The relationship between miRNAs and executive functions in patients with obsessive compulsive disorder: An exploratory analysis

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SUMMARY

Objective: Our study aimed to examine the relationship between the cognitive functions of patients with OCD, and the expression levels of 12 miRNAs that regulate glutamate and serotonin gene expressions.

Method: Seventy patients with OCD and 35 age- and educational-matched healthy controls were included in the study. The Tower of London Test (ToL), Wisconsin Card Sorting Test (WCST), Trail Making Test (TMT), Stroop Test (ST), Digit Span Test (DST), and the Verbal Fluency Test (VFT) were performed on the participants. Twelve miRNA expression levels in the venous blood of the participants were detected using real-time polymerase chain reaction.

Results: Abstraction, cognitive flexibility, psychomotor speed, and verbal fluency performances of patients with OCD were significantly worse than the healthy control group ($p<0.05$). miRNA 6740 expression levels were positively associated with ToL-total correct scores in the patients ($p=0.010$) and negatively associated with ST-interference duration in the healthy controls ($p=0.020$).

Discussion: Our study indicates that patients with OCD have impairment of executive function, and miRNA-6740 expression levels may be related to executive functions both in patients with OCD and in general. The underlying mechanisms should be investigated in future studies to better understand the relationship of miRNA-6740-5p with cognitive functions.

Key Words: miR-6740, Obsessive-compulsive disorder, cognition, executive functions, miRNA

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by recurrent obsessions and/or compulsions and significantly affects the social and daily functioning of individuals (1). Twin studies have indicated that familial transmission is observed at a high rate in OCD, and genetic factors play an important role in this; however, epigenetic factors have a complex effect through learning behaviors in the family (2). Considering the efficacy of serotonin receptor inhibitors (SRIs), glutamatergic agents, and dopamine antagonists in the treatment of OCD, studies examining the genetics of OCD focused on candidate gene studies (HTR2A, HTR2C, HTR1B, NTRK3, DLGAP1, GRID2, GRIN2B, GRIN2A HTR2A, SLC6A4, SLC6A3 and SLC1A1 transporter, COMT, and MAOA genes) over serotonin, dopamine, and glutamate neurotransmitters (3). Unfortunately, no single nucleotide gene polymorphism responsible for OCD has been found in genome-wide association studies. Moreover, the results of the studies have been inconsistent (4-6). On the other hand, the disease may have different clinical manifestations, so genetic, environmental, social, and psychological factors are blamed in its etiology, but the roles of these factors in the formation of the disease are not clearly understood (7,8). In this context, it is thought that research should be performed on a number of neurobiologic and neurocognitive parameters beyond symptoms in

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understanding the etiology.

Until now, impairments in neurocognitive functions in some areas have been reported in relation to frontostriatal network abnormalities in OCD (9,10). In one study, it was mentioned that these neurocognitive impairments were of small to medium effect size but had poor diagnostic value for OCD (11). It has been reported that patients with OCD perform worse than healthy controls, especially in cognitive areas such as planning/problem-solving, visual memory, cognitive flexibility, decision-making, inhibition, and psychomotor speed (12), but there may be some different findings in this regard (13,14). In addition, impairment in executive functions such as planning/problem-solving, decision-making, and inhibition is the endophenotype for OCD (15). On the other hand, factors such as disease severity, depression, and medication affect cognitive functions (16), so it is still unclear whether cognitive impairments are specific to OCD. In studies, neurocognitive impairments in OCD have been particularly associated with early-onset (17), familial transmission (18), and symmetry/ordering symptom clusters (19). Executive dysfunction adversely affects daily functioning (20) and the treatment response (21). In several studies, it has been reported that some variants associated with the 5-HTTLPR promoter region of the SLC6A4 gene, which regulates the transport of the serotonin neurotransmitter, which is thought to play an important role in the pathophysiology of OCD, and COMT gene polymorphisms caused worse performance in areas of executive function (22,23).

miRNAs are RNA molecules with a length of 21-24 nucleotides and they are involved in different processes that occur in the central nervous system (CNS) (24). It has been shown that miRNAs play an important role in neurodevelopment, synaptic plasticity, and other physiologic functions with their regulatory functions in the expression of genes (25). miRNA expression changes have been reported in association with cognitive disorders seen in neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases, autism, and schizophrenia (26). Studies have shown that some miRNAs affect protein synthesis, particularly associated with learning and memory functions; miR-124 affects synaptic plasticity, neurogenesis, axonal and dendritic branching (27-29), miR-132 affects synaptic plasticity (30,31), and miR-137 affects neurogenesis and neuronal differentiation (32,33), all of which cause changes in cognitive functions. In the study of Kuswanto, a difference was found in miR-137 risk variants in patients with schizophrenia in attention and processing speed and planning skills (34). In addition, Liu et al. reported a significant relationship between patients with major depression and visual memory and miR-132 (35).

Beyond being among the mechanisms regulating cognitive processes, miRNAs show promise as biomarkers in psychiatric diseases. In a few recent studies, it has been reported that some miRNA expression levels differ in OCD compared to healthy controls (36-38). However, the relationship between miRNAs and cognitive dysfunction in OCD is still unknown. Our study aimed to examine the relationship between the cognitive functions of patients with OCD and the expression levels of 12 microRNAs that regulate glutamate and serotonin gene expressions.

METHODS

Our study was designed as a branch of our project study (Project No: 2018/087) entitled “Expression of MicroRNAs in Patients with OCD and its Relationship with Resistance to Treatment” (38). Our sample was selected from patients who were diagnosed as having OCD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria, and a healthy control group was included in the project study. Participants who met the inclusion criteria and volunteered for the study were included. Patients were not receiving any previous treatment or had not been taking medication for at least 1 month. In our study, OCD patients were selected using purposive sampling from individuals seeking treatment at the outpatient clinic. The control group was chosen through snowball sampling among hospital staff who self-reported no history of psychiatric or physical illnesses. Exclusion criteria of patients from the study were as follows: (i) Not being aged 18-60 years; (ii) having intellectual

disability, psychotic disorder, bipolar disorder, dementia according to the DSM-5 diagnostic criteria ii) not having at least primary school graduate; (iii) scoring 14 or higher from the HDRS or having moderate-to-severe major depressive disorder; (iv) history of alcohol and/or drug abuse or dependence; (v) risk of active suicide; (vi) psychical diseases (such as neurologic diseases, cancer, cardiovascular diseases, and diabetes mellitus). Accordingly, 70 patients with OCD and 35 age- and educational-matched healthy controls with no psychical or psychiatric disease were included in the study.

A sociodemographic data form, the 17-item Hamilton Depression Scale (HDRS) (39), Yale-Brown Obsession Compulsion Scale (YBOCS) (40), and structured interview form for DSM-5 Disorders (SCID-5-CV) (41) were used. Afterward, the Tower of London (ToL) test, Wisconsin Card Sorting Test (WCST), Trail Making Test (TMT), Stroop Test (ST), Digit Span Test (DST), and Verbal Fluency Test (VFT) were administered to each participant by the same neuropsychologist (Table 1).

Among the patients with OCD, 17 patients had no psychiatric comorbidities; 53 patients had at least one psychiatric comorbidity (mild depression n=13, agoraphobia n=11, generalized anxiety disorder n=9, hoarding disorder n=9, unspecified anxiety disorder n=9, social anxiety disorder n=8, adult separation anxiety disorder n=7, specific phobia n=6, dysthymia n=4, eating disorder n=3, skin picking disorder n=3, trichotillomania n=2, posttraumatic stress disorder n=2, and illness anxiety disorder n=2). After explaining the purpose and design of the study, informed consent was obtained from the participants. The study was approved by the ethics committee of University of Health Sciences, Şişli Hamidiye Etfal Teaching and Research Hospital.

Genetic Analyses

miRNA Selection Process

Twelve miRNAs that were previously shown to regulate glutamate and serotonin gene regions in the relevant references were selected. miR 26a-5p specific to the SLC1A1 gene (48), miR 374b-3p (49), miR 21-3p specific to the DLGAP1 gene (50), miR 6740-5p specific to the GRID2 gene (51), miR 219a-1-3p specific to the GRİN2B gene (52), miR 320a specific to the GRİN2A gene (53), miR 106b-5p specific to the HTR2A gene (54) and miR 1296b-5p (55), SLC6A4 gene-specific miR A total of 12 miRNAs were selected: 16b-5p (56) and miR 135a-5p (57), HTR2C gene-specific miR 22-3p (58), HTR1B gene-specific miR 96b-5p (59). The following websites (http:/mirtarbase.cuhk.edu.cn and http://mirdb.org/) were also used in selecting 12 miRNAs (miR 26a-5p, miR 374b-3p, miR 21-3p, miR 6740-5p, 219a-1-3p, miR 320a, miR 106b-5p, miR 129-6b5p, miR 16b-5p, miR 135a-5p, miR 22-3p, and miR 96b-5p).

Sample Collection and MicroRNA Expression Method

It includes the stages of RNA isolation, measurement of the concentration of isolated RNA, synthesis of cDNA and RT-PCR analysis. The blood samples were centrifugated to isolated serum for 5 minutes at 4500 rpm (Allegra® X-30 Series Benchtop Centrifuges, Beckman Coulter, California, USA). A RNeasy mini kits (Qiagen, Hilden, Germany) was practiced for total RNA isolation from this serum. Spectrophotometer (NanoDrop 2000/2000c Spectrophotometer, Waltham, MA, USA) was used to valuate the purities and concentrations of the isolated RNA. cDNAs were made by the reverse transcriptase method using miRNA-specific primers. RNAs converted into cDNA acquired fluorescence properties with the SYBR Green. Real-

Table 1. Neuropsychological test battery and cognitive domain.

Executive Functions	Cognitive domain
Digit Span Test (DST) (42,43)	Attention, working memory
Stroop Test (ST) (44)	Response inhibition, resistance to interference
Trail Making Test (TMT) (45)	Sustained attention, set shifting
Verbal Fluency Test (VFT)	Attention, sustained attention, vocabulary skill scanning ability
Wisconsin Card Sorting Test (WCST) (46)	Abstraction, conceptualization
Tower of London Test (ToLT) (47)	Planning, problem solving

Table 2. Sociodemographic characteristics of the participants

	OCD(n=70)	HC (n=35)	F, t, x†	p values
Age (yr)	28–10	29.1–7.4	0.591	0.556
Sex (Female), n (%)	47(67.1)	22(62.8)	0.19	0.663
Education (yr)	11.5–3.4	11.6–2.6	0.236	0.814
Onset	18.8–8.9	-		
Duration of disorder(years)	9.1–7.4			
YBOCS	26.1–4.7	-		
Comorbidity, n (%)	53 (75.7)			

Abbreviation: HC:Healthy control;OCD:Obsessive-compulsive disorder; YBOCS:Yale Brown Obsession Compulsion Scale.

time polymerase chain reaction (RT-PCR) was used to assess miRNA expression level. RNU6 was utilized as housekeeping gene for correct appraisal. The relative expression of miRNAs was accounted with the standard delta Ct calculation method.

Statistical Analysis

The statistical analysis was performed using the SPSS 20.0 for Windows program. Mean and standard deviation for numeric variables and numbers and percentages for categorical variables were specified. Pearson's Chi-square test was analyzed divergence between categorical variables in two groups. Logarithmic transformation was provided for variables that did not meet normal distribution conditions. Neuropsychological tests of patient and control groups were compared applying analysis of covariance (ANCOVA) by fixing age and education. The relationship between the miRNA expression levels of the participants and their neuropsychological tests was examined using partial correlation analysis by fixing the variables of education and age. For the patients, the models including neurocognitive tests as the dependent variable, miRNA expression levels, comorbidity, education, and disease duration and severity as independent variables were created and tested with linear regression analysis. For the healthy control group, models including neurocognitive tests as dependent variables, miRNA expression levels, age, education levels, and body mass index (BMI) as independent variables were created and tested using linear regression analysis. The statistical alpha significance level was counted as $p<0.05$.

RESULTS

Sample

There was no significant difference between the patient and control groups in terms of age, sex, and educational status ($p>0.05$). The mean age of onset of the disease was 18.8±8.9 years, the duration of the disease was 9.1±7.4 years, and the mean YBOCS total score was 16.1±4.7 years (Table 2).

Neurocognitive Tests

In the ANCOVA analysis made by fixing age and educational status, the number of WCST-completed categories and conceptual level responses were statistically less in patients with OCD compared

Table 3. Comparison of executive functions of OCD patients and control groups

	OCD (n=70)	HC (n=35)	*F*[a]	p values	partial n2
WCST					
Number of completed category	5.3–3	7.1–2.6	19.266	<0.001	0.158
Percentage of perseverative error	20–11.7	14–7.2	17.399	<0.001	0.143
Failures to maintain set	1.3–1.3	0.9–0.9	3.064	0.083	0.029
Conceptual level responses	0.7–1	0.7–0.2	13.243	<0.001	0.115
TMT					
TMT-A (sec)	43.9–19.4	36.9–15.8	4.681	0.033	0.044
TMT-B (sec)	87.6–36.5	71.1–25.3	7.968	0.006	0.073
TMT B-A (interference)	44.5–26.1	33.8–19.6	4.877	0.03	0.046
ToL					
Total correct score	3–2	3.7–2	2.035	0.157	0.019
Total move score	34.7–17.3	42.2–19.1	3.691	0.058	0.035
Initiation time, sec	36–19	41.5–20	1.628	0.205	0.016
Total application times, sec	226.9–100.2	173.1–62.4	8.312	0.005	0.076
Total time violations, sec	0.7–1.2	0.2–0.4	4.275	0.041	0.04
VFT					
Semantic and phonetic fluency	20.4–5.4	23.1–5.4	5.152	0.025	0.049
Phonetic fluency[b]	36.1–11.1	43.2–16.2	5.435	0.022	0.051
ST					
Interference time (sec)	42.2–18.1	35.6–16.7	3.781	0.055	0.036
DST					
Forward	6.1–1.2	6.3–1.1	2.185	0.142	0.021
Backward	4.1–1.1	4.3–1.4	2.914	0.091	0.028

[a]ANCOVA analysis was performed by fixing age and educational status.
[b] Logarithmic conversion is provided.

Abbreviation: DST: Digit Span Test; HC:Healthy control; OCD: Obsessive-compulsive disorder; ST: Stroop Test; TMT: Trail making test; ToL : Tower of London Test; VFT : Verbal Fluency Test; WCST: Wisconsin Card Sorting Test.

with the control group, and the percentage of perseverative errors was significantly higher ($p<0.001$). The total application times ($p=0.005$) and total time violations ($p=0.041$) in the ToL were statistically higher in the patient group than in the control group, but there was no significant difference in the total correct scores, initiation times, and move scores ($p>0.05$). The TMT A, B, and interference times of the patient group were significantly longer than the control group ($p=0.033$, $p=0.03$, and $p=0.006$, respectively). The semantic and phonetic fluency of the patient group was significantly lower than the control group ($p=0.025$ and $p=0.022$, respectively). The ST-interference times of the patient were longer than the control group and were in a statistically significant trend ($p=0.055$). There was no statistically significant difference between the forward and backward DST of the patient group compared with the control group ($p>0.05$) (Table 3).

Relationship Between miRNA Expression Levels and Cognitive Functions

In the partial correlation analysis performed by fixing the educational status, age, and BMI variables in patients with OCD, there was a significant negative correlation between semantic fluency and miR-26 and miR-22 expression levels ($r=0.247$, $r=0.288$, $p=0.045$, $p=0.019$, respectively). There was a significant positive correlation between miR-6740 and ToL-total correct scores ($r=0.307$; $p=0.010$), and there was a significant negative correlation ($r=-0.260$; $p=0.030$) with the total move scores. There was no significant correlation between the other miRNA expression levels and neurocognitive tests ($p>0.05$). When the correlations between the miRNA expression levels of the healthy control group and cognitive tests were examined, there were positive significant correlations between miR-6740 and, DST-Forward ($r=0.430$, $p=0.010$) and

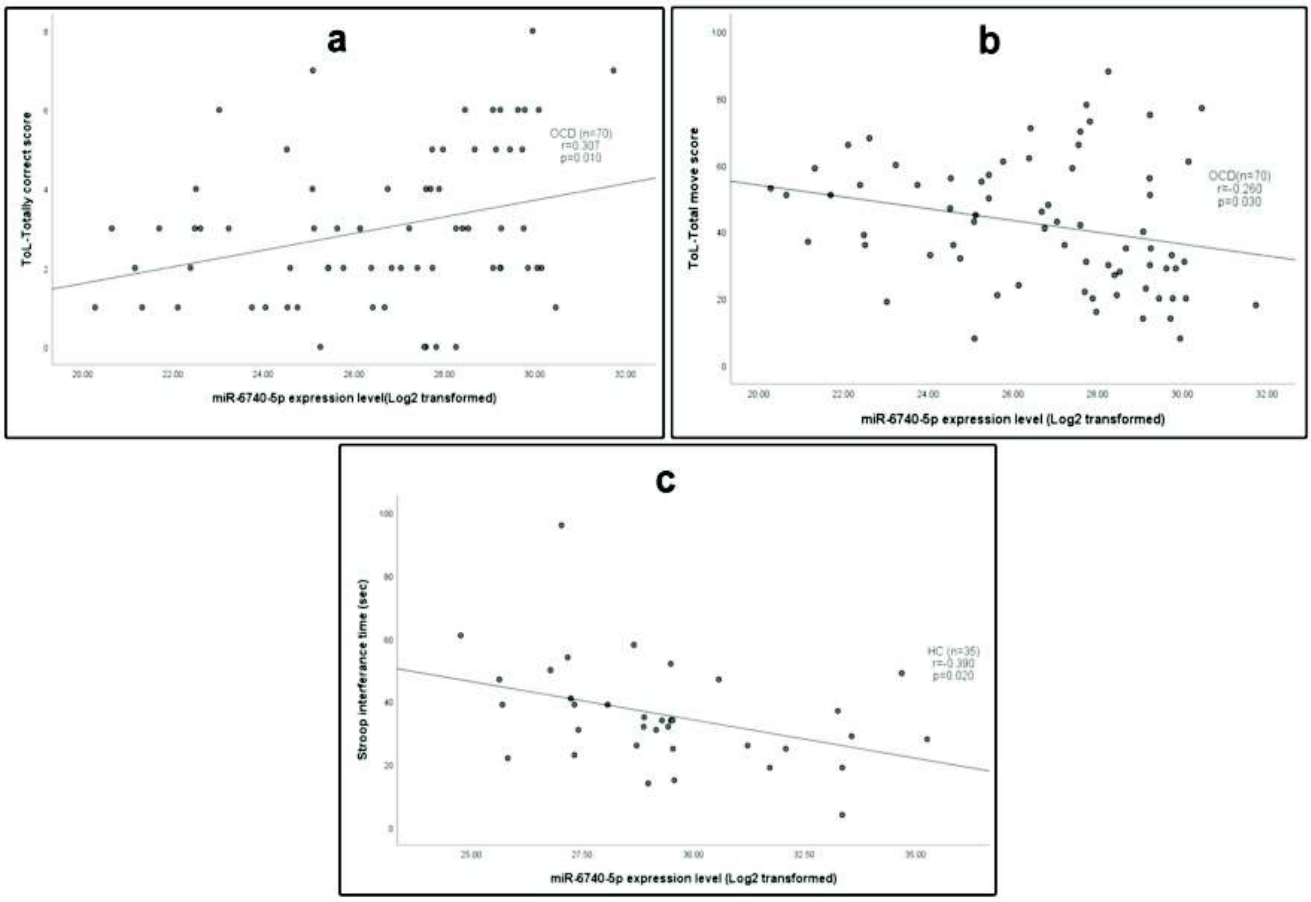

Figure 1 a,b,c. The correlation between miR-6740-5p expression levels and executive functions of participants. a) The correlation between miR-6740-5p expression levels and ToL- Total correct score of OCD patients. b) The correlation between miR-6740-5p expression levels and ToL-Total move score of patients with OCD. c) The correlation between miR-6740-5p expression levels and Stroop-interferance time of healthy controls. HC; healthy control; OCD: obsessive compulsive disorder; ToL: Tower of London test.

negative significant correlations between miR-6740 and ST-interference times (r= -0.390, p=0.020). TMT-interference time with miR-320 (r=0.403, p=0.016), ToL-application time with miR-16 (r=0.385, p=0.023), and ToL-initiation time with miR-1296 (r=0.350, p=0.039) had positive significant correlations.

Considering the significant correlations between patients' miRNAs and cognitive tests, models were created with the other variables. When variables such as education level, YBOCS score, disease duration, and comorbidity were controlled as independent variables, there was a significant association between miR-6740 expression levels (beta=0.329, t=2.732, p=0.008) and ToL-total correct scores being the dependent variable (R2=0.173, F=2.672, df=5, p=0.030). However, the model was not found significant in the further analysis where semantic fluency test scores were determined as dependent variables, and miR-22, miR-26, years of education, YBOCS score, and disease duration as independent variables (R2=0.042, F=1.433 df=7, p=0.209) (Figure 1a,1b).

There was a negative significant association between ST-interference duration and miR-6740 expression levels (beta=-0.289, t=-2.193, p=0.036) in the healthy control group when age, education level, and BMI were fixed as independent variables (R2=0.499, F=7.471, df=4, p<0.001). According to the linear regression analysis, no significant patterns were found between the other miRNA expression levels and cognitive tests (p>0.05) (Figure 1c).

DISCUSSION

In our study, we conducted an exploratory analysis comparing patients with OCD to a healthy control group in terms of cognitive functions and examined the relationship between miRNA expression levels and cognitive functions; this is the first of its kind in the literature. According to our findings, abstraction, cognitive flexibility, psychomotor speed, and verbal fluency performances of patients with OCD were significantly worse than those of the healthy control group, while there was no significant difference in planning/problem-solving skills, inhibition, attention, and working memory. In addition, miRNA 6740 expression levels of patients were positively associated with ToL-total correct scores and negatively correlated with ToL-total move scores. In the healthy control group, miRNA 6740-5p expression levels and ST-interference duration were negatively and significantly related.

OCD is a disease accompanied by rigid rituals and repetitive behaviors, and, based on this phenomenologic observation, it has been suggested that the ability of patients to change their behavior situationally, that is, their behavioral flexibility, may be reduced (60,61). In many neuropsychological studies, in which authors evaluated cognitive flexibility with TMT and WCST, perseverative error percentages, in particular, were significantly higher in patients with OCD (62-65). Similar to our study, TMT and WCST test performances of patients with OCD were worse than in healthy controls, and the percentage of perseverative errors was significantly higher. Recent studies revealed that although it has not yet been proven that it is a feature specific to OCD, there may be impairment in many cognitive areas such as executive functions, psychomotor speed, and verbal fluency in OCD (12-14).

In a meta-analysis study, it was reported that impairments in visual memory and planning skills had a great effect size, and impairments in cognitive flexibility, inhibition, verbal fluency, and psychomotor speed had a small-to-medium effect size (12). In our study, when age and educational status were fixed in patients with OCD, abstraction, cognitive flexibility, verbal fluency, and psychomotor speed impairments were prominent in the executive functions. In terms of planning skills, patients with OCD had similar performance in the ToL with the healthy control group, but the patients took longer to complete the test. In addition, in meta-analysis studies, planning skills were examined with various tests such as the Tower of Hanoi/ToL, and it was reported that patients with OCD had impaired planning skills with medium-to-large effect size (12,14).

Similar to our study, some studies reported that

patients with OCD had similar planning skills to the healthy control group (66-69) , but they took longer to initiate and perform their moves (67). In other words, it shows that OCD patients need more time to plan/problem-solve rather than having impairment in their planning/problem-solving skills. This can be interpreted as patients with OCD being unsure of the move they will make, they check frequently, and they may show obsessive slowness. On the other hand, the diversity in neuropsychological findings may be highly related to the heterogeneous appearance of patients with OCD. Studies reported that factors such as the presence of comorbidity, obsessive beliefs, drug use, and disease severity affect cognitive performance (16, 69). Although patients with moderate-to-severe depression were excluded from our study, considering that they might adversely affect cognitive tests, the results of our study may have been affected by other comorbidities because we did not include only patients with pure OCD.

Our other important finding was that as miR-6740 expression levels increase in patients with OCD, problem-solving skills increase when independent variables such as education level, disease severity and duration, and comorbidity are controlled. In the healthy control group, when the expression levels of miR-6740 increase and independent variables such as age, education year, and BMI are fixed, inhibition ability increases. In our previous study, miR-6740-5p expression levels were found to be significantly different in patients with OCD compared with the healthy control group (38). Based on current findings, it is difficult to say that miR-6740-5p's association with cognitive functions is specific to OCD. In other words, it can be said that miRNA-6740-5p expression levels are significantly related to executive functions in both patients with OCD and healthy controls.

In recent studies, the effects of some miRNAs on neurodegenerative processes, cerebrovascular disease, aging, and cognitive functions have been mentioned (26). In particular, some miRNAs have effects on synaptic plasticity, neuronal development, and neuronal morphology via LTP, where they are expressed in the hippocampus and prefrontal cortex in the CNS (70). Cognitive impairments in neurodegenerative diseases such as Alzheimer's (71, 72), Parkinson's (73), and Huntington's disease (74), and schizophrenia (75) may be affected by some miRNAs, but our knowledge on this subject is still limited. In a study, it was determined that miR-6740-5p regulated glutamate receptor subunits (GRIA2, GRID2) and GABA receptor subunit (GABRG1, GABRA4, GABRB2) genes, and miR-6740 variants might be associated with nicotine addiction (76).

The gluA2 receptor, which is AMPA type from the glutamate ionotropic receptor family, is encoded in the GRIA2 gene and the delta type GluD2 receptor is encoded in the GRID2 gene. Although it is known that each glutamate receptor plays a specific role in glutamate release, it also has effects on NMDA receptors, whose role is well-known in the etiology of some psychiatric diseases. Glutamate is the main neurotransmitter involved in functions of the brain such as memory, perception, and cognition (77). It has been indicated that miR-132 plays a role in synaptic plasticity by regulating BDNF, AMPA, and NMDA-type glutamate receptor genes and is overexpressed in the hippocampal region, thus being associated with cognitive functions such as memory (31).

In a study, visual memory impairment was associated with increased miRNA-132 expression levels in patients with depression (35). On the other hand, the exact relationship of miR-6740-5p with the CNS is not known yet and there is no study revealing its relationship with cognitive functions. However, in a study with a large sample, 21 miRNAs were detected, including miRNA-6740-5p, which is expressed at different levels in patients with Alzheimer's than in healthy controls (60). In a recent study, it was reported that miR-6740-5p was particularly associated with endothelial dysfunction, the development of atherosclerotic plaques, and cardiovascular diseases (78). In our study, we analyzed 12 miRNAs along with multiple neuropsychological tests. However, we did not apply statistical corrections for multiple comparisons, such as Bonferroni or FDR, which may have increased the risk of false positives. Therefore, our findings regarding miR-6740-5p should be interpreted as exploratory and require validation through larger, confirmatory studies to establish their reliability and significance. Considering these findings, further studies are

essential to clarify the mechanisms through which miR-6740-5p might influence cognitive functions and its broader role within the CNS.

Our study had some limitations. First, the relationship of only a limited number of miRNAs with some cognitive domains could be examined. To reveal this relationship more clearly, a study involving more miRNAs and all cognitive domains should be conducted. Secondly, given the high rate of comorbidity typically observed in OCD, anxiety, and depressive disorders, our study included a heterogeneous OCD group, which may have influenced the results. Notably, 75% of OCD patients had comorbid psychiatric disorders, while the control group had none. Considering that depression, anxiety, and PTSD are independently known to impact executive functions and gene expression, this raises uncertainty regarding the specificity of our findings to OCD. Thirdly, in our study, a 2:1 ratio was used between OCD patients and healthy controls (70 OCD vs. 35 controls). This ratio has the potential to reduce statistical power and increase group imbalances. A more balanced 1:1 ratio could have enhanced the robustness and generalizability of the findings. Therefore, the imbalance in the patient-control ratio should be acknowledged as a limitation of our study, and an equal distribution should be considered in future studies. The effects of sex on miRNA expression and executive functions were not controlled in our study, which is a limitation. Sex hormones, such as estrogens and androgens, are known to influence miRNA expression, potentially affecting neurocognitive processes. Future studies should consider controlling for sex to clarify these effects. The absence of SCID-5-CV for the control group raises the possibility of undiagnosed OCD traits or subclinical anxiety/depression, which should be acknowledged as a limitation of our study. Lastly, the mechanisms by which miRNA-6740 expression levels are related to executive functions or through which gene regulation was not examined in our study, which limits the understanding of the cause-effect relationship.

In conclusion, the performance of patients with OCD in cognitive areas such as abstraction, cognitive flexibility, verbal fluency, and psychomotor speed was significantly worse than in healthy controls. Moreover, as miRNA-6740 expression levels increased, planning/problem-solving skills increased in patients with OCD and there was an increase in motor inhibition in the healthy control group. Accordingly, it can be said that miRNA-6740 expression levels may be related to executive functions in general. In future studies, the underlying mechanisms should be investigated to better understand the relationship of miRNA-6740-5p with cognitive function.

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REFERENCES

1. American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders Fifth edition. American Psychiatric Publishing; 2013.

2. International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS). Revealing the complex genetic architecture of obsessive-compulsive disorder using meta-analysis. Mol Psychiatry. 2018 May;23(5):1181-1188. doi: 10.1038/mp.2017.154. Epub 2017 Aug 1. PMID: 28761083; PMCID: PMC6660151.

3. Bozorgmehr A, Ghadirivasfi M, Ananloo ES. Obsessive–compulsive disorder, which genes? Which functions? Which pathways? An integrated holistic view regarding OCD and its complex genetic etiology. J Neurogen 2017;31: 153-160.

4. den Braber A, Zilhão NR, Fedko IO, Hottenga JJ, Pool R, Smit DJ, Cath DC, Boomsma DI. Obsessive-compulsive symptoms in a large population-based twin-family sample are predicted by clinically based polygenic scores and by genome-wide SNPs. Transl Psychiatry. 2016 Feb 9;6(2):e731. doi: 10.1038/tp.2015.223. PMID: 26859814; PMCID: PMC4872426.

5. Mattheisen M, Samuels JF, Wang Y, Greenberg BD, Fyer AJ, McCracken JT, Geller DA, Murphy DL, Knowles JA, Grados MA, Riddle MA, Rasmussen SA, McLaughlin NC, Nurmi EL, Askland KD, Qin HD, Cullen BA, Piacentini J, Pauls DL, Bienvenu OJ, Stewart SE, Liang KY, Goes FS, Maher B, Pulver AE, Shugart YY, Valle D, Lange C, Nestadt G. Genome-wide association study in obsessive-compulsive disorder: results from the OCGAS. Mol Psychiatry. 2015 Mar;20(3):337-44. doi: 10.1038/mp.2014.43. Epub 2014 May 13. PMID: 24821223; PMCID: PMC4231023.

6. Stewart SE, Yu D, Scharf JM, Neale BM, Fagerness JA, Mathews CA, Arnold PD, Evans PD, Gamazon ER, Davis LK, Osiecki L, McGrath L, Haddad S, Crane J, Hezel D, Illman C, Mayerfeld C, Konkashbaev A, Liu C, Pluzhnikov A, Tikhomirov A, Edlund CK, Rauch SL, Moessner R, Falkai P, Maier W, Ruhrmann S, Grabe HJ, Lennertz L, Wagner M, Bellodi L, Cavallini MC, Richter MA, Cook EH Jr, Kennedy JL, Rosenberg D, Stein DJ, Hemmings SM, Lochner C, Azzam A, Chavira DA, Fournier E, Garrido H, Sheppard B, Umaña P, Murphy DL, Wendland JR, Veenstra-VanderWeele J, Denys D, Blom R, Deforce D, Van Nieuwerburgh F, Westenberg HG, Walitza S, Egberts K, Renner T, Miguel EC, Cappi C, Hounie AG, Conceição do Rosário M, Sampaio AS, Vallada H, Nicolini H, Lanzagorta N, Camarena B, Delorme R, Leboyer M, Pato CN, Pato MT, Voyiaziakis E, Heutink P, Cath DC, Posthuma D, Smit JH, Samuels J, Bienvenu OJ, Cullen B, Fyer AJ, Grados MA, Greenberg BD, McCracken JT, Riddle MA, Wang Y, Coric V, Leckman JF, Bloch M, Pittenger C, Eapen V, Black DW, Ophoff RA, Strengman E, Cusi D, Turiel M, Frau F, Macciardi F, Gibbs JR, Cookson MR, Singleton A; North American Brain Expression Consortium; Hardy J; UK Brain Expression Database; Crenshaw AT, Parkin MA, Mirel DB, Conti DV, Purcell S, Nestadt G, Hanna GL, Jenike MA, Knowles JA, Cox N, Pauls DL. Genome-wide association study of obsessive-compulsive disorder. Mol Psychiatry. 2013 Jul;18(7):788-98. doi: 10.1038/mp.2012.85. Epub 2012 Aug 14. Erratum in: Mol Psychiatry. 2013 Jul;18(7):843. Davis, L K [added]. PMID: 22889921; PMCID: PMC4218751.

7. Pauls DL, Abramovitch A, Rauch SL, Geller DA. Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. Nat Rev Neurosci 2014; 15: 410–424.

8. Sinopoli VM, Burton CL, Kronenberg S, Arnold PD. A review of the role of serotonin system genes in obsessive-compulsive disorder. Neurosci Biobehav 2017; 80: 372-81.

9. Abramovitch A, Cooperman A. The cognitive neuropsychology of obsessive-compulsive disorder: A critical review. J Obsessive Compuls Relat Disord 2015;5: 24-36.

10. Vaghi MM, Vértes PE, Kitzbichler MG, Apergis-Schoute AM, van der Flier FE, Fineberg NA, Sule A, Zaman R, Voon V, Kundu P, Bullmore ET, Robbins TW. Specific Frontostriatal Circuits for Impaired Cognitive Flexibility and Goal-Directed Planning in Obsessive-Compulsive Disorder: Evidence From Resting-State Functional Connectivity. Biol Psychiatry. 2017 Apr 15;81(8):708-717. doi: 10.1016/j.biopsych.2016.08.009. Epub 2016 Aug 11. PMID: 27769568; PMCID: PMC6020061.

11. Fullana MA, Abramovitch A, Via E, López-Sola C, Goldberg X, Reina N, Fortea L, Solanes A, Buckley MJ, Ramella-Cravaro V, Carvalho AF, Tortella-Feliu M, Vieta E, Soriano-Mas C, Lázaro L, Stein DJ, Fernández de la Cruz L, Mataix-Cols D, Radua J. Diagnostic biomarkers for obsessive-compulsive disorder: A reasonable quest or ignis fatuus? Neurosci Biobehav Rev. 2020 Nov;118:504-513. doi: 10.1016/j.neubiorev.2020.08.008. Epub 2020 Aug 28. PMID: 32866526.

12.Shin NY, Lee TY, Kim E, Kwon JS. Cognitive functioning in obsessive-compulsive disorder: A meta-analysis. Psychol Med 2014; 44:1121–1130.

13. Abramovitch A, Abramowitz JS, Mittelman A. The neuropsychology of adult obsessive–compulsive disorder: a meta-analysis. Clin Psychol Rev 2013; 33: 1163-1171.

14. Snyder HR, Kaiser RH, Warren SL, Heller W. Obsessive-compulsive disorder is associated with broad impairments in executive function: A meta-analysis. Clin Psychol Sci 2015; 3: 301-330.

15. Bora E. Meta-analysis of neurocognitive deficits in unaffected relatives of obsessive-compulsive disorder (OCD): comparison with healthy controls and patients with OCD. Psychol Med 2020; 50: 1257-1266.

16. Abramovitch A, McCormack B, Brunner D, Johnson M, Wofford N. The impact of symptom severity on cognitive function in obsessive-compulsive disorder: A meta-analysis. Clin Psychol Rev 2019; 67: 36-44.

17. Zhang J, Yang X, Yang Q. Neuropsychological dysfunction in adults with early-onset obsessive-compulsive disorder: the search for a cognitive endophenotype. Braz J Psychiatry 2015; 37: 126-132.

18. Bhattacharya M, Balachander S, Viswanath B, Reddy YJ. Comparison of neurocognitive performance in familial versus sporadic obsessive-compulsive disorder. J Obsessive Compuls Relat Disord 2021; 3: 100666.

19. McGuire JF, Crawford EA, Park JM, Storch EA, Murphy TK, Larson MJ, Lewin AB. Neuropsychological performance across symptom dimensions in pediatric obsessive compulsive disorder. Depress Anxiety. 2014 Dec;31(12):988-96. doi:

10.1002/da.22241. Epub 2014 Feb 12. PMID: 24523044.

20. Kivircik Akdede BB, Alptekin K, Akvardar Y, Kitiş A. Obsesif Kompulsif Bozuklukta Yaşam Kalitesi: Bilişsel Işlevler ve Klinik Bulgular ile Ilişkisi [Quality of life in patients with obsessive-compulsive disorder: relations with cognitive functions and clinical symptoms]. Turk Psikiyatri Derg. 2005 Spring;16(1):13-9. Turkish. PMID: 15793694.

21. D'Alcante CC, Diniz JB, Fossaluza V, Batistuzzo MC, Lopes AC, Shavitt RG, Deckersbach T, Malloy-Diniz L, Miguel EC, Hoexter MQ. Neuropsychological predictors of response to randomized treatment in obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2012 Dec 3;39(2):310-7. doi: 10.1016/j.pnpbp.2012.07.002. Epub 2012 Jul 10. PMID: 22789662.

22. Tükel R, Alkaş E, Gürvit H, Aslantaş Ertekin B, Ertekin E, Baran B, Akça Kalem Ş, Saruhan Direskeneli G. Serotonin transporter promoter polymorphism is associated with executive function impairments in patients with obsessive compulsive disorder. Clin Neuropsychol. 2016 May;30(4):536-46. doi: 10.1080/13854046.2016.1162329. Epub 2016 Mar 17. PMID: 26986829.

23. Tükel R, Gürvit H, Öztürk N, Özata B, Ertekin BA, Ertekin E, Baran B, Kalem ŞA, Büyükgök D, Direskeneli GS. COMT Val158Met polymorphism and executive functions in obsessive-compulsive disorder. J Neuropsychiatry Clin Neurosci. 2013 Summer;25(3):214-21. doi: 10.1176/appi.neuropsych.12040103. PMID: 23774999.

24. Cai Y, Yu X, Hu S, Yu J. A brief review on the mechanisms of miRNA regulation. Genomics Proteomics Bioinformatics 2009; 7: 147-154.

25. Fiorenza A, Barco A. Role of Dicer and the miRNA system in neuronal plasticity and brain function. Neurobiol Learn Mem 2016; 135: 3-12.

26. Deraredj Nadim W, Simion V, Bénédetti H, Pichon C, Baril P, Morisset-Lopez S. MicroRNAs in neurocognitive dysfunctions: new molecular targets for pharmacological treatments?. Curr Neuropharmacol 2017;15: 260-275.

27. Cheng LC, Pastrana E, Tavazoie, M, Doetsch F. miR-124 regulates adult neurogenesis in the subventricular zone stem cell niche. Nat Neurosci 2009; 12: 399-408.

28. Franke K, Otto W, Johannes S, Baumgart J, Nitsch R, Schumacher S. miR-124-regulated RhoG reduces neuronal process complexity via ELMO/Dock180/Rac1 and Cdc42 signalling. EMBO J. 2012 Jun 29;31(13):2908-21. doi: 10.1038/emboj.2012.130. Epub 2012 May 15. PMID: 22588079; PMCID: PMC3395090.

29. Rajasethupathy P, Fiumara F, Sheridan R, Betel D, Puthanveettil SV, Russo JJ, Sander C, Tuschl T, Kandel E. Characterization of small RNAs in Aplysia reveals a role for miR-124 in constraining synaptic plasticity through CREB. Neuron. 2009 Sep 24;63(6):803-17. doi: 10.1016/j.neuron.2009.05.029. PMID: 19778509; PMCID: PMC2875683.

30. Vo N, Klein ME, Varlamova O, Keller DM, Yamamoto T, Goodman RH, Impey S. A cAMP-response element binding protein-induced microRNA regulates neuronal morphogenesis. Proc Natl Acad Sci U S A. 2005 Nov 8;102(45):16426-31. doi: 10.1073/pnas.0508448102. Epub 2005 Oct 31. Erratum in: Proc Natl Acad Sci U S A. 2006 Jan 17;103(3):825. PMID: 16260724; PMCID: PMC1283476.

31. Kawashima H, Numakawa T, Kumamaru E, Adachi N, Mizuno H, Ninomiya M, Kunugi H, Hashido K. Glucocorticoid attenuates brain-derived neurotrophic factor-dependent upregulation of glutamate receptors via the suppression of microRNA-132 expression. Neuroscience. 2010 Feb 17;165(4):1301-11. doi: 10.1016/j.neuroscience.2009.11.057. Epub 2009 Dec 1. PMID: 19958814.

32. Smrt RD, Szulwach KE, Pfeiffer RL, Li X, Guo W, Pathania M, Teng ZQ, Luo Y, Peng J, Bordey A, Jin P, Zhao X. MicroRNA miR-137 regulates neuronal maturation by targeting ubiquitin ligase mind bomb-1. Stem Cells. 2010 Jun;28(6):1060-70. doi: 10.1002/stem.431. PMID: 20506192; PMCID: PMC3140955.

33. Sun G, Ye P, Murai K, Lang MF, Li S, Zhang H, Li W, Fu C, Yin J, Wang A, Ma X, Shi Y. miR-137 forms a regulatory loop with nuclear receptor TLX and LSD1 in neural stem cells. Nat Commun. 2011 Nov 8;2:529. doi: 10.1038/ncomms1532. PMID: 22068596; PMCID: PMC3298567.

34. Kuswanto CN, Sum MY, Qiu A, Sitoh YY, Liu J, Sim K. The impact of genome wide supported microRNA-137 (MIR137) risk variants on frontal and striatal white matter integrity, neurocognitive functioning, and negative symptoms in schizophrenia. Am J Med Genet B: Neuropsychiatr Genet 2015; 168: 317-326.

35. Liu Y, Yang X, Zhao L, Zhang J, Li T, Ma X. Increased miR-132 level is associated with visual memory dysfunction in patients with depression. Neuropsychiatr Dis Treat 2016; 12: 2905.

36. Kandemir H, Erdal ME, Selek S, İzci Ay Ö, Karababa İF, Ay ME, Kandemir SB, Yılmaz ŞG, Ekinci S, Taşdelen B, Bayazit H. Microribonucleic acid dysregulations in children and adolescents with obsessive-compulsive disorder. Neuropsychiatr Dis Treat. 2015 Jul 14;11:1695-701. doi: 10.2147/NDT.S81884. PMID: 26203251; PMCID: PMC4508068.

37. Yue J, Zhang B, Wang H, Hou X, Chen X, Cheng M, Wen S. Dysregulated plasma levels of miRNA-132 and miRNA-134 in patients with obsessive-compulsive disorder. Ann Transl Med. 2020 Aug;8(16):996. doi: 10.21037/atm-20-5217. PMID: 32953796; PMCID: PMC7475501.

38. Aydın EP, Alsaadoni H, Beğenen AG, Özer ÖA, Karamustafalıoğlu KO, Pençe S. Can miRNA Expression Levels Predict Treatment Resistance to Serotonin Reuptake Inhibitors in Patients with Obsessive-Compulsive Disorder? Psychiatry Clin Psychopharmacol 2022; 32: 98-106.

39. Akdemir A, Orsel SD, Dag I, Turkcapar MH, Iscan Na, Ozbay H. Hamilton depresyon derecelendirme ölçeği (HDDÖ)'nin geçerliği, güvenirliği ve klinikte kullanımı. 3P Dergisi 1996251–1996259.

40. Karamustafalıoğlu O, Üçışık A, Ulusoy M, Erkmen H. Yale Brown obsesyon kompulsiyon derecelendirme ölçeği'nin geçerlik ve güvenirlik çalışması. In: 29. Ulusal Psikiyatri Kongresi;1993: p. 86.

41. Elbir M, Alp Topbaş Ö, Bayad S, Kocabaş T, Topak OZ, Çetin Ş, Özdel O, Ateşçi F, Aydemir Ö. DSM-5 Bozuklukları

için Yapılandırılmış Klinik Görüşmenin Klinisyen Versiyonunun Türkçeye Uyarlanması ve Güvenilirlik Çalışması [Adaptation and Reliability of the Structured Clinical Interview for DSM-5-Disorders - Clinician Version (SCID-5/CV) to the Turkish Language]. Turk Psikiyatri Derg. 2019 Spring;30(1):51-56. Turkish. PMID: 31170307.

42. Reynolds CR. Book and test reviews. Arch Clin Neuropsychol 1987; 2:191–223.

43. Karakaş S. Bilnot Bataryası El Kitabı: Nöropsikolojik Testler için Araştırma ve Geliştirme Çalışmaları. 2. Baskı. Eryılmaz Ofset; 2006.

44. Karakaş S, Erdoğan E, Soysal AŞ, Ulusoy T, Ulusoy İ, Alkan S. Stroop Testi TBAG Formu : Türk Kültürüne Standardizasyon Çalışmaları, Güvenirlik ve Geçerlik. Türk Psikiyatr Derg 1999;2:75–88

45. Crowe SF. The differential contribution of mental tracking, cognitive flexibility, visual search, and motor speed to performance on parts A and B of the trail making test. J Clin Psychol 1998; 54:585–91.

46. Karakaş S. Turk kulturu icin standardizasyonu yapilmis noropsikolojik testler toplulugu. In: 32 Ulusal Noroloji Kongre Kitabi; 1996.

47. Atalay D, Cinan S. Yetiskinlerde Planlama Becerisi: Londra Kulesi Testinin Standardizasyon ve Güvenilirlik Çalismasi. Turk Psikol Derg 2007; 22: 25-38.

48. Potenza N, Mosca N, Mondola P, Damiano S, Russo A, De Felice B. Human miR-26a-5p regulates the glutamate transporter SLC1A1 (EAAT3) expression. Relevance in multiple sclerosis. Biochim Biophys Acta Mol Basis Dis 2018;1864:317-23.

49. Kan AA, van Erp S, Derijck AA, de Wit M, Hessel EV, O'Duibhir E, de Jager W, Van Rijen PC, Gosselaar PH, de Graan PN, Pasterkamp RJ. Genome-wide microRNA profiling of human temporal lobe epilepsy identifies modulators of the immune response. Cell Mol Life Sci. 2012 Sep;69(18):3127-45. doi: 10.1007/s00018-012-0992-7. Epub 2012 Apr 26. PMID: 22535415; PMCID: PMC3428527.

50. Wu YE, Parikshak NN, Belgard TG, Geschwind DH. Genome-wide, integrative analysis implicates microRNA dysregulation in autism spectrum disorder. Nat Neurosci 2016;19:1463-76.

51. Pérez-Rubio G, Pérez-Rodríguez ME, Fernández-López JC, Ramírez-Venegas A, García-Colunga J, Ávila-Moreno F, Camarena A, Sansores RH, Falfán-Valencia R. SNPs in NRXN1 and CHRNA5 are associated to smoking and regulation of GABAergic and glutamatergic pathways. Pharmacogenomics. 2016 Jul;17(10):1145-1158. doi: 10.2217/pgs-2016-0020. Epub 2016 Jun 29. PMID: 27355804.

52. Sun YJ, Yu Y, Zhu GC, Sun ZH, Xu J, Cao JH, Ge JX. Association between single nucleotide polymorphisms in MiR219-1 and MiR137 and susceptibility to schizophrenia in a Chinese population. FEBS open bio 2015;5:774-8.

53. Camkurt MA, Acar Ş, Coşkun S, Güneş M, Güneş S, Yılmaz MF, Görür A, Tamer L. Comparison of plasma MicroRNA levels in drug naive, first episode depressed patients and healthy controls. J Psychiatr Res. 2015 Oct;69:67-71. doi: 10.1016/j.jpsychires.2015.07.023. Epub 2015 Jul 23. Erratum in: J Psychiatr Res. 2016 Apr;75:23. PMID: 26343596.

54. Camkurt MA, Karababa F, Erdal ME, Bayazıt H, Kandemir SB, Ay ME, Kandemir H, Ay Öİ, Çiçek E, Selek S, Taşdelen B. Investigation of Dysregulation of Several MicroRNAs in Peripheral Blood of Schizophrenia Patients. Clin Psychopharmacol Neurosci. 2016 Aug 31;14(3):256-60. doi: 10.9758/cpn.2016.14.3.256. PMID: 27489379; PMCID: PMC4977811.

55. Marinho R, Alcântara PS, Ottoch JP, Seelaender M. Role of exosomal MicroRnAs and myomiRs in the Development of Cancer Cachexia-Associated Muscle wasting. Front Nutr 2018;4:69.

56. Baudry A, Mouillet-Richard S, Schneider B, Launay JM, Kellermann O. miR-16 targets the serotonin transporter: a new facet for adaptive responses to antidepressants. Science 2010; 329: 1537-41.

57. Issler O, Haramati S, Paul ED, Maeno H, Navon I, Zwang R. MicroRNA 135 is essential for chronic stress resiliency, antidepressant efficacy, and intact serotonergic activity. Neuron 2014; 83: 344-360.

58. Muiños-Gimeno M, Espinosa-Parrilla Y, Guidi M, Kagerbauer B, Sipilä T, Maron E, Pettai K, Kananen L, Navinés R, Martín-Santos R, Gratacòs M, Metspalu A, Hovatta I, Estivill X. Human microRNAs miR-22, miR-138-2, miR-148a, and miR-488 are associated with panic disorder and regulate several anxiety candidate genes and related pathways. Biol Psychiatry. 2011 Mar 15;69(6):526-33. doi: 10.1016/j.biopsych.2010.10.010. Epub 2010 Dec 17. PMID: 21168126.

59. Jensen KP, Covault J, Conner TS, Tennen H, Kranzler HR, Furneaux HM. A common polymorphism in serotonin receptor 1B mRNA moderates regulation by miR-96 and associates with aggressive human behaviors. Mol Psychiatry 2019; 14: 381-9.

60. Chamberlain SR, Blackwell AD, Fineberg NA, Robbins TW, Sahakian BJ. The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. Neurosci Biobehav Rev 2005; 29: 399-419.

61. Gruner P, Pittenger C. Cognitive inflexibility in obsessive-compulsive disorder. Neurosci 2017; 345:243-255.

62. Kashyap H, Kumar JK, Kandavel T, Reddy YCJ. Neuropsychological functioning in obsessive-compulsive disorder: Are executive functions the key deficit? Compr Psychiatry 2013; 54:533–40.

63. Rao NP, Reddy YCJ, Kumar KJ, Kandavel T, Chandrashekar CR. Are neuropsychological deficits trait markers in OCD? Prog. Neuropsychopharmacol. Biol Psychiatry 2008; 32:1574–9.

64. Trivedi JK, Dhyani M, Goel D, Sharma S, Singh AP, Sinha PK, Tandon R. Neurocognitive dysfunction in patients with obsessive compulsive disorder. Afr J Psychiatry (Johannesbg). 2008 Aug;11(3):204-9. doi: 10.4314/ajpsy.v11i3.30270. PMID: 19588044.

65. Tükel R, Gürvit H, Ertekin BA, Oflaz S, Ertekin E, Baran B, Kalem SA, Kandemir PE, Ozdemiroğlu FA, Atalay F. Neuropsychological function in obsessive-compulsive disorder. Compr Psychiatry. 2012 Feb;53(2):167-75. doi: 10.1016/j.comppsych.2011.03.007. Epub 2011 May 6. PMID:

21550029.

66. Rajender G, Bhatia MS, Kanwal K, Malhotra S, Singh TB, Chaudhary D. Study of neurocognitive endophenotypes in drug-naïve obsessive-compulsive disorder patients, their first-degree relatives and healthy controls: Neurocognitive endophenotypes in OCD. Acta Psychiatr Scand 2011; 124:152–61.

67. Bohne A, Savage CR, Deckersbach T, Keuthen NJ, Jenike MA, Tuschen-Caffier B, Wilhelm S. Visuospatial abilities, memory, and executive functioning in trichotillomania and obsessive-compulsive disorder. J Clin Exp Neuropsychol. 2005 May;27(4):385-99. doi: 10.1080/13803390490520418. PMID: 15962686.

68. Li B, Sun J-H, Li T, Yang Y-C. Neuropsychological study of patients with obsessive-compulsive disorder and their parents in China: searching for potential endophenotypes. Neurosci Bull 2012; 28:475–82.

69. Martínez-Esparza IC, Olivares-Olivares PJ, Rosa-Alcázar Á, Rosa-Alcázar AI, Storch EA. Executive functioning and clinical variables in patients with obsessive-compulsive disorder. Brain Sciences 2021; 11: 267.

70. Ryan B, Joilin G, Williams JM. Plasticity-related microRNA and their potential contribution to the maintenance of long-term potentiation. Front Mol Neurosci 2015; 8: 4.

71. Zovoilis A, Agbemenyah HY, Agis-Balboa RC, Stilling RM, Edbauer D, Rao P, Farinelli L, Delalle I, Schmitt A, Falkai P, Bahari-Javan S, Burkhardt S, Sananbenesi F, Fischer A. microRNA-34c is a novel target to treat dementias. EMBO J. 2011 Sep 23;30(20):4299-308. doi: 10.1038/emboj.2011.327. PMID: 21946562; PMCID: PMC3199394.

72. Lu L, Dai WZ, Zhu XC, Ma T. Analysis of Serum miRNAs in Alzheimer's disease. Am J Alzheimer's Dis Other Demen 2021; 36: 15333175211021712.

73. Fyfe I. MicroRNAs—diagnostic markers in Parkinson disease?. Nat Rev Neurol 2020; 16: 65

74. Reed ER, Latourelle JC, Bockholt JH, Bregu J, Smock J, Paulsen JS, Myers RH; PREDICT-HD CSF ancillary study investigators. MicroRNAs in CSF as prodromal biomarkers for Huntington disease in the PREDICT-HD study. Neurology. 2018 Jan 23;90(4):e264-e272. doi: 10.1212/WNL.0000000000004844. Epub 2017 Dec 27. PMID: 29282329; PMCID: PMC5798654.

75. Gou M, Pan S, Tong J, Zhou Y, Han J, Xie T, Yu T, Feng W, Li Y, Chen S, Cui Y, Tian B, Tan MDS, Wang Z, Luo X, Li CR, Zhang P, Huang J, Hong LE, Tan Y, Tian L. Effects of microRNA-181b-5p on cognitive deficits in first-episode patients with schizophrenia: Mediated by BCL-2. J Psychiatr Res. 2021 Apr;136:358-365. doi: 10.1016/j.jpsychires.2021.02.003. Epub 2021 Feb 14. PMID: 33636692.

76. Pérez-Rubio G, Pérez-Rodríguez ME, Fernández-López JC, Ramírez-Venegas A, García-Colunga J, Ávila-Moreno F, Camarena A, Sansores RH, Falfán-Valencia R. SNPs in NRXN1 and CHRNA5 are associated to smoking and regulation of GABAergic and glutamatergic pathways. Pharmacogenomics. 2016 Jul;17(10):1145-1158. doi: 10.2217/pgs-2016-0020. Epub 2016 Jun 29. PMID: 27355804.

77. Tamminga CA, Southcott S, Sacco C, Wagner AD, Ghose S. Glutamate dysfunction in hippocampus: relevance of dentate gyrus and CA3 signaling. Schizophr Bull 2012; 38:927-935.

78. Song X, Sun Z, Chen G, Shang P, You G, Zhao J, Liu S, Han D, Zhou H. Matrix stiffening induces endothelial dysfunction via the TRPV4/microRNA-6740/endothelin-1 mechanotransduction pathway. Acta Biomater. 2019 Dec;100:52-60. doi: 10.1016/j.actbio.2019.10.013. Epub 2019 Oct 10. Erratum in: Acta Biomater. 2021 Mar 1;122:387-388. doi: 10.1016/j.actbio.2021.01.009. PMID: 31606530.