Derleme
Review
Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry 2026; 18(2):487-497
doi: 10.18863/pgy.1668400

Personalized Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: Impact of Cognitive Flexibility on Treatment Outcomes

Obsesif-Kompulsif Bozuklukta Kişiselleştirilmiş Transkraniyal Manyetik Uyarım: Bilişsel Esnekliğin Tedavi Sonuçlarına Etkisi

Beyazıt Garip[1], Meriç Arda Eşmekaya[2]

[1]University of Health Sciences, Ankara
[2]Gazi University, Ankara

ABSTRACT

This systematic review evaluates the current evidence on the relationship between cognitive flexibility and transcranial magnetic stimulation (TMS) efficacy in Obsessive-compulsive disorder (OCD). Specifically, the potential of cognitive flexibility to serve as a neuropsychological marker capable of predicting treatment response and the potential of personalized TMS protocols developed on this basis to enhance therapeutic efficacy were investigated.A comprehensive search of PubMed, Scopus, and Google Scholar was conducted to identify clinical trials and observational studies examining both cognitive flexibility and response to TMS. Studies utilizing standardized neuropsychological measures such as the Wisconsin Card Sorting Test, Trail Making Test, and Verbal Fluency tasks were included. Results suggest that cognitive flexibility may play a moderating role in treatment outcomes, with about half of the reviewed studies reporting a positive association between higher cognitive flexibility and improved TMS response. Nevertheless, discrepancies across studies—particularly in assessment tools and stimulation protocols—limit the ability to draw firm conclusions. In conclusion, cognitive flexibility appears to be a potentially important factor in enhancing the effectiveness of TMS for OCD.

Keywords: Obsessive-compulsive disorder, transcranial magnetic stimulation, cognitive flexibility, neuromodulation, executive function, personalized treatment

ÖZ

Bu sistematik derleme, Obsesif-kompulsif bozukluk (OKB) hastalarında bilişsel esneklik ile ranskraniyal manyetik stimülasyon (TMS) tedavisinin etkinliği arasındaki ilişkiyi incelemektedir. Özellikle bilişsel esnekliğin, tedavi yanıtını öngörebilecek bir nöropsikolojik belirteç olup olamayacağı ve bu temelde geliştirilecek kişiselleştirilmiş TMS protokollerinin terapötik etkinliği artırma potansiyeli araştırılmıştır. PubMed, Scopus ve Google Scholar veri tabanlarında yapılan sistematik tarama ile, OKB'de bilişsel esneklik ve TMS tedavi yanıtını değerlendiren klinik deneyler ve gözlemsel çalışmalar belirlenmiştir. Wisconsin Kart Eşleme Testi, İz Sürme Testi ve Sözel Akıcılık Testi gibi standart nöropsikolojik araçları kullanan çalışmalar incelemeye alınmıştır. Bulgular, incelenen çalışmaların yaklaşık yarısında yüksek bilişsel esneklik düzeylerinin daha iyi TMS yanıtı ile pozitif yönde ilişkili olduğunu göstermektedir. Ancak bazı çalışmalarda bu ilişki doğrulanamamış; bu farklılıklar, kullanılan bilişsel değerlendirme yöntemleri ve TMS protokollerindeki metodolojik çeşitlilikle açıklanabilir. Sonuç olarak, bilişsel esneklik TMS uygulamalarının OKB tedavisinde optimize edilmesinde önemli bir faktör olabilir; ancak bu ilişkinin altında yatan mekanizmalar henüz tam olarak aydınlatılamamıştır.

Anahtar sözcükler: Obsesif-kompulsif bozukluk, transkraniyal manyetik stimülasyon, bilişsel esneklik, nöromodülasyon, yürütücü işlev, kişiselleştirilmiş tedavi

Address for Correspondence: Beyazıt Garip, University of Health Sciences Gülhane Training and Research Hospital Department of Psychiatry, Ankara, Türkiye **e-mail:** beyazitgarip@gmail.com
Received: 30.03.2025 | **Accepted:** 17.07.2025

Introduction

Cognitive flexibility refers to the mental ability to adapt one's thinking and behavior in response to changing goals, demands, or environmental conditions(Lange et al. 2017). Rigidity in the cognitive domain can significantly influence the emotional domain, which is critical for treatment responsiveness(Schwert et al. 2019).Patients diagnosed with Obsessive-Compulsive Disorder (OCD) often demonstrate cognitive rigidity and difficulty adapting to new or changing circumstances. This rigidity is thought to be associated with dysfunction in the prefrontal cortex and striatal regions, which are responsible for decision-making, behavioral adaptability, and habit formation(Ahmari and Rauch 2022).

Deficits in tasks associated with the dorsolateral prefrontal cortex (DLPFC) and/or orbitofrontal cortex (OFC) suggest interconnected neurocognitive mechanisms that contribute to OCD. These impairments include reduced response inhibition, increased error rates, and difficulties in set-shifting(Manarte et al. 2021a). The underlying pathology is thought to involve increased activity within the corticostriatothalamic-cortical (CSTC) circuitry(Jalal et al. 2023). This circuitry is a principal target for neuromodulation therapies such as repetitive transcranial magnetic stimulation (rTMS) and deep brain stimulation (DBS)(Xu et al. 2023, Dehghani-Arani et al. 2024). TMS is primarily used for treatment-resistant OCD patients who have not shown sufficient response to standard anti-obsessive treatments of at least 6 to 8 weeks in duration.

Neuromodulatory approaches, including neurostimulation, pharmacotherapy, and cognitive training, aim to rebalance dysregulated neural circuits and enhance cognitive flexibility(Ansari Esfeh et al. 2025). Improving cognitive flexibility may serve as a therapeutic target to address the underlying pathophysiology of OCD through individualized neuromodulatory interventions(Baldi et al. 2024). Brain regions commonly targeted in this context include the right DLPFC, right OFC, medial prefrontal cortex (mPFC), supplementary motor area (SMA), and anterior cingulate cortex (ACC)(Acevedo et al. 2021). These structures are interconnected within the CSTC network, the core target for advanced interventions such as DBS and deep TMS(Grassi et al. 2023).

This systematic review explores the role of cognitive flexibility in the context of TMS treatment for OCD. Specifically, it addresses three interrelated aspects: (1) predictive value — whether baseline cognitive flexibility predicts clinical response to TMS; (2) treatment effect — whether TMS improves cognitive flexibility; and (3) moderating role — whether cognitive flexibility influences the magnitude or direction of TMS efficacy across subgroups or conditions.

Method

Search Strategy

This systematic review adhered to the PRISMA guidelines. A comprehensive literature search was performed across PubMed, Scopus, and Google Scholar databases, covering the period from January 2015 to January 2025. The review aimed to investigate the role of cognitive flexibility in predicting treatment response to TMS in patients with OCD. The search strategy utilized a combination of predefined keywords relevant to the topic, including "cognitive flexibility," "executive function," "TMS," "treatment response," "predictors of response," and "neuromodulation." This approach was designed to identify all potentially relevant studies for inclusion.

Study selection was conducted by two independent reviewers who screened titles and abstracts, followed by a full-text review of eligible articles. Interrater agreement during full-text selection was assessed using Cohen's kappa coefficient, which indicated moderate to substantial agreement.

Eligibility Criteria

The inclusion criteria encompassed both randomized controlled trials (RCTs) and observational studies, acknowledging the limited number of RCTs investigating cognitive flexibility as a predictor of TMS response in OCD. Incorporating both study types enabled a broader exploration of real-world data.

However, sham-controlled studies were excluded from this review due to their primary focus on placebo effects and symptom reduction rather than on cognitive flexibility or neurocognitive predictors. Given the scarcity of clinical studies specifically addressing treatment response, studies evaluating changes in cognitive functions following TMS treatment were also included, even if they did not directly assess cognitive flexibility.

Inclusion Criteria

1. Patients diagnosed with OCD according to the Structured Clinical Interview for DSM-5-TR (SCID-5-TR) semi-structured interview.
2. Randomized controlled trials (RCTs), reviews, and observational clinical studies.
3. Studies focusing on treatment-resistant OCD.
4. Patients who did not respond to treatment despite receiving adequate duration and dosage of therapy.
5. No contraindications to TMS treatment.
6. Patients with moderate or greater OCD severity, as determined by standardized clinical scales (e.g., Yale-Brown Obsessive Compulsive Scale).
7. Studies employing neuropsychological assessments to evaluate cognitive flexibility.

Exclusion Criteria

1. Case reports, letters to the editor, and opinion articles.
2. Studies that did not adhere to standardized TMS protocols.
3. Studies that did not follow established criteria for treatment-resistant OCD in patient selection.
4. Sham-controlled TMS studies.

Data Extraction and Synthesis

Data extraction focused on key elements, including participant demographics (age, gender, diagnosis), the specific neuropsychological tests used to assess cognitive flexibility and related cognitive domains, and detailed TMS protocol parameters (e.g., frequency, intensity, duration, and stimulation site). Additional information, such as treatment duration and follow-up periods, was also recorded. To ensure data quality, the extraction process involved a thorough comparison of study methodologies, assessing consistency of findings and identifying variations in study design or reporting.

Quality Assessment

The quality assessment process involved a comprehensive evaluation of study designs, methodological rigor, appropriateness of TMS parameters, and adherence to standardized neuropsychological tests. Each study was scrutinized regarding its design (e.g., randomized controlled trials, observational studies), sample size, and the reliability and validity of the cognitive assessments employed. TMS protocols were evaluated for compliance with established guidelines, and consistency in their application across studies was considered. Only studies meeting predefined quality control criteria and demonstrating methodological rigor were included in the review to ensure the credibility of the findings.

Results

Study Selection

The systematic search yielded a total of 127 records from the PubMed, Scopus, and Google Scholar databases. After removing duplicates, 70 records were screened for eligibility. Subsequently, 30 full-text articles were assessed for inclusion. Following full-text review, 10 studies met the inclusion criteria, of which 7 were incorporated into the final analysis. Studies were primarily excluded due to irrelevant study designs (e.g., case reports) or lack of data on cognitive flexibility or TMS treatment response. A PRISMA flow diagram illustrating the study selection process is presented in Figure 1. Among the included studies, 7 were analyzed, with 4 reporting a positive correlation between cognitive flexibility and TMS treatment response. This finding suggests that cognitive flexibility may serve as a useful predictor of treatment outcomes. However, variability across studies was noted, particularly regarding the populations studied and the TMS protocols employed. Detailed characteristics of the included studies are summarized in Table 1.

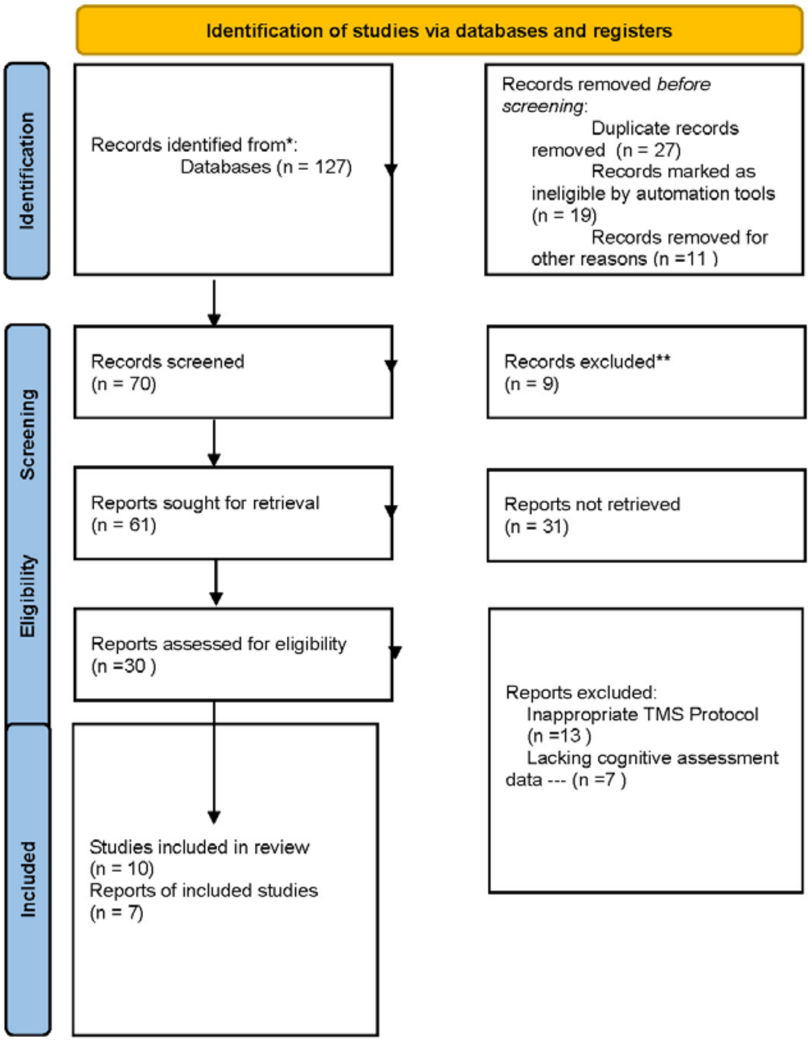

Figure 1. PRISMA flow diagram for included studies

Effects of TMS on Post-Treatment Cognitive Flexibility

TMS has been shown to influence cognitive flexibility following treatment, although findings vary across studies. Carmi et al. (2019) reported a statistically significant improvement in cognitive flexibility after high-frequency deep TMS targeting the mPFC and ACC, with enhancements measured by the Wisconsin Card Sorting Test (WCST)(Carmi et al. 2019). This suggests that TMS may enhance executive function domains critical for cognitive flexibility in patients with OCD. However, other studies, such as Shayganfard et al. (2016), did not observe significant changes in cognitive flexibility post-treatment despite applying TMS over the SMA in OCD patients (Shayganfard et al. 2016). Manarte et al. (2021b) found that good insight patients show better cognitive flexibility was associated with better clinical outcomes(Manarte et al. 2021b). Although direct measures of post-treatment changes remain limited, the available evidence indicates that TMS can positively impact cognitive flexibility in certain patient populations, potentially contributing to improved treatment responses.

Predictive Value of Baseline Cognitive Flexibility for TMS Response

Several studies have investigated the role of baseline cognitive flexibility as a predictor of response to TMS in patients with OCD. Carmi et al. (2019) found a significant positive correlation between baseline cognitive flexibility and treatment response following high-frequency deep TMS over the medial prefrontal cortex and ACC(Carmi et al. 2019). Similarly, Manarte et al. (2021b) reported that higher cognitive flexibility, assessed using the Cognitive Flexibility Inventory (CFI), was associated with greater clinical improvement as measured by the Clinical Global Impression (CGI) scale(Manarte et al. 2021b). Sachse and Widge (2025) also observed that greater baseline flexibility, assessed via task-switching paradigms, predicted a stronger response to rTMS in patients with treatment-resistant depression(Sachse and Widge 2025). In contrast, Shayganfard et al. (2016) found no significant association between cognitive flexibility and TMS response in OCD patients using the WCST(Shayganfard et al. 2016).

The meta-analysis by Dehghani-Arani et al. (2024) supports the predictive role of cognitive flexibility, with 53% of included studies demonstrating a significant link between baseline flexibility and treatment outcome(Dehghani-Arani et al. 2024). These findings indicate that, despite some variability, baseline cognitive flexibility shows promise as a biomarker for predicting TMS treatment efficacy.

Table 1. Characteristics of primary studies included in the systematic review

Reference	n	Population	TMS Protocol	Cognitive Flexibility Scales	Treatment Response Criteria	Inclusion / Exclusion Criteria	Key Findings
Carmi et al. 2019	99	OCD	dTMS, 20 Hz over mPFC/ACC, 29 sessions	WCST, Stroop Test	≥35% Y-BOCS reduction	Inclusion: Adults with treatment-resistant OCD; Exclusion: Suicidal ideation or psychosis	Positive correlation between baseline flexibility and treatment response
Shayganfard et al. 2016	36	OCD	rTMS, 1 Hz over SMA, 20 sessions	WCST	Y-BOCS score change	Inclusion: DSM-IV OCD; Exclusion: Comorbid major depression, psychosis	No significant association found
Manarte et al. 2021	42	OCD	rTMS, over DLPFC (protocol not specified)	Cognitive Flexibility Inventory (CFI)	CGI-based clinical improvement	Inclusion: DSM-5 OCD diagnosis; Exclusion: Severe depression or cognitive impairment	Higher flexibility associated with better insight and treatment outcome
Rosa-Alcázar et al. 2020	60	OCD vs GAD	Non-intervention comparative study	Stroop, Trail Making Test (TMT-B)	N/A	Inclusion: SCID-based diagnosis of OCD or GAD; Exclusion: Neurodevelopmental disorders	OCD group showed significantly lower flexibility than GAD

OCD: Obsessive-Compulsive Disorder, TRD: Treatment-Resistant Depression, GAD: Generalized Anxiety Disorder, TMS: Transcranial Magnetic Stimulation, rTMS: Repetitive TMS, dTMS: Deep TMS, DLPFC: Dorsolateral Prefrontal Cortex, mPFC: Medial Prefrontal Cortex ACC: Anterior Cingulate Cortex, SMA: Supplementary Motor Area, WCST: Wisconsin Card Sorting Test, CFI: Cognitive Flexibility Inventory CGI: Clinical Global Impression, MADRS: Montgomery–Åsberg Depression Rating Scale, SCID: Structured Clinical Interview for DSM TMT-B: Trail Making Test – Part B, Y-BOCS: Yale–Brown Obsessive Compulsive Scale

Assessment Tools for Cognitive Flexibility

Various neuropsychological instruments have been employed to assess cognitive flexibility in studies investigating TMS treatment outcomes. The WCST is one of the most commonly used tools, featured in studies such as Shayganfard et al. (2016) and Carmi et al. (2019), due to its ability to measure set-shifting and problem-solving skills. The Stroop Test, which evaluates inhibitory control and selective attention, was also utilized by Carmi et al. (2019) and Rosa-Alcázar et al. (2020) to assess cognitive flexibility deficits in OCD populations. Additionally, the CFI, a self-report measure focusing on an individual's perceived ability to adapt to changing situations, was employed by Manarte et al.(2021b). Other assessment paradigms include task-switching tests, as applied by Sachse and Widge (2025), and the Trail Making Test-B (TMT-B), used by Rosa-Alcázar et al. (2020), which measures mental flexibility and processing speed. The diversity of tools reflects the multifaceted nature of cognitive flexibility, encompassing executive functions such as set-shifting, inhibition, and problem-solving. This variability also underscores the need for standardized assessment protocols to improve comparability across studies evaluating the impact of TMS on cognitive flexibility.

Discussion

This systematic review highlights the significance of cognitive flexibility as a potential predictor of treatment response in patients with OCD undergoing TMS therapy. The findings suggest that cognitive inflexibility, a core neurocognitive feature of OCD, may influence the effectiveness of neuromodulation interventions. However, the variability in study results underscores the need for further investigation into the relationship between cognitive flexibility and clinical outcomes in OCD treatment.

Cognitive flexibility is considered an important research domain in OCD, with numerous large-scale studies focusing on its relationship with executive functions. Gruner and Pittenger (2016) identified cognitive inflexibility as a fundamental characteristic of OCD, emphasizing the limitations of traditional neuropsychological assessments in accurately capturing this deficit. They highlighted the need for complementary neuroimaging techniques to provide a more comprehensive understanding of the underlying neural mechanisms.

The study by Rosa-Alcázar et al. (2020) offers valuable insight into the association between cognitive flexibility impairments and clinical characteristics in OCD. By employing a comparative design involving patients with OCD, generalized anxiety disorder, and healthy controls, the authors demonstrated that cognitive inflexibility is significantly more pronounced in the OCD group. The use of a comprehensive neuropsychological assessment battery strengthens the methodological rigor and allows for a nuanced analysis across anxiety-spectrum disorders.

Neuroimaging studies assessing cognitive flexibility have demonstrated alterations in functional connectivity between specific brain regions. A neuroimaging study on OCD patients reported that reduced functional connectivity between the caudate and prefrontal cortex is associated with diminished cognitive flexibility (Tomiyama et al. 2019). Another key finding indicated that decreased connectivity between the putamen and DLPFC during goal-directed behaviors correlates with symptom severity (Vaghi et al. 2017). While existing research suggests increased functional activity in the frontostriatal circuitry in OCD, studies specifically examining cognitive flexibility provide critical insights into the disruption of functional connectivity and its underlying mechanisms. These findings highlight the growing importance of neurocognitive assessments in developing personalized treatment approaches.

Large-scale studies have not consistently demonstrated a strong association between cognitive flexibility and symptom severity in OCD. Although many studies suggest that OCD symptoms negatively affect executive functions, including cognitive flexibility, a meta-analysis by Abramovitch et al. (2019) reported only a small effect size for this relationship. This inconsistency may be attributed to methodological limitations, such as potential errors in administering standardized severity measures like the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), inter-rater variability, and the limited availability of validated neuropsychological tests specifically designed to assess cognitive domains in OCD.

Dysfunctional obsessive beliefs have been increasingly recognized as significant contributors to cognitive inflexibility in individuals with OCD. In this context, Şahin et al. (2018) demonstrated a negative correlation between obsessive beliefs and cognitive flexibility. Using standardized neurocognitive assessments, they found that OCD patients performed significantly worse than individuals with panic disorder, particularly on executive function tasks. The presence of rigid, maladaptive beliefs was associated with increased cognitive rigidity, which may, in turn, reinforce obsessive symptoms and perpetuate a cycle of dysfunction. These findings suggest that interventions targeting dysfunctional beliefs, such as cognitive restructuring, may help enhance cognitive flexibility and improve treatment outcomes. The inverse association between the severity of obsessive beliefs and cognitive flexibility highlights the need for individualized therapeutic approaches that integrate both cognitive and neurobiological aspects of OCD.

Although no studies to date have directly examined the relationship between cognitive flexibility and treatment outcomes following TMS in OCD, a limited body of literature has indirectly explored this association through broader evaluations of cognitive function. In our recent prospective investigation (ClinicalTrials.gov Identifier: NCT06769243; Garip, 2024), we specifically addressed this gap by assessing whether baseline cognitive flexibility could serve as a predictor of TMS treatment response in patients with treatment-resistant OCD. This study represents one of the first targeted efforts to directly evaluate the clinical utility of cognitive flexibility as a potential biomarker for TMS responsiveness in this population. Preliminary data from our study indicated no statistically significant relationship between baseline cognitive flexibility and treatment response to TMS in patients with treatment-resistant OCD.

Several potential sources of heterogeneity in TMS treatment protocols may influence therapeutic outcomes. Variability in stimulation parameters, such as frequency (e.g., 10 Hz vs. 50 Hz bursts), intensity (90% vs. 120% motor threshold), and pulse count, can lead to differing neurophysiological effects. Coil types and positioning techniques (e.g., figure-8 coil, Beam F3 method) may affect the depth and focality of stimulation. Additionally, treatment duration and session frequency (e.g., accelerated vs. standard protocols) can impact neuroplastic responses(Rossi et al. 2021).

Patient-specific factors—such as psychiatric and medical comorbidities, concurrent use of medications (e.g., benzodiazepines, antipsychotics), baseline cognitive capacity, and age—can influence TMS efficacy. These inter-individual differences may explain variability in treatment response and underscore the need for personalized approaches. Future research should account for these variables through stratification or statistical control to improve reproducibility and clinical outcomes.

Functional connectivity studies offer strong evidence for cognitive impairments in OCD. In a resting-state fMRI study, Yun et al. (2017) investigated executive function-related brain activity in OCD, focusing on the ACC and its connectivity with other regions(Yun et al. 2017). OCD patients showed significantly poorer performance on neuropsychological tasks, including increased WCST perseverative errors and prolonged Trail Making Test-B (TMT-B) reaction times ($p < 0.05$) compared to healthy controls. Notably, altered functional interaction between the ACC and right DLPFC was identified. These results suggest a network-level dysfunction underlying cognitive deficits in OCD.

The subthalamic nucleus (STN), a key component of the CSTC circuit, has emerged as a critical region implicated in both symptom severity and cognitive flexibility in OCD. A recent study by Xu et al. (2023) demonstrated that deep brain stimulation targeting the STN significantly improved OCD symptoms and cognitive performance, particularly in cognitive flexibility(Xu et al. 2023). These improvements were closely linked to STN modulation. Given the STN's role in motor control, decision-making, and executive function, its hyperactivation has been associated with cognitive rigidity and impaired response inhibition, core features of OCD. The findings reinforce the STN's functional relevance in both the neurobiology and treatment of OCD.

Recent literature increasingly highlights the impact of deep TMS on cognitive functions, particularly cognitive control. In a comprehensive review, Laskov and Klírová (2021) reported that deep TMS can enhance domains such as attention, decision-making, and executive functioning(Laskov and Klírová 2021). These effects are attributed to modulation of the CSTC circuit, which plays a central role in regulating cognitive control. By stimulating both frontal cortical areas and subcortical structures, deep TMS enhances functional connectivity among the prefrontal cortex, parietal regions, striatum, and thalamus—regions responsible for attentional regulation and higher-order cognitive organization. Given the close association between cognitive control and cognitive flexibility, these findings support the therapeutic potential of deep TMS in addressing flexibility-related impairments, particularly in neuropsychiatric conditions such as OCD.

Although various tests assess cognitive flexibility in OCD, those targeting flexible thinking, impulse control, and attentional shifting are especially valuable. The WCST is a robust tool for evaluating cognitive flexibility in neuropsychiatric disorders, including OCD. Manarte et al. (2021) found that OCD patients with poor insight performed significantly worse on the WCST compared to healthy controls(Manarte et al. 2021b). This highlights insight as a clinically and neuropsychologically important dimension. The reduced WCST performance in poor-insight patients reflects impairments in cognitive flexibility and executive functioning, contributing to perseverative thoughts and rigid behaviors in OCD.

The WCST evaluates several key aspects of cognitive flexibility, with the ability to adapt to changing conditions being one of its most critical components. During the task, participants are required to match cards based on one of three categories—color, shape, or number—which periodically change without explicit notice. The participant must deduce the new sorting rule from feedback and adjust their responses accordingly. The ability to successfully shift to a new rule reflects cognitive flexibility and is considered a core function of the prefrontal cortex(Çelik et al. 2021).

Individuals with impairments in cognitive flexibility often struggle with set-shifting, failing to abandon a previously correct rule in favor of a new one. This difficulty in adapting to novel conditions is frequently observed in clinical populations and has been linked to deficits in executive functioning(Miles et al. 2021).

Another critical parameter measured by the WCST is the perseverative error rate. Perseverative errors occur when individuals continue to apply an outdated rule despite receiving negative feedback. High rates of perseverative errors indicate difficulties in evaluating and correcting one's own mistakes, often associated with impairments in attention, goal-directed behavior, and strategic thinking(Pellegrini et al. 2024).

The neuropsychological assessment commonly used to evaluate cognitive function in OCD is the TMT, which measures task-switching ability and processing speed. Part B, involving alternating between numbers and letters, offers key insights into task-switching and is important for assessing prefrontal cortex function. The TMT primarily targets executive functions and cognitive flexibility, processes largely governed by the prefrontal cortex, which is crucial for decision-making, problem-solving, attention control, and strategy shifting. Additionally, the parietal and temporal lobes may indirectly influence attention, processing speed, and visual processing during the test. Thus, the TMT is a distinctive neurocognitive tool that evaluates multiple cognitive domains by engaging various brain regions(Manarte et al. 2021a).

The verbal fluency (VF) test is widely used to assess cognitive flexibility due to its reliance on multiple executive functions, particularly lexical retrieval, set-shifting, and strategic response generation. In both phonemic and semantic fluency tasks, individuals are required to rapidly generate words according to specific rules—for example, listing words that begin with a specific letter (such as K, A, or S) or naming items within a category (such as animals or fruits)—within a limited time. This process involves activation of semantic memory networks, inhibitory control to suppress irrelevant or repeated responses, and working memory to monitor and update output in real time. Cognitive flexibility is reflected in the individual's ability to switch between subcategories or word clusters during the task(Cintoli et al. 2024). Neuroimaging and lesion studies have consistently implicated the prefrontal cortex, particularly the DLPFC and ACC, in mediating the executive components required for verbal fluency(Park et al. 2023). Therefore, VF performance serves as a valid and sensitive behavioral indicator of cognitive flexibility, especially in clinical populations such as those with depression and schizophrenia(Neu et al. 2019).

Despite the promising insights gained from this systematic review, several limitations should be acknowledged. First, the heterogeneity in study methodologies, including variations in TMS protocols, stimulation parameters, and cognitive assessment tools, may have contributed to inconsistent findings. Different studies employed distinct neuropsychological tests to measure cognitive flexibility, which could lead to variability in reported outcomes. The reliance on traditional cognitive flexibility tests, such as the WCST and TMT, may not fully capture the complex neural mechanisms underlying cognitive adaptability in

OCD. Second, the sample sizes of included studies were often small, limiting the generalizability of findings. Larger, well-powered randomized controlled trials are needed to validate the role of cognitive flexibility in predicting TMS treatment response. Additionally, most studies did not control for potential confounding factors, such as medication use, comorbid psychiatric conditions, or illness duration, which may have influenced cognitive performance and treatment outcomes. Third, while TMS primarily targets specific brain regions involved in OCD, cognitive flexibility is a multifaceted construct involving distributed neural networks. The lack of neuroimaging integration in most studies prevents a comprehensive understanding of how TMS-induced changes in functional connectivity relate to improvements in cognitive flexibility. Future studies should incorporate multimodal approaches, including functional MRI and EEG, to better elucidate these mechanisms. Finally, the absence of long-term follow-up assessments limits our understanding of the durability of cognitive and clinical improvements following TMS. Given that neuroplasticity-related changes may evolve over time, longitudinal studies are essential to determine whether enhancements in cognitive flexibility translate into sustained therapeutic benefits for OCD patients. Addressing these limitations in future research will be crucial for refining TMS protocols, optimizing treatment outcomes, and advancing the personalization of neuromodulation therapies for OCD.

Conclusion

This systematic review examined the relationship between cognitive flexibility and treatment outcomes following TMS in patients with OCD. A total of seven original studies were included in the final analysis. The findings were categorized into two main groups: Four studies (Carmi et al. (2019), Rosa-Alcázar et al. (2020), Manarte et al. (2021b), Sachse & Widge (2025)) reported that higher baseline cognitive flexibility was associated with better clinical outcomes following TMS. For example, Carmi et al. (2019) found that participants who performed better on tests such as the WCST and Stroop Test exhibited greater symptom reduction. Similarly, Manarte et al.(2021b) reported that higher cognitive flexibility was linked to better insight and improved treatment response. Three studies (Shayganfard et al. 2016, Carmi et al. 2019, Manarte et al. 2021b) investigated whether TMS could improve cognitive flexibility itself. Among these, Carmi et al. (2019) observed improvements in executive functions after TMS sessions targeting the mPFC and ACC. In contrast, Shayganfard et al.(2016) found no significant changes in cognitive flexibility following stimulation over the supplementary motor area.

Despite these findings, results varied depending on the targeted brain regions, cognitive assessments employed, and patient characteristics. For instance, the WCST, Stroop Test, and CFI were used across studies, each measuring distinct aspects of executive function.

In conclusion, cognitive flexibility appears to be a potentially important factor in predicting and possibly enhancing treatment response to TMS in OCD. However, current evidence remains inconclusive due to methodological heterogeneity among studies. Larger, more standardized clinical trials are warranted to clarify the role of cognitive flexibility in TMS outcomes and to determine whether it can serve as a reliable biomarker for personalized treatment planning.

References

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

Acevedo N, Bosanac P, Pikoos T, Rossell S, Castle D (2021) Therapeutic neurostimulation in obsessive-compulsive and related disorders: a systematic review. Brain Sci, 11:94-98.

Ahmari SE, Rauch SL (2022) The prefrontal cortex and obsessive compulsive disorder. Neuropsychopharmacology, 47:211-224.

Ansari EM, Talesh JA, Niyasar AR, Rostami R, Khosrowabadi R (2025) Altered brain network stability in obsessive compulsive disorder following repetitive transcranial magnetic stimulation intervention: insights from structural balance theory. Psychiatry Res Neuroimaging, 346:1119-11127.

Baldi S, Schuhmann T, Goossens L, Schruers KRJ (2024) Individualized, connectome-based, non-invasive stimulation of obsessive compulsive disorder deep-brain targets: a proof-of-concept. Neuroimage, 288:1205-1227.

Carmi L, Tendler A, Bystritsky A, Hollander E, Blumberger DM, Daskalakis J, Ward H et al. (2019) Efficacy and safety of deep transcranial magnetic stimulation for obsessive-compulsive disorder: a prospective multicenter randomized double-blind placebo-controlled trial. Am J Psychiatry, 176:931-938.

Cintoli S, Favilli L, Morganti R, Siciliano G, Ceravolo R, Tognoni G 2024) Verbal fluency patterns associated with the amnestic conversion from mild cognitive impairment to dementia. Sci Rep,14:20-29.

Çelik S, Oğuz M, Konur U, Köktürk F, Atasoy N (2021) Comparison of computerized and manual versions of the wisconsin card sorting test on schizophrenia and healthy samples. Psychol Assess, 33:562-567.

Dehghani AF, Kazemi R, Hallajian AH, Sima S, Boutimaz S, Hedayati S et al. (2024) Koushamoghadam S, Safarifard R, Salehinejad MA. Meta-analysis of repetitive transcranial magnetic stimulation efficacy for obsessive compulsive disorder treatment. J Clin Med, 13:53-58.

Garip B (2024) Cognitive flexibility and response to TMS therapy (CogFlexTMS). ClinicalTrials.gov identifier: NCT06769243. Updated 10.01.2025. https://clinicaltrials.gov/study/NCT06769243 (Accessed 20.03.2025).

Grassi G, Moradei C, Cecchelli C (2023) Will transcranial magnetic stimulation improve the treatment of obsessive-compulsive disorder? a systematic review and meta-analysis of current targets and clinical evidence. Life, 13:1494.

Gruner P, Pittenger C (2016) Cognitive inflexibility in obsessive-compulsive disorder. Neuroscience, 345:243-255.

Jalal B, Chamberlain SR, Sahakian BJ (2023) Obsessive-compulsive disorder: etiology, neuropathology, and cognitive dysfunction. Brain Behav,13:e3000.

Lange F, Seer C, Kopp B (2017) Cognitive flexibility in neurological disorders: cognitive components and event-related potentials. Neurosci Biobehav Rev, 83:496-507.

Laskov O, Klírová M (2021) Effects of deep transcranial magnetic stimulation on cognition. Neurosci Lett, 755:135906.

Manarte L, Andrade AR, do Rosário L, Sampaio D, Figueira ML, Morgado P et al. (2021a) Executive functions and insight in obsessive compulsive disorder: a comparative study. BMC Psychiatry, 21:216.

Manarte L, Andrade AR, do Rosário L, Sampaio D, Figueira ML, Langley C et al. (2021b) Poor insight in obsessive compulsive disorder: associations with empathic concern and emotion recognition. Psychiatry Res, 304:114-129.

Miles S, Howlett CA, Berryman C, Nedeljkovic M, Moseley GL, Phillipou A (2021) Considerations for using the wisconsin card sorting test to assess cognitive flexibility. Behav Res Methods, 53:2083-2091.

Neu P, Gooren T, Niebuhr U, Schlattmann P (2019) Cognitive impairment in schizophrenia and depression: a comparison of stability and course. Appl Neuropsychol Adult, 26:215-228.

Park I, Ha M, Kim T, Lho SK, Moon SY, Kim M et al. (2023) Cortical gyrification differences between early- and late-onset obsessive-compulsive disorder: neurobiological evidence for neurodevelopmentally distinct subtypes. Psychol Med, 53:5976-5985.

Pellegrini L, Clarke A, Fineberg NA, Laws KR (2024) The inflexible mind: a critical factor in understanding and addressing covid-19 vaccine hesitancy. J Psychiatr Res, 179:360-365.

Rosa-Alcázar Á, Olivares-Olivares PJ, Martínez-Esparza IC, Parada-Navas JL, Rosa-Alcázar AI, Olivares-Rodríguez J (2020) Cognitive flexibility and response inhibition in patients with obsessive-compulsive disorder and generalized anxiety disorder. Int J Clin Health Psychol, 20:20-28.

Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J et al. (2021) Safety and recommendations for transcranial magnetic stimulation use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. Clin Neurophysiol, 132:269-306.

Sachse EM, Widge AS (2025) Neurostimulation to improve cognitive flexibility. Curr Opin Behav Sci, 62:101484.

Schwert C, Stohrer M, Aschenbrenner S, Weisbrod M, Schröder A (2019) Biased neurocognitive self-perception in depression - what is the reason for the discrepancy? J Affect Disord, 243:193.

Shayganfard M, Jahangard L, Nazaribadie M, Haghighi M, Ahmadpanah M, Sadeghi Bahmani D et al. (2016) Repetitive transcranial magnetic stimulation improved symptoms of obsessive-compulsive disorders but not executive functions: results from a randomized clinical trial with crossover design and sham condition. Neuropsychobiology. 74:115-124.

Şahin H, Köşger F, Eşsizoğlu A, Aksaray G (2018) The relationship between obsessive belief level and cognitive flexibility in patients with obsessive compulsive disorder. Noro Psikiyatr Ars, 55:376-379.

Tomiyama H, Nakao T, Murayama K, Nemoto K, Ikari K, Yamada S etal. (2019) Dysfunction between dorsal caudate and salience network associated with impaired cognitive flexibility in obsessive-compulsive disorder: a resting-state functional magnetic resonance imaging study. Neuroimage Clin, 24:102004.

Vaghi MM, Vértes PE, Kitzbichler MG, Apergis-Schoute AM, van der Flier FE, Fineberg NA et al. (2017) Specific frontostriatal circuits for impaired cognitive flexibility and goal-directed planning in obsessive-compulsive disorder: evidence from resting-state functional connectivity. Biol Psychiatry, 81:708-717.

Xu J, Huang T, Dana A (2023) Deep brain stimulation of the subthalamic nucleus to improve symptoms and cognitive functions in patients with refractory obsessive-compulsive disorder: a longitudinal study. Neurol Sci. 44:2385-2392.

Yun JY, Jang JH, Jung WH, Shin NY, Kim SN, Hwang JY et al. (2017) Executive dysfunction in obsessive-compulsive disorder and anterior cingulate-based resting state functional connectivity. Psychiatry Investig, 14:333-343.

Authors Contributions: The author(s) have declared that they have made a significant scientific contribution to the study and have assisted in the preparation or revision of the manuscript

Peer-review: Externally peer-reviewed.

Ethical Approval: This review study does not require ethical clearance.

Conflict of Interest: No conflict of interest was declared.

Financial Disclosure: No financial support was declared for this study..