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Neurocognitive Endophenotypes of Schizophrenia and Bipolar Disorder and Possible Associations with FKBP Variant rs3800373

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ABSTRACT

Introduction: Schizophrenia(SCZ) and Bipolar disorder (BD) are frequently occurring and impairing disorders that affect around 1% of the population. Important endophenotypes in the genetic research of SCZ and BD are cognitive functions. Core symptoms for SCZ and BD are impairments in working memory, declarative memory and attention, all of which fulfill the criteria for an endophenotype. The FK506 Binding Protein 5 (FKBP5) gene codes for a co-chaperone of the glucocorticoid receptor and has been reported to be associated with cognition. **Aim:** The aims of our research were to determine the degree of cognitive impairment in patients suffering from SCZ and BD and to explore the association of the FKBP5 variant rs3800373 genotype with the cognitive endophenotypes. **Material and Methods:** Patients and healthy controls were recruited over a period of two years from the Psychiatric Clinic, Clinical Center University of Sarajevo. Genotyping and neuropsychological assessments were performed for 263 subjects (129 SCZ, 53 BD, and 81 healthy controls [HC]). Neuropsychological assessments were performed for all patients with the Trail Making Test-A&B (TMT-A&B) and Digit-span forward&backwards tasks. The single nucleotide polymorphism (SNP) rs3800373 in the *FKBP5* gene was genotyped using Infinium PsychArray Bead Chips. **Results and Conclusion:** SCZ and BD patients performed lower than HC in the TMT-A&B and in the Digit-span backwards task, while no differences were observed between SCZ and BD patients. While SCZ patients performed lower than HC in the Digit-span forwards task, there were no differences between BD and HC or between BD and SCZ. Rs 3800373 was not associated with performance in the TMT-A&B or Digit-span forwards&backwards tasks. SCZ and BD share largely overlapping neurocognitive characteristics. Rs3800373 was not associated with performance in the neuropsychological tests. However, given the limited sample size, the results do not exclude an association with the rs3800373 variant in a larger sample. Furthermore, as the analysis was limited to one SNP, the results cannot be generalized to other genetic variants in *FKBP5*.

Keywords: Schizophrenia, endophenotypes, bipolar disorder, *tacrolimus binding protein 5.*

1. INTRODUCTION

Schizophrenia (SCZ) and bipolar disorder (BD) are complex disorders with overlapping clinical symptoms and genetic factors. Studies on SCZ and BD have explored genotype-endophenotype relationships (1, 2)). Research findings have indicated that SCZ and BD overlap both in their clinical symptoms and in certain hereditary features (3), including genetic-molecular risk variants (4). Further studies have examined the similarities and differences in cognitive impairment, neurophysiology, and damage to certain areas of the brain in SCZ and BD patients (5). Identifying disease-related genetic variants is one major focus in psychiatric research, with implications for the diagnostic boundaries of disorders and the development of a better psychopharmacological treatment.

Recent studies have shown the influence of specific genetic variations in the FK506 binding protein 5 gene (*FKBP5*), which codes for the FKBP51 protein. FKBP51 binds heat shock protein 90 (Hsp90) a chaperone of the glucocorticoid receptor. At Hsp90, FKBP51 competes with FKBP52, a homologue of FKBP51. The Hsp90 / glucocorticoid receptor complex bound to FKBP52 is preferentially transferred to the nucleus. In the nuclear compartment, Hsp90 dissociates and the glucocorticoid receptor drives gene expression of

glucocorticoid-responsive genes. Self-regulation of the glucocorticoid effects on transcription occurs because glucocorticoid receptors also induce *FKBP5* gene expression, which in turn leads to a diminished nuclear import of Hsp90-glucocorticoid receptor complexes (6). By these processes, FKBP51 is thought to affect the sensitivity of glucocorticoid receptors.*FKBP5* has been implied in gene-environment interactions for the development of psychiatric disorders (7), e.g. BD (8) and endophenotypes such as impaired cognitive function in SCZ (9). The hypothalamus-pituitary-adrenal (HPA) axis mediates the stress response through regulation of cortisol. The well-established relationship between the HPA axis and psychotic disorders is consistent with the above mentioned findings. It has been shown that polymorphisms rs3800373, rs9296158, and rs1360780, which are located in close linkage disequilibrium within *FKBP5* (see Supplementary information), are associated with increased risk of depression (10) and PTSD (11, 12), as well as with a better response to antidepressants in patients suffering from depression (13). Furthermore, rs3800373 has been linked to inadequate normalization of cortisol secretion in healthy individuals after psychosocial stress (12, 14). In line with this, changes *FKBP5* expression in the brains of patients suffering from SCZ and BD were observed (15). SCZ and BD, however, are comparably broad diagnostic categories. The association findings may therefore be refined by testing for association with more homogeneous groups or with endophenotypes of SCZ and BD. This may increase the understanding of the causal pathways from specific genetic variant to specific disorder and give further insight into the association findings that cross diagnostic boundaries.

Several neuropsychological measures have been suggested as promising endophenotypes to test the genetic underpinnings of SCZ and BD. Notably deficits in working memory,declarative memory and attention deficits (16-21) have been observed.

2. AIM

The aim of our research was to explore the degree of cognitive impairment in patients suffering from SCZ and BD. Furthermore we assessed the association of the *FKBP5* variant rs3800373 genotype with the cognitive endophenotypes working memory, declarative memory and attention deficits in patients with SCZ and BD and healthy controls(HC).

3. MATERIAL AND METHODS

The study is a partly prospective clinical and genetic case-control study that took place within a period of two years.129 patients with SCZ (83 females, 39.55 years) and 53 patients with BD(36 females, 43.40 years) from the Psychiatric Clinic, Clinical Centre, University of Sarajevo, as well as 81 healthy controls (HC; 48 females, 32.52 years), were recruited. A lifetime best-estimate diagnosis was assigned according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) with the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I). Further extensive phenotyping includ-

ed the Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale (YMRS), Beck Depression Inventory (BDI), Operational Criteria Checklist (OPCRIT), and medical treatment. To measure working memory, declarative memory, and attention, patients completed a neuropsychological assessment which included the Trail Making Test-A&B (TMT-A&B) and Digit-span forward & backwards tasks (from the Wechsler adult intelligence scale). Rs3800373 in *FKBP5* genotyping was performed with Infinium*PsychArray Bead Chips* (Illumina Inc., San Diego).

Neurophysiological assessment
Trail Making Test-A&B (TMT-A&B)

The TMT-A&B provides information on executive functions and also visual search, mental flexibility, and speed of processing. The TMT has two parts: TMT-A requires participants to draw lines to connect 25 consecutive numbers; TMT-B requires the same, but requires participants to alternate between consecutive numbers and consecutive letters. The TMT-A&B score represents the time required to complete the task (22, 23)).

Digit-span test (working memory, HAWIE-R)

Working memory, in particular number storage capacity, was evaluated by the Digit-span (forward & backward) subtest of the Hamburg-Wechsler Adult Intelligence Scale revised (HAWIE-R; Tewes, 1991) (24). Participants need to repeat verbally presented number sequences (e.g. "7, 2, 9") out loud. If they succeed, the length of the number sequence is increased. In the Digit-span forward task, the subject is asked to repeat the digits in the given order, while in the Digit-span backwards task, the subject needs to reverse the order of the numbers (25).

Biomarkers
Blood sample for DNA extraction

From each patient, around 30 ml of peripheral blood was collected in (ethylenediamine tetraacetic acid) EDTA; from inpatients at three time points, and from outpatients and controls at onetime point. DNA was isolated from 10 ml of blood according to the manufactured instructions (QIAamp DNA Blood Maxi Kit, Qiagen, Germantown, MD, USA). DNA was eluted from the column three times with 1 ml of buffer provided by the manufacturer. The DNA isolation and blood storage was done at the Laboratory for Cytogenetics and Molecular Diagnostics, Department of Pathology, Clinical Centre of the University of Sarajevo.

Genotyping and quality control

All subjects were genotyped using the Illumina Infinium Psych Array Bead Chip (Illumina Inc., San Diego). Quality control was carried our using the software PLINK (http://pngu.mgh.harvard.edu/purcell/plink/). In brief, the following quality control measures were applied to remove single nucleotide polymorphisms (SNPs): call rate <0.98; minor allele frequency <0.01; and Hardy Weinberg Disequilibrium $p<10^{-6}$. Subjects were removed if they fulfilled the following criteria: call rate <0.98; duplicated or cryptic relatedness; and outliers on the first 10 principal components (26).The SNP rs3800373 in the FKBP5 gene was selected for analy-

sis. The distribution of rs3800373 did not deviate from Hardy-Weinberg equilibrium (in cases, controls and complete samples: p-HWE > 0.35) and observed allele frequency in the controls (C: 0.26; A: 0.74) did not deviate from the one of the 1000 Genomes CEU population (C:0.26; A: 0.74; https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=3800373).

Statistical Analysis

Allele frequencies and Hardy-Weinberg equilibrium (HWE; Exact Test) proportions were calculated with the DeFinetti Program (https://ihg.gsf.de/cgi-bin/hw/hwa2.pl). The statistical analyses performed using IBM SPSS Statistics for Windows version 22. Multivariate ANOVA were used to analyze the genotype-endophenotype type associations for cognitive function. Cognitive function in the specific cognitive domains working memory, declarative memory and attention were entered as outcome variables into the model, with genotype status and case-control status (SCZ vs. BD vs. HC) as predictors. The association between genotype and psychiatric diagnosis (case-control status) analyzed with a χ^2-test.

4. RESULTS

Analysis of performance in TMT-A included data from 81 HC, 53 BD patients, and 129 SCZ patients. The diagnosis had a significant effect on the performance in the TMT-A, $F(2.260) = 20.10$, $p < .001$. Both SCZ (60.16 seconds) and BD patients (56.81 seconds) needed more time to complete the TMT-A compared to the controls (43.30 seconds); all p < .001; post hoc). There was no difference between BD and SCZ patients (p = .529, post hoc). The diagnosis also had a significant effect on the performance in the TMT-B $F(2.259) = 19.23$, $p < .001$. Both SCZ (127.57 seconds) and BD patients (116.29 seconds) needed more time to complete the TMT-B compared to the HC (98.02 seconds); all p < .01; post hoc). As in the results for the TMT-A, there was no difference between BD and SCZ patients (p = .101, post hoc).

The diagnosis had a significant effect on the performance in the Digit-span forwards test $F(2.260 = 8.90$, $p < .001$). There was neither a difference between BD (m = 8.66) and SCZ patients (m = 8.21; p = .27, post hoc) , nor between BD and HC (m = 9.27; p = .13, post hoc). However, SCZ patients performed significantly lower than HC (p < .001; post hoc). The diagnosis had a significant effect on the performance in the Digit-span backwards $F(2.260) = 10.38$, $p < .001$. Both SCZ (m = 6.44) and BD patients (m = 6.57) performed significantly lower than HC (m = 7.47); (both p < .01; post hoc). There was no difference between BD and SCZ patients (p = .89, post hoc). Time needed to complete TMT-A slightly varied according to rs3800373 alleles (AC–53.57 ± 18.33, AA–53.81 ± 20.35; CC–30.77 ± 28.65). Also for the TMT-B, the time needed was in the same distribution (AA–114.30 ± 33.56; AA–115.49 ± 35.93; CC–129.27 ± 44.47). Mean for Digit-span forwards was in order from lowest to highest from CC (8.45 ± 1.54), AC (8.55 ± 1.86) to AA (8.72 ± 1.86). The mean score on the Digit-span backwards was lowest in case of CC (6.50 ± 0.96) trough AC (6.79 ± 1.78) to AA (6.83 ± 1.72). Rs3800373 was not associated

Neuropsychological Test	Genotype rs3800373					
	AA (N = 132)		AC (N = 109)		CC (N = 22)	
	Mean	SD	Mean	SD	Mean	SD
Trail Making Test-A	53.81	20.35	53.57	18.33	60.77	28.65
Trail Making Test-B	115.49	35.93	114.30	33.56	129.27	44.47
Digit-span forwards	8.72	1.86	8.55	1.86	8.45	1.54
Digit-span backwards	6.83	1.72	6.79	1.78	6.50	0.96

Table 1. Results of TMT-A, TMT-B, Digit-span forward and backward according to rs3800373 genotype(Allele frequency (A/C) = 0.71/0.29; pHWE = 1.000).

Diagnosis Group	Genotype rs3800373			Allele frequency	Total	pHWE
	AA	AC	CC	(A/C)		
CTR	45 (54.88%)	31 (37.8%)	6 (7.2%)	0.74/0.26	82 (57:4%)	0.781
BD	30 (49.2%)	28 (45.9%)	3 (4.9%)	0.72/0.28	61 (42.6%)	0.354
Total	75 (52.5%)	59 (41.3%)	9 (6.3%)	0.73/0.27	143 (100%)	0.673

Table 2. Crosstab for testing association between diagnosis (CTR: BD) and number of alleles (linear).

Diagnosis Group	Genotype rs3800373			Allele frequency	Total	pHWE
	AA	AC	CC	(A/C)		
CTR	45 (54.9%)	31 (37.8%)	6 (7.3%)	0.74/0.26	82 (34.0%)	0.781
SCZ	76 (47.8%)	69 (43.4%)	14 (8.8%)	0.72/0.28	159 (66.0%)	0.853
Total	121 (50.2%)	100 (41.5%)	20 (8.3%)	0.73/0.27	241 (100%)	1.000

Table 3. Crosstab for testing association between diagnosis (CTR: SCZ) and number of alleles (linear)

with performance in TMT-A $F(1.257) = 0.44$, $p = .509$ & TMT-B $F(1.256) = 0.80$, $p = .737$, or Digit-span forwards $F(1.257) = 0.40$, $p = .530$, and backwards $F(1.257) = 0.37$, $p = .848$ (Table 1).

Rs3800373 was not significantly associated with BD, $\chi^2(1) = .10$, $p = .784$ (Table 2).

Rs3800373 was not significantly associated with SCZ$\chi^2(1) = .97$, $p = .326$ (Table 3)..

Rs3800373 was neither associated with BD, $\chi^2(1) = .10$, $p = .784$nor with SCZ$\chi^2(1) = .97$, $p = .326$. There was no interaction of rs3800373 with the diagnosis group on the performance in TMT-A, $F(2.257) = 0.96$, $p = .384$; TMT-B, $F(2. 256) = 0.47$, $p = .625$; Digit-span forwards, $F(2.257) = 0.59$, $p = .555$;or Digit-span backwards, $F(2.257) = 0.61$, $p = .546$, (all p >.384).

5. DISCUSSION

The endopheno types investigated in this study all belong to cognition. Cognitive capability is a complex hereditary trait shaped by a great number of genes, all with relatively weak and variable influence on the cognitive phenotype of an individual. It is well-known that general cognitive capability is an individually variable but also a highly hereditary trait (27). In our results, both SCZ and BD patients needed more time to complete the TMT-A&B compared to the HC. There was no difference between BD and SCZ patients, which is in line with the results of other studies (28-30). Previous studies demonstrated that patients with SCZ and BD have simi-

lar cognitive deficits (31, 32), including working memory, declarative memory and attention deficits (16-18). The TMT-A&B tests are sensitive to a variety of neuropsychological impairments and processes. TMT measures executive function which is an important predictor of the functional outcomes, course of illness, treatment and prognosis of SCZ and BD (33). Studies in SCZ patients have demonstrated impaired visuomotor integration and inefficient sequencing of planning and acting as assessed by TMT-B to be reliable and stable trait characteristics (34, 35).

Working memory and executive cognition is compromised in patients with SCZ and BD (36). In our study, we observed an association of working memory with SCZ and BD diagnosis. Digit-span forward & backward tasks are used to measure working memory's storage capacity. In our study, SCZ patients performed significantly lower than controls in the forward digit-span task. However, there was no difference between BD vs HC or between BD vs SCZ patients. In the backwards digit-span task, both SCZ and BD patients performed significantly lower than HC, while there was no difference between BD and SCZ patients. Our results are in line with previous studies which showed no group differences between SCZ and BD patients in different working memory measures (37, 38), although our findings are not unequivocal, as another study found more severe deficits in working memory in SCZ than in BD patients (33).

In our study, we tested the association between the *FKBP5* SNP rs3800373 and categorical diagnosis, working memory, declarative memory and attention. However, no association was found. While former studies have reported a lack of association of rs3800373 with affective disorder and psychotic disorder (38, 39), as well as cognitive performance (38, 40), there are also a series of studies that have reported a positive association between the rs3800373 variant and a diagnosis of depression (12), higher depression ratings (41), suicide attempts (34, 35, 42), response to medication, and course of disorder (43).

Two major limitations of our study are that, due to the small sample size, we i.) neither included the treatment in our analyses nor ii.) tested for specific clinical features such as psychotic symptoms. Apart from the above mentioned main limitation of our genetic association study - the small sample size - the focus on a single candidate SNP is another limitation.

6. CONCLUSION

This study investigated the role of the *FKBP5* variant rs3800373 in cognitive impairment in different neuropsychological measures, the TMT-A&B and Digit-span forwards & backwards, within the groups of BD and SCZ. The finding that SCZ as well as BD are distinct from controls with respect to most endophenotype measures of cognitive impairment is in line with previous findings and can be seen as a quality measure for the assessment of the present sample. The fact that no genetic association could be found with variation in the candidate gene *FKBP5*, neither with diagnosis nor with cognitive en-

dophenotype, does not rule out that those associations may be seen with larger samples.

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