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Cognitive Functions in Obsessive Compulsive Disorder and Its Relationship with Oxidative Metabolism

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ABSTRACT

Introduction: While data on oxidative stress in psychiatric disorders are increasing, studies on obsessive-compulsive disorder (OCD) are limited. Although many studies report neurocognitive deficits in OCD, to our knowledge, no study exists examining the relationship between neurocognitive functions and oxidative stress in OCD. This study investigated the neurocognitive functions in OCD and its relationship with OCD severity and oxidative metabolism.

Methods: In our study, 50 OCD patients and 50 healthy controls were included. The groups were well-matched for age, gender, education years, and other socio-demographic characteristics. Comorbid psychiatric diagnoses were excluded. To assess cognitive functions, a battery of neurocognitive tests was used. Oxidative metabolism parameters such as oxidants homocysteine, malondialdehyde, nitric oxide and antioxidants; sialic acid and glutathione peroxidase were measured. Obsessive-compulsive disorder severity was assessed with Yale-Brown-Obsession-Compulsion-Scale (YBOCS). Patients with OCD and control groups were compared in terms of neurocognitive functions, oxidative stress and OCD severity.

Results: OCD group performed significantly worse in various aspects of attention, memory, executive functions ($p<0.05$). Homocysteine, nitric oxide, malondialdehyde, sialic acid levels were significantly ($p<0.05$) higher, glutathione peroxidase was significantly ($p<0.05$) lower in patients versus controls. Yale-Brown-Obsession-Compulsion-Scale scores correlated negatively with most of neurocognitive functions. The relationship between oxidative parameters and cognitive tests was contradictory as some results were opposite to what was expected.

Conclusions: Cognition is affected by OCD and worsens with disorder severity. Considering oxidative parameters were meaningful in patients, oxidative metabolism may be a risk factor for OCD. However, more studies are needed to evaluate the effect of oxidative metabolism on cognitive functions.

Keywords: Obsessive-compulsive disorder, cognitive functions, oxidative metabolism

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INTRODUCTION

Obsessions are described as repetitive, frequently experienced intrusive thoughts, impulses or images that cause anxiety; compulsions are defined as behaviors or mental processes developing in response to obsessions to prevent anxiety (1).

The lifetime prevalence of OCD in adults is 2.3% (1), and approximately two-thirds of patients reported severe dysfunction. More importantly, treating OCD is challenging on several levels. In fact, on average, patients first seek professional care after 10 years of untreated symptoms and only receive appropriate treatment after 17 years. Moreover, despite the effectiveness of current treatment options such as serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT), many patients are unable to initiate or complete CBT (26% and 31%, respectively), with 40% of patients refractory to treatment (2,3).

The identification of OCD-related biomarkers is therefore of great importance and may contribute not only to more effective treatment options, but also to earlier diagnosis, more accurate prognosis, and development of prevention strategies.

Highlights

- **Cognitive functions such as attention, memory, executive functions are affected by OCD.**
- **Neurocognitive functions are worsened by severity of obsessive-compulsive symptoms.**
- **Oxidative metabolism affects OCD and might be considered as an etiological risk factor.**
- **Results are inconsistent in terms of effect of oxidative stress on cognition in OCD.**

While OCD was defined as a subtype of Anxiety Disorders in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), it has been reported to be associated with some neurobiological abnormalities different from anxiety disorders and removed from anxiety disorders in DSM-5 (1). It is considered to be a neuropsychiatric disorder including disturbing, intrusive thoughts and related compulsive behaviors (4).

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The data obtained from neuropsychological, neuroimaging and electrophysiological studies and information about its relationship with frontal functions indicate that dysfunction in prefrontal-subcortical and fronto-striato-pallido-thalamic circuits plays a role in the physiopathology of OCD (5,6). It is thought that changes in the caudate nucleus may be related to obsessive-compulsive symptoms and changes in the orbitofrontal and anterior cingulate regions may be related to mood symptoms of OCD. The changes seen in the temporal, parietal, and posterior cingulate cortex appear to be more associated with anxiety (7,8). In addition to mood and anxiety symptoms, cognitive functions are also impaired in OCD and are related to defects in fronto-striato-pallido-thalamic circuits that form the control cognition of behavior, decision-making and planning complexes (9). Cognitive defects in OCD have been determined mainly in executive functions and in attention, memory, decision making, visual-spatial functions and ability to changesets (10). Although the pathophysiology of the deterioration in these areas is not well-known, damage caused by oxidative stress and free radicals have been identified in various parts of the brain in patients with OCD (11,12).

Oxidative stress is often caused by the overproduction of reactive oxygen species (ROS) (free radicals) or the failure of systems that regulate ROS. The brain is sensitive to be damaged by free radicals; because the human brain uses up 20% of the total oxygen capacity and has high concentrations of phospholipids which make neurons more prone to lipid peroxidation and basal ganglia have large concentrations of catecholamines (13). It is suggested that oxidative stress causes diseases due to its toxic effects on the metabolism of carbohydrates, proteins, lipids and DNA. Increasing evidence supports the possibility that psychiatric disorders may be considered as multisystem disorders in patients exhibiting altered immune and oxidative markers (14). The oxidative system appears to be dysregulated in OCD and other psychiatric disorders such as major depressive disorder, bipolar disorder, or schizophrenia (15). Specifically for OCD, systemic dysregulation of inflammation and oxidative stress is increasingly being reported, although the exact etiology and pathophysiology are unknown (16–18).

There is also evidence that cognitive or memory deficits are the result of imbalances between local ROS and antioxidant capacity in the brain and it has been suggested that an unbalanced accumulation of oxidatively modified proteins in the brain enhances neurodegeneration and impairs cognitive function. Studies reporting that a number of pathological processes characterized by impairments in learning, memory, attention, and concentration are associated with increased mitochondrial deterioration within the central nervous system support these hypotheses (19).

Oxidative markers such as nitric oxide, homocysteine, malondialdehyde are associated with pathologies of the cell membrane in the central nervous system (20).

Homocysteine (Hcy), which has a role in neuropsychiatric diseases and loss of cognitive ability, plays a role in all important mechanisms of neurodegeneration such as oxidative stress, DNA damage, stimulation of apoptosis and excitotoxicity (21).

Nitric oxide (NO), a free radical, is also important in the pathophysiology of neurotoxicity in the CNS. Its role in learning and memory in the hippocampus is also known. It has been reported that SSRIs inhibit nitric oxide synthase activity and supports the role of antidopaminergics and the use of N-methyl-D-aspartate (NMDA) receptor antagonists in the treatment of OCD. Patients with OCD have been found to have high nitrate levels. This evidence points to the role of NO in obsessive-compulsive behavior as well as in the anticompulsive effects of drugs used in treatment (22).

One of the biocemicals we investigated was malondialdehyde (MDA); the most well-studied product of lipid peroxidation. Lipid peroxidation, which results in free radical production, is one of the most well-known types of damage by oxidative stress. This aldehyde is a highly toxic molecule that interacts with DNA and proteins and is known to be mutagenic (23). We aimed to investigate the effects on OCD and cognitive functions of these neurodegenerative molecules.

On the other hand, lack of sialic acid (SA) is an important risk factor for neuropsychiatric and neurodegenerative diseases and it has an important role in the protection of cell membranes and glycoprotein structures, cell-cell interactions, membrane transport, a binding molecule in membrane receptors (24). Another protective molecule we investigated was glutathione peroxidase (Gpx), which is involved in the detoxification of hydrogen peroxide (H_2O_2) and the detoxification of lipid hydroperoxides (25).

We hypothesized an impaired cognition in OCD and these parameters play a role in both OCD symptoms and cognitive impairment in OCD. Studies investigating such an association for OCD are few and to our knowledge, no studies exist examining the relationship between neurocognitive functions and oxidative stress in obsessive-compulsive disorder. We aimed to assess neurocognitive functions in patients with OCD and to examine its relationship with oxidative stress.

METHODS

Ethical Considerations

The study protocol was accepted by the ethical committees of our Atatürk University (Number:2010/3, Date: 11.06.2010).

Participants

Fifty patients diagnosed with OCD according to DSM-IV-TR criteria and 50 healthy controls matched with patients in terms of gender, age, education and other sociodemographic parameters were recruited at Atatürk University psychiatry clinic.

Our rationale for sample size was based on a pilot study conducted by Bedard et al. (26). This study found some neuropsychological differences emerged between the patients with OCD and healthy participants. Based on the use of the analysis of variance (ANOVA) statistical model, an alpha level of 0.05, a power of 90 and an effect size of 0.45, a total of 100 subjects (50 per experimental group) were needed to have sufficient power to detect the effects of neurocognitive tests on OCD.

The diagnosis of OCD in patients was confirmed and other psychiatric diagnoses of the patients and controls were excluded using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).

Inclusion Criteria

Participants between the ages of 18 and 65, literate, had no eye disorder and color blindness preventing the application of neuropsychological tests and with no comorbid psychiatric or systemic diagnosis were included.

Exclusion Criteria

Using psychotropic drugs in the last two weeks, diagnosed with a comorbid psychiatric disorder and mental retardation, infection, severe obesity, neurological disorders, organ failure, heart disease, diabetes mellitus, hypercholesterolemia and drug-substance addiction, smoking, using antioxidants and those who read the informed consent form and refused to participate in the study were excluded.

The onset age at diagnosis and duration of treatment of the patient group were not taken into consideration, the presence of the diagnosis was taken into account and this was discussed within our limitations.

Tests were applied by the researcher. Cognitive assessment was conducted in the test laboratory of our psychiatry clinic. Optimal requirements such as light, silence and external conditions were fulfilled.

SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders)
It is a Structured Clinical Interview Form for DSM-IV. The test, which was adapted to DSM III-R diagnostic criteria in 1997, was created by the American Psychiatric Association with the revision of the test according to DSM-IV diagnostic criteria. It is a semi-structured diagnostic interview schedule, translated and validated into Turkish (27). It begins with a sociodemographic data guide and covers seven diagnostic groups including mood disorders, psychotic disorders, alcohol and substance-related disorders, anxiety disorders, somatoform disorders, eating disorders, and adjustment disorders.

Sociodemographic Data Form
In the form developed by the researcher, there were questions about the individual's age, gender, educational status, marital status, occupation, residence place, income rate and family structure.

Yale–Brown Obsession-Compulsion Scale (YBOCS)
It was used to assess the severity of symptoms observed in OCD patients (28).

Neurocognitive Assessment
The neurocognitive battery included the Rey Auditory Verbal Learning Test (RAVLT), Auditory Consonant Trigram Test (ACTT), Controlled Oral Word Association Test (COWAT), Digit Span Test (DST), Trail Making Test (TMT-A/B), Wisconsin Card Sorting Test (WCST), Stroop Test (ST), Test of Variables of Attention (TOVA) (29).

Rey Auditory Verbal Learning and Memory Test (RAVLT)
Verbal episodic memory, short-term memory and learning functions were assessed with the RAVLT, in which subjects had to learn a series of words presented orally over five trials and were expected to immediately recall them after each presentation (total recall of five trials) or with a 20-minute delay (delayed recall). They were also asked to recognize target words between distracters (recognition) (30). The following measures were analyzed: total learning scores (1–5 readings), delayed recall, the number of correctly recalled words after the 20-minute delay; true positives and false positives.

Auditory Consonant Trigram Test (ACTT)
This test measured divided attention, information processing, short-term memory and working memory (31). The total number of recalled letters was evaluated.

Controlled Oral Word Association Test (COWAT)
This test was a measure of phonemic verbal fluency, in which subjects had to produce the maximum number of words with the given letters (K, A, and S, according to Turkish standardization) within one minute for each letter (32).

Trail Making Test (TMT-A/B)
This test assesses attention, mental flexibility, visual tracking, and motor abilities. In part A, dots numbered between 1 and 25 are combined with a continuous line and in part B, each letter is combined with a number alternatively. Part A evaluates psychomotor (attention) speed and focused attention whereas part B measures executive functioning and altered attention (set shifting). In this study, the times required to complete the two separate parts were evaluated.

Stroop Test (ST)
As one of the main tools for evaluating executive functioning, ST assesses the ability to flexibly direct attention in the presence of a distraction (i.e. selective attention), inhibit a habitual behavioral pattern and display unusual behavior by taking into account the individual's speed of processing in measuring resistance to interference (29).

Digit Span Test (DST)
"Digit Span" subtest of Weschler Memory Scale (WMS) is used to evaluate primary verbal attention. It has two sections, digit span forward and backward. The forward section measures verbal attention and the backward section measures verbal working memory. In the forward section, the subject repeats the numbers told by the rater, in the backward section the subject repeats the numbers told backwards. The score is the sum of the correctly recalled numbers in the forward and backward sections (34).

Wisconsin Card Sorting Test (WCST)
Executive functions such as cognitive flexibility, problem solving and abstraction abilities were assessed with the WCST-128 cards, in which participants had to classify a series of cards into three categories after having found the classification rule (color, number, or forms) (35).

In the present study, a computerized form of the test (WCST: CV4) was used. In WCST-CV4, the subjects react by choosing the appropriate card on the screen. These responses are recorded by the computer. In a study conducted; similar structures of WCST-CV4 with classical application were obtained and the results of the two applications were compatible (36).

Test of Variables of Attention (TOVA)
It measures the ability of sustained attention, continuous attention and is based on the monitoring of random changes in the stimulus flow. The TOVA test is carried out with two different stimuli that appear and disappear on the computer monitor.

During application, the subject is instructed to press the test button as fast as possible when they see the target stimulus, and not to press the button when they see the non-target stimulus. The evaluation of the TOVA is performed by the computer. Skipping correct response is evaluated as omission (TOVA 1), incorrect response as commission (TOVA 2), and response time as TOVA 3.

The obtained parameters are calculated separately for the 4-quarter periods of the test and displayed with the symbols #Q1, #Q2, #Q3, #Q4. Likewise, the first half of the test is #H1, the second half is #H2, the entire test is #T symbols (37).

Statistical Analysis
Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 11.0. The chi-square test was performed for the appropriate categorical variables based on the number or order of the table. In intergroup comparisons for numeric measure values, variables were separated as parametric and nonparametric at a significance level of 0.05 using the Kolmogorov-Smirnov and Shapiro-Wilk tests before comparison. The comparison between groups for the parametric variables was performed using the Levene test and the Index-t test. For the nonparametric variables, the Mann Whitney U test was used.

Evaluation of Nitric Oxide (NO), Malondialdehyde (MDA), Homocysteine (Hcy), Glutathione Peroxidase (Gpx), Sialic Acid (SA) Levels in Blood
10 cc of blood was drawn from the participants after a rest period of 10–15 minutes in sitting position by an experienced nurse. After centrifugation of the tubes, the serum obtained from the gel biochemistry tube was

transferred to the Eppendorf tubes. The serum was stored at -80°C until the levels of malondialedehyde, sialic acid, nitric oxide and glutathione peroxidase were determined. Homocysteine was studied from the plasma obtained from the heparin tube. Plasma homocysteine levels were studied with a commercially available homocysteine kit in the High Performance Liquid Chromatography (HPLC) device and other tests were studied manually in the Department of Biochemistry at our hospital.

The financial expenses related to the chemical materials for the manual study and commercially available homocysteine kit were covered by the researcher.

RESULTS

A total of 100 participants as 50 OCD patients and 50 healthy controls were included. The mean age of OCD patients was 29.98±11.01, mean age of controls was 31.08±10.4. Obsessive-compulsive disorder group consisted of 35 (70%) women, 15 (30%) men, control group consisted of 35 (70%) women, 15 (30%) men. The mean education year was 12.64 years in patients, 12.92 years in controls. Other sociodemographic data showed similar characteristics in both groups (p>0.05) (Table 1).

With respect to neurocognitive performance (Table 2); learning functions and short-term memory were impaired in OCD group according to RAVLT; total learning scores (1–5) were significantly lower in OCD (p=0.008) but verbal episodic memory was not affected and delayed recalling score, true positives and false positives in the recognition subtest scores did not show a significant difference (p=0.120, p=0.091, p=0.780, respectively). Obsessive-compulsive disorder group was significantly impaired in divided attention, information processing, short-term memory and working memory (ACTT; p<0.001) but psychomotor (attention) speed and focused attention were not affected (TMT-A; p=0.135). Patients performed lower in the TMT-B time scores significantly (p=0.006) meaning executive functioning and altered attention (set-shifting) was partially impaired. Obsessive-compulsive disorder group performed lower in phonemic verbal fluency assessed with the COWAT scores (p=0.027) but verbal attention seemed to be unaffected in patients assessed with the digit forward test (p=0.889). Patients performed lower in the digit back scores, meaning worse performance in verbal working memory (p=0.006). As the ST main card reading time was significantly longer (p=0.010), the patients' executive functions, altered attention (set-shifting) and selective attention seemed to be impaired. In the WCST, controls performed higher only in terms of the number of cards opened (p=0.043), meaning patients needed more cards to find the correct one. Test of Variables of Attention assessed sustained attention, continuous attention and was impaired moderately as; omission (TOVA 1) and commission (TOVA2) scores were not different between groups (p=0.784, p=0.413, respectively) but the mean response time was shorter in controls (p=0.037) meaning controls were faster than patients in giving responses to targets and nontargets.

Evaluating blood levels of biochemical parameters; oxidants; Hcy, NO, MDA levels were higher, antioxidant Gpx was lower, but antioxidant SA was higher in patients (p<0.001, p<0.001, p<0.001, p<0.001, p<0.001 respectively) (Table 3).

When the correlations between YBOCS scores and neurocognitive tests were evaluated, YBOCS scores were negatively correlated with WCST total correct scores and category score (r=-.282, r=-.301respectively) and DST total scores (r=-.280). It was determined that there was a positive correlation with the ST main card reading time (r=.403). In the TOVA test, YBOCS scores were positively correlated with response time (TOVA3) (r=279), which means delayed response and impaired continuous and sustained attention (Table 4).

With respect to the correlations between the cognitive functions and oxidative stress parameters (Table 5); Hcy effect on the cognitive tests was contradictory as it correlated positively with delayed recalling scores and true positives in RAVLT (r=0.318, r=0.313 respectively) and ACTT scores (r=0.303) contrary to the expectations and had no correlation with others. Sialic acid levels positively correlated with true positives of RAVLT (r=0.323) as expected.

Table 1. Sociodemographic characteristics of the patient and control groups

	Obsessive Compulsive Disorder (n=50)	Control (n=50)
Age (± standard deviation)	29.98±11.01	31.08±10.4
Gender	W=35 (70%), M=15 (30%)	W=35 (70%), M=15 (30%)
Educational status (years)	12.64	12.92
Marital Status		
-Married	21 (42%)	23 (46%)
-Single	28 (56)	25 (50%)
-Widow	1 (2%)	2 (4%)
Occupation		
-Housewife	16 (32%)	13 (26%)
-Government official	15 (30%)	21 (42%)
-Student	19 (38%)	16 (32%)
Income rate		
-low	1 (2%)	4 (8%)
-moderate	33 (66%)	26 (52%)
-high	16 (32%)	20 (40%)
Place of residence		
-City center	37 (74%)	42 (84)
-District	11 (22%)	7 (14%)
-Village	2 (4%)	1 (2%)
Family structure		
-Nuclear	47 (94%)	50 (100%)
-Extended	3 (6%)	0

M: Men; W: Women.

Table 2. Neurocognitive test results

Neurocognitive Tests		Group	N	Mean	Standard deviation	p	t
RAVLT	Total learning scores (1–5)	patient	50	47.3400	7.83141	0.008	-2.729
		control	50	52.5000	10.83880;		
	Delayed recalling scores	patient	50	9.9400	2.55878	0.120	-1.568
		control	50	10.7800	2.79424		
	True positives	patient	50	12.8800	1.89133	0.091	-1.708
		control	50	14.5400	6.60615		
	False positives	patient	50	1.1000	1.94044	0.780	-0.280
		control	50	1.2200	2.32370		
ACTT		patient	50	45.1400	7.55662	<0,001	-3.837
		control	50	50.4400	6.18807		
COWAT		patient	50	36.9200	15.76335	0.027	-2.249
		control	50	43.9800	15.63159		
DST	Digit forward	patient	50	6.7000	2.29685	0.889	-0.140
		control	50	6.7600	1.97495		
	Digit Back	patient	50	5.2800	1.69079	0.006	-2.793
		control	50	6.4200	2.33946		
	Digit Total	patient	50	11.9600	3.38038	0.095	-1.686
		control	50	13.1800	3.84225		
TMT	Part A	patient	50	39.6804	22.03488	0.135	1.508
		control	50	34.2574	12.70247		
	Part B	patient	50	93.0474	48.16305	0.006	2.812
		control	50	69.6658	33.73442		
TOVA Scores	Omission scores (TOVA1)	patient	50	2.3606	5.72665	0.784	-0.275
		control	50	2.6606	5.15887		
	Comission Scores (TOVA2)	patient	50	6.4930	4.57287	0.413	-0.822
		control	50	7.4524	6.87450		
	Response Time (TOVA3)	patient	50	334.6000	61.05000	0.037	2.115
		control	50	311.1800	49.05711		
WCST	Total correct scores;	patient	50	69.780	13.1122	0.401	0.843
		control	50	67.700	11.5091		
	Total error scores;	patient	50	41.760	24.0311	0.177	1.359
		control	50	34.940	26.1256		
	Category score;	patient	50	4.40	2.000	0.617	-0.501
		control	50	4.60	1.990		
	Trials to complete the first category;	patient	50	28.8000	32.52817	0.382	0.879
		control	50	23.4000	28.80830		
	Number of cards opened;	patient	50	111.5400	20.30905	0.043	2.047
		control	50	102.6400	23.08702		
ST		patient	50	26.5552	10.29242	0.010	2.630
		control	50	21.8168	7.50708		

ACTT: Auditory Consonant Trigram Test; COWAT: Controlled Word Association Test; DST: Digit Span Test; RAVLT: Rey's aAuditory Verbal Learning Test; ST: Stroop Test; TMT: Trail Making Test; TOVA: Test of Variables of Attention; WCST: Wisconsin Card Sorting Test.

Table 3. Blood levels of biochemical parameters

Group		N	Mean	Standard deviation	p	t
Hcy (nmol/mL)	patient	50	17.7042	9.70013	<0,001	6.183
	control	50	8.6732	3.54860		
MDA (nmol/mL)	patient	50	14.8014	15.99850	<0,001	4.517
	control	50	4.5000	2.01596		
NO (nmol/mL)	patient	50	23.0538	7.89758	<0,001	4.766
	control	50	11.2470	15.63433		
Gpx (nmol/mL)	patient	50	48.8170	24.88399	<0,001	-4.407
	control	50	73.0558	29.88627		
SA (nmol/mL)	patient	50	78.6498	31.21092	<0,001	7.723
	control	50	41.7008	13.05285		

Gpx: Glutathione peroxidase; Hcy: Homocysteine; MDA: Malondialdehyde; NO: Nitric oxide; SA: Sialic acid.

Table 4. Correlations between YBOCS scores and neurocognitive tests

		YBOCS
WCST total correct scores	r	-0.282(*)
	p	0.047
WCST total error scores	r	0.279(*)
	p	0.049
WCST category score	r	-0.301(*)
	p	0.034
Digit total	r	-0.280(*)
	p	0.049
Stroop test main card reading time	r	0.403(**)
	p	0.004
TOVA1#Q1	r	0.313(*)
	p	0.027
TOVA3#H1	r	0.279(*)
	p	0.050

TTOVA1#Q1: Omission (skipping correct response) scores in the first quarter of the Test of Variables of Attention; TOVA3#H1: Comission (incorrect response) scores in the first half of the Test of Variables of Attention WCST: Wisconsin Card Sorting Test; YBOCS: Yale-Brown Obsession-Compulsion Scale. *p<0.05, **p<0.01

Malondialdehyde levels did not correlate with any test scores. The effect of NO was contradictory as it negatively correlated with omission scores of TOVA (r=-0.307) as expected, but positively correlated with category score of WCST and negatively correlated with total error scores of WCST. Gpx levels were in opposition with expectations as they negatively correlated with total learning scores (r=-0.424) but positively correlated with the false positives of RAVLT (r=0.313), negatively correlated with DST backward scores (r=-0.316), positively correlated with ST main card reading time (r=292).

DISCUSSION

The main aim of this study was to determine whether a cognitive profile could be associated with OCD when using a comprehensive neuropsychological battery. Our secondary aim was to evaluate whether OCD severity and cognitive performance were related to oxidative metabolism.

In literature, there are studies showing impaired cognitive functions of patients with OCD compared to healthy controls, as well as studies showing no difference between the cognitive functions of patients and healthy controls (38-40). There may be various explanations for the lack of consistent results. Comorbidities with OCD and especially high rates of depression accompanying seem to be important causes. Whether or not the patients used drugs during the evaluation is another issue that should be taken into account when evaluating neuropsychological functions. Also, there are studies which demonstrate that serotonergic system affects cognitive functions (41).

Exclusion of depression, other comorbid psychiatric diseases and use of psychotropic drugs, and studying with similar groups in terms of age, gender and other important parameters that could affect the performance of the cognitive tests provided the means to interpret our results independently from the effects of other parameters. Therefore, we think that we could evaluate our results only in terms of OCD.

Our results were consistent with some studies indicating impairments in various aspects of attention in OCD (9,10); such that we demonstrated impairments in divided attention, information processing, altered attention (set-shifting) and partially sustained, continuous and concentrated attention.

The TMT Part A is an indicator of attention speed and focused attention and OCD subjects showed similar results with controls in attention speed as in some other studies (39, 40). But TMT Part B of patients was partially worse so it can be considered that failure is especially related to executive functions and set-shifting, rather than speed only. It can be considered that altered attention (set-shifting) and selective attention were impaired in OCD evaluated by ST similarly with some findings in the literature (42,43).

Surveys indicating impaired attention in OCD suggested impairment in those who showed high rates of depression (38, 39). Since the depression was excluded in this study, the impairments can be considered to be related to OCD only. Most of the studies revealed different results indicating interruptions in attention. Since the neurobiological basis of

Tablo 5. Statistically significant correlations between the neurocognitive tests and oxidative stress parameters

		Hcy	Gpx	NO	SA
RAVLT 1–5 total	r		-0.424(**)		
	p		0.002		
Delayed recalling scores RAVLT 7	r	0.318(*)			
	p	0.024			
True positives in RAVLT	r	0.313(*)			
	p	0.027			
False positives in RAVLT	r		0.280(*)		0.323(*)
	p		0.049		0.022
Auditory consonant trigram test	r	0.303(*)			
	p	0.033			
Digit back	r		-0.316(*)		
	p		0.025		
Stroop test main card reading time	r		0.366(**)		
	p		0.009		
TOVA1#TOT	r			-0.307(*)	
	p			0.030	
WCST total error scores	r			-0.325(*)	
	p			0.021	
WCST category score	r			0.317(*)	
	p			0.025	

Gpx: Glutatyon peroksidaz; Hcy: Homosistein; MDA: Malondialdehid; NO: Nitrik oksit; SA: Sialik asit. RAVLT: Rey's Auditory Verbal Learning Test; TOVA1#TOT: Total omission (skipping correct response) scores in the Test of Variables of Attention; WCST: Wisconsin Card Sorting Test. *p<0.05, **p<0.01

OCD is the prefrontal-striatal system, defects are expected in various aspects of attention (5,6) which our results also support.

The negative correlation of YBOCS scores between DST total scores –evaluating verbal attention– and the positive correlation between ST main card reading time –evaluating altered attention– demonstrates compatibility with previous studies indicating that attention is affected by OCD severity. A positive correlation between the TOVA response time and the YBOCS scores means that the delay in response increases with the severity of the disorder. Some studies found positive correlation between the false responses of continuous performance tests and YBOCS scores (41-43).

More results indicating lower cognitive and motor capacity were observed regarding ST performance, consistent with previous findings (42, 44). Failures in error handling and the implementation of inhibitory control may underlie deficiencies in stopping undesirable compulsive behaviors in this disorder.

Similar to other studies (45-47); OCD patients performed worse on visual-spatial memory and on tasks assessing verbal attention on the DST. These results demonstrate that attention is affected in OCD and disorder severity is associated with more attention problems. In addition to studies suggesting a significant relationship between the severity of symptoms and neuropsychological deficits in OCD, there are also studies reporting that there is no relationship between symptoms and neuropsychological test performance (48).

Some behaviors of an individual with OCD, demonstrate the presence of a memory problem. For example, a constant checking problem may indicate that the individual is not able to encode or remember behaviors by memory. Approaches on this subject indicated that OCD patients had impaired monitoring of reality and memory performance (10).

For the evaluation of memory functions; RAVLT was used to evaluate immediate and short-term memory and learning functions, DST backward and ACTT were used to evaluate working memory. When memory tests were examined together, it was found that the patients had impairments in immediate memory, working memory, short-term memory, and learning functions independently from the recall effect.

While some studies found no impairment in various memory performances of OCD patients (49, 50), some found lower memory performance (51). Memory impairment in OCD may be explained by the negative effect of OCD on cognitive functions.

Perna et al. (47) found that OCD patients have a lower spatial storage capacity, which may contribute to memory insecurity and greater dependence on external validations (52). Martoni et al. (46) concluded that the deficits in visuospatial memory in OCD appear to be more severe as the severity of symptoms increases and these may be mediated by task strategy (executive dysfunction).

Another cognitive function we investigated was the executive functions. Many studies emphasize that OCD patients have problems with executive functions. Executive functions are impaired when the frontal lobe, especially the prefrontal region is affected. Executive functions also provide coordination of other cognitive functions such as working memory and attention (9,10). Stroop Test main card reading time being longer in OCD patients than controls shows that executive functions are affected in OCD. No significant difference was found except for the number of attempts between the groups in WCST, meaning OCD patients needed to open more cards to find the correct cards, and that they could complete fewer problems with the least number of attempts possible. In addition, correlations between YBOCS and WCST mean a decrease in executive functions with the severity of OCD. Wisconsin Card Sorting Test performance includes being able to change the setup and impaired performance means perseveration, in other words, insistence on the behavior in line with the previous principles even though the behavioral principle has changed. This seems to be compatible with OCD rituals (42). As we mentioned while discussing the issue of attention, examining the ST and YBOCS relationship, it was seen that the duration time increased with the OCD severity. It is observed that the patients displayed a significantly lower performance TMT Part B (the working memory and the ability to change sets). These results tend to suggest that not only their psychomotor speed is slow, but their ability to changesets is low too. Changing the setup, planning and perseveration are frequently investigated among the executive functions in OCD.

Briefly; OCD patients performed significantly worse in all tests evaluating executive functions as demonstrated in some previous studies (53-55).

Patients also performed lower in verbal fluency in COWAT evaluations. Although few studies have reported decreases (45), most studies show intact word fluency in OCD (57-59). On the other hand, a decrease in semantic verbal fluency has been reported more consistently, reflecting decreased semantic system access (60).

The second phase of our study was to evaluate the effect of oxidative metabolism on OCD symptoms and cognitive functions. Results of oxidative metabolism indicated an impaired oxidative balance in OCD. We found a statistically significant global increase in oxidant markers in OCD patients, similar to that described for other psychiatric disorders (15). Our results were consistent with the literature reporting an increase in oxidant markers in OCD patients (12). Levels of oxidative malondialdehyde, nitric oxide, and homocysteine were high in patients. This may indicate that increased oxidative stress plays a role in the etiopathogenesis of OCD. A low level of the antioxidant enzyme glutathione peroxidase in the OCD group seems to mean a deficiency in the antioxidant system –a protective factor– which also plays a role in the etiology of OCD (15,25). The level of SA, which is a membrane component associated with cell integrity, vitality and functions, was higher in patients. The increased SA level in the blood may mean a decrease in the membrane. Losing its original position may cause membrane deformity and damage intracellular structures, especially DNA damage, which may play a role in the disease pathogenesis (15,24).

The effect of oxidative stress on cognitive functions was contradictory as Hcy correlated positively with delayed recalling scores and true positives in RAVLT (r=0.318, r=0.313 respectively) and ACTT scores (r=0.303) contrary to the expectations and had no correlation with other tests. According to previous studies, high Hcy concentration appears to be a risk factor for cognitive disability (19,21). However, this is not confirmed in all studies (61) and our results demonstrated that Hcy did not cause cognitive disability either. This may be explained by the fact that the level of Hcy in patients were relatively higher compared to controls but not far above the normal limits. The effect of SA levels on cognition was consistent with previous studies as it negatively correlated with false positives in RAVLT scores (r=-0.323) which is related to recording memory and learning (24). Since it is an antioxidant, it can be assumed that it prevents cognitive deterioration.

Malondialdehyde levels did not correlate with any test scores. It was different from the results of previous studies indicating that high MDA levels impair cognitive functions. In a comparison study between OCD patients with and without depression, MDA was found to be high and cognitive functions were affected in the group with depression (23). Malondialdehyde did not seem to affect cognitive functions in our OCD group without depression comorbidity and is consistent with this study.

NO, which is known to have effects on learning and memory in the hippocampus and has evidence for its role in OCD symptoms and treatment (22), gave contradictory results in our study and could not show a clear result on cognitive functions.

Gpx's effect on cognition was inconsistent with the literature (25) as it had a negative effect on tests demonstrating verbal working memory, executive functions, altered attention (set-shifting), selective attention, and learning functions. The fact that some tests seem to be affected negatively by the Gpx levels, which is an antioxidant enzyme, may be associated with the increase in the levels of Gpx as an antioxidant system in parallel with the increase in oxidant parameters.

As a result; it was concluded that cognitive functions are affected by OCD and cognition changes with disorder severity. Considering that oxidative parameters are meaningful in OCD patients compared to controls, our study suggests that oxidative metabolism may be a risk factor for OCD. However, more studies are needed to evaluate the effect of oxidative metabolism on cognitive functions in OCD.

Strengths and Limitations

In our study, it can be said that neurocognitive tests are rich in content because they are versatile and evaluate many areas. Evaluating several biochemical parameters, both oxidants and antioxidants, which are known to be involved in central nervous system pathologies strengthened our data. Exclusion of systemic diseases and drug use and cigarette-alcohol-substance use that may affect oxidative markers and exclusion of comorbid psychiatric diagnoses and psychotropic drug use that may affect the tests are the strengths of our study.

One of our limitations is the fact that conducting many tests consecutively can negatively affect the performance of the participants. Since the study is a comparative study, we think that this problem can be ignored due to the fact that the negative influencers were valid for both groups. Another limitation is the lack of data on the onset age, duration and treatment status of the diagnosis of OCD in the patient group. Since it is very difficult to achieve homogeneity in these features and there are studies which reported no differences between OCD participants in prior neuropsychological investigations with a wide range of tasks that ignored these features (15,26), we evaluated the test results according to current OCD severity.

Ethics Committee Approval: The study protocol was accepted by the ethics committee of Atatürk University (2010/3, Date: 11.06.2010).

Informed Consent: Informed consent was obtained from the patients.

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