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**USE OF ELECTROENCEPHALOGRAPHIC FINDINGS
IN PREDICTING RESPONSE TO NONINVASIVE
DEEP BRAIN STIMULATION IN OBSESSIVE
COMPULSIVE DISORDER**

DOCTOR OF PHILOSOPHY THESIS

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APPROVAL

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DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

17/02/2021

Özden Öksüz



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LIST OF SYMBOLS/ABBREVIATIONS

ACC	Anterior Cingulate Cortex
ALIC	Anterior Limb of the Internal Capsule
BA	Brodmann Area
BDI	Beck Depression Inventory
BG	Basal Ganglia
CBT	Cognitive Behavioral Therapy
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression-Improvement
CGI-SS	Clinical Global Impression-Severity Scale
CSTC	Cortico-Striato-Thalamo-Cortical
DAT	Dopamine Transporter
DBS	Deep Brain Stimulation
DLGAP	Discs Large Homolog-Associated Protein
DLPFC	Dorsolateral Prefrontal Cortex
DRD	Dopamine Receptor D
DSM	The Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imaging
DTMS	Deep Transcranial Magnetic Stimulation
EEG	Electroencephalography
FA	Fractional Anisotropy
FDA	Food and Drug Administration
FMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric acid
GPi/e	Globus Pallidus internus/externus
GWAS	Genome-Wide Association Studies
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
HF	High-Frequency
LF	Low-Frequency

MADRS	Montgomery-Asberg Depression Rating Scale
M-CPP	Meta-Chlorophenylpiperazine
MPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MT	Motor Threshold
M1	Primary Motor Cortex
NAc	Nucleus Accumbens
NMDA	N-methyl-D-aspartate
OCD	Obsessive Compulsive Disorder
OFC	Orbitofrontal Cortex
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
QEEG	Quantitative Electroencephalography
RCT	Randomized Controlled Trial
ROI	Region Of Interest
RTMS	Repetitive Transcranial Magnetic Stimulation
SLC1A1	Solute Carrier Family 1 Member 1
SMA	Supplementary Motor Area
SN	Substantia Nigra
SNP	Single Nucleotide Polymorphism
SPECT	Single-Photon Emission Computed Tomography
SSRI	Selective Serotonin Reuptake Inhibitor
STN	Subthalamic Nucleus
TMS	Transcranial Magnetic Stimulation
TR-OCD	Treatment-Resistant Obsessive Compulsive Disorder
VBM	Voxel-Based Morphometry
WCST	Wisconsin Card Sorting Test
Y-BOCS	Yale-Brown Obsessive Compulsive Scale
5-HT	5-hydroxytryptamine, serotonin
5-HTT	Serotonin transporter
5HTTLPR	5-HTT gene-linked polymorphic region

ABSTRACT

Öksüz, Ö. (2021). Use of Electroencephalographic Findings in Predicting Response to Noninvasive Deep Brain Stimulation in Obsessive Compulsive Disorder. Yeditepe University, Institute of Health Sciences, Doctoral Program in Neuroscience, PhD Thesis, İstanbul.

The aim of this study was to investigate the quantitative electroencephalography (QEEG) findings that affect the response to deep transcranial magnetic stimulation (dTMS) by examining the relationship between the pre-treatment resting-state QEEG data of obsessive compulsive disorder (OCD) patients and their response to dTMS. To this end, the data of 52 OCD patients (mean age: 31.88 ± 11.51 years, M/F: 23/29) aged between 18-65 years who applied to the Private Psychiatry Clinic of Prof. Dr. Kemal Arıkan (İstanbul, Turkey) between Jan 2018 and May 2019 and to whom dTMS was applied were retrospectively examined. The data were collected through sociodemographic and clinical data form, Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Beck Depression Inventory (BDI), and resting-state EEG recording. Fourier analysis was performed by averaging across eyes-closed 2-second EEG epochs without artifacts, and for each of the 19 monopolar derivations, absolute power (μV^2) was calculated for the delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-70 Hz) frequency bands. By evaluating the pre-treatment and post-treatment Y-BOCS scores of the participants, patients with a decrease in the scores of 30% and above were named “responsive group” (n=42), and those without it were named “non-responsive group” (n=10), and the pre-treatment QEEG data of both groups were statistically compared. All statistical analyses were performed using IBM SPSS Statistics 25.0. $P < 0.05$ was accepted to be statistically significant. The alpha and theta absolute power in all electrodes was found to be higher in the responsive group compared to the non-responsive group. No significant difference was observed between the two groups in terms of sociodemographic data and pre-treatment Y-BOCS_total, Y-BOCS_obsession, Y-BOCS_compulsion, and BDI scores. However, the time occupied by obsessions was found to be higher in the responsive group. In conclusion, it was revealed that the increase

in the pre-treatment alpha and theta absolute power might be beneficial in predicting OCD patients who would respond well to dTMS. We suggest that use of such biomarkers can assist clinicians in individualizing OCD treatment and thus achieving optimal treatment outcomes.

Key words: Obsessive Compulsive Disorder; Deep Transcranial Magnetic Stimulation; Electroencephalography



ÖZET

Öksüz, Ö. (2021). Obsesif Kompulsif Bozuklukta Noninvaziv Derin Beyin Stimülasyonuna Yanıt Öngörmede Elektroensefalografi Bulgularının Kullanımı. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü, Sinirbilim Doktora Programı, Doktora Tezi. İstanbul.

Bu çalışmanın amacı, obsesif kompulsif bozukluk (OKB) hastalarının tedavi öncesi dinlenim- durumu kantitatif elektroensefalografi (KEEG) verileri ile derin transkraniyal manyetik uyarıma (dTMU) verdikleri yanıt arasındaki ilişkiyi inceleyerek; dTMU'ya yanıt etkileyen KEEG bulgularını belirlemektir. Bu amaçla, Prof. Dr. Kemal Arıkan Özel Psikiyatri Kliniği'ne (İstanbul, Türkiye) Ocak 2018 ve Mayıs 2019 tarihleri arasında başvuran ve dTMU uygulanan, 18-65 yaş arasındaki 52 OKB hastasının (yaş ort: $31,88 \pm 11,51$, E/K: 23/29) bilgileri retrospektif olarak incelenmiştir. Veriler; sosyo-demografik veri formu, Yale-Brown Obsesyon Kompulsiyon Ölçeği (YBOKÖ), Beck Depresyon Ölçeği (BDÖ) ve dinlenim-durumu EEG kaydı aracılığıyla toplanmıştır. Fourier analizi, artefaktsız gözler-kapalı 2-saniyelik EEG dönemlerinin ortalaması alınarak yapılmış ve 19 monopolar derivasyonun her biri için; delta (0,5-4 Hz), teta (4-8 Hz), alfa (8-13 Hz), beta (13-30 Hz) ve gamma (30-70 Hz) frekans bantları için mutlak güç (μV^2) hesaplanmıştır. Katılımcıların tedavi öncesi ve sonrası Y-BOCS skorları değerlendirilerek; skorlarında %30 ve üzerinde azalma olan hastalar “yanıt veren grup” ($n=42$), olmayanlar ise “yanıt vermeyen grup” ($n=10$) olarak adlandırılmış ve iki grubun tedavi öncesi QEEG verileri istatistiksel olarak karşılaştırılmıştır. Tüm istatistiksel analizler IBM SPSS Statistics 25.0 kullanarak yapılmıştır. $P<0.05$ istatistiksel olarak anlamlı kabul edilmiştir. Yanıt veren grupta, yanıt vermeyen gruba göre, tüm elektrotlarda alfa ve teta mutlak gücü daha yüksek bulunmuştur. İki grup arasında; sosyodemografik veriler ve tedavi öncesi Y-BOCS_total, Y-BOCS_obsesyon, Y-BOCS_kompulsiyon ve BDI skorları açısından anlamlı fark saptanmamıştır. Bununla beraber, yanıt veren grupta obsesyonlarla geçen zaman daha yüksek bulunmuştur. Sonuç olarak; tedavi öncesi alfa ve teta mutlak güç artışının, dTMU'ya iyi yanıt verecek OKB hastalarını predikte etmede yardımcı olabileceği gösterilmiştir. Bu gibi biomarkerların

kullanımı, OKB tedavisini bireyselleřtirme ve böylece optimal tedavi sonuçlarını elde edebilme konusunda klinisyenlere yardımcı olabilecektir.

Anahtar Kelimeler: Obsesif Kompulsif Bozukluk, Derin Transkraniyal Manyetik Uyarım, Elektroensefalografi



1. INTRODUCTION AND PURPOSE

Obsessive compulsive disorder (OCD) is a psychiatric disorder that courses with obsessions and compulsions (1). Obsessions are stubborn and repetitive thoughts, impulses, or images that enter the mind out of the will, disturb the person, are foreign to self, and cannot be removed from consciousness by effort (1). Compulsions are mostly repetitive movements or mental actions to eliminate obsessions (1). The lifetime prevalence of OCD is around 2-3% (2).

Selective serotonin reuptake inhibitors (SSRIs) are recommended for the first-line treatment of OCD (3-6). However, of patients with OCD, 40-60% do not respond adequately to SSRIs (3, 7). Therefore, studies that investigate the effectiveness of adding transcranial magnetic stimulation (TMS) to SSRI treatment in OCD patients have started to be performed (8, 9). Despite the mixed results, systematic reviews and meta-analyses generally show the effectiveness of TMS in OCD treatment (10-14).

The deep TMS (dTMS) target areas in OCD are the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) in consistency with neuroimaging findings showing impairment in the cortico-striato-thalamo-cortical (CSTC) loop and observations of improvement in OCD symptoms following anterior cingulotomy or anterior capsulotomy (15). It was shown that 20 Hz dTMS applied to the ACC and mPFC through the H7-coil for six weeks in OCD patients under SSRI treatment provided a significant improvement in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores lasting for one month, and thus, dTMS was a reliable and effective method in OCD patients (16).

The baseline cortical excitability level of patients before stimulation is an important source of inter- and intra-individual variability of TMS effects (17). Electroencephalography (EEG) is a non-invasive measurement tool that reflects neural activity in the brain. (18). Therefore, differences in pre-treatment EEG measurements may be observed between patients responding and not responding to treatment. However, in the literature, there is no study that investigates the association between the response of OCD patients to dTMS and pre-treatment resting-state quantitative EEG (QEEG) findings.

The present study's goal was to determine the QEEG findings that affect the response to dTMS by examining the relationship between the pre-treatment QEEG findings of OCD patients and their response to dTMS.

Research Hypotheses:

- 1) Some of the OCD patients resistant to SSRI treatment respond when dTMS is added to the treatment.
- 2) Patients who respond to dTMS have pre-treatment QEEG findings that differ from those who do not respond to it.



2. LITERATURE REVIEW

2.1. Obsessive Compulsive Disorder

2.1.1. Definition

OCD is a psychiatric disorder that courses with obsessions and/or compulsions, which is usually chronic, sometimes with periodic exacerbations and significantly affects the functionality of the person (1). Obsessions are stubborn and repetitive thoughts, impulses or images that occur involuntarily, disturb the person, create anxiety, and cannot be removed from the mind by conscious effort (1). Compulsions are repetitive behaviors and/or mental actions developed to neutralize the obsessions (1). Compulsive actions do not have a realistic relationship to this end, or they are clearly exaggerated (19). The compulsion, which first starts to reduce the anxiety caused by obsessions, reaches an uncontrollable level over time, and this repetitive action itself creates distress and impairs the person's functionality (20). Thus, a vicious circle that is difficult to break occurs (20).

Obsessive-compulsive symptoms are usually observed as egodystonic and are considered to be unacceptable by the person, by being contrary to one's logic, moral understanding and beliefs (1). In OCD patients, obsessions at the rate of 9-36% are not regarded as absurd, and resistance to them is not shown and in this case, OCD with poor insight is mentioned (21-28).

2.1.2. History

Obsessions and compulsions are as old as human history. There are examples of behaviors that point to obsessions and compulsions in ancient religious books. Furthermore, it is observed that the source of religious and magical ceremonies is largely based on defense mechanisms similar to those in OCD (1). OCD, which had been treated as a religious event, being captured by the devil until the 15th century (29) was described in the psychiatric literature as a symptom of melancholy by Esquirol in 1838 for the first time (30). This disease, which was considered as a symptom of depression or melancholy in those years, started to be treated as a separate clinical syndrome in the early 20th century (31).

Westpahl was the first physician who distinguished obsessions from symptoms of depression and explained the syndrome close to its current definition in 1878. Westpahl stated that some thoughts came to consciousness without the will of the person and that the person could not stop his/her thoughts although he/she knew that they were meaningless and alien to him/her, and these pathological thoughts also disturbed the normal formation order of thoughts (29).

In the first part of the 20th century, the French psychiatrist Pierre Janet collected phobias, obsessions, and compulsions under one title and called it "psychasthenia". According to Janet, psychasthenia occurred as a result of the weakened willpower in an individual. Freud studied phobic neurosis and obsessive-compulsive neurosis as separate disorders, by considering that the psychological causes and mechanisms in phobias differed from the mental causes and psychodynamic mechanisms in obsessive-compulsive neurosis. The contemporary views on the psychodynamics and psychological origin of obsessive-compulsive neurosis were developed by Freud. In the 20th century, significant contributions were made to the etiology and treatment of obsessive-compulsive neurosis with learning theories. Toward the end of the 20th century, data on the possible existence of important hereditary-neurobiological factors in this disease were obtained (1).

OCD is among the anxiety disorders in Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM-IV-TR) (32). In accordance with the classification of the World Health Organization (WHO), OCD is evaluated under the title of neurotic, stress-related, and somatoform disorders (32).

In the DSM-5, OCD was removed from the title of anxiety disorders and was included under the title of "obsessive-compulsive disorder and related disorders" (33). These disorders are also referred to as "obsessive-compulsive spectrum disorders" (34). The reasons for including them under this heading are the fact that they have similar and overlapping symptoms and characteristics, deficiency in delaying or preventing repetitive behaviors, their inclusion as comorbidities, their observation in the same family, and the fact that they have some common features such as similar unusual neurotransmitter functioning and responding to similar types of treatment. As a new category in DSM-5, obsessive-compulsive spectrum disorders include the diagnoses of OCD, hoarding

disorder, body dysmorphic disorder, skin picking disorder, trichotillomania, substance/medication-induced obsessive-compulsive and related disorder, obsessive-compulsive and related disorder due to another medical condition, other specified obsessive-compulsive and related disorder, and unspecified obsessive-compulsive and related disorder (33).

2.1.3. DSM-5 Diagnostic Criteria for Obsessive Compulsive Disorder

A. The presence of obsessions, compulsions, or both of them

Obsessions are defined by (1) and (2):

1. Repetitive and constant thoughts, impulses or images, which are sometimes experienced as forced and unintentional and lead to significant anxiety or distress in most people.
2. The person tries to ignore or suppress these thoughts, impulses or images or attempts to unburden them (by performing a compulsion) with another thought or action.

Compulsions are defined by (1) and (2):

1. Repetitive behaviors (e.g., washing hands, arranging, keeping checking) or mental actions (e.g., speaking words of religious value, counting, repeating words silently) in response to the person's obsession or as if he/she is forced to act according to strict rules.
2. These behaviors or mental actions are performed for the purpose of protecting or reducing the anxiety or distress experienced, or avoiding a feared event or situation. Nevertheless, these types of behaviors or mental actions are not realistically associated with situations that are intended to be neutralized or protected from, or are clearly at an extreme level.

Note: Young children may not be able to express the goals of these behaviors or mental actions.

B. Obsessions or compulsions take the person's time (e.g., they take more than an hour a day) or cause clinically apparent distress or a decrease in functionality in social, work-related areas or other important functional areas.

C. Obsessive-compulsive symptoms cannot be attributed to the physiological impacts of a substance (a substance that can be abused, a drug) or another health condition.

D. This disorder cannot be explained better by the symptoms of another mental disorder (e.g., excessive worries as in generalized anxiety disorder; an intense focus on appearance as in body dysmorphic disorder; difficulty in disposing of possessions or disconnecting from them as in hoarding disorder; plucking your hair as in trichotillomania; picking the skin as in skin picking disorder; stereotypical behaviors as in stereotyped movement disorder; ceremonial eating behavior as in eating disorders; keeping thinking about substances or gambling as in substance-related and addictive disorders; keeping thinking that you have a disease in health anxiety; sexual impulses or fantasies as in sexual perversions; impulses as in disruptive, impulse-control and conduct disorders; guilt-related intellectual pursuits as in major depressive disorder; thought insertion or delusional pursuits as in the context of schizophrenia and in other disorders accompanied by psychosis or repetitive behavioral patterns as in the autism spectrum disorder.

Specify if:

With good or fair insight: The person distinguishes that the beliefs of obsessive-compulsive disorder are definitely or possibly not true or may be or may not be true.

With poor insight: The person thinks that his/her obsessive-compulsive disorder beliefs are possibly true.

With absent insight/delusional beliefs: The person firmly believes that obsessive-compulsive disorder beliefs are real.

Specify if:

Tic-related OCD: The person has a current or past history of a tic disorder.

2.1.4. Epidemiology

Obsessive-compulsive symptoms are not always expressed as a complaint by people, and this prevents the diagnosis of OCD and makes it difficult to determine its frequency and prevalence (1). Until the mid-1980s, OCD was accepted as a very rare disease (29). The study revealing the current epidemiological status of OCD was the Epidemiological Field Study conducted in the USA in 1984. In this study, OCD was

reported as the fourth most frequently observed psychiatric disease after phobias, substance use, and major depressive disorder. According to the results of this study conducted following the DSM criteria, the lifetime prevalence of OCD was found to be 2.5-3%, and the annual prevalence was found to be 1.5% (29).

Subsequent studies obtained results similar to these rates. In a study carried out in Canada, the prevalence of OCD was stated to be 2.9% (35). In an international epidemiological study involving the USA, Puerto Rico, Canada, Taiwan, Germany, New Zealand and Korea, Weissman et al. (1994) reported the prevalence of OCD to be 2% (at a rate varying between 0.7% and 2.5%) (36). The prevalence of OCD in Turkey was found to be 3% in accordance with the DSM-IV criteria (37).

2.1.4.1. Age of Onset

OCD usually starts between the ages of 18-25 years (1). Although it is a disorder that can also be observed in childhood, it has properties similar in content to those observed in adulthood in many ways (38).

The age of onset in males is earlier than that in females (39). When Rasmussen and Eisen (1992) investigated the age of onset of OCD in a sample group of 250 people diagnosed with OCD, they found the mean age of onset of OCD to be 20.9 in the whole group, 19.5 in male patients, and 22.0 in female patients (40). As a result, in this study, the mean age of onset of OCD in male patients was found to be statistically significantly earlier compared to female patients. They stated that most of the patients had obsessive-compulsive symptoms that did not cause labor loss before the development of OCD.

The rate of OCD and obsessive-compulsive symptoms among the relatives of people with OCD whose disease onset age was younger than 18 years was found to be two times higher than that in the relatives of people who developed OCD after the age of 18 (41). In another similar study, it was revealed that the frequency of OCD in the relatives of patients with OCD onset age younger than 14 years was higher than that in the relatives of patients with OCD onset age above 14 years (42). These studies suggest that the age of onset of OCD is important for familial transmission.

2.1.4.2. Sex

The studies conducted in the USA reported no significant difference between men and women in terms of the frequency of OCD (2). Using DSM-IV diagnostic criteria, 51% of 431 patients diagnosed with OCD were reported to be women (43). An epidemiologic study evaluating a large sample group revealed that the lifetime prevalence of OCD was slightly higher in women compared to men (36, 44). According to the "Turkey Mental Health Profile" study, the 12-month total OCD rate in the general population was 0.5%, and a three-times higher rate was found among women (0.6%) than men (0.2%) (45).

Although the prevalence of OCD is generally thought to be similar in men and women, it is known that sex difference is mainly observed in symptom subtypes. For example, the cleaning subtype is more frequently reported in women, while the checking subtype is more frequently reported in men (40). Lensi et al. (1996) examined the effects of sex difference on OCD and indicated that the age of onset of OCD was earlier, the rate of being single was higher, and sexual obsessions and symmetry obsessions were more frequently observed in male patients (39).

Eisen and Rasmussen (1993) conducted a study investigating the comorbidity of psychotic (schizophrenia, delusional disorder) or psychosis-like diseases (schizotypal personality disorder) in a group of 475 people with OCD (46). In this study, the rate of male patients was found to be 44% in the OCD group without psychosis and 85% in the OCD group with psychotic disorder. These findings suggest that comorbid conditions might affect the sex distribution.

2.1.4.3. Marital Status

When 250 people diagnosed with OCD were examined in terms of their marital status, it was observed that 43% were not married, 52% were married, and 5% were divorced (47). In many follow-up studies, although marital status was not found to be the determinant of the disease course, 107 OCD patients were examined in a prospective study, and it was reported that being married caused a significant increase in the probability of partial remission (48).

2.1.4.4. Race and Ethnic Groups

Clinical and epidemiological studies have shown that OCD affects children, adolescents, and adults without any religious and racial differences in various countries (49).

2.1.4.5. Cultural Differences

There are increasing number of studies in the recent years indicating that most of the information reported about the clinical appearance of OCD is also valid for Turkey (37, 50). Therefore, such information indicates that the disease is clinically consistent in an international context. On the other hand, it is possible to observe some cultural differences in OCD. For example, some studies examining the frequency of themes in the context of obsessions report that sexual obsessions are relatively more common in Mexico, aggressive obsessions in Brazil and England, and religious obsessions are relatively more common than others in countries such as Egypt, Israel, Saudi Arabia, Qatar and Turkey (51-54). In fact, it is reported that obsessions with religious content increase when moving toward the east in Turkey (50, 55). There are also research findings showing that there are cultural differences in some factors, such as superstitions, religiosity, moral perception, perfectionism, and thought suppression (56-58).

2.1.4.6. Socioeconomic Status

Clinical and epidemiological studies have shown that OCD affects children, adolescents, and adults without any difference in socioeconomic status in various countries (49).

2.1.4.7. Early Adverse Life Events

As a result of the retrospective studies conducted, an indirect relationship has been found between childhood emotional and physical abuse and obsessive-compulsive symptoms and even the diagnosis of OCD (59, 60).

2.1.4.8. Adverse Life Events

Stressful life events are generally reported at the onset of the disease. Pregnancy and having children, being fired, entering a new job or progressing at work, and serious physical ailments are the most prominent of these events, and the content of obsessions usually coincides with the triggering life events (61). Furthermore, it is reported that such events occurring after the disease increase the severity of symptoms (62).

2.1.4.9. Premorbid Personality Traits

Premorbid obsessive-compulsive personality traits have been found in around 15-45% of OCD patients. Nevertheless, personality traits are neither necessary nor sufficient for the development of OCD (63).

It is observed that the most common personality disorders accompanying OCD belong to the C cluster personality disorders (avoidant, dependent, obsessive-compulsive). The fact that C-cluster personality disorders are predominant suggests that OCD patients have anxious personality traits, these personality disorders can create a predisposition to the development of OCD in individuals and carry common formation processes (64).

2.1.4.10. Comorbidity

Epidemiological studies have revealed that at least 50% of OCD patients have one or more comorbid psychiatric disorders, and anxiety disorders (40-60%) (65) or major depressive disorder (65%) (19) are the most common among these.

Major depressive disorder represents one of the most frequently observed Axis I comorbidities in OCD. Lifelong association with major depressive disorder was reported to be 65%, and concurrent association was reported to be 30% (66). About 85% of them are secondary to OCD (19).

The lifetime prevalence of another anxiety disorders in patients with OCD is stated to be 40-60% (66). In OCD, it has been stated that simple phobia is observed at a

rate of 17.7%, social phobia is observed at a rate of 15.6%, generalized anxiety disorder is observed at a rate of 12.2%, and panic disorder is observed at a rate of 9.5% (67). In another study, it was found that the lifetime prevalence of phobic disorders was 46% and the prevalence of panic disorder was 13.8% in OCD patients (44).

The frequency of bipolar disorder lifetime association in OCD has been found to be 14-21% in epidemiological studies and 10-35% in clinical studies (68). It has been stated that comorbid bipolar disorder is more common in OCD cases with episodic prognosis (69).

Comorbidity between OCD and schizophrenia was found to be 12.9% (70). The views of some authors that there is a clinical subtype between schizophrenia and OCD called schizo obsessive disorder is currently a subject of debate (71).

Furthermore, there is an association between OCD and basal ganglia (BG) diseases such as Sydenham's chorea, Tourette's syndrome, Parkinson's disease and Huntington's disease (2). It is observed that 20-30% of patients have a current or past tic disorder (34). In addition to these, other obsessive-compulsive spectrum disorders, attention deficit hyperactivity disorder, and oppositional defiant disorder may also accompany OCD (33).

Axis II disorders include avoidant, dependent, histrionic, or schizotypal personality disorder (72). Although obsessive-compulsive personality disorder is thought to be closely related to OCD and frequently observed as a comorbidity, it is now reported that it coexists in a small number of cases despite some similar features (73).

2.1.5. Clinical Appearance and Findings

2.1.5.1. Clinical Picture

In OCD, obsessions that can be typically defined as unintentional, mind-occupying, repetitive, inappropriate, bizarre, egodystonic, and, thus, anxiety and distress creating thoughts, images and impulses in the individual are observed. The person who is seriously distressed by these experiences tries to control or prevent these experiences

through different methods. When these efforts are not sufficient, the person often displays compulsions that can be described as repetitive, extreme and sometimes extraordinary mental or behavioral responses in response to obsessions to relax (1). Among the important criteria specific to this diagnosis, there are symptoms such as worries beyond the simple level about real events in daily life, taking significant time, slowing down the person, causing discomfort and disrupting the functionality, accepting that obsessions are the product of his/her own mind (not being directed by someone else as in thought insertion) (1). In terms of differential diagnosis, it is emphasized that these symptoms should not be caused by any other disorder (72, 74).

2.1.5.2. Types of Obsessions and Compulsions

While contamination, harm, sexual, religious and symmetry obsessions are among the most common types of obsessions in OCD, compulsions such as cleaning/washing, checking, repeating, ordering/arranging and hoarding are the leading ones (75). As clinical manifestations, it is often possible to observe obsessive and compulsive symptoms that accompany them, such as contamination obsessions and cleaning/washing compulsions, harm obsessions and checking compulsions and hoarding obsessions and compulsions (40). Therefore, it is also possible to identify special subgroups such as checking, cleaning, hoarding in OCD as subtypes and to find separate scientific studies in this direction in the literature (34). Although patients mostly report one or more obsessions and compulsions, there are also few cases in which pure obsessions or compulsions are observed alone (75).

One of the notable studies is Lee and Kwon's classification of reactive and autogenous obsessions. Autogenous obsessions are associated with ego-dystonic sexual, aggressive and immoral thoughts and impulses without a specific triggering stimulus, while reactive obsessions are obsessions in the type of contamination/cleaning, harm/checking, and symmetry/ordering, in which triggering stimuli can be determined, which have a relatively realistic aspect and, therefore, a response is perceived naturally (76).

2.1.5.3. Quality of Life

Occasionally increasing and decreasing symptoms of OCD affect the quality of life depending on the severity and comorbid conditions. In this respect, it ranks 10th among medical conditions that adversely affect the quality of life (62). Family members, such as the patient, are also affected by this situation in a similar way, and it may be useful to address this issue at the evaluation stage since it has important effects on the disease due to their reactions to symptoms (77).

2.1.5.4. Scales

In the evaluation of OCD, it may be beneficial to get the assistance of a series of internationally validated measurement tools with supported psychometric properties, in addition to a detailed interview to be made by the clinician during the diagnosis-based evaluation. The Structured Clinical Interview for DSM-5 (SCID-5) is an assessment tool applied and rated by the clinician in line with the DSM-5 diagnostic criteria (78). Likewise, the Y-BOCS is a form applied by the clinician and is a frequently used scale in both scientific research and clinical evaluation in practice. This scale also has a self-report form that the patient can fill out (79). Apart from them, there are also scales and questionnaires such as the Clark-Beck Obsessive-Compulsive Inventory (75), Obsessive-Compulsive Inventory-Revised Form (80), Maudsley Obsessive-Compulsive Inventory (81), Padua Inventory-Washington State University Form (82), and Vancouver Obsessive-Compulsive Inventory (83), which are self-report forms, adapted into Turkish, and can also be utilized in studies and clinical practice. There are also patient-specific registration forms and standard measurement tools according to the preferred therapeutic approach (such as the Obsessive Beliefs Questionnaire prepared in line with the cognitive-behavioral model of OCD) (84).

2.1.6. Etiology

2.1.6.1. Neurotransmitters

Serotonergic System

The first studies, stating that clomipramine was effective in OCD patients, caused the development of the serotonin (5-hydroxytryptamine/5-HT) hypothesis in the etiology of OCD (85, 86). Later studies have shown that clomipramine is superior to desimipramine and amitriptyline in the treatment of OCD, by strengthening this hypothesis (87, 88). Nowadays, the acceptance of SSRIs as the most effective medications in OCD, supports the serotonin hypothesis (6). Furthermore, the exacerbation of symptoms in OCD patients by sumatriptan and meta-chlorophenylpiperazine (m-CPP), which are serotonin receptor agonists, is consistent with the serotonin hypothesis (89).

Dopaminergic System

The fact that OCD patients not benefiting enough from the treatment with SSRIs benefit from the added antipsychotic treatment suggests that there is a dysfunction in dopamine receptors in the etiopathogenesis of OCD (90). D1 receptor dysfunction has been shown in the ACC in OCD patients (91). An increase in dopamine in the mesolimbic dopaminergic pathway may adversely affect the ability of the prefrontal cortex (PFC) to suppress anxiety-related activation of the amygdala (92).

Glutamatergic System

Glutamate is the brain's primary excitatory neurotransmitter (93). Glutamate imbalance has been shown in the etiopathogenesis of OCD (94, 95). Increased glutamate levels have been found in the cerebrospinal fluid of medication-naïve OCD patients (96). Moreover, positive results have been obtained by adding riluzole, a glutamate antagonist, to treatment in OCD patients resistant to treatment, which supports the hypothesis that glutamate takes part in the etiology of OCD (97, 98).

The hypothesis that serotonin and glutamate interaction is not normal in OCD was first proposed in 1998. It is thought that corticostriatal glutamate reduces serotonin release in the caudate nucleus and serotonergic neurons play a role in glutamatergic transmission (99). OCD-like behaviors have occurred in animal experiments in which stimulation has been increased in cortico-striatal glutamatergic pathways (100). After forming a lesion in the anterior limb of the internal capsule (ALIC), which is the glutamatergic projection area extending from the orbitofrontal cortex (OFC) to the caudate nucleus, an improvement in treatment-resistant OCD (TR-OCD) patients has been detected (101). It has been reported that the metabotropic glutamate type 2 receptor (mGLUR2), which has autoreceptor properties, may be effective in reducing hyperactivity in OCD (96, 102).

2.1.6.2. Genetics

There are twin and family studies, segregation studies, linkage studies, candidate gene association studies, and genome-wide association studies (GWAS), suggesting that OCD is inherited (19, 41, 103).

Family Studies

First-degree relatives of OCD cases were interviewed directly, and it was found that the prevalence of OCD in relatives was significantly higher compared to that in the general population in the family studies (42, 104, 105). Other studies have shown that the rates of OCD and obsessive-compulsive personality disorder in the relatives of OCD patients are significantly higher compared to the general population (19, 42, 104, 106).

The prevalence of generalized anxiety disorder, agoraphobia, separation anxiety disorder, major depressive disorder, and panic disorder is high in relatives of patients with OCD (107). The prevalence of body dysmorphic disorder and grooming disorders (skin picking, nail biting or trichotillomania), which are obsessive-compulsive spectrum disorders, is significantly higher in individuals who have relatives diagnosed with OCD (108). Tic disorders are more frequently observed in relatives of OCD patients than in the normal population (109).

Twin Studies

Genetic effects in OCD have also been shown in twin studies. In studies conducted on twin groups, the rate of concordance for OCD in monozygotic twins has been found to be significantly higher than that in dizygotic twins (1). Other studies have detected that the heritability of obsessive-compulsive symptoms is 45-65%, and this situation remains at high rates as 35-55%, even in twins who do not grow up in a common environment (110-112).

Segregation Studies

Segregation studies conducted to identify whether a potentially autosomal dominant major gene takes part in the transmission of OCD show that OCD may possibly have an autosomal dominant major gene region that has a stronger effect in women (113, 114).

Linkage Studies

In the first linkage study in OCD, a linkage peak was defined in the 9p24 region of the 9th chromosome (115, 116). When this candidate region was examined in further studies, it was found to contain glutamate transporter gene Solute Carrier Family 1 Member 1 (SLC1A1) (117-120). In another genome-wide linkage study, the strongest linkage signal was determined in the 3q27-28 region on the 3rd chromosome, and other linkage signals were observed in regions on the 1st, 6th, 7th, and 15th chromosomes (121).

Candidate Gene Association Studies

Positive results obtained from family and twin studies and especially the single gene region model emphasized in segregation analyses have led to research on many candidate genes that can increase the risk of OCD. From these molecular genetic studies, findings indicating that the promoter region of the SLC6A4 gene, which is the gene encoding the serotonin transporter (5-HTT), the 5-HT1Db, 5-HT2A, 5-HT2B receptor genes, the SLC1A1 gene, which is a postsynaptic glutamate receptor gene, the discs large homolog-associated protein 3 (DLGAP3) gene encoding a protein that affects glutamate

function, the dopamine receptor D3 (DRD3), DRD4 and SLC6A3 genes associated with the dopaminergic system, the monoamine oxidase-A (MAO-A), catechol-O-methyltransferase (COMT) and μ -opioid receptor genes, myelin oligodendrocyte glycoprotein (MOG) and brain-derived neurotrophic factor (BDNF) genes may be associated with OCD inheritance (103).

Candidate Genes Related to the Serotonergic System

The effects of SSRIs on obsessive-compulsive symptoms and the fact that m-CPP leads to obsessive-compulsive symptoms are accepted as indicators that there may be a dysfunction in the serotonergic pathways in OCD (89). This has led to the investigation of genes that have a function in serotonin metabolism in OCD.

5-HT Transporter

It has been shown that there is a mutation in the promoter region of the SLC6A4 gene on 17th chromosome (5-HTT gene-linked polymorphic region, 5HTTLPR), which is the gene encoding the 5-HTT protein, in OCD (122). In the polymorphism formed by S and L alleles due to a different number of insertion/deletion repeats of a 44 bp sequence in 5HTTLPR, if the repeat sequence of 44bp is repeated 16 times, alleles called the long (L) form occur, and if it is repeated 14 times, alleles called the short (S) form occur. According to this polymorphism, the genotypes are evaluated as L/L, L/S, and S/S (123).

Lesch et al. (1996) suggested that a polymorphism in the form of the absence of the 44-bp sequence may lead to a decrease in the transcription activity of the gene (124). Especially the L allele is emphasized among the L and S variants of this polymorphism in OCD. McDougle et al. (1998) and Bengel et al. (1999) revealed a significant relationship between the L allele of 5HTTLPR and OCD (125, 126). Meira-Lima et al. (2004) reported that the L allele of 5HTTLPR was highly represented in the OCD group, but they detected no difference between patients and controls in terms of the frequency of the homogeneous LL genotype (127). On the contrary, the findings of the study, in which no relationship was found between the said polymorphism and OCD, were published (128, 129).

5-HT2A Receptor

In a meta-analysis, the allele A of rs6311 in the promoter region and the allele T of rs6313 in the coding region of the 5-HT2A receptor gene were found to be associated with OCD (130).

5-HT2B Receptor

Although the gene encoding the 5-HT2B receptor is pharmacologically regarded as a candidate gene, especially in early-onset OCD, no significant relationship was found between 5-HT2B receptor gene and early-onset OCD (131).

5-HT1Db Receptor

It has been reported that severe, repetitive behaviors in autistic patients may originate from high 5-HT1D sensitivity, and it has been suggested that the gene of this autoreceptor may be particularly associated with repetitive behaviors (132). The fact that m-CPP (non-selective 5-HT1D autoreceptor agonist) and sumatriptan (selective 5-HT1D autoreceptor agonist), cause acute worsening in OCD symptoms has led to the investigation of this autoreceptor gene as a candidate gene in OCD genetics (89). Studies investigating whether there is a relationship between the G861C polymorphism in the 5-HT1Db autoreceptor gene and OCD concluded that especially the G allele might be associated with the risk of developing OCD (133). In another study, it has been reported that the C allele of the G861C polymorphism in the 5-HT1Db autoreceptor gene in male patients is more significant in comparison with controls (134). However, di Bella et al. (2002) found no relationship between the 5-HT1Db autoreceptor gene and predisposition to OCD (135).

Candidate Genes Related to the Dopaminergic System

The possible dysfunction of dopaminergic mechanisms in Tourette's syndrome and high comorbidity rates of Tourette's syndrome and OCD have led to the investigation of dopaminergic functions in the etiology of OCD (90, 136).

Dopamine Transporter

Hemmings et al. (2003) determined that genotypes containing the A9-allele of the dopamine transporter (DAT) gene (SLC6A3) increased in OCD patients (137).

D3 Receptor

The SLC6A3 and DRD3 genes have been shown to be associated with white matter changes that emerge in early-onset OCD (138).

D4 Receptor

A correlation has been shown between the polymorphism in the gene encoding the DRD4 and OCD (139, 140). A study comparing early- and late-onset OCD in terms of genetic and clinical variables suggested that DRD4 polymorphism might have taken part in the occurrence of early-onset OCD (141). There was also an association between the 2R allele of the DRD4 gene and the symmetry dimension among the OCD symptom dimensions (142).

Candidate Genes Related to the Glutamatergic System

Dysfunction of CSTC loop regulated by glutamate is mentioned in OCD (143-147) and therefore, genes related to the glutamatergic system have started to attract researchers' attention.

Glutamate Transporter

The SLC1A1 gene encodes the postsynaptic glutamate receptor protein, and many studies have found that different variants in the gene are associated with OCD (117-120). In the studies investigating the function of isoforms of the gene, it has been stated that genes are expressed differently in participants with OCD and that they are responsible for the decrease in the function of the transporter (148). In a recent study, SLC1A1 has been demonstrated to play a role in BG-dependent repetitive behaviors in mice models with OCD (149).

DLGAP3

The DLGAP3 gene encodes a scaffolding protein, which is known to influence glutamate function (150). In the SAP90/PSD95-associated protein 3 (SAPAP3; murine homolog of DLGAP3) gene-knockout mice, compulsive behaviors responding to SSRIs and anxiety-like behaviors have been observed (150-152).

Genome-Wide Association Studies

GWAS are successful in studying complex diseases that are thought to be due to multiple genetic factors (103). Three GWAS studies on OCD have been published to date (153-155).

The International OCD Foundation Genetics Collaborative analyzed almost 500,000 single nucleotide polymorphisms (SNPs) in 1465 OCD cases, 400 trios and 5557 healthy control subjects. In the case-control analysis, the SNPs that were the most associated with OCD were found to be localized in the DLGAP1 gene, but their significance was low. As a result, in the trios analysis, an SNP (rs6131295), near to the BTB/POZ domain-containing protein 3 (BTBD3) gene, was found to have a significant relationship with OCD (153).

In the OCD Collaborative Genetics Association study, 1000 families and 500,000 SNPs were analyzed. The most consistent result was obtained for the SNP on 9th chromosome, near the protein tyrosine phosphate receptor D (PTPRD) gene, but its significance was low. The additional candidate genes that occurred in the two studies were glutamate ionotropic receptor N-methyl-D-aspartate (NMDA) type subunit 2B, FAS apoptotic inhibitory molecule 2 (FAIM2), and cadherin genes CDH9 and CDH10. It is known that many of these genes are involved in glutamatergic neurotransmission (154).

In the metanalysis of the aforementioned studies (2688 patients and 7037 controls), SNP reaching significance level was not found. The genes with the most signal domains appeared to be ankyrin repeat and SOCS box containing 13 (ASB13), R-spondin 4 (RSPO4), DLGAP1, protein tyrosine phosphate receptor D (PTPRD), geminivirus rep

interacting kinases (GRIKs), FAS apoptotic inhibitory molecule 2 (FAIM2), and cadherin 20 (CDH20). Some of these genes are candidate genes to be significant in the original GWAS studies (156).

In the third GWAS study, 7000 individuals and 31,000,000 SNPs were analyzed using the quantitative measurement of obsessive-compulsive symptoms. A significantly associated SNP with OCD was detected in the myocyte enhancer factor 2B neighbor (MEF2BNB) gene in the 9p13 region of 19th chromosome. In the gene-based tests performed additionally, MEF2B, MEF2BNB-MEF2B, and regulatory factor X associated ankyrin containing protein (RFXANK) genes in the same region were found to be significant (155).

2.1.6.3. Neuroimmunology

It has been stated that symptoms begin or exacerbate with streptococcal infection in one-third of childhood OCD cases (157). In Sydenham's chorea, which is considered to be an autoimmune disease and develops after group A hemolytic streptococcal infections, OCD symptoms are observed in three-quarters of patients, and it has been found that these symptoms begin shortly before the signs of chorea. In these patients, it has been observed that the OCD symptoms improve in parallel with neurological symptoms (157).

Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) is an autoimmune form of childhood OCD (157). In a study conducted in a group of patients meeting the PANDAS diagnostic criteria, it was found that OCD symptoms in these children started an average of 3 years earlier compared to other childhood-onset OCD, their exacerbation was sudden and dramatic, and they were associated with group A hemolytic streptococcal infections (158). Furthermore, it was stated that the symptoms of attention deficit hyperactivity disorder, such as hyperactivity, impulsivity, and attention deficit, were frequently observed, and that there were also periodic symptoms such as emotional lability, separation anxiety, and age-inappropriate behaviors associated with infections. First-degree relatives of children diagnosed with PANDAS have a high rate of tic disorder and OCD (158).

Some studies indicate that the D8/17 surface antibody of B lymphocytes creates a predisposition to PANDAS (159). This antibody was found to be at a high rate in individuals diagnosed with rheumatic fever and their relatives (159). Likewise, the D8/17 ratio is high in PANDAS cases and children with tic-related OCD (159).

2.1.6.4. Neurobiology

The separation of frontal cortex-BG connections from each other by psychosurgical methods such as capsulotomy and cingulotomy reduces OCD symptoms (101). This situation indicates the fronto-striatal pathway dysfunction in OCD (160).

The BG are the forebrain structures that provide interconnections from the cortex to the thalamus and consist of the striatum, globus pallidus (GP), substantia nigra (SN), and subthalamic nucleus (STN) and carry signals related to motor, somatosensory, cognitive and emotional functions (161). Striatum consists of the putamen and caudate nucleus and receives excitatory glutamatergic stimuli from all parts of the cortex and dopaminergic stimuli from the SN pars compacta (SNc) (nigrostriatal pathway) (161). Dopaminergic input modulates excitatory glutamatergic input from the cortex (162). Dopamine inhibits the indirect pathway through D2 receptors and stimulates the direct pathway through D1 receptors (162). There are GABAergic connections between the striatum and the GP (161). GABAergic projections are also the most important pathway from the BG to the thalamus. The stimulating glutamatergic pathway goes from the thalamus to the cortex (Figure 2.1).

The primary task of the striatum is to integrate the stimulating projections from the cortex and to regulate the thalamic stimuli going back to the cortex (163). Cell groups in the striatum provide inhibition by tonic discharges on the GP internus (GPI) (163). While pallidal cells normally inhibit thalamic cells, thanks to the tonic discharges of the striatum, the thalamus inhibition is eliminated, and cortical activation and thus movement are provided with stimulating outputs (163). For example, if there is sensory input to the striatum that hands are dirty, it is perceived as contamination through the striatal cells. Striatal discharges are initiated, and the related pallidal cells are inhibited by gamma-aminobutyric acid (GABA). Inhibitory stimuli to the thalamus decrease, and the thalamocortical pathway is released. The cortex is stimulated by glutamate, and as a

result, handwashing behavior occurs. This process occurs through the direct pathway (163). While the direct pathway creates stimulating outputs that stimulate the cortex, the indirect pathway has the opposite effect (163). The indirect pathway provides the inhibition of other involuntary movements while creating a voluntary movement (163).

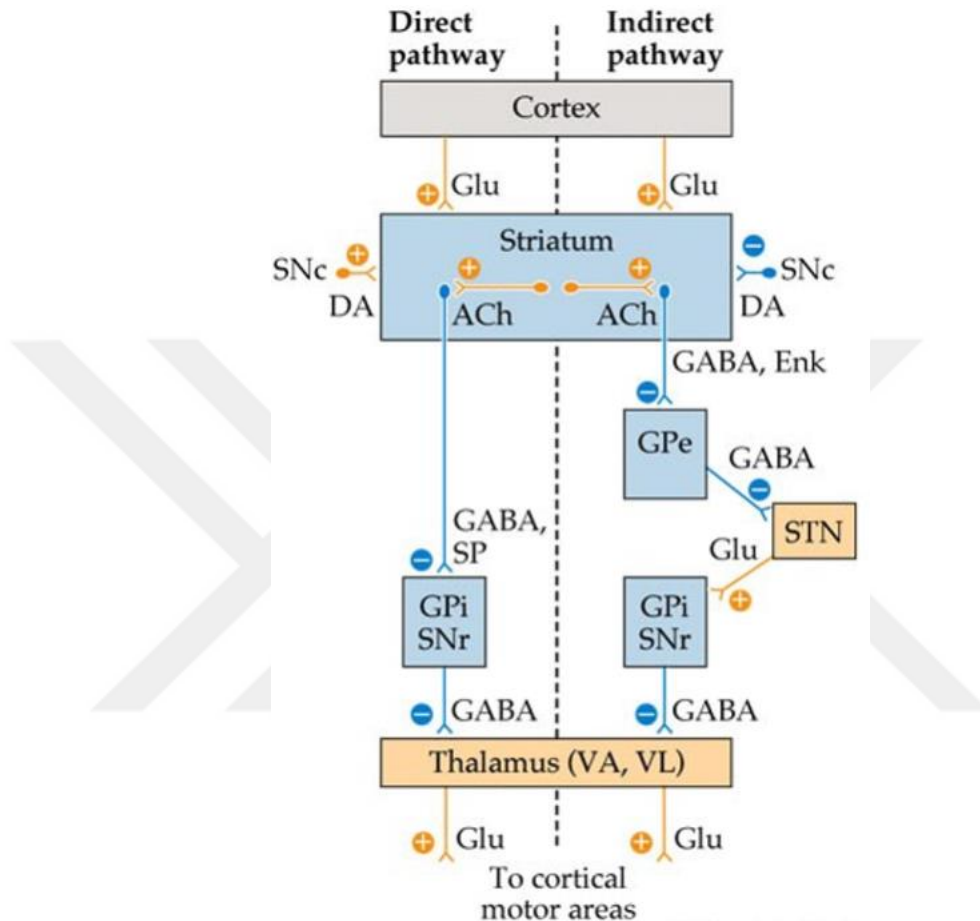


Figure 2.1. Direct and Indirect Pathways in the CSTC Loop (164). Glu: glutamate, ACh: acetylcholine, Enk: enkaphalin, DA: dopamine, SP: substance P, SNr: substantia nigra pars retri culata, SNC: substantia nigra pars compacta, GPi: globus pallidus internus, GPe: globus pallidus externus, VL: ventral lateral nucleus, STN: subthalamic nucleus, VA: ventral anterior nucleus.

Many connections that connect the BG with the cortex and thalamus have been defined, and these connections consist of 5 fronto-subcortical loops: motor (motor and oculomotor) and non-motor (lateral orbitofrontal, anterior cingulate gyrus, and dorsolateral prefrontal). The damage of non-motor loops, including the OFC, ACC, and dorsolateral PFC (DLPFC), is associated with psychiatric disorders (165). The first loop

between the OFC and the ventral part of the caudate nucleus is important in decision making and planning and is involved in the regulation of mood. In disorders in this loop, increased irritability, impulsivity, mood lability, and socially inappropriate behaviors may be observed. The second loop involves the ACC, which connects with the nucleus accumbens (NAc) and the amygdala and plays a role in attention, the assessment of reward and error, motivation, and the selection of behavior. In the disorders of this loop, decreased motivation and speech, apathy and akinesia may be observed. The third loop is between the dorsolateral part of the caudate nucleus and DLPFC and is important in executive functions. The disruption of this loop is associated with executive dysfunctions, including decreased planning and organizational skills, memory retrieval deficits, and set-shifting difficulties (Figure 2.2).

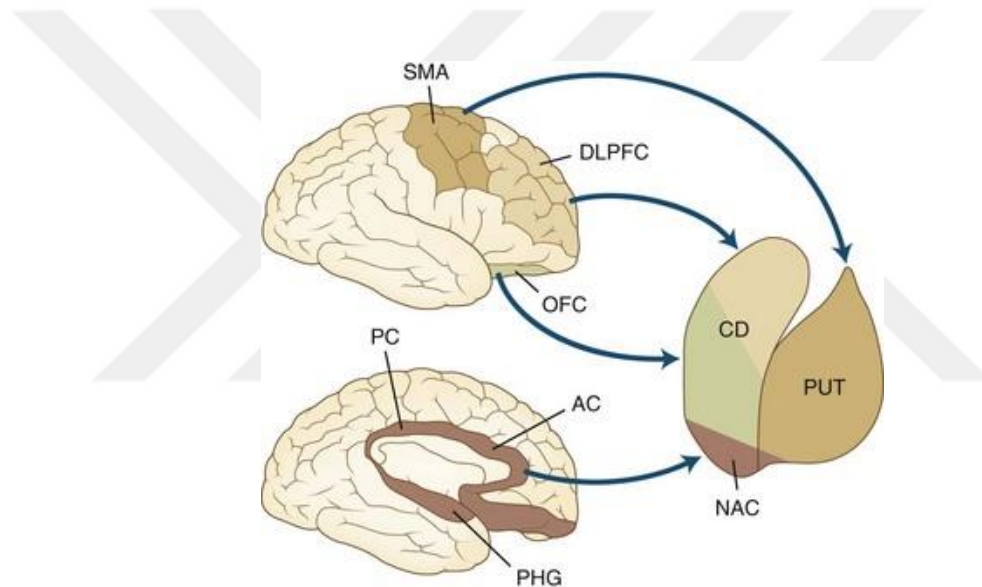


Figure 2.2. Frontostriatal Projections (166). DLPFC: dorsolateral prefrontal cortex, CD: caudate nucleus, AC: anterior cingulate gyrus, OFC: orbitofrontal cortex, NAC: nucleus accumbens, PHG: parahippocampal gyrus, PC: posterior cingulate gyrus, SMA: supplementary motor area, PUT: putamen.

In the OCD-loop model developed by Saxena et al. (1998), it was suggested that there is an imbalance between the direct (excitatory, OFC-striatum-GP-thalamus-cortical) and indirect (inhibitory, DLPFC-striatum-GP-STN-cortical) pathways in the lateral orbitofrontal loop, which includes projections from the OFC to the head of the caudate nucleus and ventral striatum, from there to the mediodorsal thalamus through GPi, and finally from the thalamus to the OFC and the activity of the direct pathway increases

(167). As a result, activity increases in the OFC, ACC, ventromedial caudate nucleus, and mediodorsal thalamus. While the reflection of hyperactivity in the OFC on symptoms is in the form of obsessions, hyperactivity in the ACC is associated with generalized anxiety (167). According to this model, compulsions are observed as repetitive movements to eliminate ineffectiveness in the striatum (Figure 2.3).

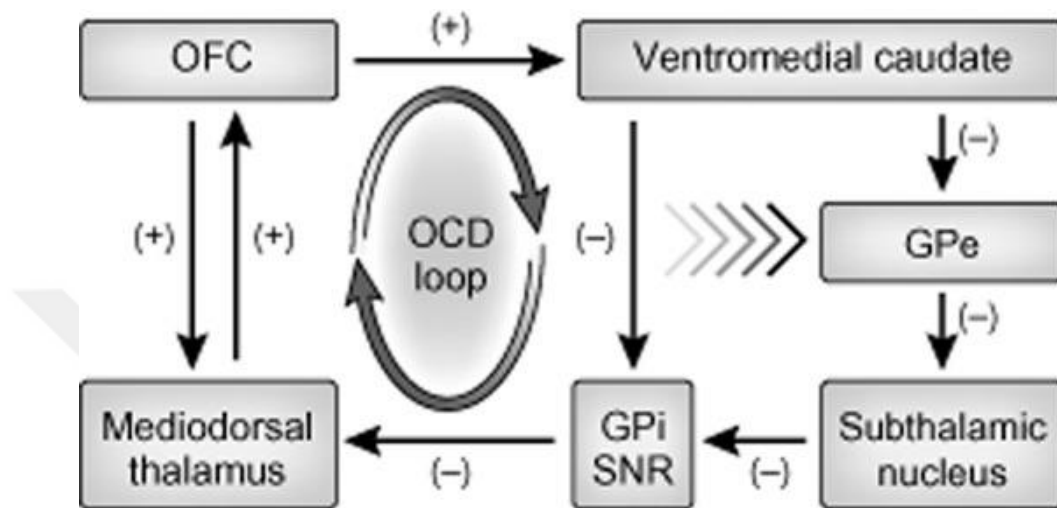


Figure 2.3. OCD-loop Model (167). SNR: substantia nigra pars reticulata, OFC: orbitofrontal cortex, GPi: globus pallidus internus, GPe: globus pallidus externus.

Savage (1998) introduced a hypothesis regarding the association between clinical symptoms and neuropsychological dysfunction. The orbitofrontal-subcortical loops (OCD-loop) in the brain of OCD patients cause executive dysfunction and lead to the occurrence of obsessive-compulsive behaviors. Ongoing obsessive-compulsive behaviors reinforce the OCD-loop in the brain and strengthen neuropsychological disorder. Eventually, a vicious circle between brain-cognition-clinical symptoms is formed. The presence of this vicious circle explains the impact of behavioral therapies in the treatment of OCD (168).

Westenberg et al. (2007) showed that in OCD, not only the OFC, but also the ACC and DLPFC regions play an essential role in decision making, and the impairment in these pathways disrupts reward assessment, error detection and behavior planning (165). Accordingly, the activity of the BG increases, and the frequency of expression of the abnormal behavior increases (165). Likewise, Menzies et al. (2008) developed an OCD

model that was not limited to the orbitofronto-striatal regions and stated that the underlying pathology might also be associated with abnormalities in the dorsolateral frontal and parietal regions, as it was associated with limbic structures, e.g., the amygdala (169).

Studies, showing that activation increases in the posterior regions including cerebellum and the parietal and occipital lobes and hyperactivation decreases in the orbitofronto-striatal regions during a cognitive task with clinical improvement in OCD, also demonstrate that the pathophysiological condition in OCD is not limited to the orbitofronto-striatal regions (170). While the orbitofronto-striatal regions (OCD-loop) are included in OCD symptomatology, a network that includes the ACC, DLPFC and posterior regions can be associated with cognitive processes in OCD (165, 170). The clinical improvement of OCD may be accompanied by the cognitive improvement and functional improvement of the brain, e.g., decision-making, visuospatial information, executive function and working memory (Figure 2.4).

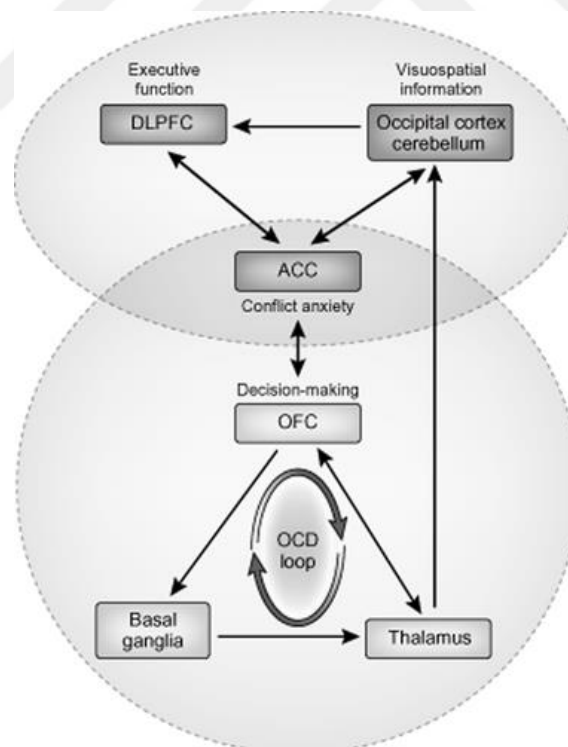


Figure 2.4. Functional Neuroanatomy of OCD (171). ACC: anterior cingulate cortex, DLPFC: dorsolateral prefrontal cortex, OFC: orbitofrontal cortex.

Mataix-Cols et al. (2004) revealed functional brain differences between OCD subtypes in their functional magnetic resonance imaging (fMRI) study (172). Accordingly, different obsessive-compulsive symptom dimensions were formed with the disruption of various components of the CSTC loop that play a role in cognition and emotion processes. When impulse inhibition is disrupted in the fronto-subcortical system, the impulse to check cannot be suppressed, and checking behavior occurs. When the emotional process is disrupted in the fronto-limbic system, emotional discomfort (the sense of disgust with dirtiness) occurs, and washing rituals emerge (173).

In their research using fMRI, Harrison et al. (2013) found that sexual/religious symptoms were associated with ventral striatal-insular connectivity, while finding that aggressive symptoms were associated with the connectivity between the amygdala, ventral striatum and ventromedial frontal cortex (174).

In their research that compared OCD patients with the healthy control group, Murayama et al. (2013) found that patients with washing rituals had hyperactivation in some bilateral cortico-cerebellar regions, while demonstrating hypoactivation in the left caudate and left OFC of patients with checking rituals (175).

Nakao et al. (2014) established a new model by revising the traditional OCD-loop model according to the results obtained from OCD subtype studies (171). In this model, while the caudate nucleus and ACC were associated with checking rituals, the major cortical brain regions were associated with washing rituals (Figure 2.5). Furthermore, in their study using voxel-based morphometry (VBM), the same group found negative relationships between aggression scores and reduction of the right cerebellum gray matter and between contamination scores and reduction of the right insula gray matter (171).

The multi-dimensional model suggested that OCD could be conceptualized as a spectrum of potentially overlapping syndromes, rather than being a unitary nosological entity (171). Moreover, this model may also explain the inconsistent findings obtained from neuroimaging studies examining OCD patients as an independent group of subtypes.

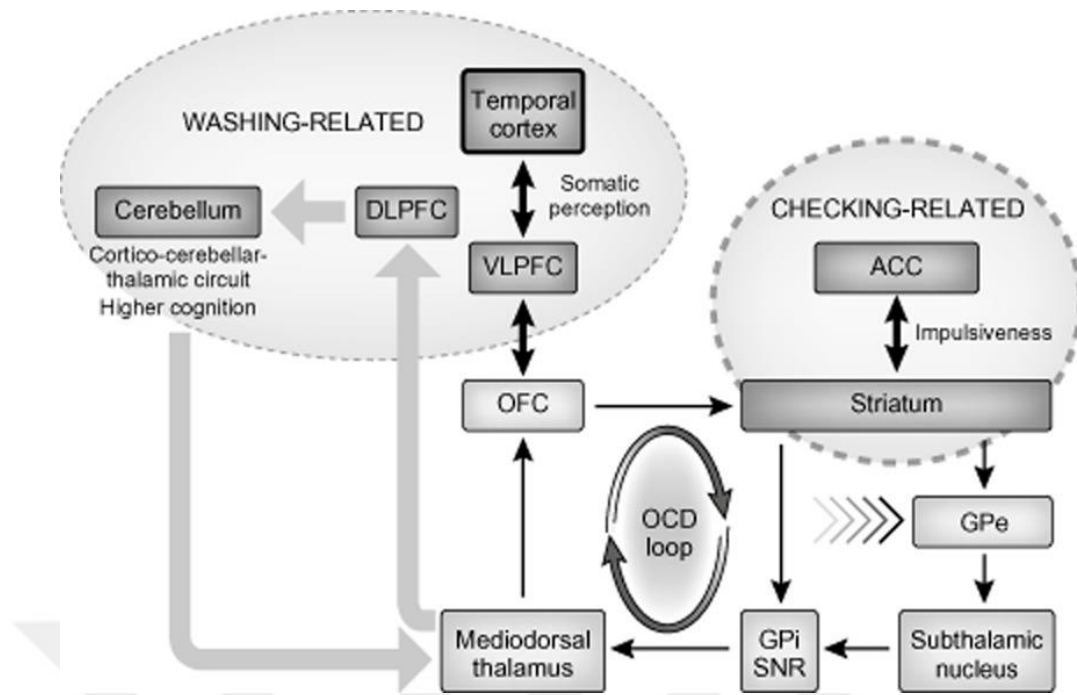


Figure 2.5. Multi-dimensional Model: OCD-loop and subtype-related loops (171).

VLPFC, ventrolateral prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; GPe, globus pallidus externus; GPi, globus pallidus internus; SNR, substantia nigra pars reticulata.

2.1.6.5. Structural Neuroimaging

Structural neuroimaging studies have reported volume alterations in regions, such as the OFC, ACC, thalamus, and caudate nucleus, in a way supporting the OCD-loop model (176-178). There are also studies supporting the idea that the regions not included in the OCD-loop model are also affected. In OCD patients, in comparison with the healthy control group, an increase in the gray matter volume has been shown in the left OFC, left inferior parietal cortex, left thalamus, left superior temporal gyrus, and bilateral hypothalamus, and a decrease in the gray matter volume has been shown in the cuneus and cerebellum (179, 180).

Region of Interest

In region of interest (ROI) studies, it has been shown that there is a decrease in volume in regions, including the OFC, caudate nucleus, thalamus, amygdala, and ACC

(176, 177, 181). In the meta-analysis of fourteen ROI studies, Rotge et al. (2009) showed that the left ACC and bilateral OFC volumes decreased and bilateral thalamic volumes increased (182). The volume increase in the ventral PFC and thalamus may be associated with increased metabolism and blood flow in these regions, as well as it may be a neurobiological marker of OCD (180).

Since the effect of medication is less in the initial period of the disease, it is significant to make an examination of pediatric patients in the early period. In the two studies comparing neuroimaging findings in certain brain regions of pediatric OCD patients and the healthy control group, the thalamus volume of treatment-naïve OCD patients was determined to be higher than that of the control group (183, 184). Furthermore, Rosenberg et al. (1997) found smaller striatal volumes and larger 3rd ventricular volumes in the OCD group in comparison with the control group (184).

Gilbert et al. (2000) initiated paroxetine treatment in 10 of the 21 pediatric OCD patients included in their study and monitored the change in the thalamus volume with repeated magnetic resonance imaging (MRI). It was determined that there was a decrease in the thalamus volume with paroxetine monotherapy in comparison with the control group, and this decrease was correlated with improvement in symptoms. Cognitive behavioral therapy (CBT) was applied to 10 patients from the same group, and MRI images were evaluated before and after the treatment. Although symptoms improved in the CBT group, there was no significant alteration in the thalamus volume. This result showed that the decrease in the thalamus volume might be associated with SSRI use, but not directly with treatment response (183).

The ROI methods measure the volumes of the brain regions that are expected to be affected in OCD. This may prevent the investigation of other brain regions that are likely to be impaired in OCD. In order to overcome this limitation, MRI studies that evaluate the whole brain with VBM analysis have been carried out.

Voxel-Based Morphometry

While Kim et al. (2001) found an increase in the regional gray matter density in multiple cortical areas, including the left OFC and subcortical areas containing the

thalamus in OCD, they demonstrated a decrease in gray matter in the posterior parts of the brain, including the left cuneus and left cerebellum (185).

As a result of MRI scanning and voxel-based morphometry (VBM) analysis they performed on 72 OCD patients and the matched control group, Pujol et al. (2004) found a decrease in gray matter volumes in the medial OFC, medial frontal gyrus, and left insular-opercular region in OCD patients and a bilateral increase in gray matter in the ventral part of the putamen and anterior cerebellum (186).

Van den Heuvel et al. (2009) showed that there was a decrease in gray matter volume in the left inferior frontal cortex, left DLPFC, left lateral OFC, and right mPFC and the bilateral prefrontal white matter volume reduction in OCD patients (143).

In the study in which they compared 23 OCD patients and 26 healthy controls by means of VBM analysis, Togao et al. (2010) showed that there was a decrease in the gray matter volume in the bilateral mPFC, right OFC, right premotor area, right DLPFC, and bilateral occipital and temporal regions in OCD patients, an increase in the white matter volume of the right ALIC and the right orbitofrontal region, and a decrease in the white matter volume of the left anterior cingulate gyrus (187).

Despite the fact that the findings obtained from VBM studies are inconsistent, Radua and Mataix-Cols (2009) performed the metaanalysis of the 12 VBM studies and found that there was a bilateral increase in the regional gray matter volumes of the lenticular nucleus (GP+putamen) extending to the caudate nucleus (predominantly in the ventral anterior putamen) and a bilateral decrease in the regional gray matter volumes of the dorsal mediofrontal/anterior cingulate gyri which extend to supplementary motor area (SMA) and the frontal eye areas in OCD patients. Interestingly, this metaanalysis did not reveal any significant intergroup difference in the OFC, the disorder of which had been consistently shown in functional neuroimaging studies in OCD patients and formed the basis of the most widely accepted OCD's neurobiological model (144).

In the meta-analysis in which Radua et al. (2010) compared OCD and other anxiety disorders in terms of VBM findings, while there was the bilateral gray matter volume increase in the lenticular/caudate nuclei in OCD, the gray matter volume decrease

was found in the left lenticular nucleus in other anxiety disorders and, thus, OCD was shown to be biologically independent of other anxiety disorders (178).

Diffusion Tensor Imaging

Szeszko et al. (2005) found that fractional anisotropy (FA) was lower in the bilateral ACC white matter in OCD patients in comparison with the healthy control group (188).

Nakamae et al. (2008) found higher FA in the subinsular white matter and higher apparent diffusion coefficient (ADC) in the left medial frontal cortex in OCD patients in comparison with the healthy control group (189).

Koch et al. (2012) demonstrated that stronger white matter deficits were related to more severe ordering symptoms by defining a negative relationship between FA and ordering symptoms (190).

Zarei et al. (2011) investigated the gray matter volume and white matter microstructure in the study in which they used diffusion tensor imaging (DTI) and VBM and revealed that the gray matter volume was higher in the right putamen and bilateral caudate in OCD patients in comparison with the healthy control group and that FA was higher in the left inferior longitudinal fasciculus, bilateral superior longitudinal fasciculus and right inferior fronto-occipital fasciculus (191).

2.1.6.6. Functional Neuroimaging

In functional neuroimaging studies such as fMRI and positron emission tomography (PET) conducted in OCD patients, the increased brain activity has been shown in the lateral OFC, ACC, and caudate nucleus. Since the medial OFC and ACC are also activated in other anxiety disorders, it may be an indicator of anxiety non-specific to OCD. However, hyperactivity in the caudate nucleus and lateral OFC appears to be specific to OCD (160).

PET and SPECT Findings

In most of the PET and single-photon emission computed tomography (SPECT) studies performed in OCD patients, it has been shown that there are abnormally high activities in the cortical and subcortical structures, including the ACC, OFC, thalamus and caudate nucleus (171, 181, 192). There are also studies in which hypoactivity was determined in the right OFC and left ACC (193). In a metaanalysis of 13 studies using PET and SPECT, OCD patients have been shown to have the OFC and caudate nucleus dysfunction, which had been previously shown to take part in OCD symptomatology (194).

In a study examining PET findings during cognitive activation in OCD, implicit learning in which the striatum was involved was investigated (195). It was shown that there was no normal activation of the striatum in OCD; instead, the medial temporal area related to conscious information processing was activated. This change, observed although learning is normal, indicates that the deterioration in the frontostriatal loop is compensated by the temporal cortex (195).

fMRI Findings

There are fMRI studies that show the increased activation in the OFC and ACC (196, 197) and in the insula, inferior frontal cortex and parahippocampus (198) during symptom provocation in OCD patients.

Cannistraro et al. (2004) demonstrated a bilateral decrease in the amygdala activation in response to human faces in OCD patients in comparison with the healthy control group (199).

Gillan et al. (2016) conducted a study that focused on the balance between habitual and goal-directed behaviors and showed that the increase in habit formation was related to the hyperactivation of the caudate nucleus in OCD patients (200).

In their resting-state fMRI study, Harrison et al. (2009) found an abnormal increase in functional connectivity along a ventral corticostriatal axis covering the OFC and surrounding areas in OCD patients (201).

In the meta-analysis of 28 fMRI studies examining executive functions in OCD, a decrease in task-relevant activation was reported in the caudate nucleus, putamen, cingulate cortex, and prefrontal regions (202). In another meta-analysis examining executive functions, frontostriatal abnormalities and parietal and cerebellar involvement were reported (147).

In a meta-analysis combining 54 fMRI studies in which cognitive and affective paradigms were applied to OCD patients, changes in the brain activation during the said paradigms were shown (203). While excessive activity was detected in the brain networks that play a role in arousal and habitual responding, salience e.g., the ACC, insula, head of the caudate nucleus, and putamen, in patients with OCD during the affective paradigm in comparison with the healthy control group, underactivation was detected in regions that play a role in cognitive control such as posterior caudate and the medial frontal region. While increased activity was observed in regions that play a role in self-referential processing, including the posterior cingulate cortex and precuneus, in patients with OCD in comparison with the healthy control group during the cognitive paradigm, underactivation was observed in the subcortical regions involved in goal-directed behavior and motor control, e.g., the ventral anterior thalamus, pallidum, and posterior part of the caudate nucleus. The findings of this study showed impaired cognitive control and an increase in habitual responding and affective processing in OCD patients (203).

Meta-Analyses Evaluating the Results of PET and fMRI Studies

In a meta-analysis combining the results of 8 studies, including 4 PET and 4 fMRI studies, it was shown that there was an increase in activation induced by symptom provocation in the ventral frontostriatal region, the left dorsal fronto-parietal network including the precuneus and DLPFC, and the left superior temporal gyrus in OCD patients in comparison with the control group (204).

In a more recent meta-analysis examining PET and fMRI studies, it was shown that there was increased activation in the bilateral amygdala, right putamen, OFC, ACC, ventromedial PFC, left inferior occipital cortex and middle temporal cortex during the emotional process induced by exposure to disease-related stimuli in OCD patients, and alterations in the amygdala were more pronounced in unmedicated patients, while changes in the right putamen were the most pronounced in medicated patients (205).

2.1.6.7. Molecular Neuroimaging

In the SPECT scanning conducted by using [^{123}I] β -CIT labeling both the DAT and the 5-HTT, Hesse et al. (2005) showed that DATs in the striatum and 5-HTTs in the thalamus and midbrain decreased (206). Moresco et al. (2007) stated that, fluvoxamine treatment increases D2 receptor availability in the BG of OCD patients in parallel with clinical improvement (207).

In MR spectroscopy (MRS) studies carried out on OCD patients, it has been shown that the N-Acetyl Aspartate level is low in the striatum and ventrolateral PFC (180, 208). In their proton-MRS study, Sumitani et al. (2007) demonstrated that the concentration of N-Acetyl Aspartate in the ACC was low in OCD patients who responded to atypical antipsychotic augmentation therapy (209).

MRS studies have indicated abnormal glutamate transmission in the brain regions associated with the CSTC loop. In MRS studies, Glx, used to represent glutamine, glutamate, homocarnosine, and GABA, was determined to be high in the caudate nucleus of OCD patients, and it normalized following SSRI treatment (180, 210-213). These results were consistent with the metabolic hyperactivity observed in the CSTC loop in OCD (167). On the contrary, Glx levels were detected to be low in the ACC (214). These findings were parallel to the inverse relationship between the ACC and BG volumes in OCD patients (95).

2.1.6.8. Neuropsychological Assessment

In neuropsychological tests applied to OCD patients, impairment in executive functions (e.g., impairment in planning, working memory, cognitive flexibility, and

response inhibition) (215, 216), attention disorder (215), verbal and nonverbal memory dysfunction (215, 216), impairment in visual-spatial abilities (215), and deteriorations in the disgust process, fear suppression, reward process, and emotion regulation (217) have been shown. These disorders point to the inadequacy in behavior inhibition and strategy formation. Moreover, Savage et al. (1999) argued that memory impairment in OCD was secondary to the impaired attention of patients to details that would be kept in memory (218). While decision-making was preserved in some patients and first-degree relatives without OCD diagnosis, impulsivity and decreased cognitive flexibility were detected (219). The inconsistency of the results regarding decision-making capacity is attributed to the heterogeneity of patients (165).

Studies combining neurocognitive tests and neuroimaging findings have suggested that there are impairments in attention, executive function, and working memory in OCD (220-224).

Attention Deficit

Schmidtke et al. (1998) showed that there were deficits in attentional processing in OCD (225). Many studies have been carried out to evaluate selective attention, based on the hypothesis stating that there is a difficulty in directing attention in OCD patients. In a PET study, decreased glucose metabolism rates in the frontal cortex of OCD patients were found to be related to the selective attention deficit (226). In a study using fMRI, decreased activation was found in the ACC and right caudate in OCD patients in comparison with the healthy control group during the Stroop task (227). In an fMRI study using the task-switching paradigm, OCD patients showed a higher error rate in the tests in comparison with the healthy control group, and decreased activation was found in the ventromedial PFC, dorsal frontal-striatal regions, and right OFC in the patients (222).

Executive Function

The executive function, which includes cognitive flexibility, set-shifting, planning, and problem-solving ability, is a higher cognitive function that controls and regulates other cognitive processes. Executive function disorders may be responsible for persistent and inflexible thoughts and behaviors in OCD (171).

The Wisconsin Card Sorting Test (WCST) represents a test appropriate for checking the set-shifting ability. While there are studies reporting that OCD patients have lower WCST scores compared to the healthy control group (228), there are also studies suggesting that this ability is not impaired (229). In a study in which SPECT was performed while applying the WCST to OCD patients, an association was detected between the number of errors in the WCST and cerebral blood flow in the left inferior frontal cortex and left caudate (230). Some other studies have suggested that the OFC dysfunction observed in OCD may impair the set-shifting ability measured by the Object Alternation Test (231, 232). In a study that utilized the Tower of London Test, cognitive inflexibility and problem-solving deficits were found in OCD (233). In an fMRI study, it was demonstrated that OCD patients had stronger left frontal cortex activation during the Word Generation Test compared to the healthy control group (234).

Working Memory

Working memory represents one of the high cognitive functions that include interim integration, process, organization, and finding of information. Working memory differs from the general memory function in that it includes active display and manipulation of information. Some researchers have shown working memory impairment in OCD by means of the Tower of London Test (233, 235).

In an fMRI study, OCD patients performed poorly at the highest level of task difficulty during the N-back task compared to the healthy control group, but considering the activation of the brain regions such as the bilateral ACC, parietal cortex and, DLPFC that serve spatial working memory, no significant difference was determined between patients and the control group (223).

In a study combining neuropsychological tests with fMRI, it was found that OCD patients showed lower scores in the delayed recall section of the Wechsler Memory Scale Revised (WMS-R) and the immediate recall section of the Rey-Osterrieth Complex Figure Test in comparison with the healthy control group and they showed more significant activation in the right DLPFC, left insula, left superior temporal gyrus, and cuneus during the two-back task. These results indicate that there is visual working

memory dysfunction in OCD patients, and this dysfunction can cause repetitive thoughts and behaviors (224).

2.1.6.9. Psychodynamic Theory

Freud defines obsessive-compulsive behaviors in the following way: “The patient’s mind is full of thoughts that really do not concern her/him, and she/he feels unfamiliar impulses. From time to time, she/he has to take actions that she/he cannot resist. These thoughts (obsessions) stuck in mind do not mean anything for the patient and often seem absurd to her/him. Although these thoughts never actually turn into action, they cause the patient to constantly escape from situations that remind her/him of these thoughts. The behaviors displayed by the patient against her/his will do not go beyond the exaggerated and ceremonial forms of actions, such as washing, which are the usual activities of daily life. However, these harmless behaviors, called obsessive acts or compulsions, are performed against the will of the person”(236).

The basic defense mechanism in the formation of OCD is regression. In these patients, in severe conflict situations caused by the impulses and desires of the oedipal period, these requests are partially or completely abandoned, and the wishes or requirements of the anal period are returned to. Therefore, while anxiety caused by impulses and requests of the oedipal period is avoided, conflicts of the anal period come to the forefront. Ambivalence (bivalence in emotions and behaviors) is a prominent feature of the anal period, and this feature manifests itself in hesitations and indecisiveness experienced during the action phase (237).

According to the psychoanalytic theory, three basic defense mechanisms specific to the anal period used in coping with aggressive and sexual impulses are defined: isolation, undoing, and reaction formation. When isolation is fully realized, the emotional component of the impulse is separated from its intellectual content and pushed into the unconscious. In this way, the patient becomes aware of an emotion-free thought at the conscious level. Compulsive actions are accepted to be the result of the undoing mechanism that aims at controlling impulses and alleviating anxiety. People who use the reaction formation, exhibit the opposite of the underlying impulse at the level of consciousness (237).

2.1.6.10. Cognitive Behavioral Theory

The cognitive model suggests that the common mechanism underlying all psychopathologies originates from dysfunctional or distorted thoughts that affect the patient's mental state. According to this model, people's emotions and behaviors are related to how they interpret the events they have experienced (238).

Automatic thoughts are negative thoughts that come to mind suddenly, spontaneously and automatically, that trigger emotions such as anger, sadness, and anxiety (239). Beck emphasized that these negative automatic thoughts were related to rules, schemes, and beliefs that people were not fully aware of (238).

Beliefs are effective in the emergence of automatic thoughts with different content. The deepest perceptions and ideas, which are shaped by the first experience of a person with the world and other people and which are generally never questioned, perceived as unchangeable truths and accepted as they are, are defined as core beliefs. Automatic thoughts are mental products on the surface and are specific to certain situations and pass through people's minds in the form of words or images. There are intermediate beliefs between core beliefs and automatic thoughts (240).

Below the automatic thoughts that are specific to the situation experienced and are on the surface, there are the attitudes, rules, and assumptions that the person cannot express and are called intermediate beliefs. Although these rules, attitudes, and assumptions are not expressed, they are considered as regulators of behavior (241). Intermediate beliefs are associated with how a person perceives any situation. These perceptions determine what a person thinks, feels, and how she/he will act (240).

Dysfunctional beliefs in the cognitive structure shape the person's thoughts and constitute the cognitive distortions specific to psychopathology. Cognitive distortions are considered to be individual biases or tendencies in the information processing. Cognitive distortions may create automatic thoughts that are not appropriate for the situation and cause emotional discomfort (241).

The cognitive behavioral theory suggests that obsessive thoughts do not differ from insistent thoughts in terms of their content. The difference between insistent thoughts and obsessions lies not in the controllability of these thoughts, but in the interpretation of these thoughts by OCD patients as indicators that they may be responsible for harm and the prevention of harm (242). People with OCD go into dysfunctional efforts, such as mental rituals or compulsive behaviors, in order to eliminate or neutralize the exaggerated sense of responsibility, since they have erroneous assessments that they have personal responsibilities over these thoughts (243).

2.1.7. Prognosis

OCD has a chronic waxing and waning course. While a significant improvement is observed in the symptoms of 20-30% of patients, a moderate improvement is observed in the symptoms in 40-50% of patients. Symptoms remain the same or worsen in 20-40% of patients (244).

The determinants of the poor prognosis in OCD are as follows: the early onset of the disease, severe initial illness, the presence of pronounced magical thinking, delusions, personality disorders (especially schizotypal, paranoid, and borderline personality), the coexistence of OCD with bipolar disorder and eating disorder, hospitalization history, not being married, poor social adaptation and inadequate social skills, and having OCD patients in the family. Good social and professional organization, the presence of an initiating event, and episodic symptoms are good prognostic factors. Obsessional content does not seem to be associated with prognosis (48).

2.1.8. Treatment

2.1.8.1. Pharmacotherapy

SSRIs are recommended for the first-line treatment of OCD (3-6). The SSRIs recommended in the first step for OCD are fluvoxamine (245), fluoxetine (246), paroxetine (247), sertraline (248), and escitalopram (249). In a meta-analysis performed on 3000 patients, the efficacy of SSRIs was not found to be different from clomipramine,

and SSRIs were better tolerated due to fewer side effects (6). Therefore, clomipramine is recommended for second-line treatment (Table 2.1).

For clinical improvement in OCD, the recommended doses of serotonergic antidepressants [Clomipramine (250-300 mg/day), sertraline (225 mg/day), fluoxetine (60-80 mg/day), paroxetine (40-60 mg/day), fluvoxamine (200-300 mg/day), escitalopram (40 mg/day), citalopram (40-60 mg/day)] should be used for a minimum of 10-12 weeks (1, 250-253).

Of patients, 40-60% do not respond adequately to SSRI treatment (3, 7). For TR-OCD, there are some recommended treatment strategies before moving to adjunctive therapies. One of these is the intravenous administration of clomipramine and citalopram. The limited number of studies indicate the importance of this practice because of its rapid onset of action (254).

Adjunctive Therapy

Antipsychotics

Half of the patients who do not respond to first-line treatment receive augmentation treatment (255). In TR-OCD, various meta-analyses and clinical trials have shown that the use of antipsychotics such as aripiprazole (256-258), risperidone (258-260), quetiapine (260, 261), olanzapine (259, 260), haloperidol (258, 260), ziprasidone (3) or amylsulpyrid (262) in combination with an SSRI is more effective in comparison with SSRI monotherapy. In most of the studies, the response was received within first month of augmentation. Approximately one-third of TR-OCD patients reported a clinically significant improvement after such treatment (263).

The first-line antipsychotics recommended in the augmentation treatment of OCD are aripiprazole and risperidone (Table 2.1).

In their meta-analysis, Bloch et al. (2006) showed that augmentation treatment with risperidone, quetiapine, olanzapine, and haloperidol increases the response to treatment (260). In another meta-analysis, while the augmentation with aripiprazole,

risperidone, and haloperidol was effective, the effect of augmentation with quetiapine, olanzapine, and paliperidone was not found to be different from placebo (258). Since pieces of evidence regarding the effectiveness of quetiapine and olanzapine are still contradictory (260, 264, 265), quetiapine ranks second, and olanzapine ranks third in augmentation treatment (3). Haloperidol, ziprasidone and amisulpride rank third in augmentation treatment (Table 2.1).

Furthermore, atypical antipsychotics acting as serotonin dopamine antagonists have the potential to induce or worsen obsessive-compulsive symptoms. This is probably associated with 5HT_{2A} receptor blockade in regions such as the ACC, dorsal posterior PFC, and OFC, which play a role in the pathophysiology of OCD (266, 267).

Glutamatergic Agents

Topiramate, an alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) glutamate receptor antagonist, may be beneficial in TR-OCD patients (268, 269). A double-blind, placebo-controlled study suggested that topiramate augmentation might be beneficial for compulsions, even if not for obsessions in TR-OCD patients (270).

In an open-label augmentation study using memantine, which is an NMDA glutamate receptor antagonist, a significant improvement in symptoms was observed in nearly half of SSRI-resistant patients (271). Some case reports also indicate the successful treatment of resistant OCD patients with memantine augmentation (272, 273).

In an open-label study, it was observed that riluzole, which is a glutamate modulator added to the current psychopharmacotherapy of TR-OCD patients, had a significant antiobsessional effect (97).

Case reports, indicating that pregabalin, which inhibits glutamate release indirectly by blocking calcium channels, will display positive impacts on OCD symptoms when administered together with serotonergic antidepressants, have been published (274, 275).

Fluoxetine, augmented with N-acetylcysteine that is a glutamate modulator, provided a significant decrease in OCD symptoms in a TR-OCD patient (276).

In the OCD treatment guide, topiramate ranks second in augmentation treatments, and memantine, riluzole, pregabalin, and N-acetylcysteine rank third (Table 2.1).

Other Pharmacological Agents

Both positive and negative results have been stated in augmentation treatment with 5-HT_{1A} and β -adrenergic receptor antagonist, pindolol (277, 278).

Ondansetron, which is a 5-HT₃ receptor antagonist, may be promising as an augmentation strategy for some OCD patients (279).

The addition of buspirone, which is a 5-HT_{1A} receptor partial agonist, to the treatment regimen did not provide additional benefits in OCD patients who had a partial improvement with clomipramine (280).

In two double-blind studies using lithium augmentation, the use of lithium in OCD was not found to be effective (281).

In a crossover double-blind study, clonazepam monotherapy caused a significant reduction in OCD symptoms in the first three weeks of the treatment, while a similar effect was not found in another 10-week double-blind placebo-controlled study (282, 283).

In the OCD treatment guide, whereas pindolol and ondansetron are in the third line in augmentation treatments, the use of buspirone, lithium, and clonazepam is not recommended (Table 2.1).

Studies on Medications not Included in the Treatment Guide

In a case report, the positive effect of augmentation therapy with perospirone (an atypical antipsychotic that is a 5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist) was mentioned (284).

In a double-blind placebo-controlled study, glycine (an NMDA glutamate receptor agonist) added to treatment was shown to be beneficial in treating OCD symptoms (285).

Although human studies are still lacking, amantadine, which is an NMDA antagonist, may be an effective medication for the treatment of OCD, in accordance with preclinical findings (286).

It has been demonstrated that response to behavioral therapy accelerates in the short term with D-cycloserine, an NMDA receptor partial agonist, but no significant difference is found between patients receiving and not receiving D-cycloserine in the following process (287).

In a double-blind placebo-controlled study performed on naltrexone, an opioid antagonist, no additional efficacy on OCD symptoms could be shown (288).

Although the addition of gabapentin to fluoxetine was shown to shorten the onset of antiobsessive effects in a study (289), it was demonstrated that gabapentin was not effective in augmentation treatment in another study (290).

Valproate in patients who could not tolerate serotonergic antidepressants increased tolerance to these medications, and it also reduced OCD symptoms (291).

A double-blind placebo-controlled study performed on lamotrigine augmentation in TR-OCD patients obtained successful results (292).

There have been few case reports indicating that TR-OCD is improved with clozapine treatment (293).

It has been reported that antiandrogenic therapy with triptorelin, a gonadotropin-releasing hormone analog, results in a significant improvement in OCD symptoms (294).

In the literature, there are reports on both positive and negative results with inositol, a secondary messenger precursor (295, 296). However, the data in this group are mostly obtained from short-term open-label studies and case reports.

Table 2.1. Pharmacological Agents Recommended in the Treatment of OCD: Taken from the Canadian Clinical Practice Guide (3).

Treatment	
First line	Fluoxetine, fluvoxamine, paroxetine, escitalopram, sertraline
Second line	Clomipramine, mirtazapine, citalopram, venlafaxine XR
Third line	IV citalopram, IV clomipramine, tramadol, tranylcypromine, duloxetine, phenelzine
Adjunctive therapy	First line: risperidone, aripiprazole Second line: quetiapine, memantine, topiramate Third line: amisulpride, celecoxib, granisetron, citalopram, haloperidol, IV ketamine, mirtazapine, N-acetylcysteine, olanzapine, riluzole, ondansetron, pindolol, pregabalin, ziprasidone Not recommended: buspirone, lithium, clonazepam, morphine
Not recommended	Clonazepam, desipramine, clonidine

IV, intravenous; XR, extended release.

2.1.8.2. Psychotherapy

Cognitive Therapies

Cognitive therapy was developed by Aeron T. Beck in the early 1960s for the treatment of depression (238). In cognitive therapy, it is aimed to change and restructure the dysfunctional thoughts and behaviors of the person applying to therapy. It is assumed that realistically re-evaluating and changing these thoughts will cause acceptable emotions and functional behaviors (297). Permanent improvements depend on changes in the person's dysfunctional core beliefs (238).

During cognitive therapy, firstly, automatic thoughts that are more on the surface and easily accessible are concentrated on. During therapy, the person is taught to identify, evaluate, and change these thoughts. After these dysfunctional automatic thoughts, the person is directed to deeper beliefs that are valid in many cases. The person's perceptions and inferences about situations and events can be changed by evaluating intermediate and core beliefs (240). Changing the core beliefs will reduce the possibility of the recurrence (240).

Cognitive therapy takes an essential place in the treatment of OCD (288, 299). The most important step in this treatment is that the patient brings new interpretations to explain her/his thoughts in a less threatening way. It is necessary to emphasize that the situation that the patient perceives as a real risk is actually only a subjective evaluation (300).

The patient may believe that thinking or imagining any action increases the frequency at which that action occurs. In treatment, such a thought is considered to be assumptions that must be shown to be true or false. In such an approach, the patient is encouraged to test whether thinking about certain things increases their chances of occurring in real life (300).

In the treatment, first of all, it is necessary to prepare the patient for change. This requires informing patients and their relatives about the disease and treatment and communicating the short and long-term advantages of therapy to ensure that the patient is connected to the treatment, in a sense, and to increase her/his motivation. At the next stage, it is reviewed with the patient through cognitive structuring to what extent the perceptions of threat-danger-excessive responsibility are realistic. In this process, it is conveyed to the patient how exaggerated threat-danger-excessive responsibility perceptions emerge as a result of various cognitive distortions (300).

In the treatment, it is taught to identify cognitive distortions and then replace these dysfunctional thoughts with thoughts that may be more compatible with the situation experienced. The goal is not to ensure more positive thinking but to develop more realistic and less threatening ways of thinking (300).

Behavioral Therapies

According to the behavioral model, thoughts that are not actually frightening and that can come to everyone's mind are associated with anxiety in the individual through conditioning and gain disturbing characteristics (classical conditioning). Such thoughts coming to mind create anxiety in the individual, and the individual displays avoidance behavior to be protected. This avoidance behavior acts as a kind of reinforcer by reducing anxiety (operant conditioning) (300).

A person with OCD tries to reduce his anxiety by developing a series of compulsive behaviors in addition to avoidance behaviors. These behaviors act as reinforcers, as in avoidance behavior, and cause the same behaviors to increase. Since the individual uses only strategies such as avoidance and repetition to cope with anxiety, as anxiety increases, she/he uses these strategies more and, thus, enters a vicious circle (300).

This view has yielded to the development of the behavioral therapy approach known as Exposure and Response Prevention (ERP) (301). In this approach, the person is made to encounter with obsessions that cause anxiety and create avoidance behaviors because they cause anxiety, and compulsions that come into play to reduce the anxiety caused by this encounter are prevented (ritual prevention). The goal is to reduce the anxiety caused by thoughts and to enable the habituation to occur (300).

Cognitive Behavioral Therapy

Cognitive therapies have provided behavioral therapies with a content they can work on. The integration of behavioralism with cognitive theory and the transformation of these two important theories into a single and holistic theory under the name of CBT has been evaluated as one of the most successful integration examples in terms of psychotherapy. Although cognitive techniques seem to be the priority in CBT, the most effective and permanent way to benefit from the cognitive technique is to use behavioral techniques (241).

2.1.8.3. Non-Pharmacological Biological Treatments

Non-pharmacological biological treatments may be useful in OCD patients not responding to adjunctive pharmacotherapy and CBT (3). Non-pharmacological biological approaches are in the last two steps in treatment. The second to last step is TMS and deep brain stimulation (DBS) applications. There are surgical applications in the last step of the treatment (302).

Psychosurgery

Patients should be diagnosed with OCD according to the DSM, be aged between 18-55 years, the disease should persist for at least five years, the Y-BOCS score should be more than 26 or obsession or compulsion subscale scores should be above 13 each, and a diagnosis of TR-OCD should be made (303). For the diagnosis of TR-OCD to be made, it is necessary to have used at least three types of SSRIs and clomipramine, to have used each medication at an effective dose for at least 12 weeks, to have applied CBT for at least 20 hours, not have a significant change in the scale scores during follow-up, and not observe an improvement despite adding at least two kinds of medications (303-306). Dementia, being under the age of 18 and older than 55 years (in some publications, being over 65 years of age), having antisocial or paranoid personality disorder, having substance addiction, pregnancy or lactation, and mental retardation are among the conditions in which this method cannot be applied (304, 305).

The results of functional and structural neuroimaging studies in OCD are that the OFC, ACC, BG structures, and the thalamus show abnormalities in this disease. Therefore, the target in TR-OCD surgery is the CSTC loop, as well as the ventral striatum, ALIC, STN, and Nac (267).

Nowadays, four methods are employed in the surgical treatment of psychiatric disorders (302, 307-309):

1. Anterior cingulotomy (Forming a lesion in the anterior cingulate gyrus)
2. Anterior capsulotomy (Forming a lesion in the fronto-limbic fibers in the ALIC)
3. Limbic leucotomy (Anterior cingulotomy+subcaudate tractotomy)

4. Subcaudate tractotomy (The destruction of the pathways between the frontal lobe and subcortical structures by forming a lesion in the substantia innominate just below the head of the caudate nucleus)

The studies conducted show that capsulotomy (101, 304, 310-312) and cingulotomy (313-315) may be effective in reducing symptoms of severe, TR-OCD patients.

Deep Brain Stimulation

DBS of the ALIC/ventral striatum is a method approved by Confirmit Europeene (CE) and the Food and Drug Administration (FDA) (316). The mechanism of action of DBS is not fully known (317).

The target anatomical regions in DBS are the ALIC (318), ventral capsule/ventral striatum (VC/VS) (319-322), Nac (322, 323), and STN (321, 324). Moreover, in meta-analyses, data on which DBS regions are more effective in TR-OCD are insufficient (325). In a review comparing anterior capsulotomy and DBS stimulating this region, it was found that both treatments were effective, but DBS was a more acceptable method in terms of side effects (326). It has been determined that there is a risk of developing hemorrhage, epileptic seizures, infection, and hypomania with DBS (327, 328).

Noninvasive Brain Stimulation

Transcranial Magnetic Stimulation

Despite mixed results, meta-analyses and systematic reviews generally show the effectiveness of neurostimulation in OCD (10-14). The use of dTMS in the treatment of OCD has been approved by the FDA (9). Studies on this subject will be detailed in the relevant section.

Transcranial Direct Current Stimulation

In a review of 12 studies targeting various brain regions, including the OFC, DLPFC, and SMA, most of the studies showed that transcranial direct current stimulation (tDCS) was effective in reducing OCD symptoms. Furthermore, it was stated that more studies were needed to determine the appropriate stimulation parameters and electrode placement (329).

Parameters Used in Treatment Follow-up

Improvement includes the condition in which obsessive-compulsive symptoms that have been the subject of complaints at the beginning disappear completely and objectively, the Y-BOCS score is ≤ 8 , and psychosocial functioning returns to the pre-illness level (260, 330).

Remission includes the condition in which the symptom severity decreases below the threshold value, the Y-BOCS score is ≤ 16 , and the improvement is evaluated as 1 (very much improved) on the clinical global impression (CGI) scale (260, 330).

CGI-Improvement (CGI-I): 1 (very much improved) or 2 (much improved) together with $\geq 35\%$ reduction in the Y-BOCS scores indicates a complete response to treatment. A decrease of more than 25% and less than 35% in the Y-BOCS scores shows a partial response to treatment, a decrease of $< 25\%$ in the Y-BOCS scores and a CGI-I: 4 (no change from baseline) show treatment unresponsiveness (260, 330). Moreover, there are studies in the literature that consider a 30% reduction in the Y-BOCS scores as the limit and divide patients into two groups as responsive and non-responsive to treatment (9).

Brain Changes Before and After Treatment

Functional neuroimaging studies examining the effect of treatment have shown that hypermetabolism in the caudate nucleus and OFC is decreased with treatment (331, 332). Moreover, some studies revealed that pre-treatment hypometabolism in the OFC

(160, 333-335) or hypermetabolism in the right caudate nucleus (334, 335) might be correlated with better response to SSRIs.

In their review including four studies (331, 336-338), Linden (2006) found that psychotherapy would lead to a decrease in metabolism in the caudate nucleus and a decrease in the correlation of thalamus and the right OFC with the ipsilateral caudate nucleus and that the effects of psychological and pharmacological interventions on cerebral metabolism were quite similar (339). At the same time, Saxena et al. (2009) argued that although thalamic activity reduction was a general result for improvement in OCD, the response to CBT requires the activation of the dorsal ACC, a region involved in the re-evaluation and suppression of negative emotions (340). According to a hypothesis, CBT will reduce obsessions and compulsions by affecting the cortical regions, including the DLPFC. On the contrary, SSRIs and antipsychotics will reduce emotions and obsessions by acting on the limbic structures and BG. Nevertheless, no finding indicating that different pathways are regulated in OCD, such as ‘top-down’ by psychotherapy and ‘bottom-up’ by pharmacotherapy, has been obtained yet (339).

Studies in which fMRI findings were evaluated before and after behavioral therapy or fluvoxamine treatment have been conducted to investigate treatment response in OCD patients. In comparison with the healthy control group, increased activation was detected in the OFC and thalamus during the symptom provocation task, and decreased activation was found in the cerebellum and parietal cortex during the Stroop task, which is related to selective attention, in untreated OCD patients (227). Hypoactivation of the posterior regions and hyperactivation of the frontal lobe improved after OCD improved with fluvoxamine treatment or behavioral therapy (170, 337). It was suggested that pre-treatment activation in the right cerebellum and left superior temporal gyrus (STG) positively correlated with improvement in the Y-BOCS scores and predicted a decrease in symptom severity (341).

Further studies are needed to elucidate the association between brain changes and treatment. Moreover, recent research shows that more widely distributed large-scale brain systems, such as the cerebellar, occipital and parietal regions, rather than the orbitofronto-striatal regions alone, may take part in the treatment of OCD (169, 170, 223).

2.2. Quantitative Electroencephalography

QEEG analysis, which is a method of detecting clinically significant changes that cannot be detected by routine visual examination, refers to converting specific EEG data into a numerical value (342). Therefore, statistical analysis can be performed by comparing the parameters of a group with the healthy control group or another group with the same pathology (343).

2.2.1. Electroencephalography Recording

In EEG recording, after subjects or patients are taken to a quiet and dimly lit room, electrodes are connected to the scalp with the help of a conductive gel and cap. Electrodes are placed on the cap in accordance with the international 10-20 system standardized by the “American Electroencephalographic Society” (Figure 2.6). Firstly, the resting-state EEG activities of participants are recorded by the computer without performing any task that may cause cognitive activity. Then, during the recording, participants are asked to open and close their eyes for a specific period of time. The recording lasts for an average of 30 minutes (342).

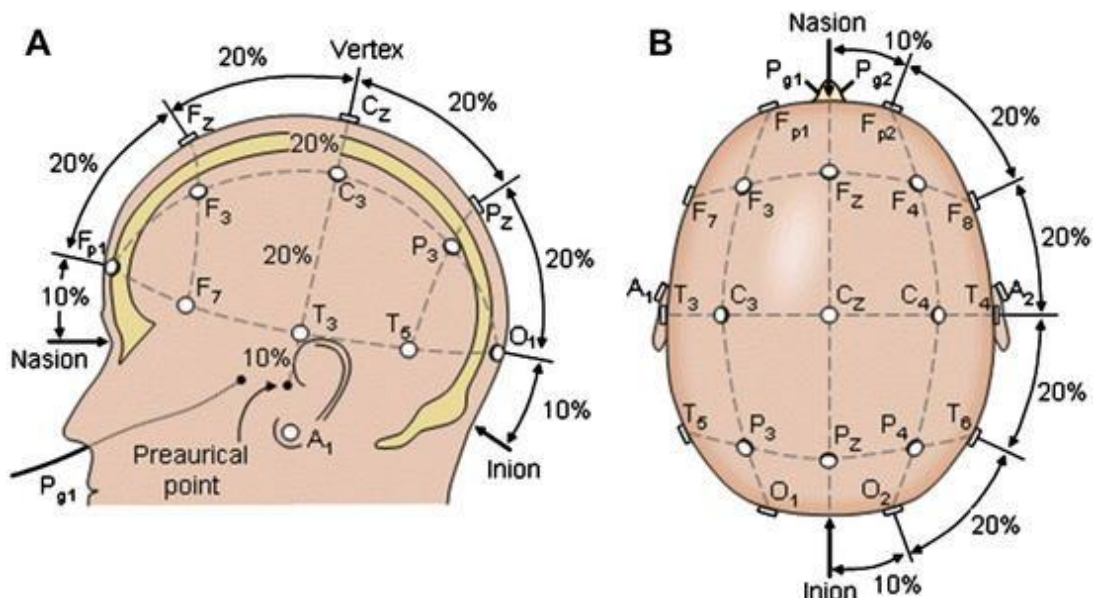


Figure 2.6. The International 10-20 System seen from (A) left and (B) above the head (344). F: frontal, FP: frontal polar, O: occipital, A: ear lobe, C: central, P: parietal, Pg: nasopharyngeal.

2.2.2. Frequency Analysis

To quantify the frequency components of the EEG signal, methods converting the EEG signal from the time domain to the frequency domain have been developed. A spectral analysis method commonly used to perform EEG analysis is Fast Fourier Transform (FFT) (343). As a result of spectral analysis, the EEG signal is separated into delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-70 Hz) frequency bands and EEG power (μV^2) is quantified in different frequency bands (345-348).

2.2.3. Quantitative Electroencephalography Studies in Obsessive Compulsive Disorder

Frontal asymmetry has been reported in alpha (349-351) and theta (352, 353) bands in OCD patients.

Resting-state frontotemporal delta (349, 353-357) and theta (349, 350, 352-355) activity has been shown to be higher in OCD patients in comparison with the healthy control group.

There are conflicting study findings reporting an increase (349, 351, 358, 359) or decrease (355, 356, 360) in the alpha activity and an increase (349, 361) or decrease (353, 355, 362) in the beta activity in OCD patients.

2.2.3.1. Frontal Asymmetry

An increase has usually been shown in the frontal alpha (349-351) and theta (352,353) band power in the left hemisphere. Asymmetries have also been reported in other bands (358, 363). Nevertheless, a number of studies have not supported these findings (355, 364).

This ambiguity may be due to the nature of frontal asymmetry that is known to reflect processes, including excessive approach (e.g., mania, substance abuse) or avoidance (e.g., depression, anxiety) or that underlie these disorders, rather than

psychiatric disorders themselves (365). Hence, the presence or absence of frontal asymmetry may be due to OCD comorbidities, including major depressive disorder or substance abuse (366). An alternative theory states that OCD patients tend to avoid particular situations and approach specific behaviors (compulsions) (367) and imbalance in this avoidance-approach process may cause frontal asymmetry (368).

2.2.3.2. Delta Band

An increase in resting-state delta activity has generally been found on the frontotemporal regions in OCD patients in comparison with the healthy control group (349, 353-356). This frontal slowing can be explained by the activation of frontal generators of delta activity (369). In two studies that utilized standardized low-resolution electromagnetic tomography (sLORETA), it was observed that this phenomenon was limited to the insula (354,363). Contrary to these findings, two studies conducted with a small sample (370) and no control group (359) demonstrated a decrease in delta power in OCD patients.

2.2.3.3. Theta Band

Resting-state frontotemporal theta activity has increased in OCD patients in comparison with the healthy control group (349, 350, 352-355).

Contrary to resting-state EEG findings, decreased frontal theta power has been determined in OCD patients in comparison with the healthy control group during the color discrimination task (371). It has been reported that frontal theta activity increases during tasks that require attention in healthy participants (372). Moreover, theta activity reflects the brain mechanism that makes a choice between competing processes such as suppressing distractions during a focused activity (373). In particular, frontal theta activity that originates from the ACC reflects active inhibition (374). It has been demonstrated that there are deficits in inhibitory regulation in OCD patients (375).

2.2.3.4. Alpha Band

It is accepted that the decrease in alpha power is related to the increase in blood-oxygen-level-dependent (BOLD) fMRI signal and reflects the increase in cortical activation (376). It has been observed that resting-state frontotemporal alpha activity is higher in OCD patients in comparison with the healthy control group (349, 351, 358, 359). Nevertheless, there are also studies indicating a decrease in alpha activity in OCD patients (355, 356, 360). This contradiction may originate from differences in study design or the heterogeneous nature of OCD symptoms.

Two studies indicated that cognitive task-related alpha activity was lower in OCD patients in comparison with the healthy control group (371, 377). The cognitive tasks utilized in the mentioned studies are the color and shape discrimination task and OCD symptom provocation task (exposure to situations that provoke OCD symptoms), respectively. The decrease in alpha activity has been reported to be associated with difficulties in suppressing distractors or task-unrelated details (378). The fact that the mind of OCD patients is often preoccupied with distractors and there is an intrinsic deficit in inhibiting obsessive thoughts can explain the alpha decrease in OCD patients during cognitive tasks.

Moreover, it has been observed that the alpha decrease during live exposure to situations that provoke OCD symptoms shifts from posterior to anterior topography, by showing frontal activation (377). The mentioned result is consistent with neuroimaging studies indicating frontal activation during symptom provocation in OCD (379).

2.2.3.5. Beta Band

Changes in beta activity are associated with cerebral metabolism (380), and a decrease in beta activity is associated with a reduction in the cerebral blood flow in that region and, thus, a decrease in metabolism. Some functional neuroimaging studies have shown that OCD is associated with cerebral metabolic abnormalities (194, 381). In the literature, there are studies reporting a decrease (353, 355, 362) and an increase in beta activity (349, 361).

OCD patients cannot show an increase in the temporal region beta band power observed in healthy individuals during olfactory stimulation (357). Although olfactory stimulation is expected to cause the desynchronization of electrical activity with increased power in the beta band (382), OCD patients have impaired neurofunctional responses to temporal activation procedures.

2.2.3.6. Relationship of Quantitative Electroencephalography Findings with Treatment Response

Prichet et al. (1993) compared the pre-treatment QEEG data of OCD patients who responded and those who did not respond to SSRIs. While increased alpha power was detected in patients responding to the treatment, increased theta power was detected, particularly in the frontal and frontotemporal regions, in patients who did not respond to the treatment (383). Hansen et al. (2003) showed that response to SSRIs in OCD was associated with an increase in pre-treatment alpha power, and increased alpha power at baseline decreased with treatment (359). These studies supported the finding that SSRIs slow down alpha activity shown in previous studies (384, 385).

An increase in the resting-state theta power is usually correlated with SSRI resistance (352, 383). On the contrary, a resting-state EEG study conducted with a younger sample reported that OCD patients with the higher pre-treatment left frontal theta activity responded better to SSRIs and this might be related to genetic differences between samples (353).

In a repetitive TMS (rTMS) study in which 1 Hz stimulation was applied to the right frontal region of 50 OCD patients, it was shown that patients who responded to the treatment (n=35) had higher theta band power in all electrodes compared to those who did not respond to the treatment (n=15) (386).

2.3. Transcranial Magnetic Stimulation

Barker et al. (1985) developed a TMS device that allowed stimulating the cerebral cortex non-invasively (387). The mechanism of TMS is based on the principle of electromagnetic induction (the conversion of electrical energy into a magnetic field and

the magnetic field into electrical energy) defined by Faraday in 1831. Although TMS was initially used to investigate the local functions of the human brain neurocognitively, it was found that it regulated cortical excitability by giving these stimuli in a repetitive manner, immediately after the development (388-393).

rTMS is based on the principle of modulating excitability of cortical neurons just below the application area by stimulating a region on the scalp by means of an electromagnetic coil (394, 395). Low-frequency rTMS (LF-rTMS) (<5 Hz) enables to reduce neuronal activity in the cortex (396), and high-frequency rTMS (HF-rTMS) (>5 Hz) provides the enhancement of cortical activity by facilitating synaptic activity (397). However, this stimulation is not limited only to the cortex where the application is made, but it also spreads to more distant regions by the connections between the brain regions (398). In dTMS, specially designed coils (H7-coils for OCD treatment) are used to reach deeper cortical structures while creating a local magnetic field (9).

2.3.1. Transcranial Magnetic Stimulation Studies in Obsessive Compulsive Disorder

Despite mixed results, systematic reviews and meta-analyses generally show the effectiveness of neurostimulation in OCD (10-14). The DLPFC, SMA, OFC/mPFC, and ACC are the brain regions shown to be associated with OCD (399). Randomized controlled TMS studies and meta-analyses targeting various brain areas affected in OCD are presented below.

2.3.1.1. Dorsolateral Prefrontal Cortex

The “dorsal (cognitive) loop” included in the CSTC loop performs executive functions such as planning, working memory, and attention (400, 401). Dorsal loop deficits in OCD are related to the indirect pathway being more dominant than the direct pathway (401, 402).

Studies Applying rTMS over the DLPFC

Studies Applying LF-rTMS over the Right DLPFC

In a double-blind, randomized controlled trial (RCT) conducted on 18 OCD patients who received or did not receive pharmacotherapy, Alonso et al. (2001) investigated the effects of sham-rTMS against 1 Hz-rTMS applied over the right DLPFC (403). The Brodmann areas (BA) 6, 8, 10, 44, and 45 that constitute the right DLPFC were stimulated 3 times a week for 6 weeks using a circular coil, and no statistically significant difference was observed between the sham-rTMS and 1 Hz-rTMS groups within 10 weeks in the average Y-BOCS scores that had been initially in the moderate-severe range ($p=0.81$). No significant difference was found between the groups according to the Hamilton Depression Rating Scale (HAM-D) scores ($p=0.95$). The authors indicated that the enrollment of TR-OCD patients in the study, heterogeneity in the medication status, uncertain disease duration, and the use of active sham coil might have caused negative results.

In an RCT they conducted with 27 TR-OCD patients, Seo et al. (2016) applied 1 Hz-rTMS over the right DLPFC using an eight-shaped coil in sessions of 20 minutes each for 3 weeks (404). In the sham protocol, the same parameters were applied, except for the use of an inactive coil. A significant difference was observed between the two groups in terms of the Y-BOCS scores after 3 weeks ($p=0.008$). At the same time, no significant difference was detected between the groups in terms of the number of patients who responded to treatment (a decrease of $\geq 25\%$ in the Y-BOCS scores) ($p=0.148$). The difference between the groups concerning the HAM-D scores ($p=0.009$) at the second week and the CGI-Severity Scale (CGI-SS) scores ($p=0.008$) at the third week was found to be significant. The limitations of this study are not mentioning whether the Y-BOCS scores improved secondary to improved mood, not being a double-blind study, the presence of a small sample, and not using neuronavigation.

Elbeh et al. (2016) investigated the impacts of 1 Hz-rTMS, 10 Hz-rTMS, or sham-rTMS applied over the right DLPFC of 45 OCD patients with a mean disease duration of 19.2 ± 11.5 months (405). Patients were followed up for three months after 10 rTMS sessions. Sham-rTMS parameters were the same as for the 10 Hz group, except for the

fact that the coil was placed at a 90° angle to the scalp. In terms of the Y-BOCS scores, while a statistically significant difference was found between the the sham group and 1 Hz group at the 2nd week ($p=0.001$) and at the 3rd month ($p=0.001$), no significant difference was detected between the 10 Hz group and the sham group, neither at the 2nd week ($p=0.08$) nor at the 3rd month ($p=0.098$). After the 3rd month, the group receiving 1 Hz-rTMS displayed a statistically significant decrease in the Y-BOCS scores in comparison with the 10 Hz group ($p=0.019$). With this study, it was demonstrated that young OCD patients not resistant to treatment with a short mean duration of illness responded well to 1 Hz-rTMS. The Hamilton Anxiety Rating Scale (HAM-A) scores in the 1 Hz group decreased significantly compared to the 10 Hz and sham groups, but it was not mentioned that this decrease might be associated with the decrease in the Y-BOCS scores.

Studies Applying HF-rTMS over the Right DLPFC

Sarkhel et al. (2010) randomly selected 42 OCD patients under medication and applied 10 sessions of 10 Hz-rTMS or sham-rTMS over the right DLPFC (406). When the Y-BOCS scores of patients were evaluated on the 14th and 28th days, although the treatment was found to be effective ($p<0.001$), it was detected that this effect was not long-lasting ($p=0.15$). On the other hand, the HAM-D scores ($p=0.035$) and HAM-A scores ($p=0.01$) improved significantly in the 10 Hz group in comparison with the sham group. Thus, in this study, rTMS was demonstrated to reduce depressive symptoms and anxiety, although it was not effective in the treatment of OCD.

In a 6-week double-blind RCT conducted with 27 TR-OCD patients with the initial Y-BOCS scores in the severe-extreme range, Mansur et al. (2011) stimulated the right DLPFC with 10 Hz-rTMS (407). These patients were then followed up with an open-label study that lasted for 6 weeks. No significant difference was determined between the groups concerning the Y-BOCS scores 6 weeks after the first stimulation ($p=0.710$). Furthermore, there was no significant difference between the groups concerning the HAM-D ($p=0.637$) and HAM-A ($p=0.539$) scores. In the open-label study, which was the continuation of the first application, 10 patients from the sham group were administered with 10 Hz-rTMS for 6 weeks, and at 8 weeks ($p=0.023$), the Y-BOCS scores decreased significantly, but then the scale scores returned to their previous state.

Clinical response was defined as much improved/very much improved in the CGI scale and $\geq 30\%$ improvement in the Y-BOCS scores, and there were no patients with clinical response to treatment in the 10 Hz group. It was stated that the existence of the disease for a long time and its severity might contribute to the decrease in the effect of the treatment.

Studies Applying LF-rTMS over the Left DLPFC

In a double-blind RCT conducted with 33 TR-OCD patients, Prasko et al. (2006) applied 1 Hz-rTMS or sham-rTMS over the left DLPFC for 2 weeks (408). In the sham group, the same stimulation parameters as in the 1 Hz group were used, except for the fact that the coil was placed at a 90° angle. At the 2nd and 4th weeks after stimulation, no statistically significant difference was detected between the Y-BOCS scores of the 1 Hz and sham groups. The significant difference between the Y-BOCS baseline scores in the 1 Hz group (Y-BOCS: 29.82 ± 5.8) and in the sham group (Y-BOCS: 23.42 ± 4.9) was considered in the final comparison between the groups.

Studies Applying HF-rTMS over the Left DLPFC

In a double-blind RCT conducted with 18 TR-OCD patients, Sachdev et al. (2007) compared the effects formed when 10 Hz-rTMS or sham-rTMS was applied over the left DLPFC (409). The sample of the study consisted of OCD patients with mild depressive disorder. Patients were randomized into two groups as 10 Hz-rTMS (n=10) and sham-rTMS (n=8). rTMS was applied for 10 sessions by using an eight-shaped coil, and the study was extended to 20 sessions. The mean disease duration of both the 10 Hz group with a mean age of 29.5 ± 9.9 years and the sham group with a mean age of 35.8 ± 8.2 years was approximately 12 years. No significant difference was found between the groups at weeks 2 or 4 ($p=0.76$, $p=0.24$) in the Y-BOCS and Maudsley Obsessive-Compulsive Inventory (MOCI) scores examined without or after correction for the Montgomery-Asberg Depression Rating Scale (MADRS) scores that improved after the 4th week. At the end of 20 sessions, a significant reduction was observed in the total Y-BOCS scores, but this decrease was not found to be significant after controlling for depression. In this study, it was concluded that 10 sessions of rTMS applied over the left DLPFC for 2 weeks were not effective in the treatment of TR-OCD.

When LF- or HF-rTMS applied over the left DLPFC were not effective, Badawy et al. (2010) increased its frequency to 20 Hz and duration to 15 sessions in 3 weeks (410). Stimulation intensity and number were not specified in this study. Since 40 of the 60 patients participating in this double-blind RCT did not use medications and were not diagnosed with major depressive disorder, the Y-BOCS scores could be evaluated more accurately. Two groups of 20 people were formed from the patients who did not use medication, and 20 Hz-rTMS was applied to one of the groups, and sham-rTMS was applied to the other. The TR-OCD group was formed with the remaining 20 patients under medication, and 20 Hz-rTMS was applied to all of them in addition to medical treatment. After three weeks, while no significant difference was revealed between the two groups who did not use medication, the Y-BOCS scores decreased significantly in the TR-OCD group using medication ($p=0.001$). When a $\geq 40\%$ reduction in the Y-BOCS scores was accepted as a treatment response, it was found that one patient (5%) who received sham-rTMS, five patients (25%) who received only 20 Hz-rTMS, and 11 patients (55%) who received 20 Hz-rTMS while under medication responded to the treatment and the difference between these three groups ($p=0.006$) was significant. The difference between the group receiving only 20 Hz-rTMS and the sham-rTMS group ($p=0.07$) and the difference between the group receiving only 20 Hz-rTMS and the 20 Hz-rTMS group when under medication ($p=0.05$) were calculated, and it was determined that the improvement in the group that received rTMS as additional treatment was more and at the limit of significance. At the same time, while no significant alteration was found in motor threshold (MT) after treatment in the group receiving sham-rTMS ($p=0.8$), MT after treatment increased significantly in the group receiving only 20 Hz-rTMS ($p=0.001$). MT also increased in the 20 Hz-rTMS group under medication ($p=0.03$). While a significant increase was observed in MT with treatment in patients with good treatment response ($p=0.001$), MT did not increase significantly in patients with poor treatment response ($p=0.11$). These findings concerning MT were interpreted that this arousal state of the networks that were overstimulated in OCD was reduced by rTMS.

Studies Applying rTMS over the Bilateral DLPFC

α -rTMS Application over the Bilateral DLPFC

By applying a new approach, Ma et al. (2014) stimulated the bilateral DLPFC with the use of individualized rTMS frequency based on the patient's α -frequency measurement (411). The average of the peak frequencies recorded from the five electrodes in the frontal region (F3-F4-F5-F8-Fz) was determined as the frequency of stimulation, and accordingly, each patient received rTMS at different frequencies, with the number of stimulations between 648 and 872 in each session. In the study, sham-rTMS or α -rTMS (8-12 Hz) was applied to 46 OCD patients under medication for 10 days. A circular coil was used in α -rTMS sessions that lasted for 20 minutes. The sham coil was in the same position as the active coil but was inactive. At week 2, a significant decrease was detected in the Y-BOCS scores of the α -rTMS group in comparison with the sham group ($p < 0.01$). The HAM-A scores decreased significantly two weeks after the treatment ($p < 0.01$) and at 1-week follow-up ($p < 0.01$), but there was no significant difference between the sham and active groups concerning the HAM-D scores ($p \geq 0.05$).

Studies Applying HF-rTMS over the Bilateral DLPFC

Haghighi et al. (2015) and Jahangard et al. (2016) conducted randomized, single-blind, and cross-over design studies to compare the impacts of sham-rTMS and 20 Hz-rTMS applied to TR-OCD patients for four weeks (412, 413). In both studies, 20 Hz-rTMS was applied sequentially over the left and right DLPFC in patients in the 20 Hz group. As a result of these studies, significant improvements were detected in the Y-BOCS scores of the 20 Hz groups in comparison with the sham groups. The common limitations of the studies are that they were designed as single-blind and did not monitor the symptoms of anxiety and depression, which could potentially affect the severity of OCD symptoms.

Sequential LF-rTMS Application over the Right DLPFC and SMA

In an RCT conducted with 20 TR-OCD patients over a 10-day period, Kang et al. (2009), after stimulating the right DLPFC at 110% MT with 1 Hz-rTMS or sham-rTMS

for 10 minutes, stimulated the SMA at 100% MT, at the same frequency (1 Hz) and for the same duration (10 min) (414). Sham-rTMS was applied by using the coil-tilt method (similar to active-rTMS, produces sound, but not similar to active-rTMS in appearance and feeling) in which the coil was placed at an angle of 45° to the scalp. The duration of OCD in the 1 Hz and sham groups was 8.17 ± 3.81 and 9.46 ± 9.41 years, respectively. The effect of time on the Y-BOCS scores was found to be significant in both groups ($p=0.009$), but there was no significant difference between the groups ($p=0.92$). There was also no significant difference between the groups in terms of depression (MADRS) or anxiety (HAM-A) scores. The limitations of this study can be listed as the presence of a small sample and the potential effects of sham stimulation.

2.3.1.2. Supplementary Motor Area

The pre-SMA (BA32/BA8) and SMA constitute a part of the sensorimotor CSTC loop, together with the premotor and primary motor (M1) cortices. After the mentioned cortical regions are topographically projected onto the putamen, they are projected to the thalamus and cortex through the direct (via GPi) and indirect (via GPe) pathways and form the sensorimotor CSTC loop (415, 416).

The rostral "associative" and caudal "sensorimotor" components of the sensorimotor cortex exhibit various functions in planning and executing motor movements (417, 418). The rostral part of the sensorimotor cortex includes the rostral cingulate motor, premotor areas, and pre-SMA plays a role in sequence generation and motor learning and is closely related to the other PFC regions (417). The caudal components consisting of the SMA, M1, premotor areas and caudal cingulate motor are responsible for the execution of movement (415).

It is thought that the SMA, thanks to its direct projections on M1, medulla spinalis, and striatum, plays a role in the internal generation of movement and construction of motor sequences (417). The Pre-SMA becomes active during the mental representation of the movement and provides the updating (419) and resolution of motor plans in the process of learning a new sequence (420). Functional change in the sensorimotor loop in OCD may prevent the suppression of internally triggered intrusive thoughts and repetitive movements (421).

A significant part of the evidence regarding abnormalities in the sensorimotor CSTC loop in OCD was obtained with structural and functional neuroimaging studies focusing on various target areas, supported by various symptom provocation tasks or neurocognitive paradigms (143-147). Inhibitory frequencies were used in the stimulation of the SMA due to high motor excitability findings, structural deficits, and pre-SMA/SMA hyperactivity in functional studies.

Studies Applying rTMS over the SMA

Following an MRS study showing the presence of hyperactivity in the dorsal ACC and SMA in OCD (422), Mantovani et al. (2010) applied 1 Hz-rTMS or sham-rTMS over the SMA in 18 patients (423). A 4-week double-blind RCT was followed by a 4-week open-label study. In the open-label study, 1 Hz-rTMS was administered for 4 weeks to patients who did not respond to sham-rTMS and responded to 1 Hz- or sham-rTMS. The groups were followed up with the Y-BOCS, self-report Y-BOCS, and CGI-SS every two weeks for 3 months. A difference was not observed between the groups concerning the Y-BOCS scores at weeks 2 ($p=0.294$) and 4 ($p=0.153$), but after the 4th week of the treatment, the self-report Y-BOCS ($p=0.031$) and CGI-SS ($p=0.044$) scores decreased in the 1 Hz-rTMS group. Although a significant improvement was observed in anxiety symptoms (HAM-A, $p=0.033$) in the sham group, OCD symptoms did not decrease significantly. A statistically significant decrease was observed in the Y-BOCS scores in the group receiving 1 Hz-rTMS for 8 weeks ($p=0.000$). The right hemisphere MT improved following 1 Hz-rTMS, but this alteration was not different from the change observed in the sham-rTMS group.

In a 2-week, double-blind RCT conducted with 22 OCD patients, Gomes et al. (2012) applied sham-rTMS or 1 Hz-rTMS over the bilateral pre-SMA (424). After the 2nd week of the treatment, a significant decrease of 15.3 ± 2.4 point was observed in the Y-BOCS scores of the 1 Hz-rTMS group in comparison with the 5.3 ± 2.6 point decrease in the sham-rTMS group ($p=0.0001$). The decrease in the Y-BOCS scores of the group receiving 1Hz-rTMS persisted for 14 weeks post-treatment. In both groups, a statistically significant improvement was observed in anxiety scores measured with HAM-A, but this did not last for 14 weeks. For both groups, no change was observed in depression scores measured with HAM-D at weeks 2 and 14. The limitations of the present research are the

small sample size, manual targeting of the pre-SMA region, sham-rTMS design, and the possibility of synergy with pharmacological treatments.

In a 6-week, multi-center RCT they conducted with 22 TR-OCD patients, Hawken et al. (2016) applied daily 20-minute 1 Hz-rTMS or sham-rTMS sessions over the bilateral SMA 5 days a week for the initial 4 weeks, 3 days a week in the 5th week, and 2 days a week in the 6th week (425). At the end of 25 sessions, a significant reduction was observed in the Y-BOCS scores of the group receiving 1 Hz-rTMS ($p=0.023$), and 80% (8/10) of the patients in the 1 Hz group had a clinical response ($>25\%$ decrease in the Y-BOCS scores). The decrease in the Y-BOCS scores of the 1 Hz group persisted for two weeks post-treatment ($p=0.044$). The group receiving 1 Hz-rTMS also displayed a significant decrease in depression scores measured by HAM-D ($p=0.021$), which did not affect the Y-BOCS results. The limitations of the current research are the small sample size, a significant difference between the groups concerning disease duration ($p=0.037$), inadequate treatment and follow-up compared to a single center, and imperfect sham design.

In a 4-week RCT they conducted with 36 TR-OCD patients, Pelissolo et al. (2016) applied 1 Hz-rTMS or sham-rTMS over the pre-SMA (426). At the end of the 4th week in both groups, there was no significant change in the Y-BOCS scores ($p=0.38$) and depression scores measured by MADRS ($p=0.64$). Of the patients, 75% had comorbid major depressive disorder. The authors suggested that the presence of severe and TR-OCD and comorbid depression could explain the negative results.

Arumugham et al. (2018) included in their double-blind RCT OCD patients whose disease had lasted for at least 1 year, who had clinically significant symptoms ($Y\text{-BOCS} \geq 16 / \text{CGI-I} \geq 4$) despite receiving appropriate SSRI therapy at least once, and who received a stable SSRI dose for at least 8 weeks (427). Forty OCD patients who had a partial response to treatment were randomly separated into two groups, with 20 patients in every group. 1 Hz-rTMS or sham-rTMS was applied over the bilateral pre-SMA regions of these patients. The pre-SMA localization was determined according to the 10/20 EEG system. As an active treatment, 18-day rTMS sessions were applied with an eight-shaped coil for 3 weeks. One thousand two hundred stimuli were delivered per day, at 100% MT, at a frequency of 1 Hz, in 4 trains, each lasting for 300 seconds, and the

inter-train interval was 2 minutes. Sham-rTMS was performed using the same parameters, time, and location, but using a sham coil with a magnetic coating for field reduction. No significant difference was revealed between the two groups concerning the baseline demographic and clinical variables. After three weeks of the treatment, there was no statistically significant difference in the Y-BOCS scores ($p=0.40$), the ratio of patients responding to treatment, HAM-D, HAM-A and CGI-SS scores between the two groups. The authors stated that 1 Hz-rTMS applied over the pre-SMA might be ineffective as a strengthening agent in patients with partial responses to SSRIs, and alternative rTMS protocols in OCD needed to be discovered. The limitations of the present research are the suboptimal sample size, small effect size and not using neuronavigation.

2.3.1.3. Orbitofrontal Cortex

The OFC, which lies on the ventral surface of the frontal lobe, forms the cortical part of the "ventral cognitive loop" and is closely associated with the "affective CSTC loop" (401, 428). OFC lesions disrupt adaptive decision making and response selection (165). It is thought that OCD symptomatology occurs as a result of excessive activity in parts involved in the "ventral cognitive loop," and this situation impairs the ability to prevent obsessions, control impulses, and eliminate the anxiety that leads to compulsive behaviors (400, 429).

Studies Applying rTMS over the OFC

In their study conducted with 23 TR-OCD patients under medication, Ruffini et al. (2009) stimulated the OFC with 1 Hz-rTMS or sham-rTMS five days a week for 3 weeks (430). For active stimulation, a 70 mm eight-shaped coil, placed over the left OFC (Fp1 in accordance with the international 10-20 system), was used. During the 10 weeks after the end of rTMS, a significant difference was found between the Y-BOCS scores of the 1 Hz- and sham-rTMS groups ($p<0.02$), but this difference disappeared after the 12th week ($p<0.06$). No significant decrease was revealed in the depression and anxiety scores of the groups. Concerning response to treatment, it was observed that the Y-BOCS scores decreased by more than 35% in 15 of 16 patients receiving 1 Hz-rTMS. The limitations of the current research are the presence of a small sample, stimulation at 80% MT, and not using neuronavigation.

In their double-blind, randomized, cross-over study conducted with 19 TR-OCD patients, Nauczyciel et al. (2014) applied 1 Hz-rTMS or sham-rTMS over the right OFC with a DB-80 coil (8). PET scan was performed at rest after 1 Hz- and sham-rTMS. After one week, the Y-BOCS scores decreased in both the 1 Hz ($p<0.01$) and sham ($p=0.02$) groups, with a larger declining trend not reaching the significance level in the 1 Hz-rTMS group ($p=0.07$). The differences between the Y-BOCS scores of the groups disappeared within 35 days. The MADRS scores did not alter over time. In the PET findings of 10 patients after 1 Hz-rTMS, hypometabolism was shown in the middle gyrus (BA10), orbital gyrus (BA47, BA11), right frontal lobe (BA9), left frontal lobe (BA11), left ACC (BA25), and left putamen. The decrease in the Y-BOCS scores was related to the decrease in the metabolic activity of the right OFC (BA47). The limitations of the research are the presence of a small sample and the possibility of patients understanding the difference between active and sham coils may have impaired the double-blind feature.

2.3.1.4. Deep Transcranial Magnetic Stimulation Studies

The development of dTMS in OCD treatment has occurred due to the observation of the effect of DBS applied to subcortical structures in OCD patients and the discovery of noninvasive methods that stimulate deep brain structures (431). The H7-coil was developed to stimulate deeper subcortical structures (15). The target areas of dTMS in OCD are the mPFC and ACC, in consistency with the neuroimaging findings showing the abnormalities in the CSTC loop and the observations of improvement in OCD symptoms following anterior capsulotomy or anterior cingulotomy (15).

In a double-blind RCT conducted with 38 OCD patients under SSRI treatment, Carmi et al. (2018) applied active-dTMS or sham-dTMS to patients for 5 weeks (9). Most of the patients in the 25-40 age range had OCD for more than 10 years. Patients were randomized into the 20 Hz-, 1 Hz-, or sham-dTMS groups, and target areas were determined to be the mPFC and ACC. The H7-coil designed to reach these areas was used in the study. Patients in the sham-dTMS group were randomized to imitate 20 Hz or 1 Hz stimulation. It was stated that the sham coil was in a similar helmet with the active coil, it imitated the senses formed in the scalp and the acoustic artifacts of the active coil, but its stimulating effect on neurons was negligible due to its distance to the skull. A

significant improvement was detected in the Y-BOCS scores of the group receiving 20 Hz-dTMS in comparison with the sham and 1 Hz groups ($p=0.0243$). Therefore, the 1 Hz stimulation was terminated. It was recorded that the treatment response rate in the 20 Hz group remained stable for the following one month and was significantly higher in comparison with the sham group. EEG measurements were made at baseline and at the end of the treatment. Clinical response in the HF group was related to the increase in Error Related Negativity (ERN) in the Stroop task, which is a qualifying electrophysiological component for the ACC activity. Among the limitations of this study, there is the presence of a small sample, unclear definition of the sham coil, and the use of the individualized stimulation protocol associated with symptom provocation. The total number of pulses applied during the 5-week treatment was different between the 20 Hz (50,000 pulses) and 1 Hz (22,500 pulses) groups, which could be an alternative explanation for the superior effectiveness of 20 Hz-dTMS.

Carmi et al. (2019) applied daily 20 Hz-dTMS or sham-dTMS to 99 OCD patients in 11 centers for 6 weeks. 89% of the group receiving 20 Hz-dTMS and 96% of the group receiving sham-dTMS completed the study (16). The Y-BOCS scores of the 20 Hz-dTMS group decreased more significantly than in the sham-dTMS group. The rates of response to treatment were found to be 38.1% in the 20 Hz group and 11.1% in the sham group. At 1-month follow-up, the response rates became 45.2% in the 20 Hz group and 17.8% in the sham group, and the significant difference between the groups persisted. In this study, it was demonstrated that 20 Hz-dTMS applied to the ACC and mPFC using the H7-coil was a reliable and effective method in improving OCD symptoms in patients who did not respond adequately to SSRIs and CBT.

2.3.1.5. Meta-analyses

By examining the studies between 1995-2012, Berlim et al. (2013) analyzed the data of 282 patients in 10 RCTs according to their pre- and post-treatment Y-BOCS scores and found a significant and medium effect size in active-rTMS results ($z=2.73$, $p=0.006$) (11). The response rates of the active and sham treatment groups were 35% and 13%, respectively ($OR=3.4$, $p=0.002$). With subgroup analysis, it was determined that LF-rTMS applications over the OFC or SMA reduced OCD symptoms. While no difference was found between the sham-rTMS and active groups with regard to the baseline

depression scores and drop rates, it was reported that baseline OCD severity was higher in patients receiving active-rTMS.

By examining RCTs published until 2014, Ma and Shi (2014) analyzed the impact of adding rTMS to the treatment in OCD patients resistant to SSRIs (12). According to the data obtained from 9 RCTs consisting of a total of 290 participants, adding active-rTMS to the current treatment was found to be effective in terms of a reduction in the Y-BOCS scores and response to treatment.

Rehn et al. (2018) examined the data obtained from 18 RCTs investigating the efficiency of rTMS in the treatment of OCD and found that active-rTMS had a consistent effect on the decrease in the Y-BOCS scores ($p < 0.001$) (432). The SMA stimulation is the region associated with the highest decreases in the Y-BOCS scores compared to other cortical regions. The subgroup analyses showed that LF-rTMS was more efficient than HF-rTMS. Furthermore, rTMS activity was found to be higher at a 12-week follow-up than at a 4-week follow-up. With this meta-analysis, it was shown that the most effective rTMS application in the treatment of OCD was LF-rTMS applied to the SMA. At the same time, it was observed that the therapeutic effects of rTMS also persisted after the treatment, and it was suggested that it might be useful regarding long-term effectiveness.

Aim of the present study is to investigate the QEEG findings that affect the response to dTMS by examining the relationship between the pre-treatment resting-state QEEG data of OCD patients and their response to dTMS.

3. MATERIALS AND METHODS

3.1. Sample

The study was planned as a retrospective study. The sample of this study consists of 52 individuals who applied to Kemal Arıkan Psychiatry Clinic (a private psychiatric practice), İstanbul Turkey, between January 2018 and May 2019, who were diagnosed with OCD in accordance with the DSM-5 diagnostic criteria (33), and whose symptoms persisted (Y-BOCS>8) (433) despite receiving SSRI treatment at a therapeutic dose for the last two months (16), who accepted the dTMS application and signed the informed consent form. By evaluating the Y-BOCS scores of the participants before and after the treatment, patients with 30% and more decrease in their scores were named as "responsive group" (n=42), those who did not were named as the "non-responsive group" (n=10), (9) and the pre-treatment QEEG data of both groups were compared.

3.2. Inclusion Criteria

1. Meeting the DSM-5 diagnostic criteria for OCD (33)
2. Being aged between 18-65 years
3. Continuation of SSRI treatment at a therapeutic dose for 8 weeks before enrollment in the study (16)
4. Persistence of OCD symptoms clinically (Y-BOCS>8) (433)

3.3. Exclusion Criteria

1. Patients who did not receive medical treatment for an adequate duration and at an adequate dose.
2. Alcohol and/or drug/stimulant use
3. Mental retardation
4. Cognitive disorders (dementia, delirium)
5. Presence of neurological disease, a history of seizures or head trauma
6. The patient's history of neurosurgical intervention.
7. The presence of another medical problem causing central nervous system involvement.

3.4. Stages of the Study

An application was made to the Ethics Committee of Üsküdar University, Faculty of Medicine, for the study, and the ethics committee approval was obtained with the letter dated 31 May 2019 and numbered 61351342-/2019-330.

In the power analysis, the effect size for the Y-BOCS scores of the groups before and after the treatment was found to be 0.33 ($\alpha=0.05$) (434). In the sample size analysis performed by taking the power value of 0.80, the total number of samples to be taken was determined to be 52 patients.

At the data collection stage, OCD was diagnosed according to DSM-5 criteria (33), and a sociodemographic and clinical data form was filled out. Y-BOCS was applied to the patients to determine the severity of OCD symptoms (433). EEG recordings were performed in all patients. Moreover, all patients filled out the Beck Depression Inventory (BDI) (435). After these procedures, dTMS was applied to all patients using the H7-coil for 5 weeks, 5 sessions a week (9). After the treatment, the Y-BOCS and BDI were applied again.

When all these data were evaluated retrospectively, patients with 30% and more decrease in the Y-BOCS scores were named as “responsive group” ($n=42$), and those who did not were named as “non-responsive group” ($n=10$) (9). These two groups were compared in terms of sociodemographic characteristics, clinical characteristics, clinical scale scores, and QEEG data.

All statistical analyses were performed using IBM SPSS Statistics 25.0. The chi-square test was applied to categorical data. The change in the pre-treatment and post-treatment scale scores was evaluated by the Wilcoxon signed-rank test. The Mann-Whitney U test was applied to compare two independent groups (responsive vs non-responsive) in terms of non-normally distributed data (age, scale scores, and QEEG data). The relationship between the decrease in the BDI scores and the decrease in the YBOCS scores was evaluated by Spearman’s correlation analysis. $p<0.05$ was accepted to be significant.

3.5. Data Collection Tools

3.5.1. Sociodemographic and Clinical Data Form

The sociodemographic and clinical data form is used to record the sociodemographic and clinical characteristics of participants. Using this form, age, major obsessive-compulsive symptom, sex, educational status, employment status, monthly income, marital status, comorbid psychiatric disorders, pharmacotherapy, physical diseases, hospitalization history, family history, and smoking were questioned.

3.5.2. Yale-Brown Obsessive Compulsive Scale

Y-BOCS is a semi-structured scale that aims to measure obsessive-compulsive symptoms in patients diagnosed with OCD in terms of their type and severity and should be applied by an interviewer who has a good command of OCD psychopathology. The Turkish validity and reliability studies of this scale, developed by Goodman et al. (1989) (79), were carried out by Karamustafalioglu et al. (1993) (433).

Although this scale consists of a total of 19 items, only the first 10 items are used for the measurement of the severity of symptoms, and these 10 items are sensitive to measuring clinical improvement. The first five items measure the severity of obsessions, and the next five items measure the severity of compulsions. Each item contains 5 options, scored between 0 and 4. Therefore, the total score, which is a value in the range of 0-40 points, is obtained together with separate obsession and compulsion sub-scores. Patients can be grouped according to the scores obtained from the scale, and disease can be grouped according to its severity (0-7: subclinical; 8-15: mild; 16-23: moderate; 24-31: severe) (433).

3.5.3. Beck Depression Inventory

BDI is a self-report scale consisting of 21 questions, developed by Beck et al. (1961) and assessing the severity of depressive symptoms (435). The score of each question ranges from 0 to 3, and the total score ranges from 0 to 63. The Turkish validity

and reliability studies of the scale were carried out by Hisli (1988), and the cut-off score was reported to be 17 (436).

3.5.4. Quantitative Electroencephalography

EEG recordings were performed in all patients before the first dTMS session. The procedures to be performed before EEG recording were explained to the patients, and their written consent was obtained with an informed consent form. In order to reduce anxiety, it was ensured that patients rested for 30 min in a quiet room. EEG recordings were performed in a soundproof, dimly lit room with appropriate ventilation. A19-channel (FP1, F7, T3, T5, F3, C3, P3, O1, FZ, CZ, PZ, F4, C4, P4, O2, FP2, F8, T4, T6) electro-cap meeting the patient's head size was properly placed on the head and fixed. Electro-gel was utilized to increase conductivity between the electrodes and the scalp and the signal/noise ratio. The gel was applied in sufficient quantity to every electrode area by a blunt tip syringe. The grounding electrode is the FPz electrode of the electro-cap. The reference electrodes are extra electrodes attached to both earlobes. The ear electrodes were pre-cleaned with cleaning gel and alcohol and placed on both earlobes using EEG paste. In EEG recording, the horizontal EOG (h-EOG) and vertical electrooculogram (v-EOG) were recorded to determine simultaneous eye movements. The Ag-AgCl disk electrodes utilized to this end were glued to the relevant area by the paste, and then the area was fixed with plaster. After all the mentioned procedures, the electrodes were checked for impedance height, and additional electro-gel was utilized if necessary. If the impedance was in the sufficient range (less than 5000 ohm), EEG recording was initiated. EEG recordings were performed by the Neuron-Spectrum-4/P device. EEG recordings were performed only at rest, and no activation method was applied during the recording. During the recording, the subjects were asked to sit comfortably, be awake and blink as little as possible.

The Neuron-Spectrum.NET software was utilized for impedance measurements in EEG recordings. The 50-Hz notch filter was set in an open position, with a scale of 10 mV/mm, and sweep of 30 mm/sec. Low-pass filter (LPF) was set to 70 Hz, and high-pass filter (HPF) was set to 0.5 Hz, as in standard EEG recordings. The EEG slices strengthened by a 0.5-70 Hz bandpass filter with a resistance of the electrodes below 5000 ohm were transferred to the memory of the computer by recording the sampling rate as

250 Hz. EEG recordings were performed in four 5-minute periods, with eyes open in half of them and eyes closed in the other half. Eyes-closed EEG data were segmented into consecutive 2-second epochs. Epochs contaminated by eye movements, blinking, and movement-related artifacts were excluded from analyses by visual inspection performed by an experienced neurologist (437).

Fourier analysis was performed by averaging across 2-second epochs without artifacts (437). Spectral analysis is one of the standard methods used for EEG quantification (438), and it enables the determination of the distribution of power in EEG according to frequency (345). Thus, it gives information about the frequency content of a signal. For every of the 19 monopolar derivations, absolute power (μV^2) was calculated for the delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (30-70 Hz) frequency bands (345-347, 386).

3.5.5. Deep Transcranial Magnetic Stimulation

The BrainsWay Deep TMS System was used in this study. The H7-coil used in the OCD protocol was designed to stimulate the mPFC and ACC (16).

The patient sits on a chair and puts his/her feet on the cart stand, at a distance of approximately 60 cm and wears earplugs. The cap is properly placed on the head, and the right and left straps are fastened back of the patient's head, and then the chin strap is fastened. The grid with horizontal and vertical lines is placed on the cap so that the red central vertical line continues with the midline of the cap and the zero arrow head mark ends up on the nasion. The stimulator is activated in single pulse mode, and the stimulator output power is set to 50% as the initial value. The system becomes ready after charging. To determine the MT, the H-coil is placed on the patient's head at the appropriate location for the tibialis motor stimulation. There is a red vertical line and a black horizontal line in the transparent plastic guide at the front end of the coil cover. The vertical line is aligned with the red vertical midline mark on the grid, and the horizontal line is aligned with the 8 cm horizontal line on the grid. If there isn't a motor response when a single pulse is applied, the stimulator output power is increased by 5%. To find the optimal position when a motor response is obtained, the coil is moved along the anterior-posterior and lateral-medial axis, and a single pulse is applied to find the position in which the

motor response is more pronounced. At the optimal position, a minimal value of MT, at which a motor response is obtained to at least 50% of the stimuli, is found. When the coil is moved 4 cm forward along the cap grid from the location found for the minimal MT, it is aligned over the mPFC. The cooling system is turned on, and the temperature is kept at 14 °C or below.

Before each session, individualized symptom provocation, which lasts for 3-5 minutes, was applied by a psychologist to activate the relevant neuronal loop (9, 16, 439, 440). To this end, a personal obsessive-compulsive symptom provocation list, which was prepared with the patient during the first assessment interview and ordered hierarchically from less stressful to more stressful, was used. A visual analog scale (VAS), scored between 1-10, was utilized to assess provocation. The patient was asked to think of the list item that causes stress at the level of 4-7 during the treatment (16).

20 Hz-dTMS was applied to patients for 5 weeks, 5 times a week (a total of 25 sessions), by giving pulses of 100% power of the MT value. The sessions consisted of 50 trains, each lasting for 2 seconds, and the inter-train interval was 20 seconds (a total of 2000 pulses) (16).

4. RESULTS

Fifty-two patients, diagnosed with OCD and aged between 18-65 years, were included in this study. Of the patients, 6 had religious obsessions (11.5%), 15 had cleaning compulsions (28.8%), 13 had mental rituals (25%), 9 had checking compulsions (17.3%), 4 had harm obsessions (7.7%), and 5 had other obsessive-compulsive symptoms (9.6%). Of the patients, 55.8% (n=29) were female, and 44.2% (n=23) were male. Five patients were primary school graduates (9.6%), 3 were secondary school graduates (5.8%), 10 were high school graduates (19.2%), and 34 were college graduates (65.4%). Of the patients, 30.8% (n=16) were students, 19.2% (n=10) were housewives, 5.8% (n=3) were retired, and 44.2% (n=23) were employed. The income of 6 patients was 2000 TL and below (11.5%), the income of 8 patients was 2000-4000 TL (15.4%), the income of 7 patients was 4000-6000 TL (13.5%), the income of 5 patients was 6000-8000 TL (9.6%), the income of 7 patients was 8000-10000 TL (13.5%), and the income of 19 patients was 10000 TL and above (36.5%). Of the patients, 50% (n=26) were single, 44.2% (n=23) were married, and 5.8% were (n=3) widow or divorced. While 22 of the patients had no psychiatric diagnosis other than OCD (42.3%), 4 had bipolar disorder (7.7%), 12 had major depressive disorder (23.1%), 2 had schizophrenia (3.8%), 6 had anxiety disorder (11.5%), 1 had functional neurological symptom disorder (1.9%), 2 had eating disorder (3.8%), 2 had autism spectrum disorder (3.8%), and 1 had Tourette's syndrome (1.9%). When the data were examined in terms of pharmacotherapy, it was observed that while all of the patients received an SSRI, 21.2% (n=11) received an antipsychotic additionally, and 11.5% (n=6) received a mood stabilizer additionally. While 39 patients did not have a physical disease (75%), 13 patients had a physical disease (25%). While 84.6% of the patients (n=44) had no hospitalization history, 15.4% (n=8) had one or more hospitalization histories. While 25 patients had no psychiatric disease in their family history (48.1%), 27 had a psychiatric disease in their family history (51.9%). Twenty-nine patients did not smoke (55.8%), and 23 patients smoked (44.2%) (Table 4.1). The mean age of the patients was 31.88 ± 11.51 years. When the mean scale scores at baseline were examined, the mean BDI score was 16.67 ± 10.17 , the mean Y-BOCS total score was 28.02 ± 10.74 , the mean Y-BOCS obsession score was 16.54 ± 5.43 , and the mean Y-BOCS compulsion score was 11.48 ± 8.38 (Table 4.2). While 42 of the patients responded to dTMS by showing a decrease of 30% and above in their Y-BOCS scores (80.8%), the adequate response was not observed in 10 of them (19.2%).

Of the 42 patients who responded to dTMS (responsive group), 6 had religious obsessions (14.3%), 11 had cleaning compulsions (26.2%), 9 had mental rituals (21.4%), 9 had checking compulsions (21.4%), 3 had harm obsessions (7.1%), and 4 (9.5%) had other obsessive-compulsive symptoms. Of the patients, 52.4% (n=22) were female, and 47.6% were male (n=20). Five patients were primary school graduates (11.9%), 3 were secondary school graduates (7.1%), 8 were high school graduates (19.0%), and 26 were college graduates (61.9%). Of the patients, 35.7% (n=15) were students, 21.4% (n=9) were housewives, 2.4% (n=1) were retired, and 40.5% (n=17) were employed. The income of 6 patients was 2000 TL and below (14.3%), the income of 6 patients was 2000-4000 TL (14.3%), the income of 6 patients was 4000-6000 TL (14.3%), the income of 4 patients was 6000-8000 TL (9.5%), the income of 6 patients was 8000-10000 TL (14.3%), and the income of 14 patients was 10000 TL and above (33.3%). Of the patients, 50% (n=21) were single, 45.2% (n=19) were married, and 4.8% (n=2) were widow or divorced. While 19 of the patients had no psychiatric diagnosis other than OCD (45.2%), 3 had bipolar disorder (7.1%), 7 had major depressive disorder (16.7%), 2 had schizophrenia (4.8%), 5 had anxiety disorder (11.9%), 1 had FNSD (2.4%), 2 had eating disorder (4.8%), 2 had autism spectrum disorder (4.8%), and 1 had Tourette's syndrome (2.4%). When the data were examined in terms of pharmacotherapy, it was observed that while all patients received an SSRI, 23.8% (n=10) received an antipsychotic additionally, and 9.5% (n=4) received a mood stabilizer additionally. While there was no physical disease in 33 patients (78.6%), 9 of them had a physical disease (21.4%). While 85.7% (n=36) of the patients had no hospitalization history, 14.3% (n=6) had one or more hospitalization histories. While 19 patients had no psychiatric disease in their family history (45.2%), 23 of them (54.8%) had a psychiatric disease in their family history. Twenty-three patients did not smoke (54.8%), and 19 patients smoked (45.2%) (Table 4.1). The mean age of the patients was 30.76 ± 11.25 years. When the mean scale scores at baseline were examined, the mean BDI score was 16.29 ± 9.83 , the mean Y-BOCS total score was 28.24 ± 10.75 , the mean Y-BOCS obsession score was 17.17 ± 4.81 , and the mean Y-BOCS compulsion score was 11.07 ± 8.52 (Table 4.2).

Of the 10 patients not responding to dTMS (non-responsive group), 4 had cleaning compulsions (40%), 4 had mental rituals (40%), 1 had harm obsessions (10%), and 1 (10%) had other obsessive-compulsive symptoms. Of the patients, 30% (n=3) were male

and, 70% (n=7) were female. Two patients were high school graduates (20%), and 8 were college graduates (80%). Of the patients, 10% (n=1) were students, 10% (n=1) were housewives, 20% (n=2) were retired, and 60% (n=6) were employed. The income of 2 patients was 2000-4000 TL (20%), the income of 1 patient was 4000-6000 TL (10%), the income of 1 patient was 6000-8000 TL (10%), the income of 1 patient was 8000-10000 TL (10%), and the income of 5 patients was 10000 TL and above (50%). Of the patients, 50% (n=5) were single, 40% (n=4) were married, and 10% (n=1) were widow or divorced. While 3 of the patients had no psychiatric diagnosis other than OCD (30%), 1 had bipolar disorder (10%), 5 had major depressive disorder (50%), and 1 had anxiety disorder (10%). When the data were examined in terms of pharmacotherapy, it was observed that while all patients received an SSRI, 10% (n=1) received an antipsychotic additionally, and 20% (n=2) received a mood stabilizer additionally. While there was no physical disease in 6 of the patients (60%), 4 of them (40%) had a physical disease. While 80% of the patients (n=8) had no hospitalization history, 20% (n=2) had one or more hospitalization histories. While 6 patients had no psychiatric disease in their family history (60%), 4 of them (40%) had a psychiatric disease in their family history. Six patients did not smoke (60%), and 4 patients smoked (40%) (Table 4.1). The mean age of the patients was 36.60 ± 11.97 years. When the mean scale scores at baseline were examined, the mean BDI score was 18.30 ± 11.91 , the mean Y-BOCS total score was 27.10 ± 11.19 , the mean Y-BOCS obsession score was 13.90 ± 7.23 , and the mean Y-BOCS compulsion score was 13.20 ± 7.96 (Table 4.2).

Between the non-responsive and responsive groups, no statistically significant difference was detected with regard to the mean age, major obsessive-compulsive symptom, sex, educational status, employment status, monthly income, marital status, comorbid psychiatric disorders (comorbidity), pharmacotherapy, physical diseases, hospitalization history, family history, smoking, mean baseline BDI, Y-BOCS total, Y-BOCS obsession and Y-BOCS compulsion scores ($p > 0.05$) (Table 4.1 and Table 4.2).

All patients' sociodemographic and clinical characteristics and the comparison of the responsive and non-responsive groups in terms of these characteristics are presented in Table 4.1, and the mean age and baseline scale scores and the comparison of the non-responsive and responsive groups in terms of these means are presented in Table 4.2.

Table 4.1. Sociodemographic and Clinical Characteristics of the Patients and the Comparison of the Responsive and Non-Responsive Groups in terms of These Characteristics

^a Chi-square test; There was no statistically significant difference between the groups ($p>0,05$).

	Total (n=52)	Responsive (n=42)	Nonresponsive (n=10)		
	n (%)	n (%)	n (%)	χ^2 value ^a	p value ^a
Major OC symptom					
Religious	6 (11.5%)	6 (14.3%)	0 (0.0%)	5,307	0,380
Cleaning	15 (28.8%)	11 (26.2%)	4 (40.0%)		
Mental rituals	13 (25.0%)	9 (21.4%)	4 (40.0%)		
Checking	9 (17.3%)	9 (21.4%)	0 (0.0%)		
Harm	4 (7.7%)	3 (7.1%)	1 (10.0%)		
Other	5 (9.6%)	4 (9.5%)	1 (10.0%)		
Sex					
Female	29 (55.8%)	22 (52.4%)	7 (70.0%)	1,016	0,313
Male	23 (44.2%)	20 (47.6%)	3 (30.0%)		
Educational status					
Primary school	5 (9.6%)	5 (11.9%)	0 (0.0%)	2,313	0,510
Secondary school	3 (5.8%)	3 (7.1%)	0 (0.0%)		
High school	10 (19.2%)	8 (19.0%)	2 (20.0%)		
College	34 (65.4%)	26 (61.9%)	8 (80.0%)		
Employment status					
Student	16 (30.8%)	15 (35.7%)	1 (10.0%)	7,326	0,062
Housewife	10 (19.2%)	9 (21.4%)	1 (10.0%)		
Retired	3 (5.8%)	1 (2.4%)	2 (20.0%)		
Employed	23 (44.2%)	17 (40.5%)	6 (60.0%)		
Monthly income					
0-2000 TL	6 (11.5%)	6 (14.3%)	0 (0.0%)	2,436	0,786
2000-4000 TL	8 (15.4%)	6 (14.3%)	2 (20.0%)		
4000-6000 TL	7 (13.5%)	6 (14.3%)	1 (10.0%)		
6000-8000 TL	5 (9.6%)	4 (9.5%)	1 (10.0%)		
8000-10000 TL	7 (13.5%)	6 (14.3%)	1 (10.0%)		
≥10000 TL	19 (36.5%)	14 (33.3%)	5 (50.0%)		

Marital status					
Single	26 (50.0%)	21 (50.0%)	5 (50.0%)	0,434	0,805
Married	23 (44.2%)	19 (45.2%)	4 (40.0%)		
Widow/divorced	3 (5.8%)	2 (4.8%)	1 (10.0%)		
Comorbidity					
No	22 (42.3%)	19 (45.2%)	3 (30.0%)	6,348	0,608
BD	4 (7.7%)	3 (7.1%)	1 (10.0%)		
MDD	12 (23.1%)	7 (16.7%)	5 (50.0%)		
SZ	2 (3.8%)	2 (4.8%)	0 (0.0%)		
AD	6 (11.5%)	5 (11.9%)	1 (10.0%)		
FNSD	1 (1.9%)	1 (2.4%)	0 (0.0%)		
ED	2 (3.8%)	2 (4.8%)	0 (0.0%)		
ASD	2 (3.8%)	2 (4.8%)	0 (0.0%)		
TS	1 (1.9%)	1 (2.4%)	0 (0.0%)		
Pharmacotherapy					
SSRI	35 (67.3%)	28 (66.7%)	7 (70.0%)	1,510	0,470
SSRI+AP	11 (21.2%)	10 (23.8%)	1 (10.0%)		
SSRI+MS	6 (11.5%)	4 (9.5%)	2 (20.0%)		
Physical disease					
Yes	13 (25.0%)	9 (21.4%)	4 (40.0%)	1,486	0,223
No	39 (75.0%)	33 (78.6%)	6 (60.0%)		
Hospitalization					
Yes	8 (15.4%)	6 (14.3%)	2 (20.0%)	0,203	0,653
No	44 (84.6%)	36 (85.7%)	8 (80.0%)		
Family history					
Yes	27 (51.9%)	23 (54.8%)	4 (40.0%)	0,705	0,401
No	25 (48.1%)	19 (45.2%)	6 (60.0%)		
Smoking					
Yes	23 (44.2%)	19 (45.2%)	4 (40.0%)	0,090	0,764
No	29 (55.8%)	23 (54.8%)	6 (60.0%)		

OC, obsessive-compulsive; SZ, schizophrenia; BD, bipolar disorder; MDD, major depressive disorder; AD, anxiety disorders; FNSD, functional neurological symptom disorder; ED, eating disorder; TS, tourette's syndrome; ASD, autism spectrum disorder; SSRI, selective serotonin reuptake inhibitor; AP, antipsychotic; MS, mood stabilizer.

Table 4.2. The Patients' Mean Age and Baseline Scale Scores and the Comparison of the Means of the Responsive and Non-Responsive Groups.

^a Mann-Whitney U test; There was no statistically significant difference between the groups ($p>0,05$).

	Total (n=52)	Responsive (n=42)	Nonresponsive (n=10)	
	Mean±SD	Mean±SD	Mean±SD	p value ^a
Age	31,88±11,51	30,76±11,25	36,60±11,97	0,130
BDI	16,67±10,17	16,29±9,83	18,30±11,91	0,693
Y-BOCS_o	16,54±5,43	17,17±4,81	13,90±7,23	0,234
Y-BOCS_c	11,48±8,38	11,07±8,52	13,20±7,96	0,433
Y-BOCS_t	28,02±10,74	28,24±10,75	27,10±11,19	0,801

SD, standart deviation; BDI, Beck depression inventory; Y-BOCS, Yale–Brown obsessive compulsive scale; o, obsession; c, compulsion; t, total.

Upon comparing the responsive and non-responsive groups in terms of the mean baseline scores of the Y-BOCS items (1-10), the time occupied by obsessive thoughts (item 1) was found to be statistically significantly higher in the responsive group (3.74 ± 0.63) in comparison with the non-responsive group (3.10 ± 1.29) ($p=0.030$). However, no statistically significant difference was determined between the mean baseline scores of the other scale items (items 2-10) ($p>0.05$) (Table 4.3).

The mean baseline scores of the Y-BOCS items of all patients and the comparison of the responsive and non-responsive groups in terms of these means are presented in Table 4.3.

Table 4.3. The Patients' Mean Baseline Y-BOCS Item Scores and the Comparison of the Means of the Responsive and Non-Responsive Groups.

^a Mann-Whitney U test; *the difference between the groups was found to be statistically significant.

	Total (n=52)	Responsive (n=42)	Nonresponsive (n=10)	
	Mean±SD	Mean±SD	Mean±SD	p value ^a
Y-BOCS_1	3,62±0,82	3,74±0,63	3,10±1,29	0,030*
Y-BOCS_2	3,29±1,16	3,40±1,06	2,80±1,48	0,163
Y-BOCS_3	3,25±1,25	3,36±1,19	2,80±1,48	0,185
Y-BOCS_4	3,15±1,29	3,29±1,20	2,60±1,58	0,195
Y-BOCS_5	3,23±1,28	3,38±1,17	2,60±1,58	0,111
Y-BOCS_6	2,50±1,64	2,45±1,69	2,70±1,49	0,666
Y-BOCS_7	2,31±1,71	2,24±1,74	2,60±1,65	0,541
Y-BOCS_8	2,17±1,74	2,07±1,76	2,60±1,65	0,380
Y-BOCS_9	2,25±1,78	2,17±1,81	2,60±1,71	0,505
Y-BOCS_10	2,25±1,79	2,14±1,82	2,70±1,70	0,451

SD, standart deviation; Y-BOCS, Yale–Brown obsessive compulsive scale; Y-BOCS_1, time occupied by obsessive thoughts; Y-BOCS_2, interference due to obsessive thoughts; Y-BOCS_3, distress associated with obsessive thoughts; Y-BOCS_4, resistance against obsessions; Y-BOCS_5, degree of control over obsessive thoughts; Y-BOCS_6, time spent performing compulsive behaviors; Y-BOCS_7, interference due to compulsive behaviors; Y-BOCS_8, distress associated with compulsive behavior; Y-BOCS_9, resistance against compulsions; Y-BOCS_10, degree of control over compulsive behavior.

When all patients' mean baseline and post-treatment scale scores was compared, it was observed that the post-treatment BDI scores (10.94±8.65) decreased significantly in comparison with the baseline scores (16.67±10.17) (p=0.000), the post-treatment Y-BOCS obsession scores (3.63±4.93) decreased significantly in comparison with the baseline scores (16.54±5.43) (p=0.000), the post-treatment Y-BOCS compulsion scores (2.62±5.07) decreased significantly in comparison with the baseline scores (11.48±8.38) (p=0.000), and the post-treatment Y-BOCS total scores (6.29±8.82) decreased significantly in comparison with the baseline scores (28.02±10.74) (p=0.000) (Table 4.4).

In the responsive group, it was observed that the post-treatment BDI scores (9.31 ± 7.99) decreased significantly in comparison with the baseline scores (16.29 ± 9.83) ($p=0.000$), the post-treatment Y-BOCS obsession scores (1.95 ± 2.21) decreased significantly in comparison with the baseline scores (17.17 ± 4.81) ($p=0.000$), the post-treatment Y-BOCS compulsion scores (0.62 ± 1.06) decreased significantly in comparison with the baseline scores (11.07 ± 8.52) ($p=0.000$), and the post-treatment Y-BOCS total scores (2.57 ± 2.80) decreased significantly in comparison with the baseline scores (28.24 ± 10.75) ($p=0.000$) (Table 4.4).

In the non-responsive group, no significant difference was detected between the baseline (18.30 ± 11.91) and post-treatment (17.80 ± 8.28) BDI scores ($p=0.959$) and between the baseline (13.20 ± 7.96) and post-treatment (11.00 ± 6.62) Y-BOCS compulsion scores ($p=0.085$), however, it was observed that the post-treatment Y-BOCS obsession scores (10.70 ± 6.85) decreased significantly in comparison with the baseline scores (13.90 ± 7.23) ($p=0.016$) and the post-treatment Y-BOCS total scores (21.90 ± 8.32) decreased significantly in comparison with the baseline scores (27.10 ± 11.19) ($p=0.005$) (Table 4.4).

The mean baseline and post-treatment scale scores of all patients and the non-responsive and responsive groups and the significance level of the change in the scale scores with treatment are demonstrated in Table 4.4.

Table 4.4. The Mean Baseline and Post-Treatment Scale Scores of the Patients and the Significance Level of the Change in These Scores with Treatment

^aWilcoxon signed-rank test; *the difference between the groups was found to be statistically significant.

	Before	After	
	Mean±SD	Mean±SD	p value ^a
Total (n=52)			
BDI	16,67±10,17	10,94±8,65	0,000*
Y-BOCS_o	16,54±5,43	3,63±4,93	0,000*
Y-BOCS_c	11,48±8,38	2,62±5,07	0,000*
Y-BOCS_t	28,02±10,74	6,29±8,82	0,000*
Responsive (n=42)			
BDI	16,29±9,83	9,31±7,99	0,000*
Y-BOCS_o	17,17±4,81	1,95±2,21	0,000*
Y-BOCS_c	11,07±8,52	0,62±1,06	0,000*
Y-BOCS_t	28,24±10,75	2,57±2,80	0,000*
Nonresponsive (n=10)			
BDI	18,30±11,91	17,80±8,28	0,959
Y-BOCS_o	13,90±7,23	10,70±6,85	0,016*
Y-BOCS_c	13,20±7,96	11,00±6,62	0,085
Y-BOCS_t	27,10±11,19	21,90±8,32	0,005*

SD, standart deviation; Y-BOCS, Yale–Brown obsessive compulsive scale; BDI, Beck depression inventory; o, obsession; c, compulsion; t, total.

While the decrease in the BDI scores of all patients and the responsive group was significant ($p=0.000$), the reduction in the BDI scores of the non-responsive group was not significant ($p=0.959$) (Table 4.4). Therefore, Spearman's correlation analysis was performed to investigate the correlation between the decrease in the BDI scores and the decrease in the Y-BOCS total scores of all patients ($r=0.147$, $p=0.297$) and the responsive group ($r=0.136$, $p=0.392$), but no significant relationship was detected between the decreases in the scores.

The responsive group showed higher mean theta absolute power in all electrodes, including FP1 ($p=0.044$), FP2 ($p=0.018$), F3 ($p=0.010$), F4 ($p=0.004$), Fz ($p=0.016$), C3 ($p=0.011$), C4 ($p=0.013$), Cz ($p=0.032$), P3 ($p=0.010$), P4 ($p=0.006$), Pz ($p=0.008$), O1 ($p=0.011$), O2 ($p=0.043$), F7 ($p=0.024$), F8 ($p=0.003$), T3 ($p=0.044$), T4 ($p=0.003$), T5 ($p=0.023$), and T6 ($p=0.009$) compared to the non-responsive group (Table 4.5).

The responsive group showed higher mean alpha absolute power in all electrodes, including FP1 ($p=0.012$), FP2 ($p=0.008$), F3 ($p=0.004$), F4 ($p=0.004$), Fz ($p=0.018$), C3 ($p=0.004$), C4 ($p=0.003$), Cz ($p=0.005$), P3 ($p=0.003$), P4 ($p=0.002$), Pz ($p=0.007$), O1 ($p=0.012$), O2 ($p=0.013$), F7 ($p=0.005$), F8 ($p=0.002$), T3 ($p=0.005$), T4 ($p=0.003$), T5 ($p=0.003$), and T6 ($p=0.005$) compared to the non-responsive group (Table 4.5).

No significant difference was found between the groups in terms of the mean delta, beta, and gamma absolute power in all electrodes ($p>0.05$) (Table 4.5).

The mean delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-70 Hz) absolute power in all electrodes (FP1, FP2, F3, F4, Fz, C3, C4, Cz, P3, P4, Pz, O1, O2, F7, F8, T3, T4, T5, T6) of all patients and the responsive and non-responsive groups and the comparison of the responsive and non-responsive groups in terms of these findings are given in Table 4.5.

Table 4.5. The Patients' Mean Delta, Theta, Alpha, Beta and Gamma Absolute Power in All Electrodes and the Comparison of the Responsive and Non-Responsive Groups in terms of These Values.

^a Mann-Whitney U test; *the difference between the groups was found to be statistically significant.

EEG Band	Total (n=52)	Responsive (n=42)	Nonresponsive (n=10)	p value ^a
	Mean±SD	Mean±SD	Mean±SD	
FP1-Delta	4,01±0,82	4,03±0,77	3,91±1,05	0,685
FP1-Theta	2,96±0,66	3,05±0,63	2,58±0,69	0,044*
FP1-Alpha	2,90±0,80	3,03±0,80	2,34±0,49	0,012*
FP1-Beta	2,45±0,50	2,48±0,50	2,31±0,49	0,315
FP1-Gamma	0,61±0,37	0,62±0,37	0,60±0,38	0,920
FP2-Delta	3,97±0,88	4,02±0,87	3,78±0,94	0,441
FP2-Theta	2,92±0,64	3,02±0,60	2,50±0,64	0,018*
FP2-Alpha	2,88±0,80	3,02±0,79	2,30±0,51	0,008*
FP2-Beta	2,42±0,47	2,45±0,46	2,28±0,49	0,295
FP2-Gamma	0,65±0,39	0,65±0,41	0,64±0,35	0,946
F3-Delta	3,41±0,64	3,43±0,63	3,29±0,73	0,534
F3-Theta	2,84±0,58	2,94±0,52	2,43±0,65	0,010*
F3-Alpha	3,00±0,81	3,15±0,79	2,35±0,60	0,004*
F3-Beta	2,50±0,50	2,55±0,48	2,25±0,51	0,088
F3-Gamma	0,49±0,25	0,49±0,24	0,47±0,29	0,833
F4-Delta	3,40±0,73	3,46±0,70	3,15±0,82	0,224
F4-Theta	2,84±0,61	2,96±0,54	2,36±0,64	0,004*
F4-Alpha	3,00±0,83	3,16±0,80	2,33±0,62	0,004*
F4-Beta	2,52±0,52	2,56±0,51	2,33±0,55	0,221
F4-Gamma	0,55±0,40	0,54±0,40	0,58±0,42	0,764
Fz-Delta	3,44±0,63	3,50±0,59	3,19±0,75	0,157
Fz-Theta	2,96±0,59	3,05±0,55	2,56±0,63	0,016*
Fz-Alpha	3,06±0,85	3,19±0,84	2,49±0,65	0,018*
Fz-Beta	2,54±0,51	2,58±0,50	2,35±0,49	0,186
Fz-Gamma	0,48±0,35	0,49±0,38	0,46±0,23	0,801
C3-Delta	3,30±0,68	3,36±0,67	3,06±0,67	0,207
C3-Theta	2,80±0,64	2,91±0,61	2,35±0,61	0,011*
C3-Alpha	3,11±0,85	3,27±0,82	2,43±0,65	0,004*
C3-Beta	2,55±0,51	2,60±0,50	2,32±0,48	0,108

C3-Gamma	0,48±0,26	0,49±0,22	0,47±0,39	0,848
C4-Delta	3,33±0,79	3,36±0,77	3,20±0,89	0,564
C4-Theta	2,79±0,65	2,90±0,62	2,34±0,59	0,013*
C4-Alpha	3,08±0,87	3,25±0,83	2,38±0,69	0,003*
C4-Beta	2,53±0,53	2,56±0,52	2,38±0,55	0,338
C4-Gamma	0,51±0,41	0,49±0,38	0,61±0,54	0,414
Cz-Delta	3,43±0,59	3,45±0,53	3,37±0,83	0,717
Cz-Theta	3,00±0,62	3,09±0,58	2,62±0,69	0,032*
Cz-Alpha	3,29±0,88	3,45±0,84	2,59±0,72	0,005*
Cz-Beta	2,65±0,52	2,71±0,51	2,39±0,48	0,081
Cz-Gamma	0,49±0,21	0,49±0,21	0,49±0,24	0,982
P3-Delta	3,20±0,60	3,23±0,59	3,07±0,66	0,450
P3-Theta	2,71±0,65	2,82±0,62	2,24±0,59	0,010*
P3-Alpha	3,49±1,03	3,70±0,97	2,65±0,88	0,003*
P3-Beta	2,63±0,53	2,69±0,51	2,36±0,55	0,077
P3-Gamma	0,43±0,19	0,44±0,19	0,41±0,21	0,643
P4-Delta	3,11±0,54	3,18±0,49	2,81±0,68	0,052
P4-Theta	2,75±0,70	2,87±0,66	2,21±0,63	0,006*
P4-Alpha	3,52±1,05	3,73±0,99	2,62±0,88	0,002*
P4-Beta	2,67±0,54	2,74±0,53	2,41±0,49	0,088
P4-Gamma	0,46±0,34	0,47±0,36	0,43±0,20	0,738
Pz-Delta	3,27±0,62	3,34±0,61	2,99±0,60	0,108
Pz-Theta	2,88±0,68	3,00±0,64	2,38±0,63	0,008*
Pz-Alpha	3,60±1,10	3,79±1,05	2,77±0,92	0,007*
Pz-Beta	2,74±0,54	2,80±0,54	2,50±0,51	0,118
Pz-Gamma	0,47±0,32	0,47±0,35	0,44±0,18	0,800
O1-Delta	3,21±0,76	3,27±0,73	2,97±0,89	0,264
O1-Theta	2,65±0,71	2,77±0,66	2,14±0,74	0,011*
O1-Alpha	3,81±1,12	4,00±1,05	3,03±1,13	0,012*
O1-Beta	2,78±0,57	2,85±0,53	2,49±0,65	0,071
O1-Gamma	0,50±0,22	0,52±0,23	0,40±0,17	0,126
O2-Delta	3,20±0,74	3,27±0,73	2,89±0,71	0,141
O2-Theta	2,69±0,69	2,78±0,66	2,29±0,70	0,043*
O2-Alpha	3,81±1,15	4,00±1,09	3,02±1,06	0,013*
O2-Beta	2,82±0,56	2,88±0,55	2,57±0,55	0,119
O2-Gamma	0,54±0,38	0,57±0,41	0,45±0,19	0,374
F7-Delta	3,45±0,81	3,46±0,81	3,38±0,86	0,768
F7-Theta	2,50±0,54	2,58±0,49	2,16±0,63	0,024*
F7-Alpha	2,57±0,72	2,70±0,70	2,00±0,50	0,005*

F7-Beta	2,29±0,49	2,33±0,49	2,10±0,47	0,171
F7-Gamma	0,57±0,36	0,59±0,37	0,51±0,35	0,543
F8-Delta	3,26±0,76	3,31±0,71	3,05±0,95	0,323
F8-Theta	2,42±0,57	2,53±0,50	1,95±0,62	0,003*
F8-Alpha	2,54±0,76	2,69±0,72	1,89±0,54	0,002*
F8-Beta	2,24±0,54	2,28±0,54	2,07±0,53	0,266
F8-Gamma	0,60±0,49	0,61±0,50	0,53±0,43	0,610
T3-Delta	2,95±0,79	2,93±0,76	3,02±0,95	0,769
T3-Theta	2,20±0,56	2,28±0,52	1,89±0,65	0,044*
T3-Alpha	2,37±0,75	2,51±0,73	1,79±0,51	0,005*
T3-Beta	2,14±0,48	2,19±0,50	1,94±0,36	0,148
T3-Gamma	0,51±0,33	0,52±0,35	0,44±0,28	0,502
T4-Delta	2,82±0,69	2,90±0,65	2,50±0,82	0,109
T4-Theta	2,12±0,58	2,23±0,52	1,65±0,63	0,003*
T4-Alpha	2,35±0,73	2,49±0,69	1,75±0,58	0,003*
T4-Beta	2,21±0,53	2,28±0,53	1,92±0,48	0,056
T4-Gamma	0,60±0,44	0,63±0,46	0,48±0,32	0,320
T5-Delta	3,04±0,79	3,04±0,77	3,03±0,88	0,973
T5-Theta	2,38±0,67	2,48±0,64	1,95±0,67	0,023*
T5-Alpha	3,12±0,90	3,30±0,83	2,37±0,83	0,003*
T5-Beta	2,37±0,50	2,42±0,48	2,12±0,56	0,087
T5-Gamma	0,42±0,22	0,43±0,23	0,36±0,19	0,362
T6-Delta	3,04±0,79	3,10±0,79	2,79±0,81	0,278
T6-Theta	2,49±0,73	2,61±0,69	1,96±0,68	0,009*
T6-Alpha	3,41±1,05	3,61±0,99	2,59±0,93	0,005*
T6-Beta	2,55±0,58	2,63±0,58	2,25±0,49	0,066
T6-Gamma	0,48±0,36	0,50±0,39	0,39±0,16	0,376

SD, standart deviation; C, central; P, parietal; FP, frontopolar; F, frontal; O, occipital;
T, temporal

5. DISCUSSION AND CONCLUSION

5.1. Sociodemographic and Clinical Characteristics of All Participants

Of the 52 patients participating in our study, 55.8% (n=29) were female, and 44.2% (n=23) were male. In other studies in the literature, OCD was observed slightly more frequently in females compared to males (36, 43) or it was determined that there was no significant difference in the prevalence of OCD between males and females (2).

When evaluated in terms of marital status, 50% of the patients (n=26) were single, 44.2% (n=23) were married, and 5.8% (n=3) were widow or divorced. In their study performed with 250 OCD patients, Rasmussen and Eisen (1991) stated that 43% of the patients were single, 52% were married, and 5% were widow or divorced (47).

Psychiatric disorders other than OCD were detected in 57.3% (n=30) of the patients participating in the study, and the most frequent of these disorders was major depressive disorder (23.1%, n=12), followed by anxiety disorders (11.5%, n=6). Epidemiological studies have shown that at least 50% of OCD patients have one or more comorbid psychiatric disorders and anxiety disorders (40-60%) (65) or major depressive disorder (65%) (19) among these accompany OCD most frequently. The rates specified in the studies show lifetime comorbidity. However, in our study, simultaneous comorbidity was evaluated, and this may explain differences between the rates. In another study, the simultaneous comorbidity rate of OCD and major depressive disorder was reported to be 30% (66). About 85% of the diagnosis of major depressive disorder is secondary to OCD (19).

Bipolar disorder (7.7%) was detected in 4 of the 52 patients participating in the study. The lifetime comorbidity of OCD and bipolar disorder was found to be 14-21% in epidemiological studies and 10-35% in clinical studies (68). There was a diagnosis of schizophrenia (3.8%) in two of the participants. In previous studies, comorbidity of OCD and schizophrenia was found to be 12.9% (70). Of the patients participating in the study, two had eating disorder (3.8%), two had autism spectrum disorder (3.8%), and one had Tourette's syndrome (1.9%). In a study carried out with 334 OCD patients, it was demonstrated that there was a diagnosis of eating disorder at a rate of 17%, autism

spectrum disorder at a rate of 3%, and Tourette's syndrome at a rate of 4-5% in the patients (441). Functional neurological symptom disorder was detected in one of the patients (1.9%). In a study carried out with 4075 OCD patients, it was demonstrated that only 1 patient had functional neurological symptom disorder (442). Evaluating only patients who received dTMS in our study may explain different rates between our results and general OCD population.

5.2. The Comparison of the Sociodemographic and Clinical Characteristics of the Responsive and Non-Responsive Groups

No statistically significant difference was detected between the responsive and non-responsive groups in terms of the mean age, major obsessive-compulsive symptom, sex, educational status, employment status, monthly income, marital status, comorbid psychiatric disorders (comorbidity), pharmacotherapy, physical diseases, hospitalization history, family history, smoking, mean baseline Y-BOCS total, BDI, Y-BOCS compulsion and Y-BOCS obsession scores ($p>0.05$). While there is no study in the literature that compares the sociodemographic characteristics of patients responding and not responding to TMS, previous studies have reported that the severity of OCD may affect the response to treatment (407, 426). The absence of a difference in terms of sociodemographic and clinical characteristics between the responsive and non-responsive groups is valuable for the homogeneity of the groups.

Furthermore, upon comparing the baseline mean Y-BOCS item scores of the non-responsive and responsive groups one by one, the time occupied by obsessive thoughts (item 1) in the responsive group was found to be statistically significantly higher than in the non-responsive group ($p=0.030$). However, there was no statistically significant difference between the means of the other scale items (items 2-10) ($p>0.05$). The longer occupation of the minds of patients in the responsive group by obsessive thoughts may have increased the response to TMS with an effect similar to symptom provocation (9, 16, 439, 440).

While the decrease in the BDI scores of all patients and the responsive group was significant ($p=0.000$), the decrease in the BDI scores of the non-responsive group was not significant ($p=0.959$). Therefore, Spearman's correlation analysis was performed to

investigate the correlation between the decrease in the BDI scores and the decrease in the Y-BOCS total scores of all patients ($r=0.147$, $p=0.297$) and the responsive group ($r=0.136$, $p=0.392$), but no significant correlation was revealed between the decreases in the scores. It is known that about 85% of the diagnosis of major depressive disorder is secondary to OCD (19). Thus, it is possible that the decrease in depression scores is secondary to the improvement of OCD.

5.3. Response Rate to Deep Transcranial Magnetic Stimulation

While 42 of the patients responded to dTMS by showing a decrease of 30% and above in their Y-BOCS scores (80.8%), an adequate response was not observed in 10 of them (19.2%). Of the 42 OCD patients to whom Carmi et al. (2019) applied dTMS, 38.1% responded to treatment (16). The reason for this difference in response rates may be the fact that while our sample consisted of patients with the Y-BOCS scores above 8, the sample of Carmi et al. (2019) consisted of patients with the Y-BOCS scores of 20 and above (16). Previous studies have reported that the severity of OCD can affect the response to treatment (407, 426). Furthermore, in the study in which Hawken et al. (2016) applied 1 Hz-rTMS over the bilateral SMA, the response rate was found to be 80% (425), in the study in which Ruffini et al. (2009) applied 1 Hz-rTMS over the OFC, the response rate was found to be 93.75% (430). Genetic differences that are not sufficiently understood yet may constitute a potential source of variation in therapeutic responses (443).

5.4. Mechanism of Action of Deep Transcranial Magnetic Stimulation

The ACC and mPFC have been found to be hyperactive in OCD patients (444, 445). According to this evidence, the ACC and mPFC appear to be suitable targets in the treatment of OCD. These brain regions can be stimulated directly by applying dTMS using the H7-coil (446).

According to the results obtained from some studies based on the motor evoked potential (MEP) measurement in healthy subjects, LF stimulation exhibits inhibitory, and HF stimulation exhibits excitatory effects (17). Since the mPFC and ACC are hyperactive in OCD patients, it can be thought that LF stimulation will be effective in the treatment

of these patients (171, 447). On the other hand, it has been demonstrated in sham-controlled studies that HF-dTMS applied over the ACC and mPFC using the H7-coil is a reliable and effective method in improving the OCD symptoms of patients not responding adequately to SSRIs, but LF-dTMS has no therapeutic effect (9, 16).

The data obtained from the studies suggest that a clear distinction that HF stimulation has excitatory effects and LF stimulation has inhibitory effects is oversimplified (448, 449). Both LF- and HF-rTMS may have excitatory and inhibitory effects (397). The baseline cortical excitability level of each subject before stimulation is an important source of the inter- and intra-individual variability of rTMS effects (17). This may explain the reason why the effects of HF-rTMS on cortical inhibition depend on individual baseline values rather than stimulation frequency (450). When cortical excitability is reduced before rTMS application, classically inhibitory LF-rTMS may exhibit excitatory effects (451). When cortical excitability is increased before rTMS, inhibitory effects may be obtained with HF-rTMS (452).

Many clinical studies have also demonstrated the inhibitory effects of HF-rTMS. Although the insula is hyperactive in nicotine addiction (453), while the application of HF-rTMS to the insula is effective in treatment, LF-rTMS has not been found to be effective (439). There is defective intracortical inhibition in patients with chronic pain, and the application of HF-rTMS over the M1 increases intracortical inhibition (454). It has been demonstrated that both the LF (424, 425, 447, 455) and HF (456) stimulation of SMA reduces the Y-BOCS scores in OCD patients.

It is known that the effects of TMS are the most pronounced when the targeted loop is active (439, 440). In OCD, it has been observed that the activity of different components of the CSTC loop increases following symptom provocation (429, 457, 458). Therefore, symptom provocation is performed before starting each dTMS session (9, 16, 439).

Symptom provocation is also used in the treatment of other psychiatric disorders with rTMS. The response to treatment is higher in post-traumatic stress disorder patients with short-term exposure to traumatic memory (440) or nicotine addicts exposed to cigarette cues (439) in comparison with the non-exposed group. It is suggested that the

retrieval of items stored in long-term memory by provocation predisposes them to change (459, 460).

Lower intracortical inhibition, higher intracortical facilitation, and lower MT were found in OCD patients compared to the control group (375, 461). Since the motor cortex is the target of the motor CSTC loop disrupted in OCD (375, 461), cortical inhibition deficits can be observed as a result of the hyperactivity of this loop and the interaction between the motor cortex neurons. Intracortical facilitation reflects the activity of the excitatory postsynaptic potentials transmitted by NMDA glutamate receptors (375). The impairment in the inhibition of unwanted intrusive thoughts in OCD is thought to depend on the impairment in GABA-B receptor-mediated inhibition and NMDA receptor activity (375).

Although OCD symptoms decreased significantly in patients treated with SSRIs compared to those who did not receive treatment, intracortical inhibition or MT did not change (461). In the study in which Badawy et al. (2010) applied 20 Hz-rTMS over the left DLPFC of OCD patients, while MT increased with treatment in patients with good treatment response, MT did not change in patients with poor treatment response (410). The post-treatment MT increase was interpreted that this excitation state of the networks over-stimulated in OCD is reduced by rTMS. All these results are compatible with the view that TMS acts by a different neuronal mechanism than SSRIs (9, 16).

5.5. The Comparison of the Baseline Quantitative Electroencephalography Findings of the Responsive and Non-Responsive Groups

The results of the present study demonstrated that responsive group have higher theta and alpha absolute power in all electrodes compared to the non-responsive group and that QEEG can help predict response to dTMS in OCD patients.

Although there is no other study in the literature that investigates the pre-treatment QEEG findings in determining the response to dTMS in OCD patients, in a study in which 1Hz-rTMS was applied over the right DLPFC, it was shown that OCD patients who responded to treatment had higher theta absolute power in all electrodes compared to those who did not respond to treatment (386).

In the pathophysiology of OCD, it has been suggested that there is an imbalance between the indirect (inhibitory, cortex-striatum-GPe-STN-GPi-thalamus-cortex) and direct (excitatory, cortex-striatum-GPi-thalamus-cortex) pathways in the CSTC loop and the activity of the direct pathway increases (167). As a result, activity increases in the ACC, OFC, caudate nucleus and thalamus (171, 181, 192). The ACC and OFC and their striatal target areas receive intense projections from the mesial temporal lobe, particularly the amygdala and hippocampus (429). It has been demonstrated that there is increased connectivity between the striatum and amygdala, hippocampus and ACC in nonmedicated OCD patients (462).

It is known that the effects of TMS are the most pronounced when the targeted loop is active (439, 440). In OCD, it has been observed that the activity of different components of the CSTC loop increases following symptom provocation (429, 458). Therefore, symptom provocation is performed before starting each dTMS session (9, 16, 439, 440).

It has been suggested that the retrieval of items stored in long-term memory by provocation may put them in the reconsolidation process in which they become susceptible to change (459, 460). The hippocampus (463) and PFC (464, 465), as well as the thalamus (466-470) and striatum (471), are structures that play a role in retrieval. The hippocampus (472) and interactions between the hippocampus and PFC (473) play a role in the reconsolidation process. The striatum (471) and the thalamus (468, 469, 474) are structures that regulate interactions between the PFC and the hippocampus.

The communication and coordination of separate brain regions is very important for a successful retrieval (468, 469, 471, 474). The memory codes are accessed through longitudinal pathways that connect the cortex with deeper brain structures such as the thalamus and hippocampal formation, and retrieval occurs (473). Theta-alpha oscillations reflect long-range information transfer in the brain (475), and this makes them suitable for facilitating communication between separate brain regions (476).

During the retrieval in healthy individuals, a positive correlation has been found between increased connectivity between the striatum, thalamus, PFC, and hippocampus

and theta and alpha power increase. Thus, theta-alpha oscillations have been shown to play a role in coordinating the interactions between the brain regions involved in the retrieval (476).

During cognitive tasks, while alpha oscillations are associated with the storage and retrieval of information (memory component), theta oscillations are associated with the manipulation and coordination of the stored information (executive component) (477-481), and alpha-theta interactions have been suggested to reflect the degree of integration between the memory (e.g. alpha) and executive (e.g. theta) components of cognition (482-487). Similar to cognitive tasks, self-generated thinking during rest also requires the interaction between the memory and executive components, and thus the retrieval and manipulation of internal information occur (488, 489).

The increase in alpha-theta power in the responsive group may have enabled memory labilization (490) by regulating communication between the brain regions involved in the retrieval (476) and made stubborn thoughts susceptible to change (459, 460). Since the effects of dTMS are the most pronounced during the retrieval (439, 440), this group is expected to respond better to treatment.

The limitations of the present study are retrospective design, not using neuronavigation, the absence of a sham group, not measuring anxiety levels, including patients with comorbidities, using medications other than SSRIs and unknown duration of disease. Furthermore, the discussion presented above should be regarded as speculative since neuroimaging methods have not been used.

As a result, we revealed that the increase in alpha and theta absolute power before treatment could help predict OCD patients who would respond well to dTMS. Based on the knowledge that these EEG waves are associated with the retrieval and manipulation of internal information (488, 489), we hypothesized that the obsessions of patients with higher theta and alpha power might be more prone to change with dTMS. The use of such biomarkers can assist clinicians in individualizing OCD treatment and thus achieving optimal treatment outcomes (491).

5.6. Future Recommendations

Prospective and large-scale studies that investigate the relationship between the response to dTMS and pre-treatment EEG findings in OCD patients without psychiatric comorbidity can be conducted in the future, and suitable candidates for dTMS can be determined before treatment. After dTMS is terminated, the symptoms of the patients can be followed and the necessity and effectiveness of the maintenance treatment can be investigated.

By combining EEG with functional neuroimaging methods, it can be investigated that the mental processes that we assume to be the source of EEG findings are related to which brain regions and how they affect the treatment response. The effect of cortical excitability parameters that can be measured by TMS device on treatment response can be investigated. In addition, the effect of chronobiological factors on treatment response can be investigated by examining the relationship between the application time of the TMS session and the treatment efficiency.

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7. APPENDICES

Appendix 1. Ethical Approval Form

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T.C. ÜSKÜDAR ÜNİVERSİTESİ GİRİŞİMSSEL OLMAYAN ARAŞTIRMALAR ETİK KURULU BAŞKANLIĞI	
SAYI: 61351342-/ 2019-330	31/05/2019
Sayın Prof.Dr.Bayram YILMAZ (Özden ÖKSÜZ) Üsküdar Üniversitesi Girişimsel Olmayan Araştırmalar Etik Kurulunun 31/05/2019 tarihinde yapılan 05 No.lu toplantısında “Obsesif kompulsif bozuklukta noninvaziv derin beyin stimülasyonuna yanıtı öngörmede elektroensefalografi bulgularının kullanımı” adlı araştırma projenizin etik açıdan uygun olduğuna karar verilmiştir. Bilgilerinize rica ederim. Doç. Dr. Cumhuri TAŞ Girişimsel Olmayan Araştırmalar Etik	
ÜÜ.ANT.FTS.001 Revizyon No: 0 (14.12.2015)	

Appendix 2. Sociodemographic and Clinical Data Form

Protokol no:

SOSYODEMOGRAFİK VE KLİNİK BİLGİ FORMU

1. Yaş:

2. Cinsiyet: 1- Kadın
2- Erkek

3. Medeni durum: 1-Evli
2-Bekar

4. Eğitim durumu: 1-İlkokul
2-Ortaokul
3-Lise
4-Lisans ve üzeri

5. Meslek: 1-Öğrenci
2-Ev hanımı
3-Emekli
4-Çalışıyor

6. Gelir düzeyi: 1-2000 TL ve altı
2-2000-4000 TL
3-4000-6000 TL
4-6000-8000 TL
5-8000-10000 TL
6-10000 TL ve üzeri

7. Sigara kullanımı: 1-Var
2-Yok

8. Başlıca OKB semptomu: 1- Dini obsesyonlar
2- Temizleme kompulsiyonları
3- Zihinsel ritüeller
4- Kontrol etme kompulsiyonları
5- Saldırganlık obsesyonları
6- Diğer

9. Komorbid psikiyatrik bozukluk varlığı (varsa nedir):

10. Mevcut psikiyatrik tedavisi:

11. Psikiyatri servisinde yatış öyküsü: 1-Var
2-Yok

12. Bilinen nörolojik/gelişimsel hastalık hikayesi: 1- Var
2- Yok

13. DM, KAH, HT, hipo-hipertiroidi, astım vb. düzenli ilaç kullanımını gerektirecek hastalık varlığı:

1-Var
2-Yok

14. Psikiyatrik hastalığı olan akraba varlığı: 1-Var
2-Yok

Appendix 3. Yale-Brown Obsessive Compulsive Scale

YALE-BROWN OBSESYON KOMPULSİYON ÖLÇEĞİ

1. OBSESİF DÜŞÜNCELERLE GEÇEN ZAMAN

Soru: Takıntılar ne kadar zamanınızı alıyor? Takıntılı düşünceler ne sıklıkla aklınıza geliyor?

0: Yok.

1: Hafif (günde 1 saatten az) veya kısa sürelerle gelip giden (günde 8 kereden az).

2: Orta (günde 1-3 saat) veya sık sık kısa sürelerle gelip giden (günde 8 kereden fazladır, ancak hasta günün büyük kısmında obsesyonlardan uzaktır).

3: Ağır (günde 3-8 saat) veya çok sık bir şekilde kısa süreli gelip giden (günde 8 kereden fazladır ve hastanın gününün büyük bir bölümünü işgal eder).

4: Çok ağır (Günde 8 saatten fazla) veya neredeyse sürekli bir şekilde gelip giden obsesif düşünceler (sayılamayacak kadar çoktur ve obsesyonlar arası süre nadiren bir saati bulur).

2. OBSESİF DÜŞÜNCELERİN YAŞAMI ETKİLEMESİ

Soru: Takıntılarınız sosyal yaşamınızı veya işinizi ne kadar etkiliyor? Bu düşünceler nedeniyle yapmak isteyip de yapamadığınız şeyler oluyor mu?

0: Hiç.

1: Hafif, sosyal ve mesleki etkinlikleri çok hafif olarak etkileyen ancak performansın tümü göz önüne alındığında pek bir değişikliğe neden olmayan derecelerde etki.

2: Orta, sosyal ve mesleki etkinlikleri etkilediği kesin olarak gözlenen ancak halen üstesinden gelinebilir durumda olan etki.

3: Ağır, sosyal ve mesleki performansı belirgin olarak olumsuz etkileyen durum.

4: Çok ağır, iş göremez durum.

3. OBSESİF DÜŞÜNCELERLE BİRLİKTE OLAN RAHATSIZLIK HİSSİ

Soru: Takıntılarınız, bu düşünceleriniz sizi ne derece rahatsız ediyor?

0: Hiç.

1: Hafif, ara sıra olan ve fazla rahatsız edici olmayan.

2: Orta derecede, sık olarak çok rahatsızlık veren ancak halen başedilebilir durumda olan.

3: Ağır, çok sık olarak çok rahatsızlık veren.

4: Çok ağır, neredeyse sürekli olan ve iş göremez duruma getiren rahatsızlık.

4. OBSESİF DÜŞÜNCELERE DİRENÇ GÖSTERME

Soru: Takıntılara direnmek için ne kadar çaba harcıyorsunuz? Bu düşünceler aklınıza gelince ne kadar sıklıkla onları kovmaya ya da dikkatinizi başka şeylere vermeye çalışıyorsunuz?

0: Her zaman takıntılara karşı direnmek için bir çaba harcamaktadır veya semptomlar o kadar azdır ki bir çaba harcama gereksinimi duymamaktadır.

1: Çoğu zaman direnmeye çalışmaktadır.

2: Direnmek için bir miktar çabalamaktadır.

3: Tüm obsesyonlara teslim olmuş durumdadır. Ancak bu durumdan hoşnut değildir.

4: Tam ve gönüllü olarak tüm obsesyonlara boyun eğmiştir durumdadır.

5. OBSESİF DÜŞÜNCELER ÜZERİNDEKİ KONTROLÜN DERECEİ

Soru: Takıntılarınız üzerinde ne kadar kontrolünüz var? Takıntılı düşünceleri durdurmada ya da dikkatinizi başka şeye yönlirmede ne kadar başarılısınız?

0: Tam kontrol edebiliyor.

1: Büyük oranda kontrol edebiliyor. Genellikle bir miktar çaba ve konsantrasyon ile obsesyonları durdurabiliyor veya dağıtabiliyor.

2: Orta derecede kontrol edebiliyor. Obsesyonları bazen durdurabiliyor veya dağıtabiliyor.

3: Az miktarda kontrol edebiliyor. Obsesyonları durdurmada nadiren başarılı olabiliyor. Sadece zorlukla dikkatini başka şeylere yönltebiliyor.

4: Kontrol edemiyor. Kendi iradesi dışında olarak algılıyor. Çok nadir olarak düşüncesini bu konudan uzaklaştırabiliyor.

6. KOMPULSİF DAVRANIŞLAR İÇİN HARCANAN SÜRE

Soru: Tekrarlanan hareketleriniz için ne kadar zaman harcıyorsunuz? Tekrarlanan hareketleri ne sıklıkla yapıyorsunuz?

0: Hiç.

1: Hafif (günde 1 saatten az zaman harcıyor) veya kompulsif davranışın sıklığı az (günde 8 kereden az).

2: Orta derecede (günde 1-3 saat) veya sık kompulsif davranışlar (günde 8 kereden fazla olmasına karşın, günün büyük kısmı kompulsiyonlardan uzak geçiyor).

3: Ağır (3-8 saat arası süre kompulsiyonlarla geçiyor) veya çok sık kompulsif davranış gösteriyor (günde 8 kereden fazla ve günün büyük bir kısmı kompulsiyonlarla geçiyor).

4: Çok ağır (günde 8 saatten fazla zaman kompulsiyonlarla geçiyor) veya neredeyse sürekli olan kompulsif davranışlar (sayılamayacak sıklıkta, kompulsif davranışların arasında nadiren bir saat boşluk olur).

7. KOMPULSİF DAVRANIŞLARIN YAŞAMI ETKİLEMESİ

Soru: Tekrarlanan hareketleriniz sosyal yaşamınızı veya işinizi ne kadar etkilemektedir? Bu davranışlar nedeniyle yapmadığınız şeyler oluyor mu?

0: Hiç.

1: Hafif, sosyal ve mesleki etkinlikleri çok hafif olarak etkileyen ancak performansın tümü göz önüne alındığında pek bir değişikliğe neden olmayan etki.

2: Orta, sosyal ve mesleki etkinlikleri kesin olarak etkilediği gözlenen ancak halen üstesinden gelinebilir durumda olan etki.

3: Ağır, sosyal ve mesleki performansı belirgin olarak olumsuz etkileyen durum.

4: Çok ağır, iş göremez durumda.

8. KOMPULSİF DAVRANIŞLA BİRLİKTE OLAN RAHATSIZLIK HİSSİ

Soru: Tekrarlanan hareketi/hareketleri yapmanız engellenseydi ne hissederdiniz? Tamamlandığı konusunda tatmin olana kadar tekrarlanan hareketlerinizi sürdürürken ne kadar sıkıntı duyarsınız?

0: Hiç.

1: Hafif. Kompulsiyonları engellendiğinde çok az sıkıntı duyuyor; veya kompulsif davranış sırasında çok az sıkıntı duyuyor.

2: Orta derecede. Kompulsiyonları engellendiğinde sıkıntısının artabileceğini ancak halen başedilebilir durumda olduğunu belirtir veya kompulsif hareketlere başladıktan sonra sıkıntısının artacağını ancak halen başedebildiğini belirtir.

3: Ağır. Eğer kompulsif davranışları engellenirse, belirgin ve çok rahatsız eden sıkıntılı durum veya kompulsif davranışlar gerçekleştirilirken anksiyetede belirgin ve rahatsız edici artış.

4: Çok ağır. Kompulsif davranışlarına müdahale edildiğinde, sıkıntıda ileri boyutlarda ve iş göremez duruma getiren artış veya kişiyi kompulsif davranışları gerçekleştirilirken iş göremez duruma sokan sıkıntı.

9. KOMPULSİF HAREKETLERE DİRENÇ GÖSTERME

Soru: Tekrarlanan hareketlere direnmek için ne kadar çaba harcıyorsunuz?

0: Sorunların üstesinden gelmek için her zaman çaba harcamaktadır veya semptomlar o kadar azdır ki bir çaba harcama gereksinimi duymaz.

1: Çoğu zaman direnmeye çalışır.

2: Direnmek için bir miktar çabalamaktadır.

3: Kompulsif davranışlara hiç direnç göstermemektedir ve teslim olmuş durumdadır. Bu durumdan hoşnut değildir.

4: Tam ve gönüllü olarak tüm kompulsiyonlara boyun eğmiş durumdadır.

10. KOMPULSİF DAVRANIŞLAR ÜZERİNDEKİ KONTROLUN DERECEİ

Soru: Sizi tekrarlanan davranışları yapmaya zorlayan duygu ne kadar kuvvetli? Tekrarlanan davranışlarınızı ne kadar kontrol edebiliyorsunuz?

0: Tam kontrol edebiliyor.

1: Büyük oranda kontrol edebiliyor. Davranışın yapılması için baskı hissetmesine karşın genellikle istemli olarak kontrol edebiliyor.

2: Orta derecede kontrol edebiliyor. Hareketleri yapmak için kuvvetli bir baskı hissediyor ancak güçlükle kontrol sağlayabiliyor.

3: Az miktarda kontrol. Kompulsiyonları durdurmak için çok fazla çaba harcaması gerekiyor. Sadece, zorlukla, geciktirebiliyor.

4: Kontrol edemiyor. Kendi iradesi dışında olarak algılıyor. Hareketi ancak anlık olarak erteleyebiliyor.

Appendix 4. Beck Depression Inventory

BECK DEPRESYON ENVANTERİ-BDE

Hastanın Soyadı, Adı:..... Tarih:.....

Bu form son bir (1) hafta içerisinde kendinizi nasıl hissettiğinizi araştırmaya yönelik 21 maddeden oluşmaktadır. Her maddenin karşısındaki dört cevabı dikkatlice okuduktan sonra, size en çok uyan, yani sizin durumunuzu en iyi anlatanı işaretlemeniz gerekmektedir.

- | | |
|--|--|
| 1 (0) Üzgün ve sıkıntılı değilim.
(1) Kendimi üzüntülü ve sıkıntılı hissediyorum.
(2) Hep üzüntülü ve sıkıntılıyım. Bundan kurtulamıyorum.
(3) O kadar üzgün ve sıkıntılıyım ki, artık dayanamıyorum. | 11 (0) Başkalarıyla görüşme, konuşma isteğini kaybetmedim.
(1) Eskisi kadar insanlarla birlikte olmak istemiyorum.
(2) Birileriyle görüşüp konuşmak hiç içimden gelmiyor.
(3) Artık çevremde hiç kimseyi istemiyorum. |
| 2 (0) Gelecek hakkında umutsuz ve karamsar değilim.
(1) Gelecek için karamsarım.
(2) Gelecekte beklediğim hiçbir şey yok.
(3) Gelecek hakkında umutsuzum ve sanki hiçbir şey düzelmeyecekmiş gibi geliyor. | 12 (0) Karar verirken eskisinden fazla güçlük çekmiyorum.
(1) Eskiden olduğu kadar kolay karar veremiyorum.
(2) Eskiye kıyasla karar vermekte çok güçlük çekiyorum.
(3) Artık hiçbir konuda karar veremiyorum. |
| 3 (0) Kendimi başarısız biri olarak görmüyorum.
(1) Başkalarından daha başarısız olduğumu hissediyorum.
(2) Geçmişe baktığımda başarısızlıklarla dolu olduğunu görüyorum.
(3) Kendimi tümüyle başarısız bir insan olarak görüyorum. | 13 (0) Her zamankinden farklı göründüğümü sanmıyorum.
(1) Aynada kendime her zamankinden kötü görünüyorum.
(2) Aynaya baktığımda kendimi yaşlanmış ve çirkinleşmiş buluyorum.
(3) Kendimi çok çirkin buluyorum. |
| 4 (0) Her şeyden eskisi kadar zevk alıyorum.
(1) Birçok şeyden eskiden olduğu gibi zevk alamıyorum.
(2) Artık hiçbir şey bana tam anlamıyla zevk vermiyor.
(3) Her şeyden sıkılıyorum. | 14 (0) Eskisi kadar iyi iş güç yapabiliyorum.
(1) Her zaman yaptığım işler şimdi gözümde büyüyor.
(2) Ufaklık bir işi bile kendimi çok zorlayarak yapabiliyorum.
(3) Artık hiçbir iş yapamıyorum. |
| 5 (0) Kendimi herhangi bir biçimde suçlu hissetmiyorum.
(1) Kendimi zaman zaman suçlu hissediyorum.
(2) Çoğu zaman kendimi suçlu hissediyorum.
(3) Kendimi her zaman suçlu hissediyorum. | 15 (0) Uykum her zamanki gibi.
(1) Eskisi gibi uyuyamıyorum.
(2) Her zamankinden 1-2 saat önce uyanıyorum ve kolay kolay tekrar uykuya dalamıyorum.
(3) Sabahları çok erken uyanıyorum ve bir daha uyuyamıyorum. |
| 6 (0) Kendimden memnunum.
(1) Kendimden pek memnun değilim.
(2) Kendime kızgınım.
(3) Kendimden nefrete ediyorum. | 16 (0) Kendimi her zamankinden yorgun hissetmiyorum.
(1) Eskiye oranla daha çabuk yoruluyorum.
(2) Her şey beni yoruyor.
(3) Kendimi hiçbir şey yapamayacak kadar yorgun ve bitkin hissediyorum. |
| 7 (0) Başkalarından daha kötü olduğumu sanmıyorum.
(1) Hatalarım ve zayıf taraflarım olduğunu düşünüyorum.
(2) Hatalarımdan dolayı kendimden utanıyorum.
(3) Herşeyi yanlış yapıyor oluşum gibi geliyor ve hep kendimi kabahatli buluyorum | 17 (0) İştahım her zamanki gibi.
(1) Eskisinden daha iştahsızım.
(2) İştahım çok azaldı.
(3) Hiçbir şey yiyemiyorum. |
| 8 (0) Kendimi öldürmek gibi düşüncülerim yok.
(1) Kimi zaman kendimi öldürmeyi düşündüğüm oluyor ama yapmıyorum.
(2) Kendimi öldürmek isterdim.
(3) Fırsatını bulsam kendimi öldürürüm. | 18 (0) Son zamanlarda zayıflamadım.
(1) Zayıflamaya çalışmadığım halde en az 2 Kg verdim.
(2) Zayıflamaya çalışmadığım halde en az 4 Kg verdim.
(3) Zayıflamaya çalışmadığım halde en az 6 Kg verdim. |
| 9 (0) İçimden ağlamak geldiği pek olmuyor.
(1) Zaman zaman içimden ağlamak geliyor.
(2) Çoğu zaman ağlıyorum.
(3) Eskiden ağlayabiliirdim ama şimdi istesem de ağlayamıyorum | 19 (0) Sağlığım ile ilgili kaygılarım yok.
(1) Ağrılar, mide sancıları, kabızlık gibi şikayetlerim oluyor ve bunlar beni tasalandırıyor.
(2) Sağlığımın bozulmasından çok kaygılanıyorum ve kafamı başka şeylere vermekte zorlanıyorum.
(3) Sağlık durumum kafama o kadar takılıyor ki, başka hiçbir şey düşünemiyorum. |
| 10 (0) Her zaman olduğumdan daha canı sıkın ve sinirli değilim.
(1) Eskisine oranla daha kolay canım sıkılıyor ve kızıyorum.
(2) Her şey canımı sıkıyor ve kendimi hep sinirli hissediyorum.
(3) Canımı sıkın şeylere bile artık kızamıyorum. | 20 (0) Sekse karşı ilimde herhangi bir değişiklik yok.
(1) Eskisine oranla sekse ilğim az.
(2) Cinsel isteğim çok azaldı.
(3) Hiç cinsel istek duymuyorum. |
| | 21 (0) Cezalandırılması gereken şeyler yapıpımı sanmıyorum.
(1) Yaptıklarımın dolayı cezalandırılabilceğimi düşünüyorum.
(2) Cezamı çekmeyi bekliyorum.
(3) Sanki cezamı bulmuşum gibi geliyor. |

Toplam BECK-D skoru:.....

8. CURRICULUM VITAE

Personal Information

First Name	Özden	Last Name	Öksüz
Place of Birth		Date of Birth	
Nationality		TC Identity Number	
E-mail		Phone Number	

Educational Status

Degree	Field	Name of the Graduated Institution	Graduation Year
Doctorate	Psychiatry	Namık Kemal University	2017
Postgraduate			
University	Medical Faculty	Akdeniz University	2009
High School		Orhan Dengiz Anatolian High School	2003

Foreign Language	Foreing Language Exam Score
English	82.500 (YÖKDİL), 66.250 (ÜDS), 63.750 (YDS)

Work Experience

Job	Institution	Time (Year – Year)
Research asistant	Department of Psychiatry, Cerrahpaşa Medical Faculty	2016 – 2017
Research asistant	Department of Psychiatry, Namık Kemal Medical Faculty	2012 – 2016
General practitioner	Kuzdere Health Center	2009 – 2010

Computer skills

Program	Ability to use
MS Office	Medium
SPSS	Medium

Scientific

Studies

Articles published in journals included in SCI, SSCI, AHCI

Psychiatry to dermatology; panic disorder. Oksuz, O. Gunver, G. Oba, MC. Arikan, K. J Clin Neurosci. 2020 Nov;81:316-20.
Quantitative EEG Findings in Patients With Psychogenic Nonepileptic Seizures. Arikan, K. Oksuz, O. Metin, B. Gunver, G. Cetin, HL. Esmeray, T. Tarhan, N. Clin EEG Neurosci. 2020 May 4;1550059420918756.
Distinct temperament and character profiles in first onset vitiligo but not in alopecia areata. Erfan, G. Albayrak, Y. Yanik, ME. Oksuz, O. Tasolar, K. Topcu, B. Unsal, C. J Dermatol. 2014 Aug;41(8):709-15.

Articles published in other journals

Kadınlarda Cinsel Ağrı Bozuklukları. Birinci Basamakta Cinsel İşlev Bozukluklarına Yaklaşım Özel Sayısı. Türkiye Klinikleri Aile Hekimliği Özel Dergisi. Öksüz Ö, Doğan S. 2015.

Papers presented at international scientific meetings and published in the proceedings book

A case of acute akathisia after a single dose paliperidone. Oksuz, O. Albayrak, Y. Unsal, C. 6th International Congress on Psychopharmacology, 2014.

Other (Projects/Certificates/Awards)

T.C. İstanbul Üniversitesi Hayvan Deneyleri Yerel Etik Kurulu Deney Hayvanları Kullanım Sertifikası (2014)

Psikofarmakoloji Derneği Bilişsel Davranışçı Terapi Temel Kuramsal Eğitimi Katılım Sertifikası (2013-2014)

Çocuk ve Ergenlerde Bilişsel Davranışçı Terapi Eğitimi Katılım Sertifikası (2015-2016)

