

Fifty Percent or more Incremental Rise in Resting Motor Threshold of the Brain Emerging as an Early Critical Biomarker in Predicting the Success of rTMS Therapy in Treatment Resistant Obsessive Compulsive Disorder: A Case Series Based Pilot Study

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Abstract

Objectives:

This pilot study aimed to evaluate whether a 50% or greater rise in Resting Motor Threshold can serve as a critical biomarker to predict the success of repetitive Transcranial Magnetic Stimulation in treatment-resistant Obsessive-Compulsive Disorder patients.

Methods:

Conducted at our advanced Neuromodulation laboratory in a tertiary care hospital, this case series-based pilot study involved 5 patients diagnosed with treatment-resistant OCD. Each underwent 12 to 18 sessions of rTMS targeting the supplementary motor area (1 Hz, 110% MT, 900 Pulses), anterior cingulate gyrus (20Hz, 100%MT, 2000 Pulses) and dorsomedial prefrontal cortex protocol (20 Hz, 100% MT, 750 Pulses). RMT was measured at baseline, after 10 sessions, and post-12 sessions, and then followed up at 3, 6, and 9 months. The clinical progress was assessed using standard OCD scales and correlated with RMT trajectory to evaluate predictive validity.

Results:

All three patients demonstrated a consistent rise in RMT by more than 50% viz: from 37% to 57% in case 1, from 32% to 53% in case 2, and from 42% to 63% in case 3 by the 12th rTMS session, aligning with significant symptomatic relief. Their MT values remained stable during remission over 12 months, reinforcing the link between early RMT elevation and sustained therapeutic benefit. This trend indicates that a more than 50% RMT rise post-initial rTMS targeted neural network sessions may signal a positive treatment trajectory in resistant OCD cases. 2 other cases where rTMS failed showed only minimal shift of RMT from 32% to only 37% at the end of 30 sessions in 4th Case while in 5th Case of failed rTMS showed 34% RMT baseline increased only to 38% after 30 sessions.

Conclusion:

To our knowledge, this is the first study in literature elucidating a 50% or greater rise in RMT as a reliable and early biomarker for successful rTMS response in treatment-resistant OCD. This finding although supports its potential role in guiding personalized, precision-based neuromodulation strategies for enhanced treatment outcomes, would require further large scale replication and validation.

Keywords: Obsessive-Compulsive Disorder, Resting Motor Threshold, Repetitive Transcranial Magnetic Stimulation, Early Response Biomarker, Precision Medicine

Background:

Obsessive-Compulsive Disorder (OCD) is a chronic condition characterized by distressing obsessions and compulsions that significantly impair daily functioning. While cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) remain the first-line treatments, approximately 30-40% of individuals with OCD fail to respond to these therapies, highlighting the need for alternative interventions.¹ One such promising approach is repetitive transcranial magnetic stimulation (rTMS), which has gained acceptance over the past decade for its ability to modulate neural activity and improve both symptoms and cognition in treatment-resistant OCD patients. Recent neurobiological research has identified that any successful task performance involves the capacity to monitor for errors and thereby to adjust behavioral response accordingly through specific brain regions, such as the orbitofrontal cortex (OFC), posterior medial prefrontal cortex (mPFC), incorporating dorsal anterior cingulate cortex (dACC), supplementary motor area (SMA) and posterior portions of pre-supplementary motor area (pre-SMA) and caudate nucleus, as key brain regions in the pathophysiology of OCD.^{2,3,4} These areas are involved in the loss of top-down inhibitory control, which contributes to the compulsive behaviors characteristic of the disorder.⁵ Neuroimaging studies have also revealed altered brain connectivity, including reduced fractional anisotropy, decreased myelination in midline tracts, and hypo-connectivity within the frontal, temporal, and parietal cortices.^{6,7} In another interesting study functional connectivity between the ventrolateral prefrontal cortex and dorsal caudate nucleus was found to be linked with worse cognitive flexibility in OCD.⁸

These findings suggest that disrupted neural circuits, particularly in the frontal-basal ganglia loop, may underlie OCD symptoms. Previous studies have highlighted the promising acute therapeutic response of rTMS applied to OFC, mPFC, dACC, SMA.^{9,10,11} OCD patients usually have lower resting motor threshold (MT) for TMS. Neurostimulation of brain but it is not clearly studied if their motor threshold rises with sustained improvement and how much shift in MT is perhaps critical for sustained remission maintenance.¹² To date, inhibitory deficits and enhanced intracortical facilitation have been implicated in OCD, with a very limited number of studies examining cortical excitability using paired-pulse TMS and later concept of MT shift is yet not mentioned in the literature.¹³ Based on this scientific fact, we designed our patient tailored treatment algorithm for specific neural region response when 5 or more sessions of TMS does not reduce neural oscillation frequency either on EEG or on rise in resting motor threshold (RMT), it suggest that rTMS stimulation of that region and intensity will not work. We discarded the group of those rTMS treatment patient who failed to respond or relapsed and were not having found to be with maintaining sequential rise in motor

threshold. The present case series also aims to understand how motor threshold rise by 50% or more can serve as an early and reliable indicator of the therapeutic response and opens up positive predictive pathway for effectiveness of rTMS in treatment resistant OCD patients, possibly shedding light on its role as critical biomarker in offering personalized, precision-based treatment in psychiatry and clinical neurosciences.

Case Vignette

Case 1

Ms D, a 25-year-old right-handed female medical internist, presented with a 18 month history of obsessive symptoms, including persistent doubts about her and interactions with colleagues, accompanied by an overwhelming need for repeated validation. Despite recognizing the irrationality of these thoughts, she repeatedly sought reassurance, particularly from senior colleagues. Additionally, she experienced ego-dystonic sexual images of opposite-gender colleagues and had compulsive tendencies to arrange objects, such as books and footwear, symmetrically. These symptoms, which caused significant anxiety, were coupled with a pronounced sense of low self-esteem. Her pre-morbid personality had been well-adjusted, with no notable family or psychiatric history. Neurologically, her brain MRI was unremarkable, and her YBOCS score was 26, indicative of severe OCD.

Ms D had trialed two courses of selective serotonin reuptake inhibitors (SSRI) therapy—150 mg/day Sertraline and 40 mg/day Fluoxetine—without notable improvement. Consequently, she was initiated on TMS, with biphasic stimulation targeting the bilateral supplementary motor area (1 Hz, 110% MT, 900 Pulses), dorsomedial prefrontal cortex protocol (20 Hz, 100% MT, 750 Pulses) and anterior cingulate gyrus (20Hz, 100%MT, 2000 Pulses using Coil DCC-03-125-C-FDA Approved). After 12 sessions of TMS, she showed significant improvement, with near-complete remission of symptoms (YBOCS- 7) following three weeks of inpatient care. Remarkably, patient's MT improved from 32% to 53% while she has remained symptom-free for since nine months and MT maintained on 53%, even clearing her national entrance exam on the first attempt.

Case 2

Ms N, a 25-year-old matriculate housewife, presented with an 8-year history of severe OCD. Her symptoms primarily involved intrusive, ego-dystonic thoughts about contamination by dirt and germs, which led to compulsive cleaning and washing rituals that consumed 4 to 5 hours daily. She also imposed strict cleaning behaviors on her family, requiring her child and husband to wash them if they were touched by others. In addition to these compulsions, Ms S experienced recurrent, distressing mental images of human feces whenever she encountered water sources or

bodies of water in her town, which she could only neutralize by mentally repeating a specific mantra eight times. She also had an obsessive need to confess her thoughts and actions to a fixed number of people, leading to further distress. In initial few years she underwent 6 months of CBT with initial partial response and again went in relapse. Despite multiple unsuccessful pharmacological interventions—including three trials of Fluoxetine (200 mg/day), Fluoxetine (60 mg/day), and Clomipramine (75 mg/day)—she continued to experience severe symptoms, resulting in significant frustration and two suicide attempts over the past three years. Her baseline Y-BOCS score was 27, indicating severe OCD. Given her refractory symptoms, Ms S was treated with regional transcranial magnetic stimulation targeting the supplementary motor area (1 Hz, 110% MT, 900 Pulses), dorsomedial prefrontal cortex protocol (20 Hz, 100% MT, 750 Pulses), and anterior cingulate gyrus (20Hz, 100%MT, 2000 Pulses using Coil DCC-03-125-C-FDA Approved). After 14 sessions of TMS, she experienced marked improvement, with her OCD symptoms almost entirely remitting. She has remained in remission for the past six months, experiencing significant relief and regained quality of life. Our patient MT was increased from 37% to 57% after her recovery and maintained same for more than 9 months till date.

Case 3

A 26-year-old male, an ice-cream vendor, presented with a 9-year history of OCD, marked by repetitive intrusive thoughts of counting pages, lines, people, and currency notes, which he would counteract through repeated rituals. In the past 4–5 years, additional checking behaviors, such as repeatedly ensuring locks, gas cylinders, and mobile messages, emerged, severely impacting his daily routine, studies, and overall quality of life. Despite two adequate trials of SSRIs — 200 mg/day of sertraline for 3 months followed by 200 mg/day of fluvoxamine for 9 months — his symptoms showed only modest improvement of 10-20%. He discontinued the medications.

Over the past three months, the patient developed significant depressive symptoms, including suicidal ideation. Escitalopram (20 mg/day, titrated to 30 mg) was initiated but failed to yield adequate symptom relief. After the family declined electroconvulsive therapy, he was referred to our tertiary care facility. With a baseline Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score of 29 and a Beck Depression Inventory (BDI) score of 34, he underwent a

combined TMS protocol, targeting the supplementary motor area, medial prefrontal cortex, and anterior cingulate cortex for OCD and the dorsolateral prefrontal cortex for both OCD and depression. After 17 sessions of TMS, significant clinical improvement was observed, particularly in both depressive and OCD symptoms, after just three weeks of inpatient care. Our patient RMT increased from 42% to 63% and his improvement persisted same for more than 12 months till date.

Case 4

A 23 years old graduate engineering student was referred for rTMS treatment from private psychiatrist with history of 7 years of treatment resistant OCD with 4 to 5 hours of time being spent on bathing and toilet cleaning every day. He was tried on adequate trials of Sertraline, Fluoxetine and Clomipramine over the years without any discernable improvement. He did not have depressive symptoms and his current medications consist of 300 mg of Fluoxetine and 1 mg of Risperidone per day. His Y-BOCS score was 35 and while he meticulously underwent rTMS therapy session targeting the supplementary motor area, medial prefrontal cortex, and anterior cingulate cortex for OCD, he showed hardly any improvement even after 30 sessions of OCD protocol. His baseline RMT was 32% and it increased to only 37% at the end of 30 sessions of TMS while his Y-BOCS shifted from 35 to 32 without any significant shift.

Case 5

A 43 years old graduate businesswoman was referred for her 22 years history of treatment resistant OCD from Kota. She has been seeking treatment from last 20 years and was helpless, hopeless and worthless after consistent failure of response from Fluoxetine, Sertraline, and Fluoxetine as well as Clomipramine adequate dose and duration with 3 hospitalizations. She would feel her body is always dirty and need to wash it again and again spending 6 to 7 hours per day in bathroom. Her Y-BOCS score was 37 and Beck Depression Inventory (BDI) score of 36. She underwent a combined TMS protocol, targeting the supplementary motor area, medial prefrontal cortex, and anterior cingulate cortex for OCD and the dorsolateral prefrontal cortex for both OCD and depression. After 12 weeks of completing the rTMS protocol, her symptoms continued with almost same intensity. Her Baseline RMT was 34% and increased only to 38% after 30 sessions while her Y-BOCS shifted from 37 to 33 without any significant improvement.

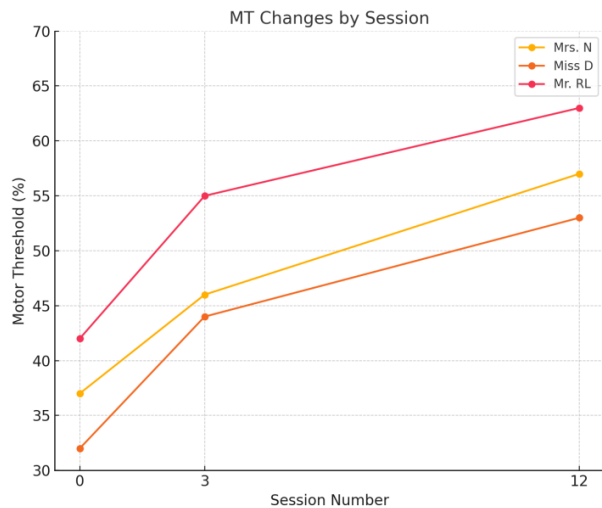


Figure 1

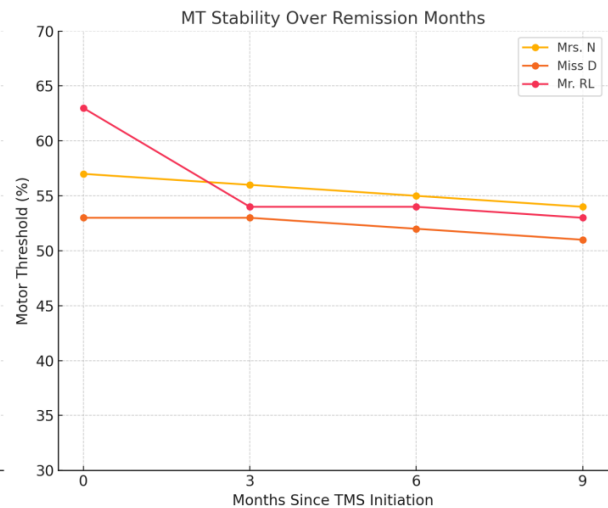


Figure 2

Figure 1: Motor Threshold Changes Across rTMS Sessions in Treatment-Resistant OCD Patients (Depicts MT progression from baseline through 3rd and 12th sessions)

Figure 2: Stability of Motor Threshold During Remission over 9 Months Post-Treatment (Shows sustained MT levels at 3, 6, and 9 months in three OCD patients)

Discussion:

rTMS is a non-invasive neuromodulatory technique rapidly advancing and commonly employed in recent years in the management of treatment-resistant neuropsychiatric disorders, particularly epilepsy, major depression and OCD. One of the technical parameters crucial to the administration of rTMS is the resting motor threshold (RMT), which is determined at the beginning of treatment and sometimes monitored over subsequent sessions. Emerging evidence suggests that an increase in RMT across rTMS sessions may serve as a surrogate marker of cortical excitability modulation and potential treatment response, but the literature remains inconsistent and underdeveloped. For OCD, the literature is more nascent. Some studies, such as Mantovani et al¹⁴, have suggested that therapeutic response is associated with neurophysiological markers of cortical modulation, including RMT. Given the hyperconnectivity and heightened excitability in cortico-striatal-thalamo-cortical loops in OCD, a rise in motor threshold might reflect a normalization of this pathological activity. However, systematic, large-scale studies quantifying motor threshold changes and correlating them with symptom reduction (e.g., Y-BOCS scores) are lacking. Present case series is an attempt to bridge this research gap by keen response of rise of motor threshold by 50% or more and its persistence in subsequent follow-ups thereby modulating neural oscillations and cortical excitability after TMS therapy in specific neural network or region thereby enhancing the predictive outcome of TMS algorithms or protocols for its effectiveness.

As in the context of epilepsy, motor threshold dynamics have been studied primarily as a safety marker, given the risk of

seizure induction. However, decades before past studies such as those by Tergau et al¹⁵ and Cantello et al¹⁶ have observed that chronic rTMS administration in epilepsy patients often leads to increased motor thresholds, implying a reduction in cortical excitability. This neurophysiological change is theorized to underpin seizure suppression, suggesting a therapeutic effect. Nonetheless, these studies remain limited in sample size, and few have directly correlated RMT changes with clinical seizure frequency reduction and for almost two decades, there were no studies focusing on significance of RMT of rTMS for its therapeutic responses.

In case of refractory depression, the increase in motor threshold has been linked with clinical improvement. Several open-label and randomized controlled trials¹⁷⁻¹⁸ have reported that patients who respond to high-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC) tend to show gradual increases in RMT, indicative of decreased cortical excitability. This aligns with the notion that rTMS may induce long-term potentiation (LTP)-like plasticity, resulting in neuroadaptive changes.¹⁹ However, not all studies replicate this trend, and RMT changes are not universally observed, potentially due to variability in coil positioning, session parameters, or inter-individual neuroplastic capacity.

Clinical observations have shown that individuals with OCD typically exhibit lower resting motor thresholds, which reflect heightened cortical excitability in the brain regions involved in the disorder. As patients undergo treatment, particularly rTMS, a change in the MT can serve as an early and reliable indicator of the therapeutic response. Specifically, as the

patients show improvement, their MT tends to increase like it happens in patients with epilepsy, signaling a reduction in cortical hyperexcitability and an overall stabilization of neural activity. A sequential motor threshold rise by 50% or more from the baseline reflect the positive predictor of effective rTMS treatment and can be considered as a critical biomarker in predicting the success of rTMS therapy, particularly in patients with OCD. We discarded the group of those rTMS treatment patient who failed to respond and does not have found to be with maintaining sequential rise in motor threshold for not even 15% to 20% increase in RMT as seen in case 4 and 5 highlighting the importance of sustained MT elevation for long-term remission.

In our treatment approach, we identified that when MT does not show a significant increase after 10 sessions of TMS, it strongly suggests that the chosen stimulation intensity or target region may not be effective. This predictive observation has proven useful in guiding clinicians to make informed decisions regarding protocol adjustments. For example, in three distinct cases of treatment-resistant OCD patients, more than 50% MT increase was observed: Mrs. N's Motor threshold (MT) rose from 37% to 46% after session 10

and 57% by 12th rTMS session, Miss D's MT increased from 32% 44% after session 10 and to 53% by 12th session, and Mr. RL's from 42% to 55% after 10 and to 63% by 12th rTMS session, as they progressed toward remission. Mrs. N MT at 3 months was 56%, at 6 months was 55% and at 9 Months was 54% during her remission. Miss D MT at 3 months was 53%, at 6 months was 52% and at 9 Months was 51% during her remission. Similarly Mr RL MT at 3 month was 54%, at 6 months was 54% and at 9 months was 53% during his remission. (Figures 1 & 2). This increase in MT correlates with their clinical recovery, underscoring the value of monitoring MT as a reliable biomarker for therapeutic success. This helped us in our 3 different long standing, treatment resistant OCD patient to understand the way clinician should validly judge and use TMS protocol. Motor threshold (MT) progression in treatment-resistant OCD patients showed consistent increases after early TMS sessions and remained relatively stable during remission over nine months. These findings reinforce MT as a dynamic biomarker for clinical response and sustainability (Figure 3). Tracking MT offers clinicians actionable insights into protocol efficacy and remission maintenance in neuromodulation therapy.



Figure 3: Radar chart visual comparison of motor threshold changes and stability during rTMS therapy in OCD patients reflecting both the early therapeutic gain and long-term maintenance of MT, supporting its use as a dynamic biomarker

Conclusion

Despite advances in neuroscience, very few validated biomarkers exist for prognostic implications in clinical psychiatry and neurosciences. The introduction of electrophysiological marker represents an essential step

forward in personalizing TMS therapy for OCD patients. By utilizing changes in MT as a clinical predictor, clinicians can tailor treatment strategies more precisely, potentially improving outcomes for those with long-standing, treatment-resistant OCD. This novel approach offers an evidence-

based framework for optimizing TMS neurostimulation and advancing the standard of care for OCD. Nevertheless, a key challenge in interpreting RMT as a biomarker is its sensitivity to extraneous variables including medication status, sleep, and hormonal cycles. Moreover, the intra-individual variability and potential for measurement error must be considered. Most importantly, there is currently no standardized protocol recommending serial motor threshold assessment during rTMS courses in clinical practice, limiting its utility as a routine biomarker.

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Conflict of Interest: None Declared

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