

Predictors of Response to Repetitive Transcranial Magnetic Stimulation in Depression: A Review of Recent Updates

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Transcranial magnetic stimulation (TMS) has been increasingly used in the treatment of various neuropsychiatric disorders including depression over the past two decades. The responses to treatment with TMS are variable as found in the recent studies. Evidences suggest that various factors influence the outcome of depression treated with TMS. Understanding the predictors of response to TMS treatment in depression will guide the clinician in appropriate selection of patients for TMS treatment as well as needful modification in the TMS technique and protocol to have a better clinical outcome. This article comprehensively reviews the factors that predict the outcome of TMS treatment in depression.

KEY WORDS: Transcranial magnetic stimulation; Depression; Response; Treatment outcome.

INTRODUCTION

Transcranial magnetic stimulation (TMS) is a newer brain stimulation technique, which has gained popularity in last three decades. TMS produces magnetic stimulus, which crosses the barrier of scalp, skull and meninges and gets converted to electrical stimulus on the brain surface and modulates the activity of cortical neurons. Repetitive TMS (rTMS) is used for therapeutic purpose in various neuropsychiatric conditions. The frequency of the magnetic stimulus delivered to brain determines, whether the underlying brain structures are stimulated or inhibited.^{1,2)} Low frequency rTMS (≤ 1 Hz) has inhibitory effect on the neurons, whereas high frequency rTMS (>1 Hz) produces neuronal excitability as well as long term potentiation of neurons.^{1,2)} The rTMS has been used in several clinical trials for management of psychiatric disorders like depression, schizophrenia, obsessive compulsive disorder, substance use disorders, autism spectrum dis-

orders, and eating disorders.^{1,3-10)}

Depression is a common neuropsychiatric disorder. Emerging evidences suggest the role of various neuro-modulation techniques including TMS in depression. Patients with depression, when treated with TMS, do not show a uniform pattern of response. Variations in the response pattern is attributed to several patient specific, illness specific as well as treatment modality specific factors. It is worthy understanding these factors, that predicts the outcome of depression treated with TMS.

A comprehensive review has been done by reviewing the existing literature on TMS in depression that describes about the predictors of response. Using the keywords "transcranial magnetic stimulation", "TMS", "Depression", "predictors of response" in popular search engines (PubMed and Google Scholar) literature were searched till the end of February 2018. All relevant articles (meta-analysis, systematic review, narrative review, original research articles, case reports/series) were evaluated in the review.

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TRANSCRANIAL MAGNETIC STIMULATION IN DEPRESSION

TMS has been approved by US Food and Drug Admin-

istration for use in cases of treatment resistant depression.⁸⁾ High frequency TMS to the left dorsolateral prefrontal cortex (DLPFC) is recommended for treatment in patients with depression.⁸⁾ The important neurobiologic structures involved in depression are predominantly left DLPFC, hippocampus, subgenual anterior cingulate cortex (ACC) and other limbic structures. Out of these brain structures, subgenual ACC is more specifically involved in depression; but it is deeply seated in the brain and could not be stimulated by TMS.⁸⁾ The subgenual ACC and DLPFC are having functional connectivity. DLPFC, being located on the cortical surface, is amenable to be modulated by TMS. Hence, left DLPFC is targeted by TMS in depression.

Though there seems to be an anticorrelation between the activity of DLPFC and subgenual ACC, functional neuroimaging studies also give some contradicting findings regarding the connectivity of left DLPFC and subgenual ACC; hence the exact neurobiologic mechanism attributing to antidepressant effect of rTMS over left DLPFC could not be ascertained.⁸⁾ Consistent evidences support the clinical relevance of two important neuronal circuits (the fronto-parietal central executive network and the medial prefrontal-medial parietal default mode network) in major depression.¹¹⁾ TMS aims these networks for bringing the therapeutic effect.

Most of the existing studies that emphasized on the efficacy of TMS in depression targeted a specific group of population. The populations studied were mostly adult population with treatment resistant depression receiving antidepressant therapy. The therapeutic effect of TMS in these patients might be augmenting effect on the ongoing antidepressants or may be the stand alone effect of TMS. It becomes challenging to predict the efficacy of TMS in depression in the general population by projecting the findings from the specific population studied. So, the findings summarized in this article need to be understood in the light of specific population studied in the individual research works.

rTMS: PREDICTORS OF TREATMENT RESPONSE IN DEPRESSION

Herrmann and Ebmeier,¹²⁾ in their review on “factors modifying efficacy of rTMS in depression” of 2006, had raised question regarding the clinical utility of TMS in de-

pression and mentioned that there is no specific predictor of TMS efficacy in depression; whatever therapeutic response observed in depression with rTMS is non-specific. However, Centre for Reviews and Dissemination had pointed out some major flaws in selection criteria, possible language bias, inadequacy of methodology and interpretation.¹²⁾ Various studies concluded about specific factors that can predict the response to TMS in depression. These factors can be broadly understood as patient related factors (e.g., age, gender), illness related factors (i.e., factors related to depression), and TMS procedure related factors (e.g., nature of protocol, site of stimulation).

Patient Related Factors

Age, gender as well as personality characteristics may have attribution to the therapeutic outcomes in depression treated with TMS. In their study of 2012, Pallanti *et al.*¹³⁾ found that rTMS was having age dependent antidepressant effect; as the age increases, the antidepressant efficacy decreases. There are many possible factors that may attribute to decreased antidepressant effect of rTMS in elderly population, which may be underlying medical condition of the elderly or related to intensity and number of pulses or due to underlying cortical atrophy.¹⁴⁾ A recent meta-analysis, which included 54 sham-controlled trials between 1997 and 2013, had revealed that gender might be a positive predictor of response as studies showing good antidepressant response to rTMS had mostly female patients.¹⁵⁾ Certain psychological characteristics also predict the response to treatment with rTMS in depression. Siddiqi *et al.* (2016)¹⁶⁾ had studied “temperament and character inventory” in patients (n=19) receiving rTMS treatment for depression to predict the response. In this study, it was found that high persistence score predicts the response to treatment with rTMS.

In their study of 2006, Fregni *et al.*¹⁷⁾ found that age and treatment refractoriness to be associated with poor antidepressant effect of rTMS and recommended rTMS for patients of younger age and less treatment resistance for a positive outcome. Aguirre *et al.* (2011)¹⁸⁾ found that the efficacy of low-frequency TMS in depression is inversely correlated with age, which emphasizes that younger individuals show better response to TMS. In this study, the patients were highly refractory to treatment, which limits its generalizability.

The activity of the brain before treatment with TMS may determine the therapeutic outcome. Activity of the brain can be measured through neurophysiological studies and functional neuroimaging. A recent study revealed that patients with better pre-TMS functional connectivity between left DLPFC and striatal connectivity respond better to TMS. Those with better above functional connectivity, show better reduction in depression severity.¹⁹⁾ Studies that evaluated the role of functional connections to cerebellum in relation to TMS treatment in depressive disorder, however the findings are not consistent.²⁰⁾ It is found that patients with major depressive disorder with low functional connectivity between cortico-striatal (dorsomedial prefrontal cortex and putamen), cortico-limbic and cortico-thalamic connectivity respond better to TMS.²⁰⁾ Philip *et al.*,²¹⁾ in their study of 2018, found that at the pretreatment level, a negative functional connectivity between subgenual ACC and default mode network as well as a positive functional connectivity of amygdala with ventromedial prefrontal cortex predicts the treatment response of comorbid depression and post-traumatic stress disorder. In another study,²²⁾ 24 patients with major depression were treated with high frequency (10 Hz) rTMS over left DLPFC for two weeks and it was found that having less treatment resistance and high pretreatment ACC volume is associated with better treatment outcome; hence can be considered as positive predictors of antidepressant response to rTMS.

Brain derived neurotrophic factor (BDNF) is a sensitive biological marker of therapeutic efficacy in electroconvulsive therapy; however, its level was found to be unchanged in patients receiving novel non-invasive brain stimulation therapies like rTMS or transcranial direct current stimulation (tDCS), as revealed in a recent systematic review and meta-analysis.²³⁾ All the patients (n=259) were having treatment resistant depression and were receiving stimulation over left DLPFC.²³⁾ Evidences are inconsistent in predicting the relevance of BDNF with response to TMS.²⁴⁾

Patients, who respond well to TMS, usually have a hyperactive hypothalamo-pituitary-adrenal axis, hence serum cortisol level may predict about the relapse of depressive episode in TMS responders.²⁴⁾ Similarly, the thyroid function test (free T3, free T4, and thyroid stimulating hormone [TSH]) was evaluated in patients with depression receiving TMS.^{24,25)} There was no difference in the pre to

post intervention free T3 and free T4 levels; however, the TSH level was found high in TMS responders.

Illness Related Factors

The illness (depression) characteristics may also predict response to treatment with TMS. Nature of depression, severity of the episode and the nature of symptoms may determine the response to TMS treatment. Brakemeier *et al.*,²⁶⁾ in their replication study of 2008 on 79 patients with major depression, evaluated the pattern of response to high frequency rTMS over left DLPFC and found the antidepressant response to be 34.2% patients only. They also found that patterns of clinical symptoms of depression may predict the rTMS related therapeutic response; depressed mood and guilt feelings being the negative predictors, whereas psychomotor retardation being the positive predictor of response. The cognitive and affective symptoms of depression significantly predict the response to rTMS treatment in comparison to the somatic symptoms.²⁷⁾ Brakemeier *et al.* (2007)²⁸⁾ concluded that sleep disturbance, low resistance and short episode duration to be the positive predictors of antidepressant effect of rTMS. A recent study²⁷⁾ revealed that there is no difference in the efficacy of rTMS in unipolar depression versus bipolar depression.

It has been also mentioned that patient of depression, who had shown poor response to electroconvulsive therapy, often poorly respond to TMS.²⁹⁾ In a more recent study, Grammer *et al.* (2015)³⁰⁾ had found that baseline severity of depressive symptoms as a predictor of response. Mild to moderate episodes of depression predict better treatment outcome; duration of treatment and number of TMS sessions carries little significance with regard to the response. Fitzgerald *et al.* (2016)³¹⁾ had done analysis of pooled data from 11 different trials of rTMS in depression and found that patients with less severe depressive episode have better response to rTMS. However, another recent naturalistic study revealed that patients with greater severity of depression at baseline respond better to TMS. In this study, the authors had used deep TMS, which has better penetrability than the conventional TMS procedures.³²⁾ The authors of this recent study considered that the patients with moderate to severe depression in naturalistic setting were less resistant to medications than the patients who received TMS for depression in other studies, which might be the reason for such

findings.³²⁾ Short duration of the depressive episode and recurrent depressive episodes are also predict a positive response to rTMS treatment.³¹⁾

Patients with depression, who had good response to TMS in their previous depressive episode, also respond to TMS in their subsequent depressive episode.³³⁾ Hence earlier good response to TMS can be considered a predictor of response to TMS in depression. TMS mediated stimulation of the left DLPFC result in release of dopamine in the striatum, which might be responsible for the therapeutic effect in depression.¹⁹⁾

TMS Procedure Related Factors

Location of DLPFC stimulation also affects the efficacy of rTMS. As per the standard technique, DLPFC is positioned 5 cm anterior to the motor cortex across the curvature of scalp.^{34,35)} However, due to anatomical variations in skull size and brain size, this measurement may not be accurate; on the other hand the activation of parts of DLPFC in major depression also varies across patients.⁸⁾ Inaccurate targeting of DLPFC is like to affect the clinical outcome. Functional neuroimaging or electroencephalography guided DLPFC may improve the clinical outcome.⁸⁾ Neuronavigation guided TMS is associated with higher amplitude and more stable motor evoked poten-

Table 1. Evidences from studies on repetitive transcranial magnetic stimulation (rTMS) in depression

| Study | Study sample | Intervention | Predictors of outcome |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Baeken <i>et al.</i> , 2009 ⁴⁵⁾ | Antidepressant free, treatment resistant depression (n=21) | High frequency rTMS over left DLPFC, 10 sessions | High baseline metabolic activities in DLPFC (left) and high anterior cingulate cortex volume associated with better outcome |
| Luborzewski <i>et al.</i> , 2007 ⁴⁶⁾ | Unipolar major depression (n=17) | High frequency (20 Hz) rTMS over left DLPFC, 10 sessions | Responders had lower baseline level (pre-treatment) of glutamate than non-responders |
| Narushima <i>et al.</i> , 2010 ⁴⁷⁾ | Patients of medication resistant vascular depression (n=65) | High frequency (10 Hz) rTMS over left DLPFC, 10 sessions | Increased low theta (4-5 Hz) activity at the subgenual anterior cingulate cortex is a good outcome predictor (to rTMS) |
| Langguth <i>et al.</i> , 2007 ²²⁾ | Patients of major depression with stable antidepressant treatment (n=24) | High frequency (10 Hz) rTMS over left DLPFC, 2 weeks | High pretreatment (rTMS) regional cerebral blood flow to anterior cingulate cortex is a good outcome predictor |
| Fitzgerald <i>et al.</i> , 2009 ³⁵⁾ | Patients with treatment resistant depression (n=51); standard 5 cm technique (n=27) and neuro-navigation technique (n=24) | High frequency (10 Hz) rTMS over left DLPFC at 100% resting motor threshold, 5 days a week for 3 weeks | At the end of 4 weeks, patients who received rTMS by neuro-navigation technique had significant reduction in depression score in comparison to those who received rTMS by standard 5 cm technique |
| Herbsman <i>et al.</i> , 2009 ³⁴⁾ | Patients with major depressive disorder (n=54) | High frequency (10 Hz) rTMS over left DLPFC with a total of 1,600 pulses/session, 15 sessions over 4 weeks | More lateral and anterior placement of TMS coil is associated with better treatment response |
| Kito <i>et al.</i> , 2008 ⁴⁸⁾ | Patients with treatment resistant depression (n=12) | High frequency (10 Hz) rTMS over left DLPFC with a total of 1,000 pulses/session at 100% resting motor threshold, 10 sessions | Increase in regional cerebral blood flow in left DLPFC, ventrolateral PFC, orbitofrontal cortex, ACC, left subgenual ACC, anterior insula, right corpus striatum is associated with antidepressant effect |
| Kito <i>et al.</i> , 2008 ⁴⁹⁾ | Patients with treatment resistant depression (n=14) | Low frequency (1 Hz) rTMS over right DLPFC with a total of 300 pulses/session, 12 sessions | Decrease in regional cerebral blood flow in limbic-paralimbic structures and increased baseline regional cerebral blood flow in left hemisphere |
| Kito <i>et al.</i> , 2011 ⁵⁰⁾ | Patients with treatment resistant depression (n=26) | Low frequency (1 Hz) rTMS over right DLPFC with a total of 300 pulses/session, 12 sessions | Decrease in regional cerebral blood flow in right PFC, bilateral orbitofrontal cortex, right subgenual ACC is associated with antidepressant effect of rTMS |
| Kito <i>et al.</i> , 2012 ⁵¹⁾ | Patients with depression (n=24) | High frequency rTMS over left DLPFC | Lower is the regional cerebral blood flow ratio between DLPFC and VMPFC, better is the response to treatment with high frequency rTMS |

PFC, prefrontal cortex; DLPFC, dorsolateral PFC; ACC, anterior cingulate cortex; VMPFC, ventromedial PFC.

tials than conventional non-navigated TMS; however, there is no difference in the motor threshold identified through these techniques.³⁶⁾ The accuracy of identifying the motor cortex with neuronavigation assisted TMS is very good.³⁷⁾

A study, used [(18)F]-fluorodeoxyglucose positron emission tomography (PET) and magnetic resonance imaging (MRI) for localizing the target zones on DLPFC for stimulation with rTMS.³⁸⁾ Patients with depression were recruited in three arms; PET-guided, standard and sham. PET-guided TMS is significantly different from sham TMS in terms of therapeutic efficacy; however, there is no significant difference between PET-guided and standard TMS.³⁸⁾

In a randomized, double blind, multicentric study on 301 medication-free patients (155 patients on active TMS group and 146 patients on sham TMS group) suffering from major depressive disorder, high frequency rTMS (10

Hz) at 120% of motor threshold, 3,000 pulses/session, five days a week for four to six weeks duration was given.³⁹⁾ The outcome in patients receiving active TMS was significantly better in comparison to the group receiving sham TMS. Gross *et al.*,⁴⁰⁾ in their meta-analysis of 2007, compared the older trials on rTMS with the recent ones and found that the effect size rTMS in depression to be higher in recent studies in comparison to the older ones. More number of rTMS sessions in therapy is associated with better clinical outcome, hence can be considered as a positive predictor of antidepressant response.⁴⁰⁾ However, it could not be replicated in the subsequent study by Brakemeier *et al.*²⁶⁾ in 2008, which found that the antidepressant effect of rTMS had significant association with treatment resistance. In a meta-analysis,¹⁵⁾ the authors concluded that lesser number of stimuli per session associated with significantly low depression scores and acute antidepressant effect; however, few other con-

Table 2. Predictors of response to rTMS in depression

| Predictor | Positive | Negative |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Neurobiologic | <ol style="list-style-type: none"> 1. 5-HT-1a gene polymorphism⁵²⁾ 2. LL genotype of the 5-HTTLPR gene polymorphism⁵²⁾ 3. Val/Val homozygotes of the BDNF gene⁵²⁾ 4. LH, FSH, progesterone, estradiol, TSH, BDNF²⁴⁾ | |
| Neuroimaging | <ol style="list-style-type: none"> 1. Decrease in task related activation of prefrontal cortex⁵³⁾ 2. Higher baseline metabolic activities of left DLPFC⁴⁵⁾ 3. High ACC volume⁴⁵⁾ 4. High baseline glucose metabolism at ACC⁴⁵⁾ 5. Lower baseline level (pre-treatment) of glutamate⁴⁶⁾ 6. Decreased metabolism at cerebellum, occipital lobe, anterior cingulate gyrus and temporal lobe⁴⁴⁾ for high frequency TMS at left DLPFC 7. Better pre-TMS functional connectivity between left DLPFC and striatum¹⁹⁾ | <ol style="list-style-type: none"> 1. Higher baseline level (pre-treatment) of glutamate⁴⁶⁾ |
| Electrophysiologic | <ol style="list-style-type: none"> 1. Increased low-theta (4-5 Hz) activity at subgenual ACC⁴⁷⁾ 2. High iAPF⁵⁴⁾ 3. Alpha power over parieto-temporal region before treatment⁵⁵⁾ | |
| TMS technique related | <ol style="list-style-type: none"> 1. TMS intensity more than 100% of motor threshold^{31,44)} 2. Number of sessions > 10⁴⁴⁾ 3. Number of pulses per session > 1,000⁴⁴⁾ | |
| Others | <ol style="list-style-type: none"> 1. Less severe episode of depression^{30,31)} 2. History of previous response to TMS⁴⁴⁾ 3. Concomitant antidepressant treatment⁴⁴⁾ 4. Short duration of depressive episode³¹⁾ 5. Recurrent depressive episode > single episode of depression³¹⁾ | <ol style="list-style-type: none"> 1. Short acute treatment (5-15 sessions)⁵⁶⁾ 2. Drug naive patients (without active maintenance treatment)⁵⁶⁾ 3. Long duration of the depressive episode⁴⁴⁾ 4. Psychotic depression⁴⁴⁾ 5. Elderly⁴⁴⁾ 6. High degree of treatment resistance^{44,57)} |

5-HT, 5-hydroxytryptamine; 5-HTTLPR, serotonin transporter linked polymorphic region; BDNF, brain derived neurotrophic factor; LH, luteinizing hormone; FSH, follicle stimulating hormone; TSH, thyroid stimulating hormone; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; TMS, transcranial magnetic stimulation; iAPF, individual alpha peak function.

temporary reviews and meta-analysis disagree with this fact.^{41,42)}

Modulation of the excitability of motor cortex prior to delivering high frequency (10 Hz) rTMS sessions over left DLPFC predicts antidepressant response.⁴³⁾ This study revealed that larger cortico-spinal excitability through motor cortex modulation is associated with better antidepressant effect.⁴³⁾ Choice of laterality (choosing right DLPFC or left DLPFC) for TMS stimulation or bilateral stimulation, does not predict the response in patients with major depressive disorder.⁴⁴⁾

Table 1^{22,34,35,45-51)} summarizes the major studies that predict the response to treatment with TMS in depression. Table 2^{19,24,30,31,44-47,52-57)} summarizes various positive and negative predictors of response to TMS treatment in depression.

IMPLICATIONS AND FUTURE DIRECTIONS

Understanding the predictors of response to TMS treatment in depression will guide the clinicians in appropriate selection of patients for treatment by TMS. It will also sensitize the clinicians to bring modifications in the TMS technique.

Recent evidences suggest that patients after receiving sessions of TMS, show increased level of neurotransmitter γ -aminobutyric acid (GABA) at the prefrontal cortex.⁵⁸⁾ Further research is needed to see, whether it can predict the response to TMS. D'Urso *et al.*,⁵⁹⁾ in their study of 2017 on patients with depression, found that individuals with prominent baseline cognitive disturbances and psychomotor retardation respond better to tDCS. Like tDCS study, these parameters can also be studied in TMS studies in patients with depression, to understand their relevance as predictors of response.

Combination of pharmacotherapy and psychotherapy is often considered as more efficacious than individual strategies alone. Combining TMS with psychotherapy is not thoroughly studied. A recent study reports that simultaneous use of rTMS and psychotherapy is associated high response (66%) and remission (56%) rate.⁶⁰⁾ The authors concluded that the baseline clinical variables did not predict the response to treatment, however early symptom improvement was highly predictive of response.

Most of the existing studies on rTMS treatment in de-

pression are limited by the small sample size.⁶¹⁾ Also there are major variations in sample selection, TMS techniques and protocols used as well as parameters of response measured. Overcoming these differences in future research may give better insight to understand the predictors of response.

LIMITATION OF THE CURRENT STUDIES

Majority of the studies on "rTMS in depression" had excluded psychotic depression, elderly and pediatric population as well as special population like pregnancy.²⁹⁾ Many studies also excluded medical co-morbidities. Though recently, it has been tried in extensively in various other clinical conditions and clinical populations, still the available evidences fall short to predict about the predictors of response to rTMS in depression. Similarly, the findings that predict therapeutic response with TMS in major depressive disorder are not consistent across various studies. The sample sizes of most of the studies that evaluated the predictors of response to TMS, were small and mostly treatment resistant. Hence, study on TMS in more number of patients and clinically diverse population may be more beneficial.

CONCLUSION

The response to TMS in depression can be predicted. Understanding the predictors of response to TMS treatment in depression will help the clinicians in appropriate selection of patients for TMS treatment and likely to improve to the treatment outcome.

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