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Do comorbid OCD-MDD patients need two separate dTMS protocols?

Major Depressive disorder (MDD) is the most common comorbidity with obsessive-compulsive disorder (OCD); more than 50% of OCD patients meet lifetime criteria for MDD or dysthymia [1]. Depression can significantly worsen OCD treatment outcomes [2] and elevate the risk for suicide [3]. While the multi-center-tested and FDA indicated deep transcranial magnetic stimulation (dTMS) treatment for OCD uses the H7 coil to target dorsomedial prefrontal cortex (dmPFC) and anterior cingulate cortex (ACC) [4], the treatment for MDD uses the H1 coil to target the dorsolateral prefrontal cortex (dlPFC) bilaterally with preference to the left [5]. However, a recent case series (N = 9) indicated the potential of effectiveness of H7 coil treatment in MDD as well [6]. This begs the question whether OCD patients with MDD comorbidity will benefit sufficiently from stimulation to the dmPFC and ACC for both their OCD symptoms and their MDD symptoms, negating the need for the standard stimulation of the left dlPFC.

To answer this question, we performed a post hoc analysis of the OCD pivotal trial [4] data and compared the Yale-Brown Obsessive Compulsive Scale (YBOCS) and Hamilton Depression Rating Scale (HDRS) data of a subset of OCD patients with MDD comorbidity (YBOCS $\geq$ 20; HDRS21 $\geq$ 16) between the active dTMS (N = 9) and sham (N = 10) groups. In the subset of patients included in this analysis, the decrease in YBOCS scores from baseline was significantly larger for the active dTMS group compared to sham starting at week 2 ($p = 0.02$) and sustained until the end of the trial (Fig. 1A). Notably, this effect was sustained and even enhanced at the 1-month follow-up assessment ($p = 0.002$). This significant difference at all time points is remarkable in light of the very small sample size. We observed a statistically significant decrease in HDRS scores from baseline at all time points ($p < 0.05$ for weeks 2–4, $p < 0.01$ for week 6, $p < 0.005$ for 1-month follow-up) in the active dTMS group. Conversely, no significant decrease in HDRS scores was observed for the sham group at any timepoint ($p > 0.05$). Although this decrease in HDRS from baseline was larger for the active dTMS group compared to the sham group, this difference wasn't statistically significant ($p > 0.1$) (Fig. 1B).

While the decrease in HDRS scores wasn't statistically significantly larger in the active dTMS group compared to the sham group, it is reasonable to assume that this could be due to the small sample size. The significant effect within the active dTMS (but not sham) group deserves attention and follow-up corroboration. It is possible that this improvement in MDD symptoms is simply the indirect result of relieving the OCD symptoms, which precedes the MDD 65% of the time. This hypothesis is supported by the timeline of HDRS improvement and separation from sham that is delayed compared to the YBOCS, in contrast to pharmacotherapy, where SRIs require twice the duration for OCD (8–12weeks) than for MDD (4–6weeks). Similarly, Zandberg et al. [7] used lagged multilevel mediational analyses, to demonstrate that reducing OCD symptoms with exposure therapy accounted for 65% of the reduction in depressive symptoms of comorbid OCD-MDD patients. Alternatively, it is possible that stimulation over the dmPFC and ACC directly improved the MDD symptoms irrespective of the OCD. The dmPFC functions as a hyper-connected hub between distinct distributed neural networks involved in depression and together with the adjacent ACC form the most consistent regions to show gray matter reduction in MDD patients [8]. In recent years evidence has accumulated demonstrating that HF stimulation of the dmPFC and ACC with deeper coils is sufficient for MDD [6,9],

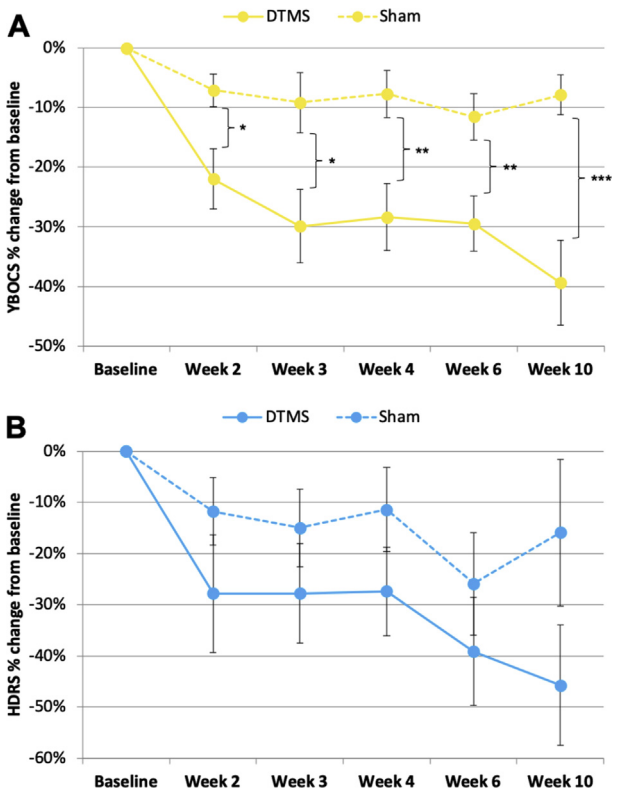

Fig. 1. Improvement in clinical symptoms of comorbid OCD-MDD patients. Mean percent change in YBOCS (A) and HDRS-21 (B) scores from baseline until the end of the trial (week 6) and at the 1-month follow-up assessment (week 10). Asterisks denote statistical significance: *-p<0.05, **-p<0.01, ***-p<0.005. dTMS – deep transcranial magnetic stimulation, YBOCS – Yale-Brown Obsessive-Compulsive Scale, HDRS-21 – Hamilton Depression Rating Scale – 21 Items. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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though the latest blinded trial over dmPFC with a figure-8 coil did not demonstrate superiority over sham [10]. Importantly, MDD is not a unitary disease, rather a heterogenous syndrome that encompasses varied co-occurring symptoms and divergent responses to treatment. Drysdale et al. [11] have shown that MDD patients can be divided into four biotypes defined by distinct patterns of dysfunctional connectivity in limbic and frontostriatal networks. However, a recent study failed to replicate these biotypes [12]. While the specific biotypes might not be clear as of yet and there also seems to be inconsistency in circuit definition, there is obvious overlap in the different neural dysfunctions identified in depression. Neuronal activity patterns within the default mode network (DMN) and the central executive network (CEN) are consistently abnormal in depression [13]. The DMN has been implicated in rumination, self-referential processing, and episodic memory retrieval and includes areas of mPFC, among other (mostly medial) areas of cingulate and parietal cortex. In depression, activity in the DMN is correlated with activity in the subgenual cingulate cortex and other limbic areas. The CEN plays a key role in regulating attention, working memory, and decision making and includes dlPFC and multiple (mostly lateral) areas of posterior parietal cortex. Early efforts to use TMS to treat depression focused on the left dlPFC, a component of the CEN, since it was consistently found to be hypoactive in depression. Likewise, hyperactivity and abnormal patterns of connectivity between the subgenual ACC and other DMN structures are also consistent findings in depression [13]. We hypothesize that patients with comorbid OCD and MDD display the latter types of circuit dysfunctions and are thus likely to benefit from stimulation of the dmPFC and ACC components of the DMN. Although further research is warranted to elucidate the mechanism that mediates clinical improvement with dTMS and target selection for individuals with MDD, we recommend, based on the available evidence, to treat comorbid OCD-MDD patients with just the OCD protocol (H7 to the dmPFC/ACC).

Declaration of competing interest

BrainsWay Ltd. funded the study (ClinicalTrials.gov identifier: NCT02229903).

Dr. Harmelech is a BrainsWay employee. Dr. Tendler serves as the chief medical officer of and has a financial interest in BrainsWay, and he has ownership interest in Advanced Mental Health Care, Inc. Dr. Roth and Dr. Zangen are key inventors of deep TMS technology and have financial interest in BrainsWay.

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