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Short communication

Deep transcranial magnetic stimulation for obsessive-compulsive disorder is efficacious even in patients who failed multiple medications and CBT

Yiftach Roth[a], Noam Barnea-Ygael[a], Lior Carmi[b], Eric A Storch[c], Aron Tendler[d], Abraham Zangen[a,*]

[a] The Department of Life Sciences and the Zlotowski Center for Neuroscience, Ben-Gurion University of the Negev, Beer-Sheva, Israel
[b] Chaim Sheba Medical Center, Ramat Gan, Israel
[c] Department of Psychiatry & Behavioral Sciences, Baylor College of Medicine, TX, USA
[d] Advanced Mental Health Care, Inc., Palm Beach, FL, USA

A B S T R A C T

OCD is a chronic and disabling disease with a lifetime prevalence of 2%-3%. About 40–60% of these patients do not adequately respond to pharmacotherapy and CBT. Deep transcranial magnetic stimulation (dTMS) was shown to be safe and effective as a treatment alternative for OCD and recently received regulatory approvals. Yet it is unclear whether patients who failed numerous medications and/or CBT can still benefit from dTMS. Here, we analyzed recent data from a double-blind multicenter dTMS study and found efficacy of this novel treatment even in OCD patient cohorts who previously failed to respond to multiple medications and CBT.

1. Introduction

Obsessive-compulsive disorder (OCD) is a disabling condition with a lifetime prevalence of 2%−3% (Ruscio et al., 2010). Cognitive behavioral therapy (CBT) and serotonin reuptake inhibitors (SRIs) have demonstrated efficacy for OCD (Öst et al., 2015), yet 40–60% of OCD patients show no or incomplete response to pharmacotherapy or CBT; in some cases, due to intolerable side-effects (Leckman et al., 2010; Mataix-Cols et al., 2005). Treatment options for these patients include switching to another SRI, augmenting with an antipsychotic, a trial of riluzole, and/or engaging in more intensive CBT. Yet, the clinical challenge still remains, and given that OCD is a chronic illness that frequently begins in adolescence (Brakoulias et al., 2017), many patients will undergo various treatment trials during their lifetime without sufficient improvement (Bloch et al., 2013; Del Casale et al., 2019). Therefore, different and novel treatment approaches are of great need.

Recently, six weeks of daily deep transcranial magnetic stimulation (dTMS) therapy have been shown to be safe and effective in OCD patients (Carmi et al., 2018, 2019) who had insufficient response to medication and/or CBT. This present a novel treatment option for OCD, but an important clinical question is how efficacious is dTMS in OCD patients with unsatisfactory symptoms reduction following multiple medication and/or CBT treatments. Here, we analyzed recent data from a multi-center double-blind clinical trial using dTMS in OCD patients (Carmi et al., 2019) to evaluate whether high number of medication trials and/or prior CBT limit the potential effectiveness of dTMS in OCD.

2. Method

The pivotal clinical trial of dTMS for OCD was performed at 11 medical centers. The study was approved by local institutional review boards and was registered at ClinicalTrials.gov (#NCT01343732). The timeline of the trial included three phases: a 3-week screening phase, a 6-week treatment phase (consisting of twenty-nine daily treatments), and a 4-week follow-up phase. The published report (Carmi et al., 2019) provides a CONSORT diagram, baseline demographic and clinical characteristics, and efficacy outcomes.

All trial participants were outpatients, aged 22–68 years, with the primary diagnosis of OCD, who did not respond to at least one past trial with SRI, were on maintenance therapy of SRI indicated for OCD ± maintenance CBT, and nevertheless had a YBOCS score ≥20. dTMS treatments were delivered after individually-based brief provocation of symptoms (Tendler et al., 2019). Stimulation intensity was 100% of foot resting motor threshold. The coil was positioned 4 cm anterior to the foot motor cortex, targeting medial prefrontal and cingulate cortices and each treatment session consisted 50 trains of 2 s at 20 Hz (40 pulses per train, 2000 pulses per session), separated by 20-s inter-train intervals. Participants remained blinded to treatment type (active/sham) as

* Corresponding author at: Department of Life Sciences and the Zlotowski Center for Neuroscience, Ben-Gurion University, Israel.
E-mail address: azangen@bgu.ac.il (A. Zangen).

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detailed in the original manuscript (Tendler et al., 2019).

Efficacy and safety ratings were administered at baseline, at treatment weeks 2, 3, 4, 6, and at the 1-month follow-up visit. The primary efficacy measure for this subset analysis was response, defined as ≥30% improvement in YBOCS total score at the end of treatment compared to baseline (as defined in the original study (Tendler et al., 2019)). For the current analysis the sample was divided into groups containing subjects with insufficient response to one or two medications (1–2 Meds cohort) versus subjects with insufficient response to three or more medications (3+ Meds cohort). A medication was counted into the cohort based on the site principal investigator's (PI) decision following a patient interview, generally with supporting documentation that the medication was prescribed for at least two months above the minimum dosage required for OCD treatment. In addition, subjects were divided into cohorts who either received prior CBT (of at least 2 months with a therapist) or did not receive prior CBT (Past CBT/No CBT).

Response rates and YBOCS change from baseline over time were assessed in each subset. Paired comparisons were made with Fisher's exact test.

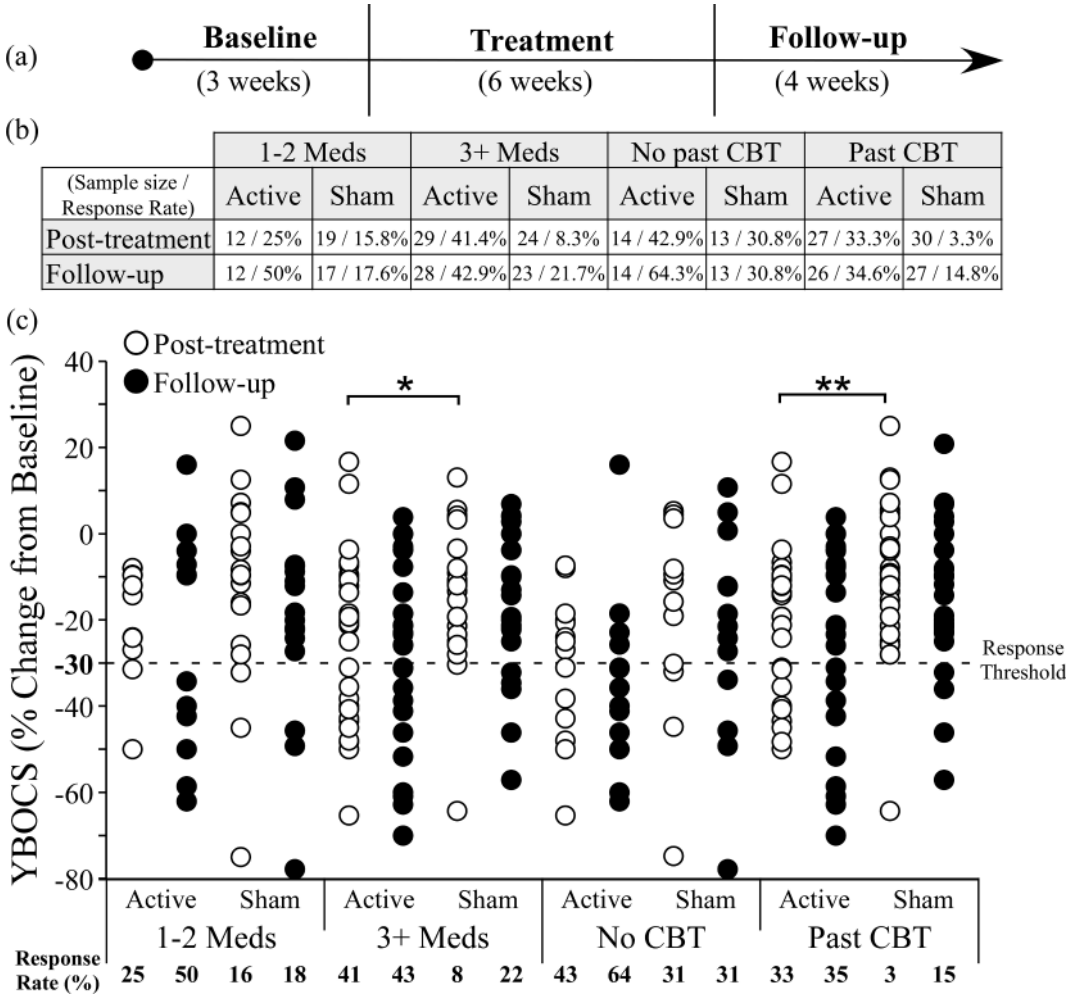
3. Results

The majority of patients were in the 3+ Meds (63%, 53/84 completers) or Past CBT (68%, 57/84) cohorts. There were no significant differences in age or gender between the cohorts. Fig. 1 presents a schematic timeline of the study (a), sample sizes and response rates (b), and the percent of change in YBOCS score from baseline for each individual (c) in the post-treatment and follow-up time points, for patients treated with dTMS or sham in each cohort.

Response at post-treatment was significantly higher in the dTMS group compare to sham in the larger cohorts of 3+ meds (dTMS: 41.4%; sham: 8.3%; $p = 0.0109$) and of Past CBT (dTMS: 33.3%; sham: 3.3%; $p = 0.0041$).

4. Discussion

In the double-blind sham-controlled multi-center dTMS trial, the vast majority of patients had insufficient responses to 3 or more medications as well as prior CBT. Due to the fact that the trial was not powered to show significance in each cohort, statistically significant differences between active and sham arms, or between Post-treatment and Follow-up, were not expected within specific cohorts. Nevertheless,



(Sample size / Response Rate)	1-2 Meds		3+ Meds		No past CBT		Past CBT	
	Active	Sham	Active	Sham	Active	Sham	Active	Sham
Post-treatment	12 / 25%	19 / 15.8%	29 / 41.4%	24 / 8.3%	14 / 42.9%	13 / 30.8%	27 / 33.3%	30 / 3.3%
Follow-up	12 / 50%	17 / 17.6%	28 / 42.9%	23 / 21.7%	14 / 64.3%	13 / 30.8%	26 / 34.6%	27 / 14.8%

Fig. 1. Schematic timeline of the study (a), samples sizes and response rates (b), and the percent of change in YBOCS score from baseline for each individual from the different cohorts at the end of the 6-weeks treatment and at the 10-weeks Follow-up (c). Asterix denote a significant response rate difference between the indicated groups, where $*p < 0.05$, $**p < 0.01$ (Fisher's exact test).

active dTMS treatment induced higher response rates than those in the sham group, within all cohorts and time points. In the larger cohorts of more treatment resistant patients, response rates at the primary time point (following 6-weeks of treatment) were significantly higher in the active dTMS group than those in the sham group. It is possible that the advantage of the active treatment did not reach significance in the smaller cohorts of less prior treatments due to the smaller sample size. In addition, our analysis suggests that treatment history affected both the timing and degree of response rates. More specifically, for the more resistant patients (3+ Meds and Past CBT groups), the difference between active and sham stimulation was significant following treatment and unchanged during follow-up, while for their respective (less resistant) subgroups the difference between active and sham was not significant following treatment but greatly increased during follow-up, exceeding those of the more resistant patients. These different patterns of effects may be due to the interaction between the pathological circuitry's level of activation following symptoms provocation and the levels of dTMS-induced plasticity. More specifically, dTMS beneficial effects may be achieved faster with background of CBT or multiple pharmacological interventions, while "rewiring" of neural networks in more naïve patients require longer incubation time.

This analysis demonstrates that dTMS is an effective treatment option for OCD patients, regardless of prior non-response to SRIs ± antipsychotics or CBT sessions. This supports the hypothesis that the mechanism of action of dTMS for OCD is different from that of pharmacotherapy or CBT and may be based on direct modulation of the cortical-striatal-thalamic-cortical circuitry (Carmi et al., 2018, 2019).

Limitations of this analysis, other than the reduction of sample size to smaller cohorts, include the lack of controlled monitoring of prior pharmacological treatments and regimens. Since OCD is a chronic disorder and patients are prescribed medications from different providers over the course of their lifetime, the medication history gathered is generally an underestimation of medication exposure. Furthermore, patients who are recalling benefits from medications at a time when they are doing poorly, might be underestimating those prior benefits as those medications could have been discontinued after the patient responded and plateaued but lost perspective. There is no simple solution for this, as pharmacy records are only available for two years, and clinician records for seven years. We also found that the patient and therapist reports on CBT for OCD do not necessarily correlate with exposure and response prevention (ERP) for OCD. In several cases, patients were receiving reassurance or relaxation techniques on a weekly basis, or told to do brief exposures without the time for habituation. A formal test on the components of ERP is warranted, to determine that someone truly did not respond to CBT/ERP for OCD.

Nevertheless, the present analysis suggests that dTMS is beneficial for OCD patients with different treatment history, including those with unsatisfactory response to multiple medications and CBT.

Declaration of Competing Interest

Dr. Roth and Prof. Zangen are key inventors of deep TMS and have financial interest in Brainsway; Dr. Barnea-Ygael is a Brainsway employee; Dr. Carmi has received research and travel support from Brainsway; Dr. Tendler serves as the chief medical officer of and has a financial interest in Brainsway; Dr. Storch has no conflict of interests.

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