HHS Public Access

Author manuscript

*Int J Geriatr Psychiatry*. Author manuscript; available in PMC 2020 June 01.

Published in final edited form as:

*Int J Geriatr Psychiatry*. 2019 June ; 34(6): 822–827. doi:10.1002/gps.5091.

# Unilateral and Bilateral Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Late-Life Depression

**Alisson Paulino Trevizol, MD, PhD**[1,2], **Kyle W. Goldberger, MD**[3], **Benoit H. Mulsant, MD, MS, FRCPC**[1], **Tarek K. Rajji, MD, FRCPC**[1,2], **Jonathan Downar, MD, PhD, FRCPC**[1,4], **Zafiris J. Daskalakis, MD, PhD, FRCPC**[1,2], and **Daniel M. Blumberger, MD, MSc, FRCPC**[1,2]

[1]Department of Psychiatry, University of Toronto

[2]Temerty Centre for Therapeutic Brain Intervention and Campbell Family Research Institute, Centre for Addiction and Mental Health

[3]Michael G. DeGroote School of Medicine, McMaster University

[4]MRI Guided rTMS Clinic, Toronto Western Hospital, University Health Network

## Abstract

**Background:** The management of late-life depression is challenged by high rates of treatment-resistance and adverse effects, along with medical comorbidities and polypharmacy. Together with the limited data on managing treatment-resistant depression in older adults, there is a need for investigating the efficacy of non-pharmacological treatment strategies. Repetitive transcranial magnetic stimulation (rTMS) is one modality that may better serve this patient population.

**Methods:** The present study examines data from two previous clinical trials (NCT00305045 and NCT01515215) to explore the efficacy of bilateral and unilateral high-frequency left-sided (HFL) rTMS in older adults suffering from treatment-resistant depression. A total of 43 adults aged 60 or older, with a current major depressive episode, were randomized to bilateral sequential, unilateral HFL, or sham. Bilateral sequential stimulation involved low frequency (1Hz) right dorsolateral prefrontal cortex (DLPFC) stimulation followed immediately by high frequency (10Hz) left DLPFC. The unilateral condition was HFL stimulation alone and the placebo condition was either HFL or sequential bilateral form of sham. The primary outcome was remission of depression.

**Results:** Participants receiving bilateral rTMS experienced greater remission rates (40%) compared to unilateral (0%) or sham (0%) groups. Response to rTMS in the Hamilton Depression Rating Scale scores similarly favored the efficacy of bilateral rTMS.

Corresponding Author: Daniel M. Blumberger, MD, MSc, FRCPC, Medical Head and Co-Director, Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, Associate Professor, Department of Psychiatry, University of Toronto, Mailing: 1001 Queen St. W. Unit 4, Room 115, Toronto, ON M6J 1H4, Tel: 416-535-8501, Fax: 416-583-4613, daniel.blumberger@camh.ca.

DISCLOSURES

Conflicts of Interest:

APT reports no biomedical interests or conflicts.

KWG reports no biomedical interests or conflicts.

**Conclusion:** This study suggests that sequential bilateral treatment may be an optimal form of rTMS when used for treatment-resistant depression in older adults. Further large-scale comparative effectiveness trials of bilateral rTMS in this population are warranted.

### Keywords

late-life depression; transcranial magnetic stimulation; geriatrics; treatment-resistance; clinical trial

## INTRODUCTION

Clinically, late-life depression (LLD) complicates medical comorbidities and patient wellbeing with increased functional impairment and mortality[1–4]. The management of depression in older adults presents further challenges as patients often present with complicated medical histories, frailty, polypharmacy, and pharmacologic adverse events, the latter of which may be more frequent and more serious than in their younger counterparts[5,6].

The burden of depression can be further compounded by the failure of first-line therapies, as treatment-resistant depression (TRD) is associated with longer illness duration and higher medication doses[7]. Accordingly, the impact of TRD is more pronounced in older adults[8–11]. In this context, more effective interventions for the management of treatment-resistant LLD, especially through novel non-pharmacologic approaches, are urgently needed.

One emerging non-pharmacological intervention for TRD is repetitive transcranial magnetic stimulation (rTMS). To date, the most common rTMS target in TRD has been the dorsolateral prefrontal cortex (DLPFC). The DLPFC is known to subserve the cognitive regulation of emotions and its dysfunction has been implicated in the neurobiology of depression[12]. The most thoroughly explored types of rTMS include: unilateral high-frequency left-sided (HFL), unilateral low-frequency right-sided (LFR), and a sequential bilateral combination of LFR promptly followed by HFL.

All three of these types of DLPFC-rTMS have demonstrated efficacy when compared to sham stimulation for TRD. According to a recent meta-analysis, almost 30% of patients responded to HFL compared to only 10% of those undergoing sham treatment[13]. LFR designs have also demonstrated greater efficacy relative to sham stimulation, with one meta-analysis identifying response rates of 38% and 15% to LFR and sham rTMS, respectively[14]. The superiority of bilateral rTMS to sham has also been demonstrated in a separate meta-analysis, with 25% of patients considered responders to treatment, compared to 7% among controls[15]. Finally, in a recent network meta-analysis evaluating the effect of multiple brain stimulation techniques for MDD, Brunoni et al. (2017) reported that bilateral rTMS was significantly more effective than sham for response and remission, with an OR of 3.39 (95% CI, 1.91 – 6.02) and 5.75 (95 % CI, 1.93 – 17.24), being ranked in the first two positions for response[16]. In addition, bilateral rTMS was more effective than HFL and LFR, with direct evidence showing the superiority of bilateral rTMS to HFL for remission, with an OR of 4.02 (95% CI, 1.3 – 12.35)[16]. It is less clear whether bilateral rTMS is consistently superior to HFL or LFR rTMS, with some studies supportive[14,16] and others showing no advantage[15] However, a recent randomized, double-blind, sham-controlled clinical trial conducted by

Kaster et al. (2018) demonstrated the superiority of bilateral deep TMS over sham using the H1 coil for the treatment of MDD in 55 subjects from 60 to 85 years old (6012 pulses, 18 Hz, 120% of resting motor threshold, delivered over the dorsolateral and ventrolateral prefrontal cortex 5 days per week over 4 weeks)[17]. Authors reported a significantly higher remission rate in the active group (40% vs. 14.8%), with a number needed to treat of 4 (95% CI: 2.1 – 56.5). No changes on any executive function were reported, as well as no severe adverse effect, contributing to the hypothesis that bilateral rTMS is superior to sham, safe, and well tolerated in the treatment of LLD[17].

While support for rTMS in TRD accumulates, there remains limited evidence regarding its efficacy in older adults. Earlier studies suggest that advanced age predicts a poorer response to rTMS, possibly due to prefrontal atrophy and a greater coil-to-cortex distance[18–21]. Thus, we undertook a sub-analysis from two randomized controlled trials (RCTs) with adults over the age of 60 with treatment-resistant LLD who were submitted to bilateral, unilateral HFL, or sham rTMS. We hypothesize that bilateral rTMS achieves higher response and remission rates, in comparison to HFL and sham stimulation.

## MATERIALS AND METHODS

### Participants

Participants were recruited at an urban tertiary mental health centre (Centre for Addiction and Mental Health, Toronto, ON, Canada). The complete details of the inclusion criteria are available in the original published studies, ClinicalTrials.gov IDs NCT00305045 [22] and NCT01515215 [23]. The present study included data obtained from participants who were between the ages of 60–85, meeting criteria for a major depressive episode without psychotic features (as diagnosed by SCID-IV-TR), a score above 19 on the 17-item Hamilton-Depression Rating Scale (HDRS), non-response or intolerability of two antidepressant trials (across separate classes and at adequate doses), and were on four or more weeks of a stable dose of all psychotropic medication preceding randomization. Individuals meeting DSM-IV criteria for non-nicotine substance dependence (within the preceding six months) or substance abuse (within the preceding month), borderline personality disorder, or antisocial personality disorder were excluded from participation. Other exclusion criteria were: active suicidality, metal implants in the cranium, an unstable medical or neurologic illness, previous seizures, a diagnosis of dementia, or a Mini-Mental Status Exam (MMSE) score less than 24. Participants provided written informed consent, with study approval via the research ethics board of the Centre for Addiction and Mental Health.

### Treatment Protocol

Participants were randomized to bilateral, HFL, or sham rTMS. Clinical operators were aware of the treatment condition as they applied the rTMS, but participants and evaluators were blinded.

Both studies followed similar treatment protocols comprising two phases. First, a total of 15 treatment sessions were administered at five sessions/week over three weeks. At the

conclusion of the first phase, a blinded evaluator would determine whether the participants had achieved remission, defined as a 17-item HDRS ≤ 10. Remitters terminated treatment, while non-remitters continued treatment for an additional 15 sessions.

If a participant failed to attend greater than two consecutive sessions, he/she was withdrawn from the trial. Missed sessions were added to the end of each treatment course.

The rTMS used was the Magventure RX-100 Repetitive Magnetic Stimulation (Tonika/Magventure, Denmark) with a cool B-65 figure-of-8 coil. Stimulation was applied at intensities drawn from previously published protocols[24,25]. In one of the contributing clinical trials, stimulation intensity was adjusted for coil-to-cortex distance, specifically at 120% of the distance-adjusted resting motor threshold[23]. Participants in the other trial received stimulation at 120% of the RMT unadjusted for coil-to-cortex distance[22]. Localizing the DLPFC was determined either as 5cm anterior to the site of maximal stimulation of the abductor *pollicis brevis*[22] (study 1) or through MRI (magnetic resonance imaging) neuronavigation[23] (study 2). Treatment parameters, outlined in Table 1, were in accordance with safety guidelines. The bilateral stimulation was performed starting with the LFR stimulation, followed by the HFL stimulation, with no interval between each side, except for the time of repositioning the coil. The sham procedure included placing the coil at 90˚ off the scalp in a single-wing tilt position, out of the view of participants, creating an experience comparable to active rTMS[26]. Participants were asked after the treatment phase whether their assignment was to the active or sham group.

## Assessments

The Structured Clinical Interview for the DSM-IV (SCID) and the 17-item HDRS were used to evaluate diagnosis and depression severity at baseline, respectively. The SCID-II was used to assess for antisocial and borderline personality disorders, while the MMSE was used to identify participants with dementia.

The end-time point for outcome comparisons was defined as the final week of treatment for each participant (i.e., week 3 or week 6). The rates of remission (a score ≤ 10 on the 17-item HDRS) were compared between groups as the primary outcome. Response rates (> 50% reduction in HDRS scores) were also assessed. Adverse events and tolerability data were recorded in a separate log.

## Statistical Analysis

Data analysis was performed using SPSS statistical software (SPSS for Windows 22.0; SPSS Inc. Chicago, Ill.) with an intention-to-treat design using the *last observation carried over* approach. Categorical variables were assessed with $\chi^2$ or 2-tailed Fisher's exact tests. Fisher's exact tests were used for two-way pairwise comparisons between groups. Demographic and clinical variables at baseline were analyzed between groups. Analyses were two-tailed, with a significance level of alpha = 0.05.

## RESULTS

A total of 43 participants were included in the intention-to-treat analysis. Subjects were allocated to: (1) sham (n=12; three in study 1); (2) HFL (n=11; 4 in study 1); (3) bilateral rTMS (n=20; 12 in study 1). We observed no differences in the proportion of subjects who were treated using the MRI neuronavigation system and the 5-cm rule in each arm (Fisher's exact p = .146). Demographic and baseline clinical variables are outlined in Table 2. By six weeks, 39 participants (90.7%) had completed treatment. There was no significant difference between participants who did not follow-up and those who completed treatment with reference to any demographic or baseline clinical variables. Of 41 participants where data was available, 25 (58.1%) accurately guessed their placement to active or sham, although there were no significant group differences, $\chi^2(2) = 0.83$, p = .662.

Remission rates differed significantly between treatment conditions: bilateral (8 of 20, 40%), unilateral HFL (0 of 11, 0%), and sham (0 of 12, 0%), Fisher's exact = .004. In the intention-to-treat analysis, remission for bilateral rTMS was significantly greater compared to unilateral (Fisher's exact p = .028) and sham (Fisher's exact p = .014); with no difference between the unilateral and sham (Fisher's exact p = 1).

The proportion of participants responding to treatment significantly differed between conditions: bilateral (9 of 20, 45%), unilateral HFL (0 of 11, 0%), and sham (2 of 12, 16.7%), (Fisher's exact p = .016). Response to bilateral rTMS was greater compared to unilateral (Fisher's exact p = .012), but not sham (Fisher's exact p = .139); with no difference between unilateral and sham (Fisher's exact p = .478).

A total of four patients (9.3%) dropped out of the study. Three dropped out due to lack of response; one subject could not tolerate the treatment. Only two patients reported moderate to severe adverse effects that were thought to be associated with treatment, both in the HFL group, with no significant difference between groups (Fisher's exact p = .140). One patient reported moderate-to-severe insomnia, and another patient reported moderate-to-severe headaches. No moderate to severe adverse events were reported in the sham or the bilateral groups. The proportion of participants who dropped out did not differ significantly across groups: bilateral (1 of 20, 5%), unilateral (2 of 11, 18.2%), and sham (1 of 12, 8.3%) Fisher's exact p= 0.798.

## DISCUSSION

The present study compared the efficacy of bilateral, unilateral HFL, and sham rTMS for treatment-resistant depression in older adults. It was hypothesized that bilateral rTMS would demonstrate superior efficacy compared to the other treatment groups. Consistent with this prediction, remission rates for the bilateral group were significantly greater than for the unilateral and sham groups. Response rates and changes in HDRS scores were also significantly different across treatment conditions, with bilateral rTMS achieving a significantly greater response rate compared to unilateral or sham rTMS. These findings are supported by a recent network meta-analysis that suggests the superior efficacy of bilateral rTMS compared to other rTMS designs, including unilateral and sham[16].

One possible explanation for the comparative success of bilateral over unilateral stimulation follows the presence of dysfunction in both right and left DLPFC in patients with LLD. For instance, Chang et al. (2011) used structural MRI to identify reduced cortical volume in both the right and left DLPFC among older adults with depression[27]. Functional studies associated with executive-control tasks identified attenuated activity in the left DLPFC, and reduced functional connectivity within the right DLPFC-DACC (dorsal anterior cingulate cortex) cognitive circuit[28]. Bilateral stimulation may thus target the neural substrates of MDD more broadly than unilateral stimulation.

From a mechanistic perspective, it has been proposed that depression may ensue from functional insufficiency of both left and right prefrontal regions, each responsible for different symptom clusters[29]. In a more detailed recent model, it has been proposed that depression may involve dysfunction in two goal-pursuit systems: a left DLPFC 'promotion system' related to goal-directed activity, and a right DLPFC 'prevention system' related to anxiety and avoidance [30]. In support of this proposal, Rossini et al. (2010) reported HFL stimulation to achieve less improvement in patients with high psychic anxiety symptoms, and LFR stimulation to achieve less improvement in patients with high levels of psychomotor retardation/impaired work and activities [31]. Targeting both hemispheres could therefore potentially achieve greater efficacy by addressing a wider spectrum of pathology and thus a larger proportion of LLD patients, compared to unilateral stimulation. Future work in a larger sample may help to clarify whether HFL and LFR stimulation address different aspects of MDD pathology.

Limitations of the present study include the small sample and the unbalanced number of participants across the three groups, with smaller sample sizes in the unilateral and sham groups compared to the bilateral group. The smaller sample sizes may not have provided sufficient power to assess for clinically significant differences between the unilateral and sham groups. The small sample size of the HFL group may have contributed to the lack of remitters in this group.

Another limitation arises from the different DLPFC localizing methods employed in the two studies. One of the contributing clinical trials[22] localized the DLPFC using the original 5cm method. This method has been shown to miss the DLPFC in up to 1/3 of patients[32] and has been associated with an inferior treatment response when compared to neuronavigation capable of incorporating anatomical variability across patients[33,34]. In addition, the two studies employed a passive form of sham stimulation which has been criticized as an inferior form of sham stimulation. However, we did not see a differential correct guess rate in the three groups. Further limitations include the lack of a formal method of assessment of anxiety symptoms and the use of different psychotropic medications, including benzodiazepines and augmentation with atypical antipsychotics (Table 2). Nevertheless, given the potential for benzodiazepines to interfere with the efficacy of the rTMS, we limited the doses of benzodiazepines to a maximum of 2mg equivalents of lorazepam per day.

Despite these limitations, the present analysis provides further evidence for the potential value of rTMS in LLD, specifically when bilateral stimulation is employed. This finding contrasts with previous work suggesting that advanced age portends a weaker response to

rTMS[18–21]. Previous reports suggest that prefrontal atrophy, manifesting as an increased distance from the rTMS coil to the DLPFC, may contribute to the attenuated response to rTMS among older adults[19,20]. Indeed, one protocol that adjusted for the greater coil-to-cortex distance, by increasing stimulation intensity, ultimately generated modest rates of remission [35]. Of note, the aforementioned studies profiling the weaker response to rTMS among older adults only examined unilateral HFL stimulation[18–21]. This may further explain the absence of remission or response to unilateral rTMS in the present study. The marked contrast between the remission rates of 0% among participants following unilateral stimulation compared to the 40% remission rates following bilateral stimulation may suggest that the challenges associated with treating older adults may be overcome with bilateral stimulation.

Alternatively, bilateral stimulation may achieve greater efficacy in LLD by addressing both left- and right-hemisphere components of the broader pattern of network dysfunction reported in imaging studies of MDD[27,28]. The stronger remission rates and treatment response observed in the present analysis may thus reflect a combination of the adjusted stimulation intensity employed in each trial, in addition to the broader-spectrum effects of bilateral stimulation in addressing more cortical regions that are potentially involved in depression.

Taken together, these secondary analyses support the efficacy of bilateral rTMS in older adults with treatment-resistant depression. Although exploratory, the remission rate of 40% among older adults, who have failed more than two adequate medication trials, is clinically meaningful and may compare favourably to the outcomes for additional trials of medication (35). In fact, our findings are in line with the recent meta-analysis that suggests a possible superiority of bilateral rTMS over sham[17] and over HFL[16]. Overall the procedures were well-tolerated, with few participants dropping out. These preliminary findings call for future confirmatory research exploring the utility of bilateral rTMS in treatment-resistant late-life depression.

## ACKNOWLEDGEMENTS

This work was funded in part by a Canadian Institutes of Health Research Post-Doctoral Fellowship and an operating grant from the Ontario Mental Health Foundation.

Source of Funding:

BHM receives research support from the Canadian Institutes of Health Research (CIHR), National Institute of Health (NIH), Brain Canada, and the CAMH Foundation. He has received medications and matched placebo tablets for NIH-funded clinical trials from Bristol-Myers Squibb, Eli-Lilly, and Pfizer.

T.K.R. receives research support from Brain Canada, Brain and Behavior Research Foundation, Canada Foundation for Innovation, the CIHR, Ontario Ministry of Health and Long–Term Care, Ontario Ministry of Research and Innovation, the US National Institute of Health (NIH), and the W. Garfield Weston Foundation.

JD has received research support from CIHR, Brain Canada, the Canadian Biomarker Integration Network in Depression, the Ontario Brain Institute, the Klarman Family Foundation, the Edgstone Foundation, a travel stipend from Lundbeck and from ANT Neuro, and in-kind equipment support for an investigator-initiated trial from MagVenture.

ZJD has received within the last 3 years both research and equipment in-kind support for an investigator-initiated study through Brainsway Inc. and Magventure Inc. ZJD has also received monies for participation on an advisory board from Sunovion Inc. Finally, ZJD owns>$10,000 (CAD) in stock of Biogen Inc.

DMB has received research support from the CIHR, NIH, Brain Canada and the Temerty Family through the CAMH Foundation and the Campbell Research Institute. He received research support and in-kind equipment support for an investigator-initiated study from Brainsway Ltd. and he is the site principal investigator for three sponsor-initiated studies for Brainsway Ltd. He received in-kind equipment support from Magventure for an investigator-initiated study. He received medication supplies for an investigator-initiated trial from Indivior.

## REFERENCES


1. Schulz R, Drayer RA, Rollman BL. Depression as a risk factor for non-suicide mortality in the elderly. Biol Psychiatry. 2002;52(3):205–225. [PubMed: 12182927]
2. Rovner BW, German PS, Brant LJ, Clark R, Burton L, Folstein MF. Depression and mortality in nursing homes. JAMA. 1991;265(8):993–996. [PubMed: 1992213]
3. Lenze EJ, Rogers JC, Martire LM, et al. The association of late-life depression and anxiety with physical disability: a review of the literature and prospectus for future research. Am J Geriatr Psychiatry. 2001;9(2):113–135. [PubMed: 11316616]
4. Blazer DG. Depression in late life: review and commentary. J Gerontol A Biol Sci Med Sci. 2003;58(3):249–265. [PubMed: 12634292]
5. Reynolds CF 3rd, Dew MA, Pollock BG, et al. Maintenance treatment of major depression in old age. N Engl J Med. 2006;354(11):1130–1138. doi:10.1056/NEJMoa052619 [PubMed: 16540613]
6. Mark TL, Joish VN, Hay JW, Sheehan D V, Johnston SS, Cao Z. Antidepressant use in geriatric populations: the burden of side effects and interactions and their impact on adherence and costs. Am J Geriatr Psychiatry. 2011;19(3):211–221. [PubMed: 21425504]
7. Rizvi SJ, Grima E, Tan M, et al. Treatment-resistant depression in primary care across Canada. Can J Psychiatry. 2014;59(7):349–357. doi:10.1177/070674371405900702 [PubMed: 25007419]
8. Schatzberg A, Roose S. A double-blind, placebo-controlled study of venlafaxine and fluoxetine in geriatric outpatients with major depression. Am J Geriatr Psychiatry. 2006;14(4):361–370. doi: 10.1097/01.JGP.0000194645.70869.3b [PubMed: 16582045]
9. Raskin J, Wiltse CG, Siegal A, et al. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. Am J Psychiatry. 2007;164(6):900–909. doi:10.1176/ajp.2007.164.6.900 [PubMed: 17541049]
10. Kok RM, Nolen WA, Heeren TJ. Venlafaxine versus nortriptyline in the treatment of elderly depressed inpatients: a randomised, double-blind, controlled trial. Int J Geriatr Psychiatry. 2007;22(12):1247–1254. doi:10.1002/gps.1823 [PubMed: 17562523]
11. Allard P, Gram L, Timdahl K, Behnke K, Hanson M, Sogaard J. Efficacy and tolerability of venlafaxine in geriatric outpatients with major depression: a double-blind, randomised 6-month comparative trial with citalopram. Int J Geriatr Psychiatry. 2004;19(12):1123–1130. doi:10.1002/gps.1190 [PubMed: 15526307]
12. Naismith SL, Norrie LM, Mowszowski L, Hickie IB. The neurobiology of depression in later-life: clinical, neuropsychological, neuroimaging and pathophysiological features. Prog Neurobiol. 2012;98(1):99–143. doi:10.1016/j.pneurobio.2012.05.009 [PubMed: 22609700]
13. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med. 2014;44(2):225–239. doi:10.1017/s0033291713000512 [PubMed: 23507264]
14. Berlim MT, Van den Eynde F, Jeff Daskalakis Z. Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: a meta-analysis of randomized, double-blind and sham-controlled trials. Neuropsychopharmacology. 2013;38(4):543–551. doi:10.1038/npp.2012.237 [PubMed: 23249815]
15. Berlim MT, Van den Eynde F, Daskalakis ZJ. A systematic review and meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for

treating major depression. Psychol Med. 2013;43(11):2245–2254. doi:10.1017/S0033291712002802 [PubMed: 23200131]

16. Brunoni AR, Chaimani A, Moffa AH, et al. Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review With Network Meta-analysis. JAMA Psychiatry. 2017;74(2):143–152. doi:10.1001/jamapsychiatry.2016.3644 [PubMed: 28030740]
17. Kaster TS, Daskalakis ZJ, Noda Y, et al. Efficacy, tolerability, and cognitive effects of deep transcranial magnetic stimulation for late-life depression: a prospective randomized controlled trial. Neuropsychopharmacology. 6 2018. doi:10.1038/s41386-018-0121-x
18. Fregni F, Marcolin MA, Myczkowski M, et al. Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. Int J Neuropsychopharmacol. 2006;9(6):641–654. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16939662. [PubMed: 16939662]
19. Manes F, Jorge R, Morcuende M, Yamada T, Paradiso S, Robinson RG. A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. Int psychogeriatrics. 2001;13(2):225–231.
20. Mosimann UP, Marre SC, Werlen S, et al. Antidepressant effects of repetitive transcranial magnetic stimulation in the elderly: correlation between effect size and coil-cortex distance. Arch Gen Psychiatry. 2002;59(6):560–561. [PubMed: 12044199]
21. Mosimann UP, Schmitt W, Greenberg BD, et al. Repetitive transcranial magnetic stimulation: a putative add-on treatment for major depression in elderly patients. Psychiatry Res. 2004;126(2):123–133. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15123391. [PubMed: 15123391]
22. Blumberger DM, Mulsant BH, Fitzgerald PB, et al. A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression. World J Biol Psychiatry. 2012;13(6):423–435. doi:10.3109/15622975.2011.579163 [PubMed: 21736507]
23. Blumberger DM, Maller JJ, Thomson L, et al. Unilateral and bilateral MRI-targeted repetitive transcranial magnetic stimulation for treatment-resistant depression: a randomized controlled study. J Psychiatry Neurosci. 2016;41(4):E58–66. [PubMed: 27269205]
24. Pascual-Leone A, Rubio B, Pallardo F, Catala MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet. 1996;348(9022):233–237. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8684201. [PubMed: 8684201]
25. Rossini PM, Burke D, Chen R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol. 2015;126(6):1071–1107. doi:10.1016/j.clinph.2015.02.001 [PubMed: 25797650]
26. Lisanby SH, Gutman D, Luber B, Schroeder C, Sackeim HA. Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. Biol Psychiatry. 2001;49(5):460–463. [PubMed: 11274658]
27. Chang C-C, Yu S- C, McQuoid DR, et al. Reduction of dorsolateral prefrontal cortex gray matter in late-life depression. Psychiatry Res. 2011;193(1):1–6. doi:10.1016/j.pscychresns.2011.01.003 [PubMed: 21596532]
28. Aizenstein HJ, Butters MA, Wu M, et al. Altered functioning of the executive control circuit in late-life depression: episodic and persistent phenomena. Am J Geriatr Psychiatry. 2009;17(1):30–42. doi:10.1097/JGP.0b013e31817b60af [PubMed: 19001356]
29. Rotenberg VS. Functional brain asymmetry as a determinative factor in the treatment of depression: theoretical implications. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(8):1772–1777. doi:10.1016/j.pnpbp.2008.08.011 [PubMed: 18775761]
30. Luber BM, Davis S, Bernhardt E, et al. Using neuroimaging to individualize TMS treatment for depression: Toward a new paradigm for imaging-guided intervention. Neuroimage. 2017;148:1–7. doi:10.1016/j.neuroimage.2016.12.083 [PubMed: 28062252]

31. Rossini D, Lucca A, Magri L, et al. A symptom-specific analysis of the effect of high-frequency left or low-frequency right transcranial magnetic stimulation over the dorsolateral prefrontal cortex in major depression. Neuropsychobiology. 2010;62(2):91–97. doi:10.1159/000315439 [PubMed: 20523080]

32. George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry. 2010;67(5):507–516. doi:67/5/507 [pii]10.1001/archgenpsychiatry.2010.46 [PubMed: 20439832]

33. Fitzgerald PB, Hoy K, McQueen S, et al. A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. Neuropsychopharmacology. 2009;34(5):1255–1262. doi:10.1038/npp.2008.233 [PubMed: 19145228]

34. Herwig U, Padberg F, Unger J, Spitzer M, Schonfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: examination of the reliability of “standard” coil positioning by neuronavigation. Biol Psychiatry. 2001;50(1):58–61. [PubMed: 11457424]

35. Nahas Z, Li X, Kozel FA, et al. Safety and benefits of distance-adjusted prefrontal transcranial magnetic stimulation in depressed patients 55–75 years of age: a pilot study. Depress Anxiety. 2004;19(4):249–256. doi:10.1002/da.20015 [PubMed: 15274174]

**Key points**

- Bilateral rTMS was superior to unilateral high frequency rTMS and sham stimulation for remission and response rates according to the Hamilton Depression Rating Scale
- The proportion of participants who dropped out did not differ significantly across groups, as well as the adverse effects severity or frequency.
- Sequential bilateral treatment may be an optimal form of rTMS when used for treatment-resistant depression in older adults.
- Further large-scale comparative effectiveness trials of bilateral rTMS for Treatment-Resistant Late-Life Depression are warranted.

**Table 1.**

Treatment Parameters

| Study | Blumberger et al. 2012 (120% RMT) | Blumberger et al. 2016 (120% AdjRMT ) |
|---|---|---|
| **High Frequency Unilateral (HFL)** | Frequency: 10Hz<br>Pulses Per Train: 30<br>Trains: 48 + 1 (10 pulses)<br>Total Pulses: 1450 | Frequency: 10Hz<br>Pulses per train: 30<br>Trains: 70<br>Total pulses: 2100 |
| **Bilateral** | Frequency: 1 Hz<br>Pulses Per Train: 100<br>Trains: 4 + 1 (65 pulses)<br>Total Pulses: 465<br>Frequency: 10Hz<br>Pulses Per Train: 30<br>Trains: 25<br>Total Pulses: 750 | Frequency: 1 Hz<br>Pulses per train: 100<br>Trains: 6<br>Total pulses: 600<br>Frequency: 10Hz<br>Pulses Per Train: 30<br>Trains: 50<br>Total Pulses: 1500 |

AdjRMT: RMT adjusted for coil-cortex distance

**Table 2.**

Demographic and Baseline Clinical Variables

| Characteristic | Bilateral (n=20) | Unilateral (n=11) | Sham (n=12) |
|---|---|---|---|
| Age, y, mean (SD) | 66.8 (5.8) | 66.1 (8.5) | 64.1 (3.7) |
| Gender, M/F | 13/7 | 4/7 | 3/9 |
| Years of education, mean (SD) | 14.5 (3.2) | 12.6 (2.7) | 16.9 (4.1) |
| Onset age, y, mean (SD) | 32.1 (16.7) | 20.1 (14.7) | 38.5 (14.7) |
| Duration of current episode, months, mean (SD) | 27.2 (16.3) | 17.7 (10.1) | 31.4 (28.1) |
| Number of episodes, mean (SD) | 2.9 (2.7) | 3.3 (3.2) | 3.9 (4) |
| Current episode severe (%) | 2 (10) | 4 (36.4) | 1 (8.3) |
| Current episode moderate (%) | 18 (90) | 7 (63.6) | 11 (91.7) |
| Atypical features (%) | 2 (10) | 2 (18.2) | 1 (8.3) |
| Melancholic features (%) | 3 (15) | 0 (0) | 0 (0) |
| *Prior Medication History* | | | |
| SSRI (%) | 10 (50) | 5 (45.5) | 7 (58.3) |
| SNRI (%) | 6 (30) | 4 (36.4) | 5 (41.7) |
| TCA (%) | 7 (35) | 6 (54.5) | 8 (66.7) |
| Mirtazapine (%) | 4 (20) | 1 (9.1) | 1 (8.3) |
| Lithium (%) | 1 (5) | 0 (0) | 0 (0) |
| *Active Medication During Study* | | | |
| Benzodiazepine (%) | 6 (30) | 4 (36.4) | 5 (41.7) |
| Antipsychotic (%) | 4 (20) | 3 (27.3) | 2 (16.7) |
| No antidepressant (%) | 3 (15) | 0 (0) | 0 (0) |
| ATHF score, mean (SD) | 6.8 (4.0) | 5.7 (2.2) | 4.6 (2.1) |
| Baseline HDRS, mean (SD) | 24.6 (4.2) | 26.5 (3.4) | 24.5 (3.5) |

SD = standard deviation; y = years; M/F = male/female; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; ATHF = antidepressant treatment history form; HDRS = 17-item Hamilton Depression Rating Scale.