INVESTIGATION OF COGNITIVE DYSFUNCTIONS IN PATIENTS WITH BIPOLAR AFFECTIVE DISORDER, SCHIZOPHRENIA, THEIR RELATIVES AND CONNECTION WITH SOME GENETIC MARKERS

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Abstract. The current study is about cognitive dysfunctions in patients with bipolar affective disorder and schizophrenia and is focused on the genetic markers of these cognitive dysfunctions. 132 people are investigated and divided in the following groups: patients with schizophrenia and bipolar affective disorder, their healthy relatives and controls without relatives with psychiatric disorder. The cognitive status is investigated with a test battery, which contains Trail Making Test (TMT-A and B), Digit Symbol Test (DST) and Verbal Fluency Test (VFT). Demographic and clinical data are collected with semi structured interview Diagnostic Interview for Psychosis (DIP). The genetic analysis is conducted in collaboration with the Centre of Molecular Medicine in MU Sofia. The statistics is used to check the distributio,to compare mean values and also correlation analysis, regression analysis logistic regression and other methods are used.

Results. The cognitive dysfunctions are more pronounced in schizophrenic patients than in pat ientswith bipolar affective disorder. The healthy relatives of the patients with schizophrenia and bipolar affective disorder have significant differences in the cognitive capacity compared to controls, which have no relatives with psychiatric disorder.

Some of the investigated genetic polymorphisms (rs12363494)have a great impact on the cog nition.

Key words: bipolar affective disorder, cognitive dysfunctions, genetic markers, polymorphis ms, rs12363494, MUC5B

INTRODUCTION

Bipolar Affective Disorder (BAD) and schizophrenia are chronic disorders with big social significance. More schizophrenia, but also bipolar affective disorder leads to limitations in the possibilities of social adaptation and slow working capacity. One of the leading causes for these disease consequences are impairments in the cognitive abilities associated with these disorders, such as impairments in attention, memory, executive functions. In the last decades, the scientific view on the lack of cognitive impairments in bipolar affective disorder has changed. Evidences for significant changes in cognition not only in schizophrenia, but also in bipolar affective disorder were found. The cognitive changes in patients with bipolar affective disorder are not so great, as in schizophrenia, but are an indisputable fact. The etiology of these impairments in both disorders is still unclear. The efforts of the scientific community are directed towards search for the genetic basis of both the etiology of these disorders and of cognitive impairment in particular.

The aim of the present work is to investigate the cognitive impairments in bipolar affective disorder and schizophrenia and the putative genetic causes of these impairments. The results of the conducted cognitive tests, which reflect the impairments, are presented. The results of the genetic tests performed on patients with both disorders and their relatives are also presented. The results of the patients and their relatives were compared with the results of the controls.

MATERIALS AND METHODS

The present study has a cross-sectional design and is carried out in cooperation with the Center for molecular medicine at the Medical University - Sofia. A 10 ml venous blood was taken from patients and controls for genetic analysis. The research is a part of an international project with the participation of a scientific team from Cardiff University and the Center for molecular medicine, Sofia University. Inclusion criteria for patients were: men and women over 18 years of age with diagnosed bipolar affective disorder or schizophrenic disorder according to ICD-10 diagnostic criteria (in remission to the time of the study). The exclusion criteria: presence of organic mood disorder, mood disorder, due to the use of psychoactive substances or other medications, diagnostic uncertainty. For the group of controls respectively including criteria: men and women over the age of 18, with or without a relation to the patients, exclusion criteria: presence of a mental disorder according to the ICD-10 diagnostic criteria. All procedures were performed after signing an informed consent in accordance with international ethical requirements. The Diagnostic Interview for Psychosis (DIP) - a semi-structured interview [1] was used to establish a diagnosis and data on the course of the disease. Cognitive status was assessed with the Trail Making Test – A, B (TMT-A, TMT-B) [2], Digit Symbol Test (DST) [3], Verbal Fluency Test (VFT) [4]. Genetic methods include DNA extraction and targeted next-generation sequencing. DNA extraction was performed at the Center for Molecular Medicine, Sofia University, using a semi-automated magnetic particle isolation system (Chemagic Magnetic Separation Module). A panel of 187 genes was used for next-generation sequencing. Targeted sequencing was performed in collaboration with a team from the Institute of Medical Psychology and Clinical Neurosciences in Cardiff, Wales. The panel includes candidate genes encoding sodium and calcium channels related to neurotransmitter systems such as dopaminergic, serotonergic and glutamatergic, and genes related to synaptic plasticity. The panel also includes genes found in genome-wide association studies or that overlap between several different phenotypes and are relevant to neurocognitive functions. The statistical processing of the results is performed using SPSS – 19. Methods for examining distributions, comparing means, correlation analysis, regression analysis, logistic regression, and others were used.

RESULTS

The distribution of study participants by sex, diagnosis, age, and consanguinity is demonstrated in Table 1.

gender	Controls non-relatives	Controls Relatives	Bipolar disorder	Schizophrenia	Total
male					
number	5	12 (sch-5; bd-7)	15	28	60
age					
mean	25,67 sd 4,9	26,52 sd 5,1	30,73 sd 5,2	29,79 sd 5,0	28,73 sd 5,0
Female					
number	6	14 (sch-6; bd-8)	27	25	72
age					
mean	26,25 sd 4,5	27,35 sd 4,7	30,78 sd 5,4	29,56 sd 5,1	28,86 sd 5,0
Total					
number	11	26	42	53	132
age					
mean	26,11 sd 4,7	26,93 sd 5,0	30,76 sd 5,3	29,68 sd 5,0	28,85 sd 5,0

Table 1. Distribution of participants by gender, diagnosis, consanguinity and age

Controls in the present study were divided into two groups. The first group was healthy participants (controls) who have a first- or second-degree relative with a person with schizophrenia or bipolar affective disorder. The second group of controls was composed of healthy participants who were not related to a mentally ill person. This division was necessitated by the objectives and nature of the study. No statistical differences were found between controls and relatives of patients when solving BMT-A, although controls completed the test on average 22 seconds faster. The differences between the controls and the two groups of patients were significant, with the greater difference between the controls and the schizophrenic patients (58 sec on average). An interesting finding is that there was no statistically significant difference between healthy relatives and patients with bipolar disorder (p=0.986). Our data show that the tested TMT-A cognitive functions were affected to a small extent in patients with BAD, and also in the relatives of patients with BAD and schizophrenia. However, the relatives performed significantly better than the schizophrenic patients (p=0.016). The difference between bipolar and schizophrenic patients was also statistically significant (table 2).

Test	Participants	Difference in means	Standard deviation	Significance
Тмт-А	Contr. unrelated/Contr. relatives	-22,792	11,977	0,229
	Contr. unrelated/BAD	-26,927	6,824	0,001
	Contr. unrelated/schizophr.	-58,014	6,267	0,000
	Contr. relatives/BAD	-4,135	12,124	0,986
	Contr. relatives/schizophr.	-35,222	11,819	0,016
	BAD/Schizophr.	-31,087	6,543	0,000
Тмт-В	Contr. unrelated/Contr. relatives	-43,122	34,068	0,586
	Contr. unrelated/BAD	-75,928	19,412	0,001
	Contr. unrelated/schizophr.	-170,246	17,826	0,000
	Contr. relatives/BAD	-32,806	34,486	0,777
	Contr. relatives/schizophr.	-127,125	33,619	0,001

	BAD/Schizophr.	-94,319	18,612	0,000
DST	Contr. unrelated/Contr. relatives	14,490	2,866	0,000
	Contr. unrelated/BAD	20,632	1,633	0,000
	Contr. unrelated/schizophr.	27,998	1,500	0,000
	Contr. relatives/BAD	6,142	2,901	0,150
	Contr. relatives/schizophr.	13,508	2,828	0,000
	BAD/Schizophr.	7,367	1,566	0,000
VFT	Contr. unrelated/Contr. relatives	5,341	1,466	0,002
	Contr. unrelated/BAD	5,577	0,835	0,000
	Contr. unrelated/schizophr.	9,518	0,767	0,000
	Contr. relatives/BAD	,236	1,484	0,999
	Contr. relatives/schizophr.	4,177	1,447	0,022
	BAD/Schizophr.	3,941	0,801	0,000

Table 2. Comparison of the results of the different groups of participants in the study when solving the cognitive tests

The results of the test of executive functions (TMT-B) were similar. There was no statistically significant difference between controls and healthy relatives (p=0.586). The minus sign indicates that the controls were about 43 seconds faster on the test. No statistical difference was found between relatives of patients and patients with BAD (p=0.777), but such a difference was present between controls and patients with BAD (p=0.001). Patients with schizophrenia performed statistically significantly worse than all other groups. The DST showed results that were significantly different from the above two tests. A significant difference was observed between controls and relatives of patients (p<0.000). The absence of a statistically significant difference between the relatives and patients with BAD is also striking (p=0.150). We can conclude that in terms of attention and working memory, relatives of patients were affected to a degree close to that of patients with bipolar disorder. The sign in front of the mean values is positive, because in the cases of DST and VFT, the larger result is the better, in contrast to TMT-A and B, where the smaller number of seconds is the better result (table 2). In verbal fluency, we again found a statistically significant difference between controls and relatives of patients (p=0.002). Controls did significantly better than both groups of patients. Relatives and patients with BAD were presented in an absolutely equal way. This was proved from the difference in means equal to 0.236 and the p-value which was approximately one (p=0.999). This result was very similar to the DST result. We can say that in terms of verbal fluency, relatives of patients were affected commensurately with patients with bipolar disorder. Patients with schizophrenia were again the most affected. The difference in means between schizophrenics and controls was approximately 10 enumerated animals in favor of controls.

When comparing the results of relatives of bipolar patients with those who are relatives of schizophrenic patients, no statistically significant differences were found between the two groups (table 3).

Participants	Test	Mean values	Standard deviation	Significance
Relatives - BAD	Тмт-А	25,48sec.	6,36	0,723
Relatives – schizophrenia		24,66sec.	7,90	
Relatives - BAD	Тмт-В	49,44sec.	17,38	0,467
Relatives – schizophrenia		45,46sec.	14,99	
Relatives - BAD	DST	53,60sym.	10,82	0,127
Relatives – schizophrenia		58,42sym.	5,28	
Relatives - BAD	VFT	25,32an.	5,75	0,748
Relatives – schizophrenia		24,71an.	5,31	

Table 3. Comparison of cognitive test scores of relatives of bipolar patients with those who are relatives of schizophrenic patients

In the present study, we compared high school graduation success in controls, healthy relatives of patients, and patients. All patients were free of clinical manifestations of mental disorder at the time of high school graduation. Table 4 shows that patients (bipolar and schizophrenic in one group) had the lowest success rate, followed by their relatives, and controls with no patient relatives had the highest success rate.

Participants	**Difference in means**	**Standard deviation**	**Significance**
Controls unrelated/controls related	0,65	0,20	0,004
Controls unrelated/patients	1,14	0,19	0,000
controls related/ patients	0,49	0,16	0,008

Table 4. Comparison of high school achievement among controls, relatives of patients, and patients

It can be assumed that the patients had some cognitive problems even before the clinical manifestation of the disease. On the other hand, the difference in mean success between controls and healthy relatives was greater than the difference between relatives and patients (before they got sick). In other words, in terms of average school performance, the results of healthy relatives were closer to these of the patients than to controls.

Table 5 presents a comparison between patients with schizophrenia and bipolar disorder. Patients with schizophrenia had less success than patients with bipolar disorder.

Participants	**Difference in means**	**Standard deviation**	**Significance**
Patients with schizophrenia/patients with bipolar disorder	0,40	0,11	0,009

Table 5. Comparison of high school achievement between patients with schizophrenia and patients with bipolar disorder

Together with the Center for Molecular Medicine at MU-Sofia, we looked for a relationship between the results in solving the cognitive tests and the success in finishing school of the participants, on the one hand, and the presence of certain polymorphisms in candidate genes,

on the other. The polymorphisms we investigated were selected as a result of sequencing a panel of 187 candidate genes, jointly with Cardiff University, associated with schizophrenia and bipolar affective disorder. These genes are genes encoding electrolyte channels, neurotransmitter systems, participants in synaptic plasticity and related to neurocognitive functions. Table 6 presents the frequency of variants according to diagnoses.

Polymorphism	Gene	Controls	Number BD	Number sch.	Total
rs140604077	LAMA2	1 (relative)	0	1	2
rs41280102	SCN4A	2 (relative)	2	6	10
rs12363494	MUC5B	1(relative) 2(non-relative)	9	9	21
rs1433652	WDR55	1 (relative)	0	2	3
rs41285288	LAMA2	1 (non-relative)	1	2	4
rs765685405	CACNA1S	1 (relative)	0	2	3
rs117843717	SHANK2	1 (relative)	0	3	4
rs202161651	MUC5B	0	0	2	2
rs373965587	MUC6	0	0	1	1
rs376920234	DLGAP2	0	0	1	1
rs137853319	FLNA	0	0	1	1
rs991492074	IQSEC1	0	0	1	1
rs376744130	GSN	0	1	0	1
Total 13	13	10	13	31	44

Table 6.The frequency of established single nucleotide polymorphisms according to diagnosis

It is noteworthy that most polymorphisms occurred only in patients but none only in controls. Two of the polymorphisms were found in patients and in healthy controls. The term Single-nucleotide polymorphism (SNP) refers to the replacement of one nucleotide, which is located at a specific position in the human genome, with another, which is observed with different frequencies in different populations.

We examined the influence of the different polymorphisms on the participants' test-solving results (all groups in total). Through linear regression, we identified several polymorphisms that showed a statistically significant association with cognitive ability. The first of them was polymorphism rs12363494 in the MUC5B gene, which negatively affects cognitive abilities ($p<0.000$). The other polymorphism with a similar effect was rs765685405 in the CACNA1S gene ($p=0.031$). On the other hand, the rs1433652 polymorphism in the WDR55 gene was likely to have a positive effect on cognitive abilities, as shown by the opposite sign in front of the coefficient "B" ($p=0.048$) (Table 7).

Polymorphism	Coefficient B	Stand. deviation	Stand. Coeff. β	Significance (P)
rs140604077	-4,651	3,535	-0,077	0,189
rs41280102	1,655	1,353	0,072	0,222
rs12363494	4,245	0,869	0,275	0,000
rs1433652	-6,711	3,379	-0,112	0,048
rs765685405	5,038	2,321	0,145	0,031
rs117843717	-,899	3,276	-0,021	0,784
rs41285288	-,336	1,898	-0,010	0,860
rs376744130	5,884	3,276	0,098	0,074
rs137853319	3,324	4,005	0,055	0,407

rs202161651	2,092	3,276	0,035	0,524
rs373965587	5,353	4,625	0,089	0,248
rs991492074	-0,713	0,901	-0,021	0,672
rs376920234	-1,564	1,723	-0,097	0,365

Table 7. Influence of polymorphisms on cognitive abilities (total result of solving the four tests, reduced to Z-score)

When checking the influence of polymorphisms on the average success from secondary education, rs12363494 in the MUC5B gene and rs765685405 in the CACNA1S gene were striking, which also significantly affected the performance of cognitive tests (p=0.047 and p=0.092, respectively). Another confirmation of the possibility that cognitive impairments manifest themselves at a young age, even before the clinical manifestation, and therefore affect the ability to achieve higher success in school. The data are presented in Table 8.

Polymorphism	Coefficient B	Stand. deviation	Stand. Coeff. β	Significance (P)
rs140604077	0,983	0,938	0,086	0,296
rs41280102	-0,222	0,339	-0,041	0,513
rs12363494	-0,433	0,218	-0,111	0,047
rs1433652	0,118	0,629	0,013	0,851
rs765685405	-1,049	0,621	-0,112	0,092
rs117843717	-0,049	0,877	-0,004	0,956
rs41285288	-0,615	0,508	-0,076	0,227
rs376744130	0,301	0,877	0,019	0,732
rs376920234	-1,564	1,723	-0,097	0,365
rs202161651	-0,749	0,877	-0,066	0,394
rs373965587	0,820	1,239	0,051	0,508
rs991492074	-0,713	0,901	-0,021	0,672
rs137853319	-0,552	0,871	-0,045	0,459

Table 8. Influence of polymorphisms on the average success rate at the completion of secondary education

The sign in front of the coefficient "B" of the negatively influencing polymorphisms here was negative, since their presence was associated with lower success, i.e. "move" in opposite directions. Some of the polymorphisms that were studied caught our attention, so we think it is appropriate to highlight them in a separate Table 9.

Polymorphism	Gene	Role in relation to cognitive abilities
rs12363494	MUC5B	Harmful
rs765685405	CACNA1S	Harmful
rs1433652	WDR55	Protective

Table 9. Polymorphisms in candidate genes showed significant association with certain cognitive characteristics

Regarding the functions of the described genes, we will mention that MUC5B encodes one of the members of the mucin protein family, its expression in the brain was found in the neuronal cells of the cortex and the neuronal cells of the caudate body. It is possible that mucins are

expressed by the neuroepithelial lining of the ventricular system of the brain and of the central canal of the spinal cord. CACNA1S encodes a protein that is a member of the calcium voltage-gated ion channel family. WDR55 encodes WD repeat-containing protein 55. This protein is a core modulator of ribosomal RNA biogenesis, cell cycle progression, and organ development.

DISCUSSION

In her dissertation work on cognitive disorders in patients with bipolar affective disorder, Pandova notes that the cognitive profile of patients with BAD type 1 is characterized by a small number of specific, qualitatively distinguishable and quantifiable impairments of memory, attention, executive functions and speed of processing the information [5]. The author also registered cognitive problems in first-degree relatives of patients with bipolar affective disorder. Previous research on the cognitive abilities of patients with schizophrenia compared to healthy controls, in which the average age of patients and controls was 25 years, was conducted in 2009 [6]. The study is a meta-analysis of 47 studies on cognitive impairment in patients with first-episode schizophrenia. The total number of patients was 2,204 and controls were 2,775. The authors found significant neurocognitive impairments in patients with first-episode schizophrenia in 10 neurocognitive domains. It is concluded that neurocognitive impairments in patients with a first schizophrenic attack are widely and demonstratively represented. Verbal memory and procedural speed are most affected. In addition, in a large proportion of patients, general intelligence appears to be affected compared to a premorbid level. We present the cited study because of the compact and young sample, which is similar to ours in mean age. In search of endophenotypes in bipolar disorder, Bora, Yucel and Pantelis summarized in a meta-analysis 45 studies on cognitive impairment in patients with bipolar affective disorder - a total of 1423 patients and 17 studies on the cognitive abilities of first-degree relatives of patients with bipolar affective disorder - a total of 433 participants [7]. The authors found that common domains in the cognitive impairment of patients and patients' relatives were attention switching, verbal memory, and attention concentration. On the other hand, procedural speed, visual memory and verbal fluency were only affected in the patient group according to the cited meta-analysis. A similar meta-analysis examining cognitive impairment in relatives of schizophrenic patients was published by Sitskoorn et al., 2004. 37 studies that compared 1639 healthy relatives of schizophrenic patients with 1380 controls were included. The largest differences between the two groups were found in verbal memory (similar to relatives of patients with bipolar disorder) and executive functions. In attention, differences between controls and relatives were not as large as in the first two domains [8]. The authors hypothesize that the differences are due to the predisposition to schizophrenic disorder in relatives of schizophrenic patients as an expression of phenotype. It is emphasized that the results cannot be directly addressed to specific genetic markers. Zammit et al. (2004) set out to investigate in a longitudinal study the influence of the premorbid level of intelligence on the risk of developing schizophrenia, bipolar affective disorder and depressive disorder [9]. The cited study is a retrospective cohort of medical histories of patients followed over a 27-year period. The study group included 50,087

participants with various psychiatric illnesses, and conclusions about premorbid level of functioning were based on the studied intellectual quotient, taking into account other social and psychological data about the participants. The following results are obtained: lower premorbid IQ is associated with an increased risk of developing schizophrenia, major depressive disorder and other non-affective psychoses, but not with developing bipolar affective disorder. The level of intelligence is inversely proportional to the risk of developing schizophrenic disorder. Based on the results, the authors conclude that, to a certain extent, bipolar affective disorder is distinguished in the context of neurodevelopment theory from the others (schizophrenic disorder, non-affective psychoses, and major depressive disorder).

In recent decades, the efforts of the scientific community have been highly concentrated on the search of the influence of different genes and variants in them on the clinical picture and the course of various mental disorders. This trend is especially true for severe mental disorders. In the present study, together with the Center for Molecular Medicine at the Sofia University, we investigated the frequency and influence of certain rare genetic variants on the cognitive abilities of patients and controls. In general, the selected variants are rare and therefore not found in all participants. We found that certain polymorphisms (rs12363494 and rs765685405) negatively affect cognitive ability and success in completing secondary education. However, other polymorphisms (rs1433652) may have a protective effect on cognition. Scientific data on the influence of polymorphisms in certain genes on the cognition of patient groups are not many. The vast majority of studies look for an association between gene polymorphisms and the diseases themselves, but do not detail their impact on cognitive abilities. A cognition-focused study on the impact of gene polymorphisms was conducted in 2013. In it, the authors focused on polymorphisms in the D3 receptor genes, in the dopamine transporter SLC6A3, the vesicular monoamine transporter SLC18A2, the catechol-ortho-methyl transferase COMT and the dopamine beta-hydroxylase DBH [10]. An association was found between schizophrenic disorder and polymorphisms rs7631540, rs2046496 in the D3 receptor, as well as with rs363399, rs10082463 in SLC18A2, rs4680, rs4646315, rs9332377 in COMT. The study included 601 trios, 468 controls and 118 trios-controls. A slight association was found between rs10082463 in SLC18A2 and psychomotor functions and of rs363285 with executive functions examined with BMT, but after analytical corrections these associations were not confirmed. In a genome-wide association study conducted by Wong et al. (2017), found an association of two variants in the MUC5B gene with depression [11]. The CACNA1S gene has not yet been associated with psychiatric diseases. Product of gene expression is the alpha subunit of Cav1.1 ion channels. They are found most often in the transverse tubules of muscle tissue. Mutations in CACNA1S lead to hypokalemic periodic paralysis, predisposition to malignant hyperthermia, and predisposition to thyrotoxic periodic paralysis [13, 14]. An important paralog of the CACNA1S gene is CACNA1C. Paralogs are known to be homologous genes that arose through duplication mechanisms and encode proteins with similar but non-identical functions. The CACNA1C gene, in turn, encodes the alpha subunit of Cav1.2 ion channels. This category of calcium channels is found in the brain and more specifically in the dendrites and cell body of neurons. In recent years, there has been growing evidence of an association of Cav1.2 with psychiatric disorders. In a genome-wide association study, the statistically strongest result for association with mental disorders was

obtained for rs1006737 in the CACNA1C gene [15, 16]. Another genome-wide association study conducted by the Psychiatric Genomics Consortium found an association for another variant rs4765905 in the CACNA1C gene [17].

In recent years, the number of studies that are looking for the answer to the question: "Which is the gene of the psychiatric diseases?" are extremely a lot. We want to emphasize that one of the goals of the present work was to look for an association between certain polymorphisms in candidate genes and cognitive disorders, but not between gene polymorphisms and a certain disorder.

CONCLUSION

Patients with bipolar affective disorder and schizophrenic disorder had distinct and statistically significant impairments in cognitive abilities compared to healthy controls. Cognitive impairments in schizophrenic patients were quantitatively more pronounced than those in patients with bipolar disorder. Healthy relatives of patients with schizophrenia and bipolar affective disorder had significant differences in cognitive ability compared to unrelated controls. Cognitive disorders were observed even before the clinical manifestation of the disease in both groups of patients, which is judged by their significantly lower success rate at the end of secondary education. There was no statistically significant difference between the cognitive impairments in the relatives of the two groups of patients (patients with schizophrenic disorder and patients with bipolar disorder). Some rare polymorphisms in the MUC5B genes, CACNA1S and WDR55 genes, were associated with cognitive ability.

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