

Cognitive-Affective Variability in TMS for Depression: Investigating Anxiety Exacerbation as a Treatment Outcome

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INTRODUCTION

- Repetitive Transcranial Magnetic Stimulation (rTMS) therapy is an effective treatment for patients with treatment-resistant MDD, with evidence suggesting it may also alleviate comorbid anxiety (O'Reardon, 2007), (George, 2007).
- Common side effects include headache, discomfort at the stimulation site, and lightheadedness (Mayo Clinic)
- Clinical experience indicates that different cognitive-affective profiles may show varied responses to TMS, sometimes requiring a change in protocol or medication.
- However, anxiety is not typically listed among the possible adverse effects of TMS, and the frequency of TMS-emergent anxiety has not been quantified.

METHODS

- A retrospective chart analysis was undertaken for patients who underwent rTMS treatment for MDD at the McLean TMS Clinic.
- Inclusion criteria:
 - >29 sessions
 - Primary diagnosis of MDD
 - Valid pre and post GAD-7, QIDS, and PHQ-9 scores
- PHQ-9, QIDS, GAD-7 scores were normalized across patients. Additionally, percent change in scores across treatment per patient was calculated.

RESULTS

| Title | Authors | Protocol & Population | Anxiety as an Adverse Event |
|---|----------------------------------|---|--|
| Low-Frequency Right Repetitive Transcranial Magnetic Stimulation for the Treatment of Depression After Traumatic Brain Injury: A Randomized Sham-Controlled Pilot Study | Rao V et al. 2019 | Protocol: Low Frequency Right Sided DLPFC Population: Adults with Depression after Traumatic Brain Injury | 1 patient in rTMS intervention group (N=13) and 1 patient in sham (N=17) in week 4 follow up. |
| Motor cortex repetitive transcranial magnetic stimulation in major depressive disorder - A preliminary randomized controlled clinical trial | Hu, Y.-T. et al. 2024 | Protocol: DLPFC or MC group, 10 Hz rTMS over five days. Population: Adults with MDD | Listed as an adverse effect experienced by some participants both active and sham, no mention as to frequency. |
| Treatment of Vascular Depression Using Repetitive Transcranial Magnetic Stimulation | Ricardo E. Jorge, MD et al. 2008 | Protocol: 10 Hz to L-DLPFC over 10 day period Population: Adults with Vascular Depression | 2 (13%) of participants in active condition |
| Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial | Blumberger, D.M. et al. 2018 | Protocol: 10 hz L-DLPFC vs Intermittent theta burst stimulation (iTBS) Population: Adults with TRD | 8 participants (4%) in rTMS group and 9 (4%) in iTBS group. |
| Clustered repetitive transcranial magnetic stimulation for the prevention of depressive relapse/recurrence: A randomized controlled trial | Wang, H.-N. et al. 2017 | Protocol: 10hz to DLPFC Population: Adults with MDD who had stable full or partial remission on a 6-month antidepressant (ADP) | 2 participants (2.4%) in rTMS+ADP (antidepressant) group. 7 (7.7%) in rTMS group |
| Efficacy and safety of deep transcranial magnetic stimulation for major depression: A prospective multicenter randomized controlled trial | Levkovitz, Y. et al. 2015 | Protocol: 18 Hz dTMS to PFC were applied during 4 weeks acutely, and then biweekly for 12 weeks Population: Adults with MDD | 2 participants (1.8%) in sham group None in active dTMS group |

Figure 1: Previous rTMS studies that focus on treating depression and contain anxiety as an adverse effect

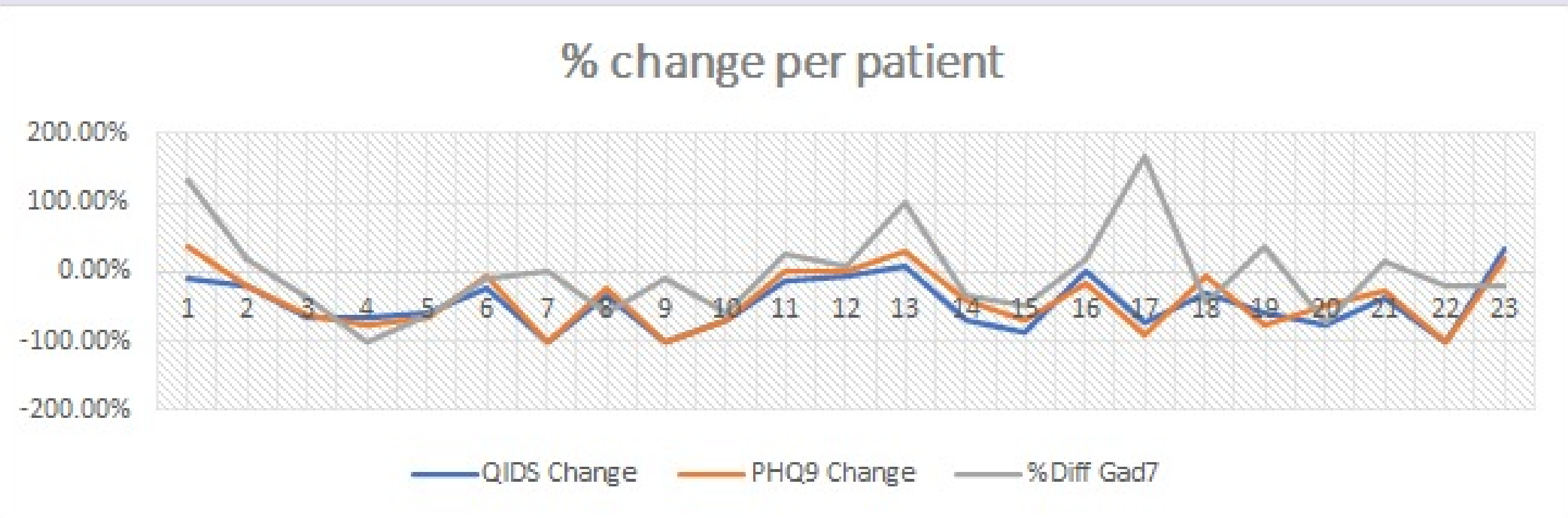


Figure 2: Comparison of QIDS, PHQ9, and GAD-7 score percent changes per patient (N=23) receiving rTMS treatment for depression.

RESULTS

- Nine of 23 patients (39%) had higher anxiety scores after treatment relative to their baseline.
- Four of these nine patients exhibited a greater than 30% worsening of their GAD-7 scores, with three of these patients exhibiting an increase of 100% or more.
- PHQ-9 and QIDS showed substantial and correlated improvement. GAD-7 responses varied and did not closely track with depression improvements.
- Switching from left to right stimulation or between deep and focal coils did not clearly mitigate this effect.

CONCLUSION

- Consistent with prior literature, anxiety improved on average.
- Nevertheless, a sizable minority of patients experienced worsening anxiety, suggesting the need to counsel patients about this adverse effect.
- Further work is needed to test this among larger patient samples and to quantify the anxiolytic effect of changing protocols, such as right low-frequency.
- Identifying cognitive-affective and neurobiological markers of anxiety exacerbation may enable more targeted, personalized brain-based interventions.

CITATIONS

O'Reardon JP, Solvason HB, Janicak PG, et al. "Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial." *Biological Psychiatry*, 2007;62(11):1208–1216.

George, M. S., Taylor, J. J., & Short, E. B. (2013). The expanding evidence base for rTMS treatment of depression. *Current opinion in psychiatry*, 26(1), 13–18.