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# Age as a determinant of transcranial magnetic stimulation efficacy for major depressive disorder in a naturalistic clinic setting

## 1. Introduction

Major depressive disorder (MDD) is a highly prevalent, debilitating public health issue that is a leading cause of disease burden throughout the world [1]. Pharmacotherapy is typically used as a first line treatment for MDD [2]. Treatment resistant depression (TRD) is commonly defined as failure to respond or achieve remission after two or more trials of antidepressant medication of adequate dose and duration. Each year, 30.9% of adults develop TRD [3] (see ).

One non-medication treatment alternative for TRD is repetitive transcranial magnetic stimulation (rTMS). Approved by the Food and Drug Administration in 2008 [4], rTMS is a noninvasive neurostimulation therapy that uses focally targeted magnetic pulses to modulate neuronal activity in cortical brain regions associated with mood regulation [5]. rTMS is well-established as a safe and efficacious treatment for patients with TRD. There are, however, mixed research findings regarding whether advanced age is a poor prognostic indicator for rTMS efficacy [6–9]. The present study evaluated the efficacy of rTMS for MDD in a naturalistic setting for individuals aged 15 to 78 with MDD.

## 2. Methods

This study is a retrospective chart review of 495 patients aged 15–78 with moderate or greater severity MDD (based on DSM-V diagnostic criteria and a 9-item Patient Health Questionnaire [PHQ-9] score $\geq$10) who underwent acute, bilateral rTMS therapy at one of four Neuro Wellness Spa clinical sites between 2017 and 2020 (Table 1).

rTMS was delivered using the MagPro R30 equipped with a figure-of-eight coil (C-B60). The rTMS protocol consisted of five sessions per week for a total of 30 acute sessions, followed by 6–8 taper sessions. The MT location and value were determined by visual observation of finger movement. Stimulation site was 5.5 cm forward from the MT location. Based on co-morbid anxiety symptom severity, patients were prescribed either a depression or an anxiety protocol. All patients received both theta burst (TBS) and single pulse (SP) stimulation at each session. Most patients received 50Hz intermittent TBS to the left dorsolateral prefrontal cortex (DPFC) at 80% motor threshold (MT) for 200 pulses followed sequentially by 10Hz intermittent SP stimulation to the left DPFC at 120%MT for 3000 pulses and 50Hz continuous TBS to the right DPFC at 80%MT for 1200 pulses. Some patients with significant co-morbid anxiety received 50Hz intermittent TBS to the left dorsolateral prefrontal cortex (DPFC) at 80% motor threshold (MT) for 200 pulses followed sequentially by 1Hz intermittent single pulse stimulation to the right DPFC at 120%MT for 1500 pulses. These are atypical rTMS protocols utilized by this treatment site. Medication changes were discouraged during rTMS treatment. Ongoing psychotherapy was supported.

Patients were categorized by age: 15–24, 25–34, 35–44, 45–54 and 55–78. PHQ-9 and GAD-7 (a 7-item Generalized Anxiety Disorder assessment) were assessed at baseline and at end of acute treatment. A response to rTMS treatment was defined as $\geq$ 50% decrease in PHQ-9 score from baseline to end of acute treatment, and remission was defined as a PHQ-9 score $\leq$5 at end of acute treatment. Sex, baseline anxiety and baseline depression severity were analyzed to eliminate confounding variables.

A paired sample *t*-test was used to determine differences in PHQ-9 scores between the two timepoints. Significance values for the paired *t*-test were adjusted using a Bonferroni adjustment test (BF). A change variable was created to represent change in PHQ-9 score over the observation period. To determine if this change score was significantly different between different age categories, a one-way ANOVA test was conducted. To model the association between age in years and this change score while controlling for other important covariates (e.g., sex and baseline anxiety), a multiple linear regression was conducted. To determine if the frequency distribution of achieving no response, response, or remission following rTMS treatment varied based on age category a chi-squared test. All statistical analyses were checked against the assumptions of each test (e.g. homogeneity of variance).

## 3. Results

We examined the difference in PHQ-9 score pre- and post-treatment. All age categories showed a significant reduction in PHQ-9 (mean PHQ-9 score change = −11.45, p = 4.4e-16). Response and remission rates did not significantly differ between age groups ($x^2 = 4.92$, p = 0.766) or sex ($x^2 = 3.33$, p = 0.189). There were no statistically significant differences in baseline PHQ-9 scores or sex between age cohorts.

## 4. Discussion

This study suggests that, for these patients aged 15–78 with MDD, rTMS was equally effective for all age cohorts and offers support for the use of rTMS for the treatment of MDD across the lifespan.

By 2030, adults aged 65 and over will make up more than 20% of U.S. residents [10]. The growing elderly population, prevalence of

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**Table 1**
Displays age categories, number of patients per category, sex distributions, mean baseline PHQ-9 and GAD-7, mean final PHQ-9, number and percent of patients who achieved response, and number and percent of patients who achieved remission.

| Age Category | 15–24 | 25–34 | 35–44 | 45–54 | 55–78 |
|---|---|---|---|---|---|
| Number of Patients (n) | 120 | 126 | 87 | 94 | 68 |
| % Female | 42 | 54 | 68 | 67 | 63 |
| Mean Baseline PHQ-9 | 17.78 | 17.99 | 18.83 | 18.64 | 18.88 |
| Mean Baseline GAD-7 | 14.74 | 14.73 | 14.84 | 13.94 | 13.96 |
| Mean Final PHQ-9 | 7.21 | 6.98 | 6.85 | 6.27 | 6.98 |
| Percent Response (n) | 72.5 (87) | 73.01 (92) | 79.3 (69) | 78.71 (74) | 70.58 (48) |
| Percent Remission (n) | 45 (54) | 50 (63) | 56.32 (49) | 55.31 (52) | 50 (34) |

geriatric depression, and high incidence of adverse reactions to pharmacotherapy in the elderly substantiate the need for non-medication, treatment alternatives for geriatric MDD.

A unique, valuable feature of the present study is that age was analyzed over a continuum of five cohorts. To our knowledge, all recent literature examining rTMS outcomes by age used only two cohorts ($\geq$60/65 or $<$ 60/65). Other beneficial characteristics of this study include the large sample size and the use of objective, validated rating scales.

Limitations of this study are intrinsic to those of retrospective research conducted in a naturalistic setting. A sham rTMS group was not used to control for placebo effects. Additionally, the present study used an atypical rTMS treatment protocol and did not control for concurrent medications or psychotherapy.

Continued research in the form of double blind, randomized control trials that examine rTMS depression outcomes over an age continuum should be conducted to further assesses the effect of age on rTMS efficacy for MDD.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

[1] Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Vos T. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 2013;382(9904):1575–86.
[2] Gautam S, Jain A, Gautam M, Vahia VN, Grover S. Clinical practice guidelines for the management of depression. Indian J Psychiatr 2017;59(Suppl 1). S34.
[3] Zhdanava M, Pilon D, Ghelerter I, Chow W, Joshi K, Lefebvre P, Sheehan JJ. The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. J Clin Psychiatr 2021;82(2):29169.
[4] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120(12):2008–39.
[5] Ontario Health Quality. Repetitive transcranial magnetic stimulation for people with treatment-resistant depression: a health technology assessment. Ont Health Technol Assess Ser 2021 May 6;21(4):1–232. PMID: 34055112; PMCID: PMC8129638.
[6] Pallanti Stefano, et al. rTMS age-dependent response in treatment-resistant depressed subjects: a mini-review. CNS Spectr 2012;17(1):24–30.
[7] Sackeim HA, Aaronson ST, Carpenter LL, Hutton TM, Mina M, Pages K, et al. Clinical outcomes in a large registry of patients with major depressive disorder treated with transcranial magnetic stimulation. J Affect Disord 2020;277:65–74.
[8] Licht-Strunk E, van der Windt DA, Van Marwijk HW, de Haan M, Beekman AT. The prognosis of depression in older patients in general practice and the community. A systematic review. Fam Pract 2007;24(2):168–80.
[9] Fitzgerald PB, Hoy KE, Anderson RJ, Daskalakis ZJ. A study of the pattern of response to rTMS treatment in depression. Depress Anxiety 2016;33(8):746–53.
[10] Cheruvu Vinay K, Chiyaka Edward T. Prevalence of depressive symptoms among older adults who reported medical cost as a barrier to seeking health care: findings from a nationally representative sample. BMC Geriatr 2019;19(1):1–10.

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