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A case series of a novel 1 Hz right-sided dorsolateral prefrontal cortex rTMS protocol in major depression

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To the Editor,

Although effective in treatment-resistant depression (TRD) and superior in tolerability to medication, repetitive transcranial magnetic stimulation (rTMS) is currently burdened by high costs of equipment acquisition, operation and technical complexity, precluding its widespread use [1]. Simplifying the treatment technique could facilitate more widespread uptake of rTMS in community settings. To this end, we investigated a non-cooled parabolic coil that is less expensive than cooled figure of eight (Fo8) coils and allow simplified positioning because of its central opening and wide stimulation area.

Between August 2018 and June 2019, 43 TRD patients completed at least fifteen (15) sessions of 1 Hz right-sided dorsolateral prefrontal cortex (DLPFC) rTMS at our clinic using a MagPro R30 and a MMC-140 parabolic coil (MagVenture, Farum, Denmark). Patient selection process is described in our previous reports [2,3]. All patients provided informed consent and this study was approved by the Research Ethics Board of the University Health Network.

Patients underwent once-daily right DLPFC-rTMS, with the center of the coil over F4 (calculated using a right-flipped adjusted BeamF3 algorithm [4]) for 15–30 sessions, 5 times/week (1 Hz, 60 s on and 30 s off, 6 trains, 8.5 min total stimulation time, 360 pulses/day [5]), at 120% of resting motor threshold for the hand muscles. Patients completed a Beck Depression Inventory - II (BDI-II) before every treatment session. Response was defined as an improvement of $\geq$50% from baseline; remission was defined as a final treatment score $\leq$12 [6].

Overall, 43 patients underwent treatment (mean course length 22.4 ± 5.9 sessions) for a total 979 sessions in this series. Regarding baseline characteristics, mean age was 40.6 ± 13.3, with 63% female patients. Mean pre-treatment BDI-II was 36.4 ± 10.0. Number of previous failed medication trials averaged 1.8 ± 1.5, and length of current episode 37.5 ± 54.9 months. 42 patients had a diagnosis of unipolar depression, 1 patient had bipolar depression and 20 (46.5%) patients had a comorbid anxiety disorder.

No serious adverse events occurred. All patients experienced manageable pain levels, with reported VAS scores ranging from 1 to 7 (VAS scale 1–10, 10 = maximum tolerable pain). First-session mean pain rating was 6.5 ± 1.9, decreasing to 5.0 ± 2.4 by the final session. No patient discontinued prematurely due to pain or any other adverse symptoms such as headache, fatigue or vertigo. Mean motor threshold (MT) was 37.2 ± 9.0% of maximal stimulator output. Average treatment intensity (120% of MT) was 44.1 ± 9.0%, with 2.3 ± 3.8 days to reach target intensity.

Sixteen of the 43 patients (37.2%) achieved response ($\geq$50% improvement from baseline) and 10/43 (23.3%) achieved remission (mean improvement, $32.9\% \pm 31.8$). Responders showed steady improvement to maximal effect at their final week of treatment (Fig. 1A). An Epanechnikov kernel with bandwidth of 15%, probability density estimate of the percent improvement revealed a trimodal distribution of outcomes (Fig. 1B), with a notch near 50% improvement, distinguishing a responsive subgroup (50–70%) from a non-responsive subgroup (20–30%), similar to our previous reports [3]. Another notch around 0% distinguished non-responders from a third group having experienced slight deterioration (−10 to −20%) with treatment. Comparing deteriorating with non-deteriorating patients using independent-samples *t*-test and logistic regression analysis wielded no statistically significant differences ($p < 0.05$) in baseline characteristics (sex, age, comorbid anxiety, duration of the depressive episode and number of medication). No association was also found between these and response ($p < 0.05$).

To our knowledge, this is the first case series investigating the use of a parabolic coil with 1 Hz stimulation in patients with MDD. The current results are superior to what was reported in one of our recently published study [3] and in the classic and highly cited meta-analysis of high-frequency (HF) rTMS by Berlim et al. [7]. While encouraging, those results are below what was reported in a large randomized controlled trial (RCT) by our group [8].

The main goal of this study was to test the use of this novel coil design. With conventional Fo8 coils, targeting requires expertise, since scalp landmarks are hidden under the coil. Due to its central opening, this coil allows for direct visualization of the landmarks, and hence easier placement (Fig. 1C). This could potentially facilitate the delivery of rTMS in a wider range of settings. The use of 1 Hz stimulation likewise facilitates more widespread use of rTMS since it can be delivered on inexpensive stimulators.

Of note, the magnetic field is weaker in the central area of the parabolic coil, where the opening is located (Fig. 1D). This raises the possibility that centering the coil over DLPFC could in fact lead to less DLPFC stimulation and more stimulation of adjacent regions such as lateral orbitofrontal cortex. Notably, stimulation of

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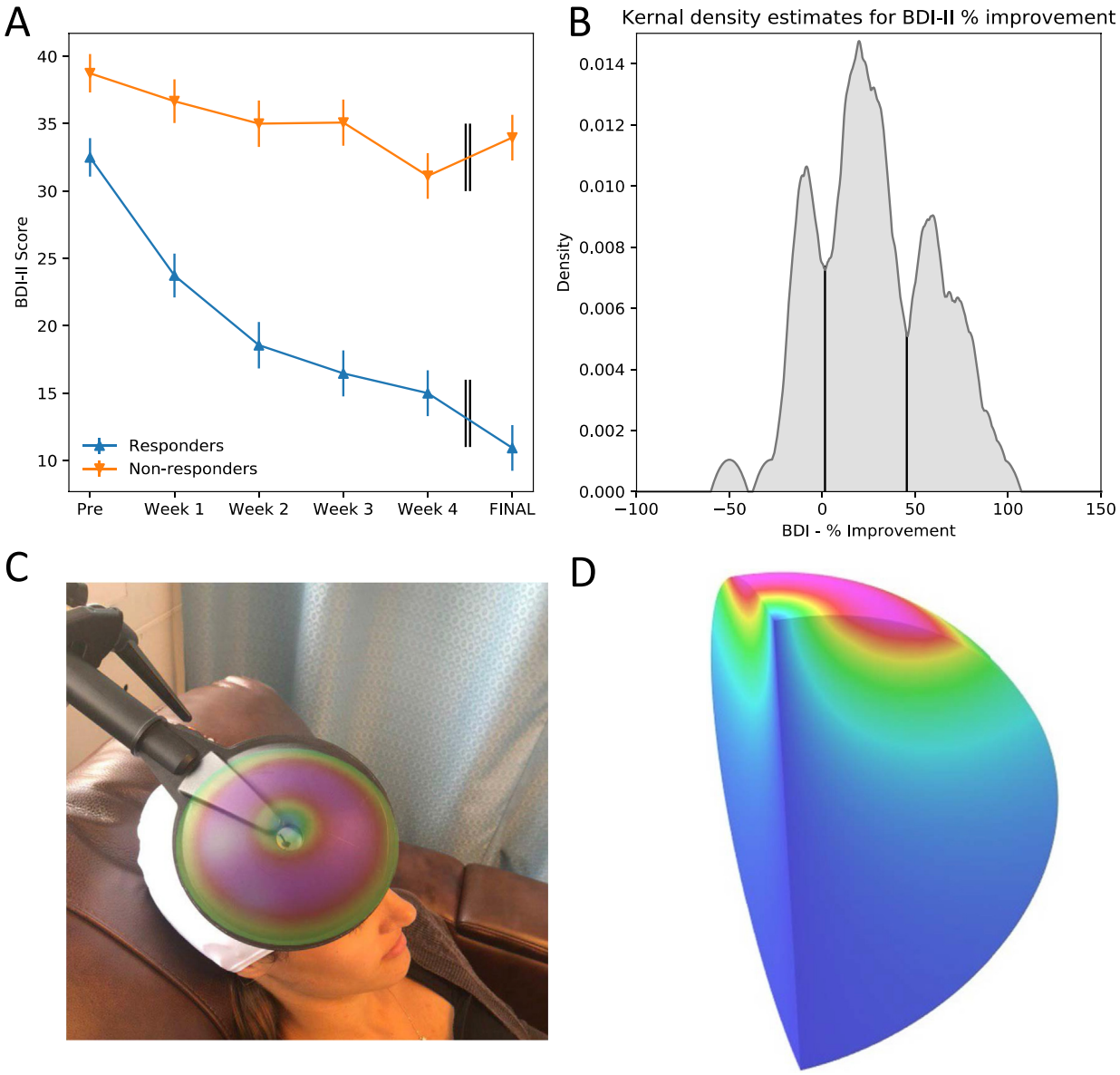

Fig. 1. **A)** Trajectories of improvement. Non-responders showed little improvement over the course of treatment, while responders showed steady improvement to meet criteria for clinical response on the BDI-II (≥50% reduction in symptoms from baseline). "Final" represents the last BDI-II score for every participant, irrespective of the total number of sessions received (i.e. if they finished on week 4, 5 or 6). **B)** Distribution of outcomes. An Epanechnikov kernel with bandwidth of 15% probability density estimate of the percent improvement (expressed as percentage improvement from baseline to final score on the BDI-II) revealed a trimodal distribution of outcomes, with a notch in the distribution at 50% improvement, distinguishing a responsive subgroup (50–70%) from a non-responsive subgroup (20–30%), and another around 0%, distinguishing non-responders from a third group (−10 to −20%) having experienced slightly worst outcomes with the treatment (improvement beyond 100% is an artifact of the statistical procedure). The **C)** Example of MMC-140 coil placement over F4, with central opening allowing direct visualization of scalp landmark, and electric field modelling overlay. **D)** Other perspective of the electric field modelling of the MMC-140 coil (credit: MagVenture). BDI-II, Beck Depression Inventory-II.

this area with rTMS [2] and intracortical electrodes [9] has been shown to decrease depressive symptoms. Another study has also shown efficacy of larger coils in TRD [10]. Placement of the parabolic coil more medially, to enhance stimulation of DLPFC proper, may be worth future study.

An interesting and novel observation is the presence of patients who seem to have experienced a deterioration in their mood with this protocol. This was not seen in previous studies [2,3]. If replicated, this could warrant another study to determine if there are any predictors of this trajectory of outcome.

Limitations of this case series include the use of only patient-rated scales, heterogeneity of comorbidities and medications, and are similar to another case series from our group [3].

In summary, this series suggests that 1 Hz right DLPFC-rTMS delivered with parabolic coils is safe, well tolerated, and effective in MDD patients with mild to moderate TRD. Although the positioning of this coil might bear future optimization, the simplicity of the technique and its applicability via low-cost equipment could greatly expand the reach of rTMS beyond specialized centers in developed countries. Given the widespread global burden of MDD, more affordable, scalable, and simplified rTMS techniques

could markedly enhance the delivery and overall impact of the technique on patient health around the world.

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