

The efficacy of cognitive rehabilitation with RehaCom programme in schizophrenia patients. The role of selected genetic polymorphisms in successful cognitive rehabilitation

Monika Mak¹, Jerzy Samochowiec¹, Piotr Tybura¹, Przemysław Bieńkowski², Beata Karakiewicz³, Liliana Zaremba-Pechmann³, Bożena Mroczek³

¹ Department of Psychiatry, Pomeranian Medical University, Szczecin, Poland

² Department of Pharmacology, Institute of Psychiatry and Neurology, Warsaw, Poland

³ Public Health Department, Pomeranian Medical University, Szczecin, Poland

Mak M, Samochowiec J, Tybura P, Bieńkowski P, Karakiewicz B, Zaremba-Pechmann L, Mroczek B. The efficacy of cognitive rehabilitation with RehaCom programme in schizophrenia patients. The role of selected genetic polymorphisms in successful cognitive rehabilitation. *Ann Agric Environ Med.* 2013; 20(1): 77-81.

Abstract

Introduction. Schizophrenic patients present cognitive dysfunctions which are regarded to be one of endophenotypical markers predisposing to schizophrenia. Currently, schizophrenia can be treated as a neurodegenerative and neurodeveloping disease with genetic background.

Objective. Assessment of the possible positive effect of neuropsychological rehabilitation in schizophrenia, in patients presenting cognitive dysfunctions. An additional aim was to verify the hypothesis that some genetic polymorphisms can be a prognostic factor for success in neuropsychological rehabilitation.

Material and methods. 41 participants and 40 control subjects were randomly selected. Both groups had the diagnosis of paranoid schizophrenia. Cognitive functions were checked with the Wisconsin Card Sorting Test, Trail Making Test, and Stroop Test at the beginning and end of the experiment. In the research group, each patient trained with the rehabilitation programme RehaCom, whereas the control group did not receive such training. Genes COMT rs4680 and BDNF rs6265 were analysed in the genetic part of study.

Results. RehaCom procedures appear to be useful in the neuropsychological rehabilitation of cognitive dysfunctions in patients diagnosed with schizophrenia. The research group showed a moderate improvement in the training programmes. Analysis of parameters obtained in the neuropsychological tests showed a slight improvement in both groups. At the present time, analysis of the polymorphisms of genes cannot be treated as a prognostic factor for the success of neuropsychological rehabilitation because statistical analyses showed few dependences with little statistical significance.

Conclusions. Cognitive rehabilitation produces moderate improvement in cognitive functioning.

Key words

cognitive functions, neurorehabilitation, schizophrenia, RehaCom, Wisconsin Card Sorting Test, genes' polymorphisms, BDNF, COMT

INTRODUCTION

Neurons in brain, as proven, have modification ability called neuroplasticity [1]. On account of neuroplasticity, an injured brain is able to recover partially or improve impaired functions. Pharmacological treatment and environmental stimuli can influence neuroplasticity. According to many scientific researches, schizophrenic patients examined neuropsychologically present cognitive dysfunctions, as far as working memory and executive functions (connected with prefrontal cortex) are concerned [2, 3, 4, 5, 6]. Some authors even suppose that for the quality of life of schizophrenia patients, cognitive deficits are more crucial than the psychopathological symptoms [7]. Cognitive dysfunctions are currently regarded to be one of endophenotypical markers predisposing to

schizophrenia. Working memory and executive functions are the functions most often discussed as being disturbed in schizophrenia. Deficits of these functions are the result of structural and functional abnormalities in the prefrontal cortex [8, 9, 10, 11]. These abnormalities are reflected in poor neuropsychological tests results (Wisconsin Cards Sorting Test, Trail Making Test, and Stroop Test) [12, 13, 14]. This indicates that neurostructural changes underly schizophrenia, which can be treated as a neurodegenerative and neurodeveloping disease. Some genetic factors in cognitive performance in schizophrenia are under consideration. The COMT gene is functionally expressed in neural systems considered essential in schizophrenia. The COMT Met allele are associated with a lower activity form of COMT and with better cognitive performance, while the COMT Val allele is associated with a poorer one [15]. The brain-derived neurotrophic factor (BDNF) plays a crucial role in neurodevelopment and plasticity. Allele BDNF66Met is associated with reduced hippocampal engagement during memory processing. A lower level of BDNF may contribute to worse cognitive functioning [16].

Address for correspondence: Jerzy Samochowiec, Department of Psychiatry, Pomeranian Medical University, Szczecin, Broniewskiego 26, 71-460 Szczecin, Poland
E-mail: samoj@pum.edu.pl

Received: 24 February 2012; accepted: 18 December 2012



RehaCom is a software package, enabling focus on various cognitive areas that need to be trained [17]. It was constructed for neurological patients and patients after brain injuries. Due to cognitive dysfunctions connected with prefrontal cortex present in schizophrenia, there are reasons to believe that neuropsychological rehabilitation, for example with RehaCom, could be useful in improving cognitive disorders in patients with schizophrenia [18, 19, 20].

MATERIALS AND METHODS

Patient population. Eighty-one Caucasian patients of Polish descent with paranoid schizophrenia were recruited to the study. Main inclusion criteria: diagnosis of paranoid schizophrenia, cognitive dysfunctions measured with neuropsychological tests, remission period, and pharmacological monotherapy. Main exclusion criteria: double diagnosis, acute phase, neurological and/or somatic disorders. There were 2 groups; the research group subjected to cognitive training, and the control group which was not trained. Each patient was assigned to a group according to a simple randomization method [21]. The research group consisted of 41 participants, and the control group consisted of 40 patients (Tab. 1). Both groups did not show significant differences in gender, age and illness duration.

Table 1. Demographic Data of Subjects

	research group	control group
gender	M 19 F 22	M 18 F 22
age/mean value/SD	34+/- 11.07	39 +/- 12.99
age in first episode /mean value/SD	26+/- 5.12	28+/- 8.37
number of psychotic episodes/mean value/SD	3 +/- 1.09	3 +/- 1.34
illness duration/mean value/SD	9 +/- 7.21	11 +/- 8.56
education: higher/secondary/vocational/primary	7/24/8/2	12/17/7/4

Every participant suffered from diagnosed schizophrenia and previously medicated with antipsychotic drugs. The Polish version of ICD-10 criteria was used to confirm a diagnosis of paranoid schizophrenia. All patients were patients received neuroleptics (Tab. 2).

Table 2. Neuroleptics in the Research and Control Groups

	research group	control group
olanzapine	18	16
ziprasidone	5	12
perazine	7	9
clozapinum	3	0
quetiapinum	1	0
amisulpridum	1	0
risperidone	2	3
zuclopenthixol	3	0

The ranges of doses of neuroleptics used in the presented study were in accordance with the Polish standards for schizophrenia treatment, and followed manufacturer's recommendations

[22]. Every participant was informed about the aim of research and study conditions. Informed consent was obtained from each participant, both written and verbal. The study was approved by the Ethics Committee of Pomeranian Medical University in Szczecin, Protocol No. BN-001/88/06.

Assessment methods. First, the psychopathological status of each patient was measured using PANSS. Cognitive functions were checked with the Wisconsin Card Sorting Test, Trail Making Test, and Stroop Test at the beginning of the experiment, and after 60 days. In the research group, each patient was trained for 16 sessions (twice a week) with the training program RehaCom. RehaCom is a software package containing many procedures focused on different areas of cognitive functioning. Training sessions lasted about forty minutes, twenty minutes for each procedure.

For presented study, 2 procedures were selected: attention/concentration (the patient should find among many pictures the one that is identical with a pattern), and topological memory (pictures on a screen that the patient should memorize after they are covered up; the patient is then shown one of the pictures and must find its correct location). This group was compared with the control group not treated with RehaCom.

For genetic analysis, a blood sample was taken from every participant. Genes COMT rs4680 and BDNF rs6265 were analysed. DNA was extracted with a simple salting out procedure from blood. Genotyping was made by using the PCR method with RFLR techniques.

Data analysis. The normality of continuous variables distributions was checked with the Kolmogorov-Smirnov test. Variables were described by mean values, standard deviations and 2 proportion test. Considering the small number of patients in the groups, the non-parametric Mann-Whitney test was used for statistical differences analysis. Differences between the first and second assessment were assessed by the Wilcoxon test. Statistical analyses were made with STATA 11.

RESULTS

Analysis of the parameters obtained in the neuropsychological tests showed some improvement in neuropsychological assessment in both groups. In the research group, the participants achieved significantly improved results in both parts of the TMT test, the control group only in part B (Tab. 3-7). Comparing both groups, there

Table 3. Mean values and standard deviations in the Positive and Negative Syndrome Scale in the control and research groups

PANSS parameters	Group	Mean value	Standard deviation
Global score	research	47.34	13.99
	control	68.98	20.75
Positive scale	research	9.10	2.25
	control	14.45	7.10
Negative scale	research	13.68	5.99
	control	20.98	7.07
General psychopathology scale	research	24.59	7.14
	control	33.73	9.22



Table 4. Mean values and standard deviations in the Trail Making Test in the control and research groups in first and second assessments

	mean value/SD – time in seconds		p value	
	research group	control group	research group	control group
TMT part A first assessment	35.12 +/- 12.32	37.2 +/-15.24	0.02336	0.03047
TMT part A second assessment	33.8 +/-11.82	36.58 +/-20.54		
TMT part B first assessment	60.83 +/-27.67	86.28 +/-37.78	0.07262	0.00079
TMT part B second assessment	58.71 +/-27.63	76.1 +/-27.59		

Table 5. Mean values and standard deviations in the Stroop Test in the control and research groups in first and second assessments

	mean value/ SD		p value	
	research group	control group	research group	control group
Stroop I first assessment time in seconds	35.93 +/-11.46	31.53 +/-8.45	0.01093	0.2797
Stroop I second assessment time in seconds	34.66 +/-10.58	31.3 +/-9.11		
Stroop II first assessment time in seconds	65.56 +/-24.15	75.48 +/-33.93	0.00793	0.00684
Stroop II second assessment time in seconds	62.71 +/-20.91	63.08 +/-23.06		

Table 6. Scores of the two proportion test for the number of errors in the Stroop test. Comparison of control and research groups in first and second assessments

Stroop number of errors	control group first assessment		research group first assessment		p value	control group second assessment		research group second assessment		p value
	N	%	N	%		N	%	N	%	
0	17	42.50	18	43.90	0.4496	18	45.00	23	56.09	0.1606
1	6	15.00	6	14.63	0.4814	8	20.00	5	12.20	0.1710
2	5	12.50	3	7.32	0.2185	3	7.50	8	19.51	0.0593
3/more	12	30.00	14	34.15	0.3451	11	27.50	5	12.20	0.0438
Total	40	100.00	41	100.00		40	100.00	41	100.00	

Table 7. Mean values in the Wisconsin Sorting Card Test parameters in the control and research groups in first and second assessments

	research group/ first assessment MV	research group/ second assessment MV	p value	control group/ first assessment MV	control group/ second assessment MV	p value
total cards	112.22	98.27	0.00059	106.98	99.68	0.01008
total correct	74.85	69.44	0.05502	68.58	68.4	0.86152
total errors	37.37	28.83	0.00708	37.28	31.28	0.02466
perseverative responses	20.15	17.88	0.10854	30.03	17.25	0.00246
perseverative errors	17.9	15.59	0.10746	24.78	15.5	0.00256
non-perseverative errors	19.46	13.24	0.00944	13.53	15.78	0.97493
conceptual responses	64.66	61.54	0.21501	57.15	60.95	0.29642
categories completed	4.17	5	0.00123	4.43	4.83	0.23433
trials in the first category	23.02	22.2	0.69511	20.23	24.3	0.74943
failure to maintain the set	2.05	0.66	0.00078	1.18	0.85	0.52301
learning to learn	-3.43	-1.89	0.04173	-4.79	-3.15	0.04717

were no significant differences in the TMT test (Tab. 8). In the Stroop test, the research group made less errors in the second assessment; other significant results, however, were not attained. In the Wisconsin Cards Sorting Test, the research group improved their results in the following parameters: total cards, total correct, total errors, nonperseverative errors, conceptual responses level, categories complete, and failure to maintain set, learning to learn (Tab. 7). The control group improved their results in the following parameters: total cards, total correct, perseverative responses, perseverative errors and learning to learn.

In first examination, the research group obtained better scores than the control group in the parameters: total correct, perseverative responses, perseverative errors, nonperseverative errors, conceptual responses level and failure to maintain set. Statistical analysis of RehaCom results showed that the final results in both employed procedures were better than in the beginning, especially in the attention/concentration procedure.

For the purpose of the analysis of genetics, the research group was divided according to genotypes. Analysis of differences in RehaCom procedures scores did not show significant differences between the groups, but some slight tendencies were observe at the beginning attention/concentration procedure (Tab. 9-11). Subjects with G/G genotype (caused by polymorphism val/val) in BDNF started with better scores (from higher level of difficulty) than subjects with A/G genotype (caused by polymorphism val/met) ($p=0.0801$). Subjects with A/G genotype achieved a lower score than the others ($p=0.0550$), and subjects with G/G val/met genotype gained better scores than others in the same point ($p=0.0897$).



Table 8. P- values in TMT, Stroop and WCST parameters. Significant differences in the first and second assessments between control and research groups

control group/research group	Mann-Whitney Test
	p value
TMT part A	0.78014
first assessment /second assessment	0.66009
TMT part B	0.00007
first assessment /second assessment	0.00031
Stroop część pierwsza	0.10677
first assessment /second assessment	0.15886
Stroop part II	0.24131
first assessment /second assessment	0.62319
Stroop errors	0.7147
first assessment /second assessment	0.30184
WCST total cards	0.23293
first assessment /second assessment	0.57509
WCST total correct	0.07798
first assessment /second assessment	0.83515
WCST total errors	0.78405
first assessment /second assessment	0.33695
WCST perseverative responses	0.39731
first assessment /second assessment	0.58285
WCST perseverative errors	0.48990
first assessment /second assessment	0.50431
WCST nonperseverative errors	0.04494
first assessment /second assessment	0.41773
WCST conceptual responses	0.07254
first assessment /second assessment	0.83871
WCST categories completed	0.36883
first assessment /second assessment	0.92071
WCST trials in the first category	0.17849
first assessment /second assessment	0.95728
WCST failure to maintain the set	0.02806
first assessment /second assessment	0.56752
WCST learning to learn	0.54590
first assessment /second assessment	0.64407

Table 9. Results of the research group trained with RehaCom, concerning attention/concentration, and topological memory procedures

	START/mean value/SD	END/mean value/SD	p
topological memory level of difficulty	5.12 +/-1.83	8.95+/-3.36	0
attention/concentration level of difficulty	7.44 +/-2.88	22+/-3.18	0

Table 10. The Hardy-Weinberg equilibrium for control and research groups

	Group	Hardy-Weinberg equilibrium	
		Chi ²	p
BDNF	research	0.76	0.38274
BDNF	control	1.25	0.26438
COMT	research	3.29	0.06964
COMT	control	0.06	0.80028

Table 11. Significant values in statistical comparison of genetic groups trained in RehaCom procedures

Mann-Whitney Test							
start or end of procedure	compared groups			RehaCom procedure	p value	N1	N2
Start	BDNF	GG	AG	attention	0.0801	26	9
Start	-	all others	AG val/met	attention	0.0550	29	6
Start	-	all others	GG val/met	attention	0.0897	20	15

DISCUSSION

Some researches have confirmed improvement of cognitive functioning (especially executive functions: working memory and attention), measured with neuropsychological tests [19, 23, 24]. Unfortunately, in most of such researches the results were not compared with those of the untrained control groups of schizophrenic patients. In the presented study, significant differences in neuropsychological tests between research and control groups were not confirmed. This could be explained by the limited battery of tests, or too short time of training. Applying a wider battery of tests could be useful in the assessment of more subtle deficits, and further in verifying them in a second examination.

Some researchers have already used the RehaCom as a tool probably useful for cognitive rehabilitation. Similar results have been obtained by Pflieger using RehaCom in a group of patients with diagnosed schizophrenia and trained with RehaCom for 7 weeks. The procedures used were identical to those in the presented study – attention concentration and topological memory. The patients tested neuropsychologically improved their results in the final assessment [19]. Dellagi et.al presented the case study of patient who was also trained with RehaCom, and who had improved results in the neuropsychological tests, PANSS and social functioning [24]. In other research, scientists used even 4 procedures, and to assess eventual improvement of cognitive functioning used not only neuropsychological tests but also social functioning scales and PANSS. The authors confirmed improvement in every examined dimension [25]. RehaCom was also used by An et al. with the attention concentration procedure. The conclusion was also encouraging for using such methods in trying to help patients improving their cognitive functions [23]. In the presented study, it was not possible to compare the scores of PANSS and social functioning quality after training. The PANSS groups were assessed only at the beginning of study to compare them, because the influence of training on positive or negative symptoms was not taken into consideration.

A meta-analysis conducted by McGurk et al. in 2007 showed that methods of cognitive rehabilitation produce moderate improvements in cognitive functioning and, together with psychiatric rehabilitation, can also positively influence functional outcomes [26]. The meta-analysis contains data of 26 randomized, controlled trials of cognitive remediation in schizophrenia in a group of 1,151 patients. The results suggest that the cognitive training was associated with significant improvements:

- medium effect size for cognitive performance (0.41);
- lower effect size for psychosocial functioning (0.36);
- small effect size for symptoms (0.28).



The effects of cognitive remediation on psychosocial functioning were stronger in studies that combined psychiatric rehabilitation with cognitive remediation [26]. In the presented study, cognitive rehabilitation was combined with pharmacological treatment and psychiatric rehabilitation, which finally resulted in slightly improved cognitive functioning.

Considering BDNF and COMT, there are many researches proving that schizophrenic patients characterized by some polymorphisms obtain better scores in cognitive tests. In the presented study, the patients were analysed according to their success in cognitive rehabilitation procedures.

Patients described as G/G genotype in BDNF started from a higher level of difficulty than patients with A/G genotype. The explanation could be that polymorphism BDNF Val66Met has a possible negative influence on cognitive functioning.

Subjects with A/G (BDNF) val/met (COMT) genotype gained a lower score than the others, and subjects with G/G (BDNF) val/met (COMT) genotype gained better scores than others at the same point. The COMT gene with functional polymorphism 108/158 (Val58Met) is possibly a factor conditioning better cognitive functioning through decreasing activity of the enzyme decomposing dopamine in the prefrontal cortex. In these conditions, the G/G (BDNF) val/met (COMT) genotype can especially positively influence cognitive performance. At the end of training, there were no significant differences between groups. Unfortunately, the authors of the presented study did not find any similar publications, and therefore did not have the possibility to compare research results with other researches.

The study has its limitations: a battery of neuropsychological tests that was too limited, short time of cognitive training, and a low number of patients in the genetic part of study; however, the number was sufficient to perform statistical analysis, but not to draw final conclusions.

CONCLUSIONS

In contrast to some previous publications, cognitive rehabilitation produces moderate improvement in cognitive functioning.

RehaCom procedures apparently can be useful in neuropsychological rehabilitation of cognitive dysfunctions in patients with diagnosed schizophrenia.

A comprehensive treatment using also new technologies supporting pharmacological treatments and other therapies should show results in increased cognitive functioning, and in consequence improve the quality of a patient's life.

Analysis of genes' polymorphisms cannot at the present time be treated as a prognostic factor for neuropsychological rehabilitation success, because statistical analyses showed few dependences with little statistical significance.

Acknowledgments

The study was supported by the Ministry of Higher Education Grant No. N N402020335.

REFERENCES

- Konorski J. Conditioned reflexes and neuron organization. Tr. from the Polish ms. under the author's supervision. Cambridge University Press 1948: 98.

- Caspi A, Reichenberg A, Weiser M, Rabinowitz J, Kaplan Z, Knobler H, et al. Cognitive performance in schizophrenia patients assessed before and following the first psychotic episode. *Schizophrenic Res.* 2003; 65: 87-94.
- David AS, Malmberg A, Brandt L, Allebeck P, Lewis G. IQ and risk for schizophrenia: a population-based cohort study. *Psycho Med.* 1997; 27: 1311-23.
- Fuller R, Nopoulos P, O'Leary D. Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. *Am J of Psychiatry.* 2002; 159: 1183-89.
- Jones P, Rodgers B, Murray RM. Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet.* 1994; 344: 1398-402.
- Keefe RS, Eesley CE, Poe MP. Defining a cognitive function decrement in schizophrenia. *Biol Psychiatry.* 2005; 57: 688-91.
- Green MF, Kern RS, Braff DL. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull.* 2000; 26: 119-36.
- Carter CS, Robertson LC, Nordahl TE, Chaderjian M, Oshora-Celaya L. Perceptual and attentional asymmetries in schizophrenia: further evidence for a left hemisphere deficit. *Psychiatry Res.* 1998; 62: 111-119.
- Goldman-Rakic P. Prefrontal cortical dysfunction in schizophrenia. The relevance of working memory. *Psychopathology and brain.* New York, Raven Press, 1991.
- Pierri JN, Volk CL, Auh S, Sampson A, Lewis DA. Somal size of cortical pyramidal neurons in schizophrenia: differential effects across neuronal populations. *Biol Psychiatry.* 2003; 54: 111-20.
- Selemon LD, Goldman-Rakic PS. The reduced neuropil hypothesis: a circuit based model of schizophrenia. *Biol Psychiatry.* 1999; 45: 17-25.
- Everett J, Lavoie K, Gagnon J, Gosselin N. Performance of patients with schizophrenia on the Wisconsin Card Sorting Test (WCST). *J Psychiatry Neurosci.* 2001; 26: 123-30.
- Perlstein WM, Elbert T, Stenger VA. Dissociation in human prefrontal cortex of affective influences on working memory-related activity. *Proc Natl Acad Sci USA* 2002; 99: 1736-41.
- Rybakowski JK, Borkowska A, Czerski PM, Hauser J. Performance on Wisconsin Card Sorting Test and polymorphism of DRD3 and COMT gene in schizophrenic patients. *Mol Psychiatry.* 2001; 6: 718-24.
- Egan MF, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci. USA* 2001; 98: 6917-6922.
- Hariri AR, et al. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *J Neurosci.* 2003; 23: 6690-6694.
- Regel H, Fritsch A. Evaluationsstudie zum computergestützten Training psychischer Basisfunktionen. Abschlussbericht zum geförderten Forschungsprojekt. Bonn: Kuratorium ZNS 1997.
- Mateer CA. The rehabilitation of executive disorders. In *Cognitive neurorehabilitation* D.T. Stuss, G. Winocur & I. H. Robertson. London: Cambridge University Press 1999.
- Pfleger U. Computerunterstütztes kognitives Trainingsprogramm mit schizophrenen Patienten. Münster/New York: Waxmann – Internationale Hochschulschriften 1996; Bd. 204.
- Sablier J, Stip E, Franck N. Cognitive remediation and cognitive assistive technologies in schizophrenia. *Encephale.* 2009; 35: 160-7.
- Everitt BS, Vessely S. *Clinical Trials in Psychiatry*, 2nd Edition. Wiley, January 2008.
- Jarema M, Kiejna A, Landowski J, Meder J, Rabe-Jabłońska J, Rybakowski J. Standardy leczenia farmakologicznego schizofrenii. *Psychiatr Pol.* 2006; 6: 1171-6.
- An SK, Oh BH, Hyun MH, Yoo KJ. The Effect of Attention Training Using Computer-Aided Cognitive Rehabilitation Program (REHACOM) in Chronic Schizophrenics. *J Korean Neuropsychiatry Assoc.* 1997; 36: 72-79.
- Dellagi L, Ben Azouz O, Johnson I, Kebir O, Amado I, Tabbane K. Cognitive remediation therapy in schizophrenia: a case report. *Tunis Med.* 2009; 87: 660-3.
- Cochet A, Saoud M, Gabriele S, Broallier V, El Asmar C, Daléry J, et al. Impact of a new cognitive remediation strategy on interpersonal problem solving skills and social autonomy in schizophrenia. *Encephale.* 2006; 32: 189-95.
- McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A Meta-Analysis of Cognitive Remediation in Schizophrenia. *Am J Psychiatry.* 2007; 164: 1791-802.

