention in males and executive functions in females).

Sex differences in the association between clinical correlates and cognitive impairment in patients with schizophrenia are rarely studied. In the study of Li and colleagues[41] on a large sample of 360 first-episode adult-onset psychosis patients, it was shown that considerable heterogeneity exists in associations of symptoms and cognition in males and females. In first-episode male patients most neurocognitive domains studied correlated with negative symptoms, while females demonstrated negative associations between neurocognitive domains and general symptomatology.[42] The other study demonstrated that attention was independently associated with negative symptoms in female patients and general psychopathology in male patients.[43] Negative symptoms were also independently associated with verbal learning, memory, and social cognition only in male patients, while general psychopathology was independently associated with symbol coding only in female patients.

The results of our study suggest that the interaction between cognitive functions and clinical symptoms in schizophrenia is not linear but rather a more complex pattern involving the factor of the patient's sex, and this may have contributed to the inconsistency of the data from previous studies on this issue.

In general, the sex specificity of the cognitive profile and the interactions between cognition and clinical symptoms of schizophrenia indicate differences in the functional and possibly anatomical and biochemical mechanisms underlying these processes.

We assume that this study is the first attempt to establish a pattern in the relationship between psychopathological manifestations and cognitive functioning in patients with schizophrenia, depending on the degree of cognitive decline in subjects of one of the sexes.

The limitations of the study include the absence of a control or comparison group (for example, healthy subjects or patients with diagnoses other than schizophrenia), as well as the use of only quantitative (not qualitative) methods of assessment. All patients included in the study received stable antipsychotic therapy at an adequate dosage. It is known that some neuroleptics, for example, clozapine, may have an effect on cognitive functions,[44] but the factor of pharmacotherapy was not taken into account in this study. The sample size is relatively small for gender studies; together with the lack of papers in this area, this makes our conclusions about the nature of the observed sex differences preliminary and restricts the generalizability of the study results.

In conclusion, male and female patients with comparable symptomatologies of schizophrenia have differences in their cognitive profiles and in the pattern of links between cognitive functioning and clinical symptoms. Our results suggest that patients' sex is a crucial factor mediating cognitive functioning and the symptomatology of schizophrenia.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of the Mental Health Research Center (Approval no: 185, Date: September 16, 2013).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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