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Real-world efficacy of deep TMS for obsessive-compulsive disorder: Post-marketing data collected from twenty-two clinical sites

Yiftach Roth [a,b,*], Aron Tendler [a,b,c], Mehmet Kemal Arikan [d], Ryan Vidrine [e], David Kent [f], Owen Muir [g], Carlene MacMillan [h], Leah Casuto [i], Geoffrey Grammer [j], William Sauve [j], Kellie Tolin [k], Steven Harvey [l], Misty Borst [m], Robert Rifkin [l], Manish Sheth [n], Brandon Cornejo [o], Raul Rodriguez [p], Saad Shakir [q], Taylor Porter [r], Deborah Kim [s], Brent Peterson [t], Julia Swofford [u], Brendan Roe [u], Rebecca Sinclair [g], Tal Harmelech [b], 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] BrainsWay Ltd, Israel
[c] Advanced Mental Health Care, 11903 Southern Blvd. Royal Palm Beach, FL 33411, USA
[d] AKADEMIK Psychiatry& Psychotherapy Center Halaskargazi Cad. No: 103, Gün Apt, apartment: 4B 34371 Osmanbey – Istanbul, Turkey
[e] TMS Health Solutions, 3300 WEBSTER STREET, SUITE #402 OAKLAND, CA, 94609, USA
[f] NuMe TMS, 2375 S Cobalt Point Way #102, Meridian, ID, 83642, USA
[g] Brooklyn Minds, 347 Grand St, Brooklyn, NY, 11211, USA
[h] Brooklyn Minds, 10 W 37th Street, 5th Floor, New York, NY, 10018, USA
[i] Lindner Center of Hope, 4075 Old Western Row Rd, Mason, OH, 45040, USA
[j] Greenbrook TMS, 8405 Greensboro Drive, Suite 120 McLean, VA 22102, USA
[k] Greenbrook TMS, 1500 Sunday Dr #200, Raleigh, NC, 27607, USA
[l] Greenbrook TMS, 11477, Olde Cabin Rd, Suite 210 St. Louis MO 63141, USA
[m] Greenbrook TMS, 8850, Stanford Boulevard, Suite 3300Columbia, MD 21045, USA
[n] Achieve TMS, 5060 Shoreham Place Suite 100 San Diego, CA, 92122, USA
[o] Achieve TMS, 516 SE Morrison St. Suite #309 Portland, OR, 97214, USA
[p] Delray Center for Healing, 403 SE 1st St, Delray Beach, FL, 33483, USA
[q] Silicon Valley TMS, 2039 Forest Ave Esthetician Freshman Classroom, San Jose, CA, 95128, USA
[r] Prime TMS, 1811 Wakarusa Dr #102, Lawrence, KS, 66047, USA
[s] 3535 Market St, Philadelphia, PA, 19104, USA
[t] The family Living Institute, 1307 Jamestown Rd STE 202, Williamsburg, VA 23185, USA
[u] TMS NW, 5512 NE 109th Ct ste n, Vancouver, WA, 98662, USA

A B S T R A C T

Background: Deep transcranial magnetic stimulation (dTMS) with the H7-coil was FDA cleared for obsessive-compulsive disorder (OCD) in August 2018 based on multicenter sham-controlled studies. Here we look at the efficacy of dTMS for OCD in real world practices.

Methods: All dTMS clinics were asked to supply their data on treatment details and outcome measures. The primary outcome measure was response, defined by at least a 30% reduction in the Yale Brown Obsessive Compulsive Scale (YBOCS) score from baseline to endpoint. Secondary outcome measures included first response, defined as the first time the YBOCS score has met response criteria, and at least one-month sustained response. Analyses included response rate at the endpoint (after 29 dTMS sessions), number of sessions and days required to reach first response and sustained response.

Results: Twenty-two clinical sites with H7-coils provided data on details of treatment and outcome (YBOCS) measures from a total of 219 patients. One-hundred-sixty-seven patients who had at least one post-baseline YBOCS measure were included in the main analyses. Overall first and sustained response rates were 72.6% and 52.4%, respectively. The response rate was 57.9% in patients who had YBOCS scores after 29 dTMS sessions. First response was achieved in average after 18.5 sessions (SD = 9.4) or 31.6 days (SD = 25.2). Onset of sustained one-month response was achieved in average after 20 sessions (SD = 9.8) or 32.1 days (SD = 20.5). Average YBOCS scores demonstrated continuous reduction with increasing numbers of dTMS sessions.

Conclusions: In real-world clinical practice, the majority of OCD patients benefitted from dTMS, and the onset of improvement usually occurs within 20 sessions. Extending the treatment course beyond 29 sessions results in continued reduction of OCD symptoms, raising the prospect of value for extended treatment protocols in non-responders.

* Corresponding author. The Department of Life Sciences and the Zlotowski Center for Neuroscience, Ben-Gurion University of the Negev, Beer-Sheva, Israel.
E-mail address: yiftach@brainsway.com (Y. Roth).

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1. Introduction

Obsessive-compulsive disorder (OCD) is a chronic disabling condition with a lifetime prevalence of 2%–3% (Ruscio et al., 2010). 30–60% of OCD patients do not adequately respond to pharmacotherapy or cognitive behavioral therapy (CBT) (Pallanti et al., 2004; Mataix-Cols et al., 2005; Simpson et al., 2006; Leckman et al., 2010). Deep repetitive transcranial magnetic stimulation (dTMS) utilizes specially designed H-coils to induce neuronal depolarization in broad and deep cortical regions. The H7-coil targets neural networks in the medial prefrontal and anterior cingulate cortices. Abnormalities in these regions have been implicated in the pathophysiology of OCD (Alexander et al., 1986; Haber 2003). The safety and efficacy of H7-coil dTMS for OCD was demonstrated in a sham-controlled pilot study (Carmi et al., 2018) and later replicated in a subsequent multicenter sham-controlled study resulting in FDA clearance (Carmi et al., 2019b). Following adoption of this new treatment method for OCD patients in clinical practice, it is important to evaluate the safety and efficacy of dTMS in a naturalistic study. The outcomes in sham-controlled studies often do not accurately reflect outcomes in community practice, for a variety of reasons (Anglemyer et al., 2014). It was possible that the intervention would have decreased efficacy in the real world due to the requirement of a brief moderately distressing individually tailored provocation prior to each dTMS session (Tendler et al., 2019) as part of the dTMS treatment procedure (Carmi et al., 2018, 2019b). During the multicenter sham-controlled study, all the provocations were reviewed by an exposure therapy expert, whereas in real-world practice greater variability in provocations is expected.

The present study presents the first dTMS treatment data for OCD under naturalistic conditions. The goals of this study were to analyze the response rates after an adequate dose of 29 dTMS sessions (Carmi et al., 2019b), to characterize time and number of sessions required to reach response, and to investigate the pattern of clinical outcome as a function of number of treatment sessions.

2. Methods

The post marketing data collection project was designed to collect all of the treatment information, demographic data, and outcome data, on subjects treated with dTMS for OCD. The protocol was reviewed by Sterling IRB and granted an exemption from informed consent provided patients were assigned only a patient code (not name or initials) and age (year not date of birth). dTMS providers were contacted about this project through email, through their account managers, through a dedicated project manager and the Chief Medical Officer. All dTMS clinics were asked to participate and sent instructions along with a template excel database to complete. The excel sheet template is available in the supplementary information and includes illness and treatment history, various patient and clinician rating scales such as the Yale-Brown Obsessive Compulsive Severity Scale (YBOCS) (Goodman et al., 1989), considered the gold standard for OCD symptoms assessment.

To incentivize participation and to support the work of data entry, clinics could receive $5 per line of excel data and $70 per YBOCS or Hamilton depression rating scale (HDRS) (Kyle et al., 2016) evaluation. A line of excel data corresponded to one day treatment in detail (motor threshold, treatment intensity, inter-train interval, number of pulses, frequency, side effects etc.). Clinicians were required to submit scores at least at baseline and endpoint. When the patient came in for retreatment, the same code would be used to inform regarding durability.

All sites received training and certification on the device, YBOCS symptom checklist (Goodman et al., 1989), YBOCS severity scale and how to create individualized provocations.

Recruited patients had diagnosis of OCD as a primary or secondary disorder, confirmed by a psychiatrist or psychologist.

Response was defined as a reduction of $\geq$30% in YBOCS score compared to baseline, as in the multicenter trial (Carmi et al., 2019b), given the severity of OCD patients typically joining a demanding treatment (in terms of time and money) such as dTMS.

Patients were usually treated with a high frequency (HF) protocol. Some patients (15/219, 7%) were treated with an intermittent theta burst (iTBS) protocol (Huang et al., 2009; Suppa et al., 2016), or both HF and iTBS sequentially. A tailored provocation preceded each dTMS session (Tendler et al., 2019; Carmi et al., 2018, 2019b). In short, a 3–5 min individualize symptom provocation was performed before each treatment session to activate the relevant neuronal circuit. A hierarchically ordered list of personalized obsessive-compulsive symptom provocations was designed by a clinician together with the patient during the first assessment meeting. Before each treatment session, the staff member guided the patient through the hierarchical list and chose the item that triggered the highest distress score. Once the score was achieved, the patient was asked to keep thinking about this specific obsession during the treatment. dTMS was performed using the H7-coil (BrainsWay Company, Jerusalem, Israel) and a BrainsWay (BrainsWay Company, Jerusalem, Israel) or Magstim Rapid^2 (Magstim Company, Spring Gardens, UK) stimulator. For the HF protocol, dTMS was typically administered with the FDA approved protocol (20 Hz, 100% of the leg resting motor threshold (MT), 50 trains of 2s duration, inter-train interval (ITI) 20s, 2000 pulses per session). The iTBS protocol typically consisted of bursts of 3 pulses at 50 Hz, 5 Hz bursts frequency, 2s on and 8s off, 1800 pulses per session at 80 or 90% of the leg resting MT. Patients generally received daily dTMS sessions, and foot motor threshold was measured once a week. The H7 coil was advanced 4 cm anterior to the foot motor cortex, and attached to the head. YBOCS assessment was done usually once a week, yet there were patients for whom YBOCS scores were reported only after a large number of sessions (e.g. 20 or 29).

Analyses included response rates after 29 dTMS sessions, the number of sessions and time in days required to reach first response, and number of sessions and days required to the onset of a period of sustained response of at least one month. The analysis of first response included patients who had at least one YBOCS score after receiving less than 29 sessions, in order to obtain estimation on the number of sessions and time in days required to reach first response. Rates of response after 29 sessions were compared between groups of patients with/without concomitant SSRI medications and with/without comorbid diagnosis in addition to OCD, using Fisher's exact test. Kaplan-Meier survival analysis was used to examine the time course of achieving first response. The event was first occurrence of response among patients who remained in the study. Hence, the Kaplan–Meier function censors observations at each time point representing patients who have achieved response or dropped out, and only patients at a risk of the event (remained in the study and have not reached response) are accounted for at each time point. The change in YBOCS score as a function of number of dTMS sessions was analyzed using Student's t-test. Analyses were done with GraphPad Prism Version 5.03.

3. Results

Twenty-two sites with H7-coils had provided treatment information and outcome data, primarily from late 2018 through 2019.

Demographic and clinical data of subjects are shown in Table 1.

Most subjects had concomitant SSRI medications (Table 1), and about 66% had comorbid diagnosis in addition to OCD. Post-hoc analyses found no correlation between comorbidity ($p = 0.77$) or concomitant SSRI medications ($p = 0.25$) and treatment outcome.

Data from 219 OCD patients was collected. Of them, 182 patients had at least one post-baseline YBOCS score and were included in the analysis (Fig. 1). 15 subjects received iTBS protocol and were analyzed separately, and 167 patients who received the FDA-cleared protocol were included in the main analyses.

No seizures or other serious adverse events were reported. Overall, the treatment was well tolerated. Adverse events were reported for 18

Table 1
Demographic data of subjects.

Age, Years mean (SD) [N]	37.7 (16.7) [125]
Gender,% Female (n/N)	37.3% (41/110)
Ethnicity, % Caucasian (n/N)	84.2% (64/76)
OCD Diagnosis, % comorbidity (n/N)	65.9% (81/123)
Number of life-time failed medications, mean (SD) [N]	5.8 (4.6) [81]
Concomitant SSRI medications, % (n/N)	72.3% (73/101)

patients and were either unrelated to the device or typical to TMS, such as transient headaches and application site pain.

The main database used for analysis included 121 patients who completed the 29 treatment sessions required by the standard FDA-approved protocol and had YBOCS score at this timepoint. Out of these, 70 patients (57.9%) reached response at this primary time point. Out of 45 patients who had YBOCS scores and stopped treatment before receiving 29 sessions, 26 (57.8%) reached responder status. There were 135 patients who had post-baseline YBOCS measures after receiving less than29 sessions, hence they were included in the analysis of first response. Among them the number of patients who achieved first response (after any number of sessions) was 98 (72.6%). Among 63 patients who had at least one-month follow-up and did not reach response, or had at least one-month follow-up after they reached response, the number of patients who achieved sustained response was 33 (52.4%). Yet, 92 of 113 patients (81.4%) who reached response at any time point, were in responder status in their last YBOCS assessment. The number of sessions and number of days required to reach first response and sustained 1-month or longer response, are shown in Fig. 2. First response was achieved in average after 18.5 (SD = 9.4) sessions, or 31.6 (SD = 25.2) days. The onset of a one-month or longer period of sustained response was in average after 20 (SD = 9.8) sessions, or 32.1 (SD = 20.5) days.

Kaplan-Meier survival analysis revealed that after 31 days the rate of response was 50%, and after 60 days it was 78% (Fig. 3).

The cumulative survival table is shown in Table S1 in the supplementary Material.

The improvement in YBOCS score from baseline was statistically significant ($p < 0.0001$; $t = 45.02$, $df = 4405$), and up to 40 dTMS sessions a continuous gradual reduction in the YBOCS scores is evident. Beyond that point there were too few subjects to draw any conclusions.

The means and SEM of % change in YBOCS score from baseline, as well as the total YBOCS score, as a function of the number of sessions, are plotted in Fig. 4. The numbers of patients who received a certain number of sessions are plotted above the X axis.

Among 15 patients who received the iTBS protocol, 14 (93.3%) achieved first response, 5/6 (83.3%) who had one-month follow-up achieved sustained response, and 6/8 (75%) who had YBOCS scores after 29 sessions were responders at this time point.

4. Discussion

This post-marketing study covering 219 OCD patients is the first naturalistic study of dTMS for OCD. We observed a first response rate of 72.6% and a sustained ≥ one-month response rate of 52.4%. Additionally, 57.9% of patients reach response after 29 dTMS sessions, a higher response rate than the 38.1% reported in the active arm of the sham-controlled multicenter study (Carmi et al., 2019b). This result demonstrates that variations in application did not degrade outcomes compared to the clinical trial settings, and outcomes of many interventions in real-life practice vary when compared to clinical trial settings (Anglemyer et al., 2014). In the original multicenter clinical trial, study subjects in the active treatment group may have had a reduced therapeutic effect due to the uncertainty on whether they are receiving a placebo or an active treatment (Jonas, 2019). Following the success of the multicenter study, there were concerns regarding the feasibility of obtaining the same degree of success in resistant patients in the community. These concerns stemmed primarily from the expected variance in application of provocations resulting from the absence of a singular exposure therapy expert which benefited the multicenter study. The present study refutes this concern and to the contrary, response rates are even higher in a real-world clinical setting than was seen in the multicenter clinical trial. Another possible reason for the higher response rate noticed in the real-world clinical practice is the clinicians' option to increase frequency of exposure therapy or use augmentation medications, neither of which were allowed in the rigorous sham-controlled study.

There are several theories to account for symptoms in OCD, but deficiencies in extinction and inhibitory learning are well accepted (McGuire et al., 2016; Shayganfard et al., 2016; Coutinho et al., 2017; Norman et al., 2018; Seo et al., 2018; McGuire and Storch 2019). In this analysis, perhaps the treatment was effective without the use of exposure therapy experts because all that is necessary from the brief provocation is activation of the underlying OCD circuitry, which is

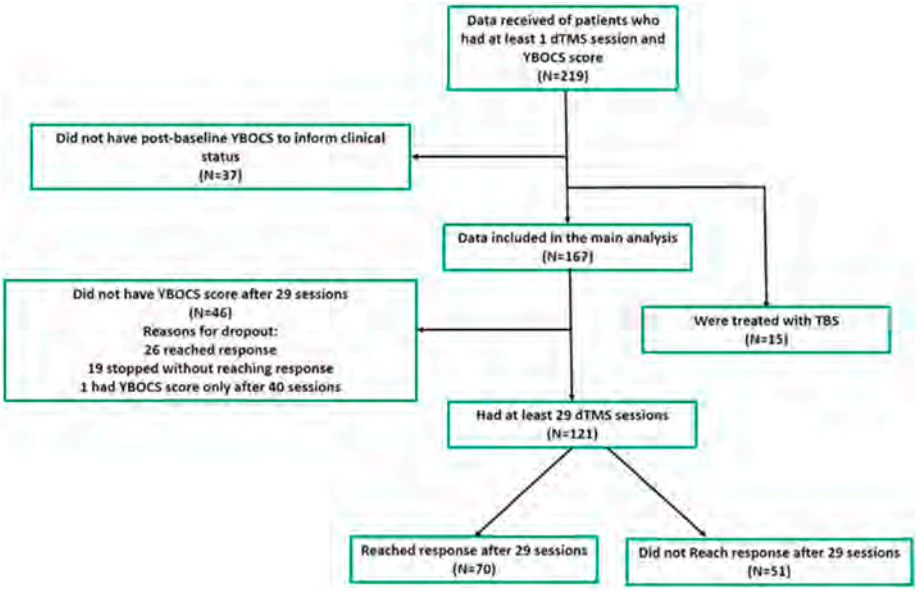

Fig. 1. CONSORT flow diagram for the real-world data collection of OCD patients treated with dTMS.

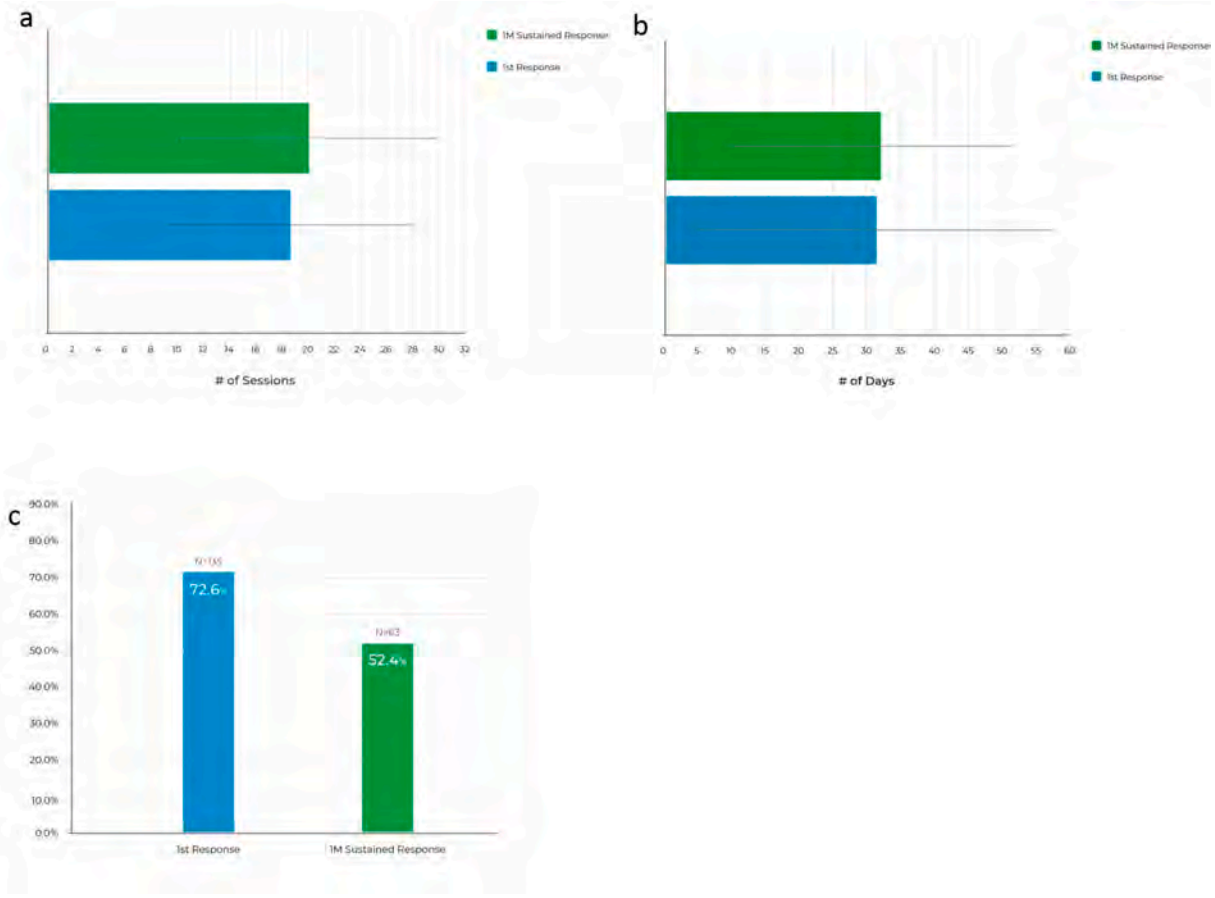

Fig. 2. a. Number of dTMS sessions required to reach first response and sustained ≥1-month response, based on the YBOCS score. b. Number of days required to reach first response and sustained response. Shown are means±SDs. c. Percentages of patients who reached the respective goal (first response and sustained response). Numbers of subjects N for each case are shown above the % of benefited subjects.

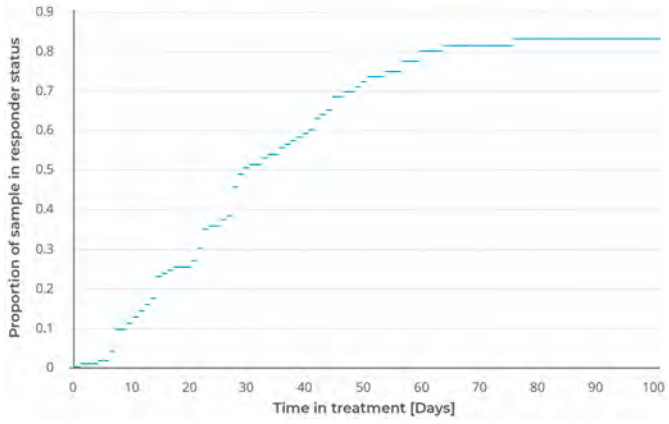

Fig. 3. Cumulative incidence (1- survival) plot of response. The event is first occurrence of ≥30% improvement from baseline YBOCS score among subjects remaining in the study at a given time point.

accomplished by creating a few minutes of doubt and not allowing the patient to alleviate it through a compulsion. We postulated that such activated circuitry is more amenable to change and long-term modulation by repeated stimulation through Hebbian plasticity mechanisms (Hebb 1949; Chiappini et al., 2018; Zibman et al., 2019). A putative mechanism is that dTMS interferes with or interrupts this circuitry during a period of reconsolidation (Birbaumer, 2010; Censor et al., 2010) and subsequently strengthens compensatory activity. A hint to this was seen in the pilot study, where responders expressed enhanced error related negativity (Carmi et al. 2018, 2019a). However, these mechanistic speculations warrant further investigation.

An important question for OCD patients is the time to onset of response. A meta-analysis of studies of SRIs for OCD found that clinical effect was usually manifested after 10–13 weeks (Soomro et al., 2008). In the current analysis, we found that over 70% of patients reached response and over 50% attained sustained response of at least one month after an average of 18–20 dTMS sessions or 31–32 days. There was high degree of variability, with the standard deviation of first response ranging between 9 and 28 sessions (6–57 days). Yet, part of this variability stems from the scarcity of the data, since for many patients, post-baseline YBOCS scores were reported only after more than 20 sessions, and part of them were in response at that time point. Hence, the number of sessions and days to reach response are most probably over-estimated, and more accurate data may lead to shorter estimates and lower variability. Regardless, the vast majority of OCD patients gain clinical benefit from dTMS and the onset of effect is relatively quick compared to psychotherapy and pharmacotherapy. Moreover, the data of first response (after 18.5 sessions) and 1-month sustained response (after 20 sessions) seems to indicate that once a subject reaches response the improvement will last at least 1-month. Therefore, besides the acute and relatively quick efficacy, dTMS seems to induce neuroplastic changes that may explain the long-term clinical effect. Additionally, OCD symptoms as assessed by the average YBOCS score seem to indicate continuous improvement with increasing number of dTMS sessions (Fig. 4), and the rate of response increases dramatically with the time in treatment (Fig. 3). Hence, many initial non-responders may benefit from continued dTMS treatment.

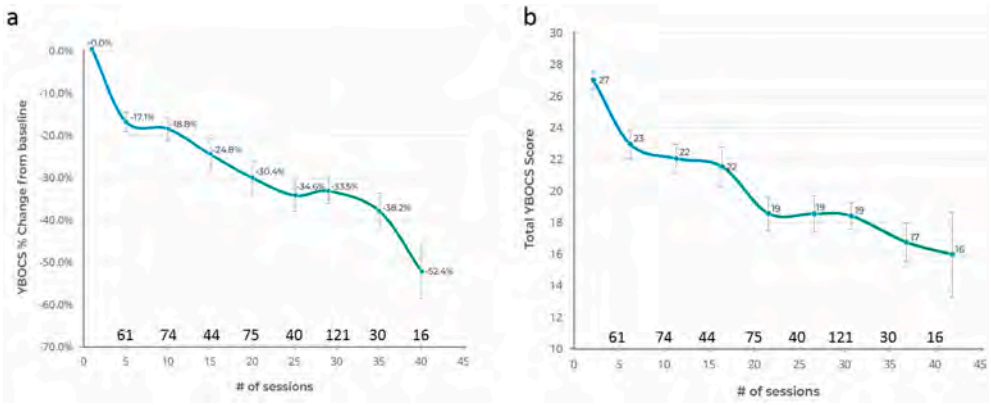

Fig. 4. The % change in YBOCS score compared to baseline (a), and the total YBOCS score (b), as a function of number of dTMS sessions. Shown are means±SEMs. The numbers above the x axis indicate numbers of subjects who had YBOCS scores at the respective number of sessions.

This real-world analysis is primarily limited by the amount of information that sites were able to submit for analysis. A minority of the sites did not fill out demographic information and only shared the number of treatments and YBOCS scores. The main limitation is that only a small percentage of the sites took the time to participate, even though we know the utilization patterns from many more sites that are treating OCD patients with anecdotal reports of very high success rates. Their focus is treating patients and not consistent detailed documentation or research. Potential solutions to the deficiencies in real world evidence data collection require interoperable technologies to enable consensual effortless sharing between electronic health records, patient mobile health applications or wearables and surveys (Evans 2016; Scholte et al., 2016; Shickel et al., 2018). We hope to use these in the future in order to gain information from a larger cohort of patients in a naturalistic setting, such as in the present study. Moreover, the naturalistic data is by its nature incomplete and may lead to bias. For example, the data on response after 29 sessions may be biased by the patients who dropped out at an earlier stage. 57.8% of those earlier quitters reached response. Hence it is possible that the dropout led to decreased measured response rates after 29 sessions. Likewise, data of one-month follow-up after response or one-month without response was available for only 63 patients. Yet, the vast majority of patients who reached response at any time point (92 of 113, 81.4%) were responders in their last YBOCS assessment. Hence, it is possible that sustained response is attained by much more than 52.4% found in this study among the patients who had one-month follow-up data. Another limitation is that dTMS treatment for OCD is currently not reimbursed by insurance. Hence the patients payed out-of-pocket for the treatment. This may introduce a bias towards increased response rates due to cognitive dissonance.

Ethics approval and consent to participate

Study exempt from informed consent by Sterling IRB as discussed in the manuscript.

Availability of Data: It is still being actively collected to answer further questions, and is only available for co-contributors to analyze, not the general public.

Authors' contribution

Aron Tendler, Yiftach Roth, Abraham Zangen: Post marketing project design, manuscript writing and data analysis. Tal Harmelech: Data collection, manuscript writing and data analysis. Aron Tendler, Kemal Arikan, Ryan Vidrine, David Kent, Owen Muir, Carlene MacMillan, Leah Casuto, Deborah Kim, Brent Peterson, Geoffrey Grammer, William Sauve, Kellie Tolin, Steven Harvey, Misty Borst, Robert Rifkin, Manish Sheth, Brandon Cornejo, Raul Rodriguez, Saad Shakir, Taylor Porter, Julia Swofford, Brendan Roe, Rebecca Sinclair: Data contribution and manuscript review.

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Declaration of competing interest

Aron Tendler, Abraham Zangen, Yiftach Roth and Tal Harmelech have a financial interest in BrainsWay. Aron Tendler, Kemal Arikan, Mark DeLuca, Ryan Vidrine, David Kent, Owen Muir, Carlene MacMillan, Leah Casuto, Deborah Kim, Brent Peterson, Geoffrey Grammer, William Sauve, Kellie Tolin, Steven Harvey, Misty Borst, Robert Rifkin, Manish Sheth, Brandon Cornejo, Raul Rodriguez, Saad Shakir, Taylor Porter, Piper Buersmeyer, Julia Swofford and Brendan Roe have a financial interest in commercial TMS.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.11.009.

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