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Cognitive dysfunction progression in schizophrenia – relation to functional and clinical outcome

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Summary

Aim. In the present work we tested the hypothesis of cognitive function disorder progression in schizophrenia.
Methods. Current cognitive, clinical and functional status of 34 chronic schizophrenic patients (13 males, 21 females), with mean 31 year-long duration of illness, was assessed. For neuropsychological assessment we used WCST, TMT, Stroop Test and Verbal Fluency Test. Results were compared with performance of 30 age, sex and educational level matched healthy controls and 20 first-episode subjects investigated before starting the first pharmacological treatment.
Results. Compared to first-episode drug-free patients, individuals with chronic schizophrenia performed worse on tests measuring psychomotor speed and shifting abilities (TMT A and B) and cognitive flexibility (more perseverative errors in the WCST). They also had more perseverations in letter and category Verbal Fluency Test.
Discussion. These results are in accordance with data from studies indicating rapid cognitive dysfunction progression in later stages of schizophrenia. Obtained differences cannot be explained only in terms of age differences. In group of chronic schizophrenic patients, worse cognitive abilities were related to poor functional outcome in individuals with longer duration of illness.
Conclusion. The results suggest that cognitive dysfunctions seem to have progressive character in the course of illness and are associated with present clinical and functional outcome.

schizophrenia / psychopathology / cognitive function / executive function / chronic schizophrenia / first-episode schizophrenia

INTRODUCTION

Cognition in schizophrenia has been widely investigated in the last years; however, there are still different opinions about relations between cognitive disturbances and the course of illness. Although deficits are present in many cognitive domains (e.g. attention, vigilance, memory and learning, verbal functions, reasoning and problem solving); according to most data, working memory and executive function disturbances, related to prefrontal cortex function impairment, are the most robust in this illness and are considered to be associated with poor patient's functional outcome [1, 2, 3]. As found also in healthy relatives of schizophrenic subjects; cognitive dysfunctions became known as endophenotype markers of the illness. Among them, cognitive flexibility disorders are found to be one of the most significant for schizophrenia. In neuropsychological studies, this parameter is often measured by Wisconsin Card Sorting Test (WCST), occurring in higher number of perseverative errors [4, 5, 6].

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Some authors claim that cognitive deficits increase during the course of illness, and that is associated with progression of structural and functional changes in the brain, observed in chronic schizophrenic patients [7, 8, 9]. However, other studies suggest that this decline appears only in early stages of disease and becomes stable in further course of illness [10]. According to some data [11], there is a significant relationship between early age of onset, longer duration of untreated psychosis and greater cognitive dysfunction.

The nature of cognitive dysfunction progression in schizophrenia is not clear. There are some evidences that, in general, patients with chronic schizophrenia have worse results of neuropsychological tests comparing to first-episode individuals. However, significant differences are not always found between particular patients [12]. There are first-episode subjects who have as intense disorders as chronic schizophrenic patients. Therefore, it cannot be excluded that cognitive dysfunction progression in some individuals is more rapid than in the others. Some authors [13] claim that cognitive dysfunction profile of first-episode and of a chronic schizophrenic subject are very similar; and not duration of the disease but intensity and nature of psychopathological symptoms (especially disorganization symptoms) should be taken into account.

The purpose of this observational, cross-sectional research was to confirm the hypothesis of cognitive function disorders progression in schizophrenia. Assuming that cognitive function status in chronic schizophrenic patients must be worse not only than in healthy age, sex and education level-matched subjects; but also than in first-episode patients; we decided to compare remitted chronic schizophrenic patients with first-episode individuals, who were just before the beginning of pharmacological treatment. Our aim was also to find associations between cognitive, clinical and functional outcome in schizophrenic patients, taking closer look into the group of subjects in late stages of illness.

METHODS

The investigated group consisted of 34 subjects with chronic schizophrenia, 13 males and 21 females, aged 48–80 years, diagnosed with paranoid schizophrenia according to ICD-10 criteria. Mean duration of illness was 31±SD (range 29–36 years).

Most of the investigated subjects were outpatients living independently or with their families, 3 persons came from the residential institution for mentally ill patients, 5 subjects were inpatients just before the end of their hospitalization. All these subjects were in full or partial remission period. At their illness onset, all of them received typical antipsychotics. Currently, 18 patients were treated with typical and 15 with atypical drugs. There were no statistically significant differences in results of psychiatric rating scales and scores of neuropsychological tests between patients treated with different types of medication.

The obtained results were compared with the results of: 1) first episode schizophrenic patients and 2) healthy controls matched according to age, sex and educational level.

1) The first comparative group consisted of 20 first-episode patients diagnosed with schizophrenia according to ICD-10 criteria (11 males and 9 females), aged 18-29, (mean 22.5±3.8) before the beginning of pharmacological treatment. All these patients were assessed in outpatient clinic of Clinical Neuropsychology Department in Bydgoszcz, Poland.

2) In the second comparative group there were 30 healthy subjects (10 males and 15 females), aged 47–75 (mean 56±8.0) sex and educational level matched to the chronic schizophrenic patients.

Individuals with severe neurological diseases, brain trauma and alcohol or drug abuse were excluded from the study. The present work has been approved by Ethics Committee of Institute of Psychiatry and Neurology, Warsaw, Poland; and therefore has been performed in accordance with ethical standards laid down in the 1964 Declaration of Helsinki. All persons stated in the text gave their written informed consent prior to their inclusion to the study.

To assess current cognitive functioning, the following neuropsychological tests were used:

1. **Wisconsin Card Sorting Test (WCST)** designed by Heaton at al. [14] computer version, was used to assess executive function and work-

ing memory. Percentage of perseverative (PE), and nonperseverative errors (NPE), number of correctly completed categories (CC), number of conceptual level responses (%CONC) and number of trials to complete first category (1 CAT) were taken into account.

2. **Stroop Test**

Stroop A – Reading Color Names in Black (RCNb) was used for the evaluation of verbal abilities and attention. In this test, patient is asked to read color names printed in black ink on the white card as quickly as possible.

Stroop B – Naming the Color Word – different (NCWd) was used to assess verbal working memory, attention and executive function. The subject is asked to name color of each printed word, which is different from the color described by the word [15].

3. **Trial Making Test**: part A was used for the measurement of psychomotor speed, and part B for the assessment of visuospatial working memory, ability to shift strategy and executive function [16].

4. **Verbal Fluency Test** to assesses the ability to generate words by subject in 60-second time according to given category (in Category Test) and letter (in F, A, S Letter Test), was used. Letters FAS show similar frequency in Polish language and this version is commonly used in neuropsychological evaluation in Poland.

Psychopathological assessment

To assess intensity of psychopathological symptoms we used Brief Psychiatric Rating Scale (BPRS). Clinical Global Impairment Scale (CGI) was used to measure severity of disease and Global Assessment Scale (GAS) for evaluation of patient's global social functioning.

STATISTICAL ANALYSIS

Statistical analysis was performed using STATISTICA computer version. For the assessment of distribution of the variables Shapiro-Wilk and median test were used. For the comparison of results and significant differences between three groups, ANOVA Kruskal-Wallis test was used. The U-Mann-Whitney Test for evaluation of significance of differences between two groups, and R- Spearman tests for correlations between variables, were used. The Bonferroni correction and G-power test were calculated to assess statistical power of the results.

RESULTS

As is shown in Tab. 1 – *next page*, significant differences in performance on neuropsychological tests between chronic schizophrenic patients and age, sex and educational level matched healthy controls were found. Chronic schizophrenic patients performed significantly worse on all neuropsychological tests in comparison to healthy subjects, excluding Stroop Test. Chronic schizophrenic group performed worse on TMT A and B, had more perseverations in Verbal Fluency Test (Letter and Category Test), generated less correct words in letter (F, A, S) Verbal Fluency Test and showed impairment in performance in all domains of the WCST.

In comparison to first episode schizophrenic patients, chronic schizophrenic subjects achieved also worse results in TMT A and B and more perseverations in letter and category Verbal Fluency Test. They also had higher number of perseverative errors in the WCST which was an indicator of greater cognitive flexibility disorders, in comparison to the results of first-episode schizophrenic patients.

In the group of chronic schizophrenic subjects; worse performance on neuropsychological tests (Tab. 2 – *next page*) correlated with higher intensity of psychopathological symptoms (measured with BPRS), greater severity of disease (assessed with CGI) and worse global social functioning (measured with GAS). The mean result of BPRS scale in the investigated group was 22.3 points (0-57$\pm$15.9) and the most frequent symptoms were blunted affect and autism. Mean value of CGI was 3.2 points (1– 6$\pm$1.6) which was an indicator of moderate severity of disease. Mean result of GAS was 67.4 point (21– 100$\pm$17.3) which meant moderate difficulties in patient's global social functioning.

Tab 1. Demographic characteristic and the results of neuropsychological tests (mean values±SD) in groups of: chronic schizophrenic patients (n=34), first-episode schizophrenic patients (n=20) and healthy controls (n=30)

	Chronic schizophrenic patients n=34	First -episode schizophrenic subjects (drug-free) n=20	Healthy controls n=30
Age	56.5±8.9 (48-80)	22.5±3.8 (18-29)	56.4±8.0 (45-75)
Education (years)	13.2±3.1 (9-20)	11.3±1.7 (8-14)	13.4±2.4 (10-19)
Duration of disease	31.2±3.8 (29-36)	1.4±0.7 (1-3)	_____
Number of hospitalizations	14.36±16.2 (1-80)	_____	_____
TMT A (seconds)	52.70±23.0 *	35.05±10.5##	30.36±8.7
TMT B (seconds)	113.45±56.6*	81.80±30.2#	53.56±19.2
Stroop A (seconds)	26.73±8.6	26.60±9.5	25.44±6.1
Stroop B (seconds)	76.97±27.0	81.45±20.7	65.16±13.0
Verbal Fluency Test category Test			
correct words	39.67±10.9	35.20± 1.5	43.00±9.7
perseverations	1.63±1.7**	0.90±1.6#	0.32±0.6
intrusions	0.33±0.8	0.20±0.5	0.08±0.3
Verbal Fluency Test letter test (F.A.S)			
correct words	23.82±9.2**	30.15±11.8	47.8±7.8
perseverations	0.33±0.6	1.40±2.0#	0.32±0.7
intrusions	0.76 ±1.0*	0.25±0.4	0.20±0.5
WCST PE	17.24±9.6**	11.95±7.6#	8.66±3.2
WCST NPE	20.00±11.4**	19.24±9.0	8.6±0.4
WCST CC	3.48±2.5**	5.1±0.9#	5.8±0.4
WCST % CONC	50.96±26.3**	69.7±7.0	75.96±8.0
WCST 1 CAT	40.36±46.5	26.2±5.9	13.4±43.0

Difference between chronic schizophrenic patients and healthy controls significant *p<0.05, ** p<0.01.
Difference between patients with chronic schizophrenia and first-episode subjects significant #, <0.05, ## p<0.01.

Analysis of demographic and clinical variables in the group of patients with chronic schizophrenia has revealed (Tab. 3 – *next page*) significant correlation between later age of onset and worse results in all domains of WCST, which indicates greater disturbances of executive functioning in these patients. No associations between the age of onset and the performance on other neuropsychological tests were found. Higher level of education was connected with better results in Stroop A and Verbal Fluency Test, which suggests educational level beneficial influence on verbal abilities (reading and word generation). Patients with higher number of hospitalizations in the first 9 years of disease, at present had greater psychomotor slowing (worse results on TMT A) and worse shifting abilities (worse results on TMT B). Patients with higher number of hospitalizations presented less intrusions in Verbal Fluency Test.

DISCUSSION

Cognitive outcome of first-episode unremitted patients turned out to be significantly better comparing to status of remitted patients with chronic schizophrenia. Higher age of chronic schizophrenic subjects was a significant factor associated with worse executive functioning; also with greater cognitive flexibility disorders. Neuropsychological test performance results significantly differed group of chronic schizophrenic patients from age, sex and education level matched

Table 2. R- Spearman correlations between the results of psychiatric rating scales and neuropsychological tests in 34 chronic schizophrenic patients.

Psychiatric rating scales & neuropsychological tests	R-Spearman
BPRS &:	
TMT A	0.33*
TMT B	0.51 **
Stroop B	0.37*
Verbal Fluency Test (Category Test) intrusions	0.47 *
CGI &:	
TMT A	0.42*
TMT B	0.59**
Stroop B	0.47 *
Verbal Fluency Test (Category Test)	-0.39 *
correct words	0.44 *
VFT (Category Test) perseverations	-0.46**
VFT (F.A.S) correct words	0.47 **
VFT (F.A.S) intrusions	
GAS &:	
TMT A	-0.36 *
TMT B	-0.47**
VFT (F.A.S) correct words	0.48 **
VFT (F.A.S) intrusions	-0.37 *

Table 3. R-Spearman correlations in group of patients with chronic schizophrenia (n=34); between age of onset and years of education. Number of hospitalizations and results of neuropsychological tests.

Correlations	R-Spearman
Age of onset &:	
TMT A	ns
TMT B	ns
Stroop A	ns
Stroop B	ns
Verbal FluencyTest (CategoryTest) correct words	ns
VFT (CategoryTest) perseverations	ns
VFT (CategoryTest) intrusions	ns
VFT(F.A.S) correct words	ns
VFT (F.A.S) perseverations	ns
VFT (F.A.S) intrusions	ns
WCSTNPE	0.55*
WCSTPE	0.51*
WCSTCC	-0.54*
WCST% CONC	-0.60*
WCST 1st Cat	0.32

table continued on next page

Education (years) &:	
TMTA	ns
TMTB	ns
StroopA	-0.42*
StroopB	ns
Verbal Fluency Test (CategoryTest) correct words	0.46**
VFT (CategoryTest) perseverations	ns
VFT (CategoryTest) intrusions	ns
VFT(F.A.S) correct words	0.61**
VFT (F.A.S) perseverations	ns
VFT (F.A.S) intrusions	ns
WCSTNPE	ns
WCSTPE	ns
WCSTCC	ns
WCST%CONC	ns
WCST1stCat	ns
Number of hospitalizations &:	
TMT A	0.42*
TMT B	0.47*
Stroop A	ns
StroopB	ns
Verbal Fluency Test (Category Test) correct words	ns
VFT (CategoryTest) perseverations	ns
VFT (CategoryTest) intrusions	-0.45*
VFT (F.A.S) correct words	ns
VFT (F.A.S) perseverations	ns
VFT (F.A.S) number of intrusions	ns
WCSTNPE	ns
WCSTPE	ns
WCSTCC	ns
WCST% CONC	ns
WCST 1st Cat	ns

R-Spearman correlations significant *p<0.05, **p<0.01

healthy controls. Therefore, we cannot explain the result differences between chronic and first-episode patients only in terms of natural ageing of cognitive functions. That would be an argument for general cognitive dysfunction progression in schizophrenia. The association found between longer duration of illness and worsening of performance on the WCST may additionally suggest progressive character of executive dysfunctions in patients with chronic schizophrenia. This data correspond with previous results showing significantly worse performance on "frontal" tests in patients with longer duration of illness [17, 18].

In the group of chronic schizophrenic subjects, patients with later onset of illness had more disorders in cognitive flexibility (higher number of perseverative errors) and attention (more non-perseverative errors) as well as lower ability to complete correctly categories on the WCST and to generate conceptual level responses. These results are in accordance with data from studies indicating that patients with later onset of schizophrenia may present different profile of cogni-

tive dysfunctions in comparison to early-onset patients. Moreover, some authors suggest possibility of rapid cognitive dysfunction progression in later stages of schizophrenia [19, 20, 21]. Pantelis at al. [22] claim that this process is associated with later development of executive functions and working memory associated with later myelienation of prefrontal cortex. Patients with long-term duration of disease presented significant impairment in psychomotor speed, shifting abilities, verbal fluency and especially in working memory, executive function and that were connected with serious disturbances in their current psychosocial functioning. This may support data obtained by other authors who pointed out that worse cognitive abilities are related to poor functional outcome in patients with longer duration of illness [12, 23, 24]. Cognitive dysfunctions, especially those related to frontal impairment, may affect abilities of interpersonal problem-solving in chronic schizophrenic patients. Zanello et al. [25] explored the relationships between functioning of different cognitive areas and social problem-solving skills in chronic schizophrenic patients (in comparison with the group of healthy subjects) and described the existing deficit in social problem-solving skills in chronic schizophrenic group. Authors have suggested that alterations in social problem-solving skills may reflect social anxiety and/or „theory of mind" impairment in chronic schizophrenia.

In the group of chronic schizophrenic patients, executive functions measured with paper-and pencil tests, but not with WCST , occurred significantly for clinical and functional outcome measured with psychiatric rating scales. Those results are not fully consistent with data emphasizing that "prefrontal" functions abnormalities (e.g. cognitive flexibility disorders) are crucial for worsening of the patient's social functioning. It may be an effect of limitations of the present work: first of all small sample size, but also lack of previous cognitive evaluation of chronic schizophrenic patients. However, according to the present state of knowledge, the influence of cognitive dysfunctions on psychopathological symptoms is not clear. According to some authors, these deficits are independent from clinical outcome [21] or associated only with negative and disorganization symptoms [26, 27, 28].

A significant correlation between severity of disease and cognitive deficits was found, suggesting that more severe course of disease, higher intensity of psychopathological symptoms and worse global social functioning are connected with greater disturbances of working memory, verbal fluency and psychomotor speed. In the investigated group, greater cognitive and functional disturbances were associated with higher number of hospitalizations and lower number of years of education. These observations indicate that education may be a protecting factor of cognitive and social functioning in chronic schizophrenia. This may support the hypothesis that cognitive reserve is important in neuropsychiatric disorders including schizophrenia, bipolar disorders and depression [29]. Authors suggest that cognitive failure below a certain threshold may alone, or in combination with common psychiatric symptoms, produce neuropsychiatric syndromes. Therefore, there might be a possibility for chronic schizophrenic patients to enhance cognitive abilities through pharmacological treatment or non-pharmacological interventions, such as education and neurocognitive training.

In the present work some arguments for cognitive function progression, but not for the specificity of cognitive impairment in schizophrenia, were found. Chronic schizophrenic patients in comparison to first-episode subjects, have achieved worse results in neuropsychological tests measuring psychomotor speed, set shifting as well as showed greater tendency for perseverations on verbal fluency and for cognitive flexibility impairment. These results correspond with other author's findings which indicate greater frontal functions disturbances in chronic schizophrenia [23, 30]. The present work, not only has indicated signifcant occurence of "prefrontal" (working memory and executive functions) disturbances but also of verbal functions connected with activity of different brain regions. This suggests that in schizophrenia there is no specific area of cognitive dysfunction, as other authors claim [31]. Similar (although less severe) impairment is observed in other severe psychiatric disorders [32] although information from genetic studies [33, 34] indicate different biological mechanism of frontal dysfunction measured by WCST in schizophrenia and bipolar disorders.

CONCLUSION

Results of the present work show progressive nature of cognitive impairment; that in chronic schizophrenic patients is associated with poor cognitive and functional outcome.

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