Brain Stimulation 12 (2019) 1319–1321

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Safety, tolerability and effectiveness of a novel 20 Hz rTMS protocol targeting dorsomedial prefrontal cortex in major depression: An open-label case series

Keywords:
Treatment-resistant depression
TRD
Transcranial magnetic stimulation
TMS
High-frequency
DMPFC

To the Editor

Repetitive transcranial magnetic stimulation (rTMS) of the dorsomedial prefrontal cortex (DMPFC) in treatment-resistant depression (TRD) has been recently studied as an alternative to conventional dorsolateral prefrontal cortex (DLPFC) rTMS [1,2]. Across both targets, intermittent theta-burst stimulation (iTBS) reduces treatment duration while achieving comparable outcomes to conventional 10 Hz stimulation [1,3]. However, iTBS can require more costly devices than conventional high-frequency rTMS, and the consistency of excitatory effect varies across individuals [4].

Neurophysiological and functional magnetic resonance imaging (fMRI) evidence suggests that 20 Hz stimulation may have a more consistent excitatory effect versus 1 Hz, 10 Hz, or iTBS [5]. Recently, a study by Cash and collaborators [6] demonstrated that excitatory effects for 20 Hz were most consistently obtained with a duty cycle of 2 s on, 4 s off (versus 8, 16, or 32 s off). On this duty cycle, a 1200 pulse session may be delivered in just 3 min, enabling rapid sessions without device upgrades. However, the therapeutic outcomes for this 2 s on, 4 s off 20 Hz protocol remain undocumented. Here, we report open-label data on the safety, tolerability and effectiveness of this 20 Hz DMPFC-rTMS protocol in 123 patients with TRD.

Between January 2016 and May 2018, 123 TRD patients were treated with 20 Hz bilateral DMPFC-rTMS at our clinic. Baseline characteristics and comorbidities are presented in the supplementary material. Referral and assessment process and inclusion/exclusion criteria were the same as in our previous reports [1,7,8]. All patients provided informed consent following University Health Network guidelines. This study was approved by the Research Ethics Board of the University Health Network.

Procedures for DMPFC-rTMS (lower extremity motor threshold determination and coil positioning over DMPFC at 25% of the nasion-inion distance along the midline) follow those previously reported by our group [1]. Treatment was delivered using a MagPro R30 device equipped with a Cool DB80 Coil (MagVenture, Farum, Denmark). Patients underwent once-daily sequential bilateral (right then left hemisphere) DMPFC-rTMS sessions, 5 times/week (20 Hz, 2 s on and 4 s off, 30 trains per hemisphere, 1200 pulses/hemisphere, total of 2400 pulses/day, 6 min total stimulation time), at 120% of resting motor threshold for lower extremity. Patients completed a Beck Depression Inventory – II (BDI-II) before every treatment session. After 15 sessions, a decision was made based on clinical improvement (>20%) whether to continue to 20–30 sessions, with follow-up 1–2 weeks after the final session. Response was defined as an improvement of ≥50% from baseline; remission was defined as a final treatment score ≤12 on BDI-II.

123 patients completed 2528 sessions in this series. 95 patients completed an acute course of ≥15 sessions (completers) and 28 patients dropped out at <15 sessions (non-completers). Of the 95 completers, 29 who achieved response/remission underwent a maintenance course of 3–16 sessions afterwards (weekly or biweekly). Regarding safety, no serious adverse events (seizures, syncopal episode, manic/hypomanic switch or other treatment-limiting incidents) occurred in any patient. All patients reported tolerable pain levels (VAS 3–9, 10 = intolerable). First-session mean pain rating was 7.4 ± 1.3 SD, decreasing to 6.3 ± 2.2 by the final session. No patient discontinued prematurely due to pain or any other adverse symptoms such as headache, fatigue or vertigo.

Treatment outcomes are presented in the supplementary material. Among completers, 28/95 (29.5%) achieved response and 18/95 (18.9%) achieved remission. Among non-completers, 10/28 (35.7%) achieved response and 8/28 (28.6%) achieved remission. Overall (intention-to-treat), 38/123 (30.9%) achieved response and 26/123 (21.2%) achieved remission. Responders showed steady improvement to maximal effect at their final week of treatment (Fig. 1A). Kernel density estimation revealed a bimodal distribution of outcomes (Fig. 1B), with a notch in the distribution at 37% improvement, distinguishing a responsive subgroup (40–60%) from a non-responsive subgroup (0–20%), as noted in our previous reports on DMFPC-rTMS [1,9].

This report suggests that the 20 Hz DMPFC rTMS protocol can be delivered with a 4 s ITI, in a safe, tolerable and effective manner [6]. No serious adverse events were reported, and treatment was well-tolerated, with no non-completers having dropped-out for side-effects. Response and remission rates were comparable to those previously reported in meta-analyses of DLPFC-rTMS [10]. This protocol may also be clinically advantageous, increasing the cost-efficacy of rTMS, and with more patients able to receive treatment in a given time span.

https://doi.org/10.1016/j.brs.2019.06.020

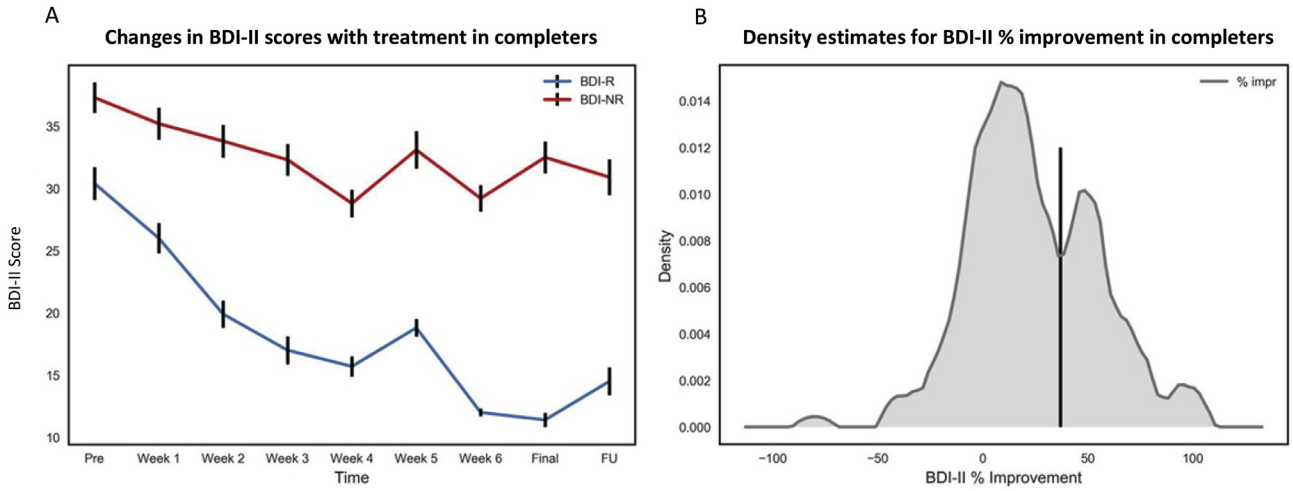

Fig. 1. A) Trajectories of improvement in overall responders and non-responders who completed a full treatment course (≥15 sessions). Non-responders showed little improvement over the course of the 3 min 20 Hz DMPFC-rTMS protocol, while responders showed steady improvement to meet the criteria for clinical response on the BDI-II (≥50% reduction in symptoms from baseline). "Final" represents the last BDI-II score for every participant, irrespective of the total number of sessions received (i.e. if they finished on week 4, 5 or 6). B) Distribution of outcomes for 3 min 20 Hz DMPFC-rTMS. A kernel density estimates of the probability distribution function of clinical outcomes (expressed as percentage improvement from baseline to final score on the BDI-II) revealed a sharply bimodal distribution with a notch around 37% improvement distinguishing non-responders from partial and full responders to the of 3 min 20 Hz DMPFC-rTMS protocol. BDI-II, Beck Depression Inventory-II; FU, follow-up; R, responders; NR, non-responders.

Limitations include the use of open-label data, which although naturalistic, do not allow estimates of efficacy, but only effectiveness. Given the open nature of the trial, it is to be expected that estimates of response and remission rates may be higher than what would be obtained in sham-controlled randomized controlled trial, which would also be required for direct comparison with iTBS or 10 Hz rTMS. Another limitation is the use of self-report rather than clinician-rated scales. The heterogeneity of comorbidities and medications in this naturalistic case series can be considered as a limitation or strength. Finally, baseline BDI-II scores were higher in non-responders compared to responders, although higher depression severity is a known negative predictive factor of response to rTMS [10].

In summary, our data from 2528 sessions in 123 individuals suggest that the brief 20 Hz DMPFC-rTMS protocol is safe and tolerable even at the high stimulation intensities employed. Overall response and remission rates were comparable to those previously reported in meta-analyses of rTMS [10]. Thus, the 20 Hz protocol previously studied in motor cortex [6] appears safe and efficacious for DMPFC stimulation. Rapid sessions (<5–10 min) may thus be viable not only for iTBS, but also for 20 Hz stimulation (without a stimulator upgrade). Given that our protocol requires a sequential bilateral stimulation of the DMPFC, unilateral DLPFC stimulation would thus only require 3 min. Future trials assessing the efficacy of a 3 min 20 Hz rTMS protocol to the left DLPFC, equal in length to the recently FDA-approved 3 min iTBS protocol, may be warranted.

Conflicts of interest

Authors JPM, KF, DD, JMSK, PF, RFHC and PG report no conflicts of interest. JD reports research grants from CIHR, the National Institute of Mental Health, Brain Canada, the Canadian Biomarker Integration Network in Depression, the Ontario Brain Institute, the Weston Foundation, the Klarman Family Foundation, the Arrell Family Foundation, and the Buchan Family Foundation, travel stipends from Lundbeck and ANT Neuro, in-kind equipment support for investigator-initiated trials from MagVenture, and is an advisor for BrainCheck, TMS Neuro Solutions, and Restorative Brain Clinics. 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 principal site investigator for three sponsor-initiated studies for Brainsway Ltd. He received in-kind equipment support from Magventure for investigator-initiated research. He received medication supplies for an investigator-initiated trial from Indivior. He has participated in an advisory board for Janssen. In the last 5 years, ZJD has received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc and Magventure Inc. His work was supported by the Ontario Mental Health Foundation (OMHF), the Canadian Institutes of Health Research (CIHR), the National Institutes of Mental Health (NIMH) and the Temerty Family and Grant Family and through the Centre for Addiction and Mental Health (CAMH) Foundation and the Campbell Institute.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.06.020.

References

[1] Bakker N, Shahab S, Giacobbe P, Blumberger DM, Daskalakis ZJ, Kennedy SH, et al. rTMS of the dorsomedial prefrontal cortex for major depression: safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. Brain Stimul. 2015;8:208–15. https://doi.org/10.1016/j.brs.2014.11.002.

[2] Kreuzer PM, Downar J, De Ridder D, Schwarzbach J, Schecklmann M, Langguth B. A comprehensive review of dorsomedial prefrontal cortex rTMS utilizing a double cone coil. Neuromodulation: Technol. Neural Interface 2018;26:13–5. https://doi.org/10.1111/ner.12874.

[3] Blumberger D, Vila-Rodriguez F, Thorpe K, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. The Lancet 2018;391:1683–92. https://doi.org/10.1016/S0140-6736(18)30295-2.

[4] Hamada M, Murase N, Hasan A, Balaratnam M, Rothwell JC. The role of interneuron networks in driving human motor cortical plasticity. Cerebr Cortex 2013;23:1593–605. https://doi.org/10.1093/cercor/bhs147.
[5] Eldaief MC, Halko MA, Buckner RL, Pascual-Leone A. Transcranial magnetic stimulation modulates the brain's intrinsic activity in a frequency-dependent manner. Proc Natl Acad Sci USA 2011;108:21229–34. https://doi.org/10.1073/pnas.1113103109.
[6] Cash RFH, Dar A, Hui J, De Ruiter L, Baarbé J, Fettes P, et al. Influence of inter-train interval on the plastic effects of rTMS. Brain Stimul. 2017:1–7. https://doi.org/10.1016/j.brs.2017.02.012.
[7] Schulze L, Remington G, Giacobbe P, Kennedy SH, Blumberger DM, Daskalakis ZJ, et al. Effect of antipsychotic pharmacotherapy on clinical outcomes of intermittent theta-burst stimulation for refractory depression. J Psychopharmacol 2017;31:312–9. https://doi.org/10.1177/0269881116675516.
[8] Feffer K, Lee HH, Mansouri F, Giacobbe P, Vila-Rodriguez F, Kennedy SH, et al. Early symptom improvement at 10 sessions as a predictor of rTMS treatment outcome in major depression. Brain Stimul. 2017:1–31. https://doi.org/10.1016/j.brs.2017.10.010.
[9] Downar J, Geraci J, Salomons TV, Dunlop K, Wheeler S, McAndrews MP, et al. Anhedonia and reward-circuit connectivity distinguish nonresponders from responders to dorsomedial prefrontal repetitive transcranial magnetic stimulation in major depression. Biol Psychiatry 2014;76:176–85. https://doi.org/10.1016/j.biopsych.2013.10.026.
[10] 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;44:225–39. https://doi.org/10.1017/S0033291713000512.

Jean-Philippe Miron*
MRI-Guided rTMS Clinic and Krembil Research Institute, University Health Network, Toronto, Canada

Department of Psychiatry and Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Unité de Neuromodulation Psychiatrique (UNP), Centre Hospitalier de l'Université de Montréal (CHUM), Université de Montréal, Montréal, Canada

Kfir Feffer
Lev-Hasharon Mental Health Center, Tzur-Moshe and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Robin F.H. Cash
Departments of Psychiatry and Biomedical Engineering, University of Melbourne, Melbourne, Victoria, Australia

Dorsa Derakhshan
Department of Psychiatry and Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

John Min Seok Kim
Department of Psychiatry and Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Peter Fettes
Department of Psychiatry and Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Peter Giacobbe
Department of Psychiatry and Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Harquail Centre for Neuromodulation, Sunnybrook Health Sciences Centre, Toronto, Canada

Daniel M. Blumberger
Department of Psychiatry and Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Temerty Centre for Therapeutic Brain Intervention at the Centre for Addiction and Mental Health, Toronto, ON, Canada

Zafiris J. Daskalakis
Department of Psychiatry and Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Temerty Centre for Therapeutic Brain Intervention at the Centre for Addiction and Mental Health, Toronto, ON, Canada

Jonathan Downar
MRI-Guided rTMS Clinic and Krembil Research Institute, University Health Network, Toronto, Canada

Department of Psychiatry and Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

* Corresponding author. MRI-Guided rTMS Clinic and Krembil Research Institute, University Health Network, Toronto, Canada.
E-mail address: mironjp@icloud.com (J.-P. Miron).

4 May 2019
Available online 20 June 2019