ARTICLE IN PRESS

Brain Stimulation xxx (2017) 1–8

Contents lists available at ScienceDirect

Brain Stimulation

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

Clinical and electrophysiological outcomes of deep TMS over the medial prefrontal and anterior cingulate cortices in OCD patients

Lior Carmi [a,b], Uri Alyagon [b], Noam Barnea-Ygael [b], Joseph Zohar [c], Reuven Dar [a], Abraham Zangen [b,*]

[a] School of Psychological Sciences, Tel Aviv University, Tel Aviv, Israel
[b] Department of Life Sciences and the Zlotowski Center for Neuroscience, Ben-Gurion University of the Negev, Beer-Sheva 84105, Israel
[c] Tel Aviv University, Sackler Faculty of Medicine, Tel- Aviv, Israel

ARTICLE INFO

Article history:
Received 17 March 2017
Received in revised form
3 July 2017
Accepted 4 September 2017
Available online xxx

Keywords:
dTMS
ACC
ERN
OCD

ABSTRACT

Background: Obsessive Compulsive Disorder (OCD) is a chronic and disabling disorder with poor response to pharmacological treatments. Converging evidences suggest that OCD patients suffer from dysfunction of the cortico-striato-thalamo-cortical (CSTC) circuit, including in the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC).
Objective: To examine whether modulation of mPFC-ACC activity by deep transcranial magnetic stimulation (DTMS) affects OCD symptoms.
Methods: Treatment resistant OCD participants were treated with either high-frequency (HF; 20 Hz), low-frequency (LF; 1 Hz), or sham DTMS of the mPFC and ACC for five weeks, in a double-blinded manner. All treatments were administered following symptoms provocation, and EEG measurements during a Stroop task were acquired to examine changes in error-related activity. Clinical response to treatment was determined using the Yale-Brown-Obsessive-Compulsive Scale (YBOCS).
Results: Interim analysis revealed that YBOCS scores were significantly improved following HF ($n = 7$), but not LF stimulation ($n = 8$), compared to sham ($n = 8$), and thus recruitment for the LF group was terminated. Following completion of the study, the response rate in the HF group ($n = 18$) was significantly higher than that of the sham group ($n = 15$) for at least one month following the end of the treatment. Notably, the clinical response in the HF group correlated with increased Error Related Negativity (ERN) in the Stroop task, an electrophysiological component that is attributed to ACC activity.
Conclusion: HF DTMS over the mPFC-ACC alleviates OCD symptoms and may be used as a novel therapeutic intervention. Notwithstanding alternative explanations, this may stem from DTMS ability to directly modify ACC activity.

Introduction

Obsessive Compulsive Disorder (OCD) is a chronic condition with a life time prevalence of ~2.3% [1], which is considered by the World Health Organization as one of the ten most disabling disorders [2]. Although the combination of cognitive behavioral therapy (CBT) and serotonin reuptake inhibitors (SRIs) stands as a first line treatment for OCD [3], the clinical challenge still remains. This is due to the complexity and heterogeneity of the disorder [4], the high percentage of patients that are drug-resistant or that cannot tolerate the drug-related side effects [5,6], and the relative low percentage of patients that receive CBT [7].

One alternative treatment is non-invasive brain stimulation using transcranial magnetic stimulation (TMS). TMS enables alteration of neural activity in specific brain regions, molding plasticity at the network level [8], and modulating cortical excitability in both motor and non-motor areas [9]. Low-frequency (LF) TMS (~1 Hz) is generally thought to produce inhibitory effects, whereas high-frequency (HF) TMS ($\geq$5 Hz) is generally thought to produce excitatory outcomes [10]. Several studies have tried to harness TMS to treat OCD, and a recent meta-analysis concluded that although active TMS was found to be clinically and statistically superior to sham TMS, a consensus intervention protocol has yet to emerge

* Corresponding author. Department of Life Sciences and the Zlotowski center for Neuroscience, Ben-Gurion University, PO Box 653, Beer Sheva 84105, Israel.
E-mail address: azangen@bgu.ac.il (A. Zangen).

http://dx.doi.org/10.1016/j.brs.2017.09.004

[11]. Up until now, most studies targeted the supplementary motor area (SMA) or components of the cortico-striato-thalamo-cortical (CSTC) circuits - the dorsolateral PFC (DLPFC) and orbitofrontal cortex (OFC). Indeed, converging evidence points towards the involvement of the CSTC circuits in the etiology of OCD [12], including structural abnormalities [13,14] and impaired function of the CSTC circuit as a whole [15–17], or of its different components [15,18–22]. For example, the anterior cingulate cortex (ACC) and the medial prefrontal cortex (mPFC) were found to be hyperactive in OCD patients while detecting cognitive conflicts [23] or making an error [24].

Over-reaction to errors is a common feature to many individuals with OCD [15,25]. Patients often report a distressing sense of incompleteness and a drive to perform an action until this sensation is reduced and things look, feel, or sound “just right” [15,25]. One example for such over-reaction can be evident in tasks that include commission of a mistake, such as Stop-Signal, Flanker, or Stroop tasks [26–31]. In these tasks, OCD patients display an increased Error-Related Negativity (ERN) electroencephalogram (EEG) signal following a mistake [16,23,26,28,32–34]. This ERN signal is attributed to ACC activity and is most evident within the theta frequency band (4–8 Hz) recorded over the mPFC [35]. Notably, deep rTMS treatment over the mPFC with a double-cone coil improved both OCD symptoms and post-error slowing, which suggests a correlation between error monitoring impairment and OCD pathophysiology [36].

Taken together, the ACC and mPFC may stand as favorable targets for intervention in OCD. These brain regions can be stimulated directly using deep TMS with the H7-coil (Fig. S1 and [37]). However, the most effective frequency of stimulation cannot be predicted. On the one hand, the mPFC and ACC are hyperactive in OCD and thus an inhibitory LF stimulation may be efficacious (e.g., [38]). On the other hand, HF stimulation can disrupt activity and induce long term effects, as recently shown for nicotine addiction, where high (but not low) frequency stimulation of the insula was effective [39] although the insula is actually thought to be hyperactive in addicts [40]. Moreover, HF in animal models produces more consistent and lasting neuroplastic effects [41]. Hence, in the current study, in an attempt to affect OCD symptoms, we tested either HF or LF stimulation over the mPFC and ACC using the H7-coil. We also hypothesized that clinically-beneficial stimulation will affect ACC activity, which will be evident as modified ERN response and therefore providing a potential electrophysiological biomarker for the treatment effect.

Methods and materials

Procedure

The experiment included baseline clinical and electrophysiological measurements in 41 OCD patients, a 5-weeks treatment phase, corresponding measurements, and a one month follow-up phase. The study was performed at Chaim Sheba Medical Center, Israel (2012–2014), and the protocol was approved by the local Institutional Review Board and the Israeli Ministry of Health.

Participants

Forty one OCD participants who met stage III criteria (failure of two SRI trials plus CBT, Table S1) [42] were recruited via newspapers and internet advertisements, and from the outpatient program at Chaim Sheba Medical Center. The inclusion criteria were: 18–65 years old; current DSM-IV diagnosis of OCD; a score of ≥20 in the Y-BOCS (20 items) [43]; CBT at maintenance phase (if conducted); and stable SSRI medications maintenance for 8 weeks prior to enrollment, and unchanged during treatment. Exclusion criteria included any other Axis-I psychopathology or a current depressive episode. All participants signed a written informed consent form.

Clinical procedure

All participants underwent clinical assessment that included the Mini-International Neuropsychiatric Interview (MINI) [44], the Yale-Brown-Obsessive-Compulsive Scale (YBOCS) [43], an IQ assessment using the Raven's Progressive Matrices test (RSPM) [45], the Hamilton's depression rating scale (HAM-D; 24-item) [46], and the Clinical Global Impressions of severity (CGI-S) [47]. Participants were randomly assigned to receive 1 Hz stimulation (LF), 20 Hz stimulation (HF), or sham stimulation, using a computer program (Interactive Web Randomization System; Medpace's ClinTrak, USA). All groups were treated five times per week for five weeks (for a total of 25 sessions), and each treatment session began with an exposure to personalized obsessive-compulsive cues.

The primary and secondary efficacy measures, YBOCS and CGI-I [47], were performed at baseline (pre-treatment), prior to the second treatment session in weeks 2–4, prior to the last treatment session (post-treatment), and at 1-week and 1-month follow-ups (1 W and 1M FU) visits. Evaluations were performed by clinically trained raters in a blinded manner, and the efficacy outcome in these measures was the change from Pre-to Post-treatment. For YBOCS, the clinical response was defined as a reduction of 30% [42]. This threshold was set in accordance with the literature, taking into account the study population (stage III criteria [42]). Nevertheless, results using the more common threshold of 35% reduction in YBOCS scores are also reported. For CGI-I, response was defined as a score≤2 (very much improved or much improved).

Provocation of OCD symptoms

The effects of DTMS seem to be most pronounced when the targeted circuit is active. For example, a brief exposure to the traumatic memory in post-traumatic stress disorder (PTSD) participants [48], or to smoking cues in heavy smokers [39], increased treatment response compared to the unexposed group. This phenomenon can be explained, at least in part, by accumulating evidences suggesting that items that are stored in long-term memory become prone to change (e.g., by stimulation) upon their retrieval (e.g., following provocation) [49,50].

Specifically for OCD, hyperactivity of different components of the CSTC circuit was observed following symptom provocation [17,51,52]. Therefore, prior to each session a provocation was administrated by the operator. For each patient, a list of personalized provocations was designed by a clinician during the first assessment meeting. These provocations were designed to achieve a self-report score between 4 and 7 on a 1 to 10 visual analog scale (VAS), and were recorded on the case report forms (CRFs). Following each treatment, participants were allowed to perform any relevant ritual they desired.

Deep rTMS

DTMS offers a non-invasive tool to stimulate deep-located regions such as the ACC. DTMS was administered using a Magstim Rapid[2] TMS stimulator (The Magstim Co. Ltd., Whitland, Carmarthenshire, United Kingdom) equipped with an H7-coil (specifically designed to stimulate the ACC, Supplementary material 1.1).

During each DTMS session, the optimal spot on the scalp for leg motor cortex stimulation was localized, and the leg resting motor threshold (RMT) was defined. The coil was then moved forward 4 cm anterior to the motor spot and aligned symmetrically over the mPFC. HF and LF stimulation trains of pulses were delivered at 100% and 110% of the leg RMT, respectively (different intensities were employed for safety reasons, taking into account patients with augmentation medications such as D2 antagonists and the higher risk for HF stimulation). HF (20 Hz) sessions consisted of 50 trains lasting 2 s each, with an inter-train interval of 20 s (2000 pulses in total), while LF (1 Hz) sessions consisted of 900 consecutive pulses. Sham stimulation (randomized to mimic either HF and LF stimulation), and the determination of the type of stimulation for each individual (HF, LF or sham) were performed as previously described [39,53] (Supplementary material 1.4). Participants were told that physical sensations may be induced by both real and sham coils, operators and raters were blind to the type of treatment, and raters were not allowed to be present during treatments. Following the first treatment, participants were asked to guess which treatment they were assigned to (active\sham) by choosing one of the following answers: 1. I do not know, 2. Uncertain that I received active\sham treatment, 3. Strong feeling that I received active\sham treatment. 4. Active\sham group.

Electrophysiological recording during a stroop task

EEG recordings during a Stroop task were performed at Pre- and Post-treatment time-points. The Stroop task was administered using E-Prime software (Psychology Software Tools, Inc.) on a 17 inch computer screen, as previously described [54]. Participants were instructed to press the key associated with the color of the word while ignoring the word's meaning (Supplementary material 1.5). EEG was recorded using the ASA lab (A.N.T. Enschede, Netherlands), with a 32 channels cap (Waveguard) and two Electrooculography (EOG) channels. Electrode impedances were kept below 10 KΩ, and all channels were average referenced. Data were collected at 250 samples per second and digitized with a 24-bit AD converter.

EEG analysis

Detailed description is provided in the Supplementary material 1.6. In brief, continuous EEG data were filtered using 1–100 Hz band-pass and 50 Hz notch, and were segmented into trials that were time-locked to the participants' response. The segmented data were baseline corrected, and noisy segments or channels were removed. Data were then gathered according to conditions (congruent/incongruent), divided by response type (correct/mistake) and filtered to the theta band (4–8 Hz). Since most of the mistakes (93%) were made within the incongruent trials, analysis was carried out solely for this condition. The amplitudes following responses (0–120 ms, see supplementary material 1.6) were computed using an adaptive mean measure. In addition, we used a wavelet transform analysis to convert the data from a time to a frequency domain. Thus, the mean theta power from the Cz electrode, ranging between 0 and 120 ms post response, was converted to decibels (dB) [27], and the power spectral perturbation was expressed as a change from baseline (in dB). All EEG analysis was performed using MATLAB's EEGLAB toolbox.

Statistical analysis

Data analysis was performed using STATISTICA software, version 12 (StatSoft, Tulsa, OK).

Interim analysis - In an attempt to maximize the clinical benefit to the participants, an interim analysis was carried out midway through the experiment ($n = 7$, 8, and 8 for the HF, LF, and sham groups, respectively). We used a mixed model ANOVA with Group (HF, LF and sham) and Time (baseline and weeks 2–5) as independent variables and YBOCS scores as the dependent variable. Thereafter, we performed a 3X2 ANOVA analysis with Group (HF, LF and sham) and Time (Pre- and Post-treatment) to compare the effect of stimulation. Following this analysis, the LF group was excluded from the study due to the lack of consistent response in this group (as detailed below) and given the limited rate of recruitment of the study population.

Final analysis - For the behavioral data, we used a mixed-model ANOVA with Group (HF and sham) and Time (baseline and weeks 2–5) as independent variables, and the scores of YBOCS and CGI-I as dependent variables. Significant results were further analyzed with Tukie post-hoc. Analyses of 1 W and 1M FU results were compared using T-tests and the required p value for significance was corrected (p_C) for the relevant number of comparisons. Chi-square test was used to compare blinding and response rates.

EEG amplitude and power were analyzed using a mixed-model measure ANOVA with Group (HF and sham), Time (Pre- and Post-treatment), and Response type (correct and mistake) as independent variables, and with theta band dB mean power (0–120 ms post response) as the dependent variable. Significant results were further analyzed using Tukey post-hoc. All data are presented as mean±SEM.

Results

The three groups did not differ in their baseline characteristics of gender, age, IQ, concomitant medication, depression, or OCD severity (Table 1). No severe adverse events were recorded, and the treatment was well-tolerated by most participants. Side-effects that included headaches and fatigue were reported by four participants (three from the HF group and 1 from the sham group). Three participants dropped out during treatment - one due to conflicting schedule (sham group) and two due to inconvenience with the treatment (HF group). Thus, the final analysis consisted of 38 participants (out of 41 randomized) that completed the treatment (see Consort chart in Fig. S2). Most of the participants did not guess which group (active \ sham) they were assigned to (75%, 88% and 86% chose option #1 (“I don't Know”) from the LF, HF, and sham groups, respectively; $\chi^2 = 0.66$, $p = 0.71$). One participant out of each group correctly chose option #2 (uncertain that I received active\sham), and one out of each group falsely chose option #3 (Strong feeling that I received active\sham treatment). These percentages imply that the blinding process was well established.

Interim analysis

Repeated measures analysis for the five weeks of treatment revealed a near significant Group X Time interaction ($F_{8, 80} = 1.81$, $p < 0.08$), and analysis comparing the change from Pre to Post

Table 1
Baseline demographic and clinical characteristics.

	Sham	LF[a]	HF	p
Sample size	14	8	16	
Female\Male	7/7	4/4	7/9	n.s.
Age	35 ± 3.5	28 ± 3.1	36 ± 2.1	n.s.
Raven IQ	38 ± 5.8	34 ± 6.3	47 ± 6.6	n.s.
YBOCS	26 ± 1	25 ± 1.2	28 ± 0.7	n.s.
HAMD-21	9 ± 0.88	10 ± 1.2	9 ± 0.97	n.s.
CGI - S	5 ± 0.6	5 ± 0.5	5 ± 0.5	n.s.
D2 antagonist augmentation	6/14	3/8	5/16	n.s

YBOCS, Yale–Brown Obsessive Compulsive Scale; HAMD-24, Hamilton Depression Rating Scale – 24-item; CGI-S, Clinical Global Impression – Severity. All means are accompanied with SEM scores.
[a] See interim analysis for differences in sample size.

Please cite this article in press as: Carmi L, et al., Clinical and electrophysiological outcomes of deep TMS over the medial prefrontal and anterior cingulate cortices in OCD patients, Brain Stimulation (2017), http://dx.doi.org/10.1016/j.brs.2017.09.004

treatment revealed a near significant effect for the HF ($F_{1, 20} = 5.38$, $p = 0.055$), but not for the LF ($F_{1, 20} = 1.23$, $p = 0.28$) treatment over sham (see details in Supplementary material 2.1). Taking into account the lack of trend in the LF group, the fact that 2 out of 8 patients in the LF group demonstrated an increased YBOCS score following treatment, and given the limitation of resources and slow recruitment rate, the LF arm of the study was omitted. Further recruitment was carried out only for the HF and sham groups, using the same double-blind arrangements, and all forthcoming analysis will compare the results of these two groups.

Final analysis

Sixteen participants in the HF group and 14 participants from the sham group completed all stages of the study and were included in the final analysis.

Clinical results

The primary analysis for the efficacy of the treatment was the percent change in YBOCS scores. This analysis revealed a significant Group X Time interaction ($F_{4, 112} = 7.81$, $p < 0.001$), and a post-hoc analysis revealed significant differences between the groups at weeks 4 ($p < 0.01$) and 5 ($p < 0.01$; Fig. 1a). In accordance with these results, a significantly higher proportion of participants from the HF group (seven participants; 43.75%) compared to the sham group (one participant; 7.14%) reached the predefined response criteria (i.e. 30% reduction in YBOCS relative to baseline) after five weeks of treatment ($\chi^2 = 5.11$, $p < 0.05$; Fig. 1b). Calculating the response rate using the more restrictive criteria of 35%, we found that five participants (29.41%) from the HF group and one participant (7.14%) from the sham group were defined as responders ($\chi 2 = 2.71$, $p < 0.10$).

Analysis of the YBOCS scores during follow-up visits revealed a significant difference between the HF and sham groups at the 1 W FU visit (n = 11 and 13, respectively; $t_{22} = 3.46$, $p_C < 0.05$). At this time point, 5 participants (45.45%; only one with less than 35% score reduction) of the HF group and 1 participant (7.69%) from the sham group were defined as responders ($\chi 2 = 4.53$, $p < 0.05$). During the 1M FU, YBOCS scores continued to be stable, but significance was lost (n = 9 and 9, respectively; $t_{16} = 2.06$, $p_C < 0.6$). At this time point, 4 participants (44.44%; only one with less than 35% score reduction) of the HF group and none of the participant from the sham group were defined as responders ($\chi 2 = 5.14$, $p < 0.05$).

Analysis of the CGI–I scores revealed a significant main effect for Group ($F_{1, 24} = 10.55$, $p < 0.01$; Fig. 1c). In accordance with this result, a significantly higher proportion of participants from the HF group (11 participants; 64.7%), compared to the sham group (one participant; 7.1%), reached the predefined response criteria after five weeks of treatment ($\chi^2 = 11.80$, $p < 0.001$; Fig. 1d). Here again, there was a significant difference between the HF and sham groups in the 1 W FU ($t_{20} = 3.40$, $p_C < 0.05$), while 1M FU scores remain low but without a significant difference between the groups ($t_{16} = 2.23$; $p_C = 0.23$). During the 1 W FU, 7 participants (63.63%) of the HF group and 1 participant (7.69%) from the sham group were defined as responders ($\chi 2 = 8.39$, $p < 0.01$); while during the 1M FU, 5 participants (55.55%) of the HF group and 3 participants (33.33%) from the sham group were defined as responders ($\chi 2 = 0.9$, $p < 0.35$).

Stroop-EEG analysis

We excluded from the analysis patients who had more than 90% mistakes (2 from the HF group and 3 from the sham group), and

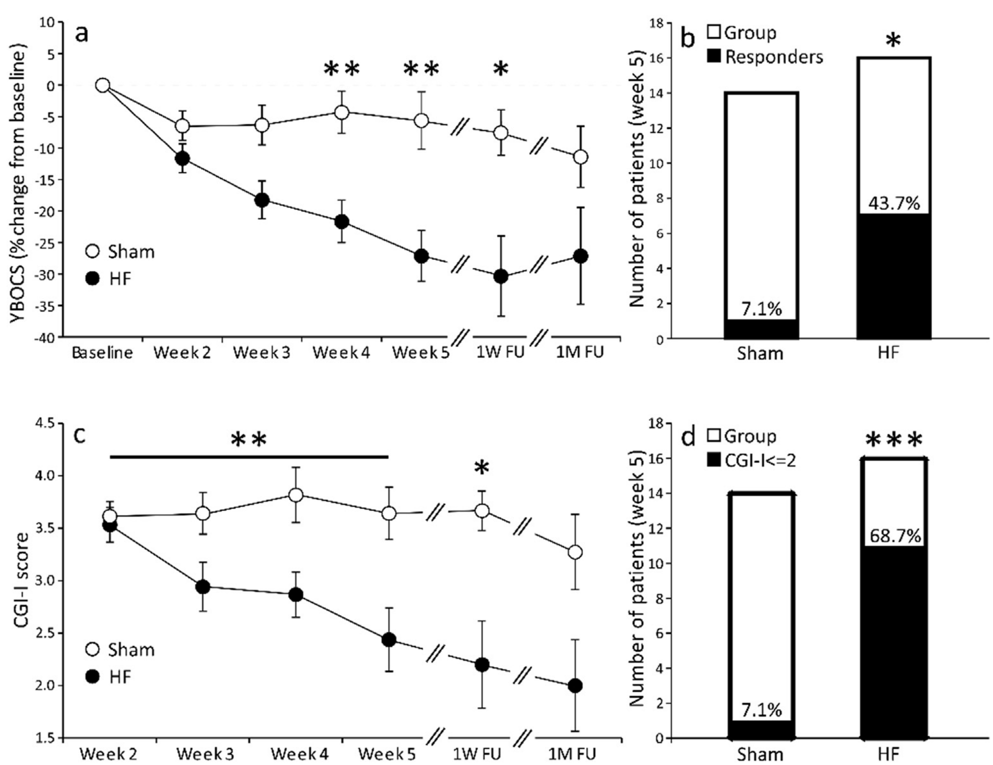

Fig. 1. Clinical effect of the treatment. **Panel a** presents mean + SEM changes in YBOCS scores from baseline along the study, for the HF and sham groups. **Panel b** presents the number and percentage of participants who responded to treatment (i.e. 30% reduction in symptoms at week 5) in each group. **Panel c** and **d** presents changes from baseline in CGI-I scores and the percentage of participants that benefit from the treatment, in each group. *p < 0.05, **p < 0.01, ***p < 0.001.

patients who had no mistakes at all (1 from HF group and 2 from the sham group). Thus, the final ERN analysis included 13 participants from the HF group and 9 participants from the sham group, with no differences in behavioral mistake percentage at baseline (13 ± 3.4% and 8 ± 2.3%, respectively), or following treatment (14 ± 2% and 12 ± 2.5%, respectively).

The ERN response expressed in the theta band (0–120 ms post response) was similar in both groups at baseline, but there was a shift towards increased ERN in the HF group, and decreased ERN in the sham group following treatment (Fig. 2).

Analysis of the theta power revealed a significant Group X Time X Response interaction ($F_{1,\ 20}$ = 4.11, $p < 0.05$); and post-hoc analysis revealed significant post-treatment differences between the groups. Specifically, theta activity in response to a mistake following treatment was higher in the HF group when compared to that of the sham group ($F_{1,\ 20}$ = 6.8, $p > 0.01$; Fig. 3).

Notably, the effect of treatment on ERN correlated with its effect on symptom severity in the HF group ($r = 0.63$, $p < 0.01$), but not in the sham group ($r = -0.42$, $p < 0.26$; Fig. 4).

Finally, a secondary analysis revealed gender differences in response to treatment, such that men were significantly more prone to respond than women (Supplementary material 2.2).

Discussion

The present study is the first to explore the safety, tolerability, and efficacy of multiple sessions of DTMS in the treatment of OCD. The results indicate that HF stimulation over the mPFC and ACC is a safe and effective intervention for the alleviation of OCD symptoms in participants who failed to receive sufficient benefit from previous treatments. We found that compared to sham treatment, the response rate following HF treatment was significantly higher for up to one month, and that the reduction in symptoms severity was related to the magnitude of changes in the ERN response.

In this study, both HF and LF DTMS using the H7 coil turned out to be safe and overall well tolerated by OCD participants. No severe adverse events such as seizures occurred, and the most frequent side-effects included mild headaches during, or immediately following, stimulation; a pattern that is in line with a recent comprehensive review [55]. In addition, response within the sham group was very low and in agreement with former sham-controlled TMS studies [56], implying that the obtained results are due to stimulation and are not merely a consequence of provocation-induced exposure therapy.

The fact that HF stimulation was superior over LF stimulation seems counterintuitive, as it would be expected that reducing excitability, rather than increasing it in the hyperactive mPFC and ACC of OCD patients would induce a therapeutic effect [57]. Nevertheless, cumulative data suggest that the notion of excitatory HF vs. inhibitory LF stimulation is oversimplified [55,58]. High-frequency stimulation, which is considered to be excitatory, can also disrupt neural activity, and was shown to be a more effective tool when attempting to induce long-term clinical effects. For example, in cigarette smokers high (but not low) frequency rTMS directed to the insula reduced cigarette consumption [39] which mimics the effect of damage to this area. In addition, stimulation of the SMA with both LF [36,59–61] and HF [62] were shown to reduce YBOCS scores in OCD patients, and several other studies reported successful intervention by either HF or LF targeting the right, left or bilateral DLPFC [63–66], or the left OFC [67], while others reported no difference between real or sham stimulation [68–74].

One mechanism that can explain the observed results is that neuromodulations induced by HF stimulation in the mPFC and ACC reinforced participants' ability to exert inhibitory control over their compulsive behavior. An additional factor that may contribute to the effect of stimulation is the state of the relevant neuronal circuit. Specifically, this provocation-DTMS procedure that was applied here may interfere with the dysfunctional information flow in the frontal-basal ganglia circuit, which is mediated by the ACC and was suggested to be a core pathology of OCD [75]. According to this hypothesis, initiation of behavioral sequences that are stored in the PFC results in motivational distress that is only relieved upon completion of the sequences. However, in OCD participants, hyper-activation of the ACC retards the feeling of completion and generates the compulsive behavior. Consequently, provocation of personalized OCD symptoms that trigger the behavioral sequence, followed by mPFC-ACC stimulation that modulate its activity, may disrupt circuits associated with the feeling of incompleteness and may alter the dysfunctional monitoring activity. Consistent with this hypothesis, our results imply that the beneficial effect of the treatment was associated with modified theta activation over the mPFC and the ACC, which is considered to be the generator and the locus of the ERN response [76]. Particularly, the HF treatment resulted with increased ERN theta activity that was correlated with reduction of symptom's severity. To the best of our knowledge, no TMS protocols or pharmacological interventions [77] have shown such a change in ERN signal in OCD patients. Here again, the finding is somewhat counterintuitive considering that enhanced ERN is generally elicited in OCD participants in comparison to control [33], and that general hyper-activation of the ACC is commonly found in OCD participants [33]. Nevertheless, similar findings were previously observed following beneficial interventions in OCD. For example, increased resting state [78] and task-related activity [79] in the dorsal ACC (dACC) were found in participants that improved after CBT treatment. Saxena and colleges [78] suggested that

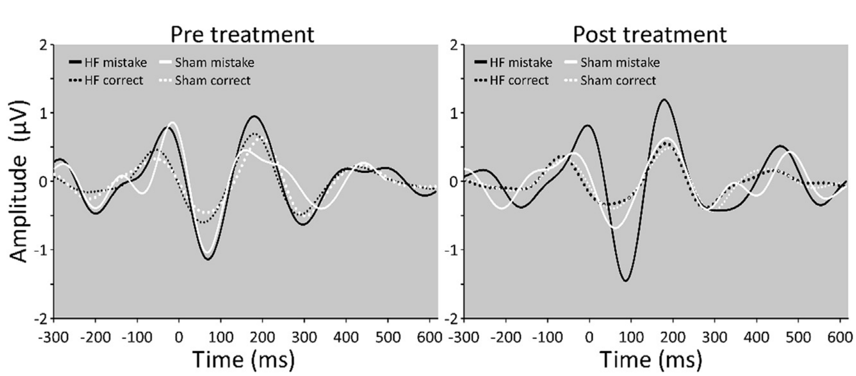

Fig. 2. Electrophysiological effect of the treatment. Grand averages of pre- and post-treatment EEG measurements during correct and mistake responses in the Stroop task, as recorded from the Cz electrode in theta band (4–8 Hz), are presented. Time point 0 is set at the motor response.

Please cite this article in press as: Carmi L, et al., Clinical and electrophysiological outcomes of deep TMS over the medial prefrontal and anterior cingulate cortices in OCD patients, Brain Stimulation (2017), http://dx.doi.org/10.1016/j.brs.2017.09.004

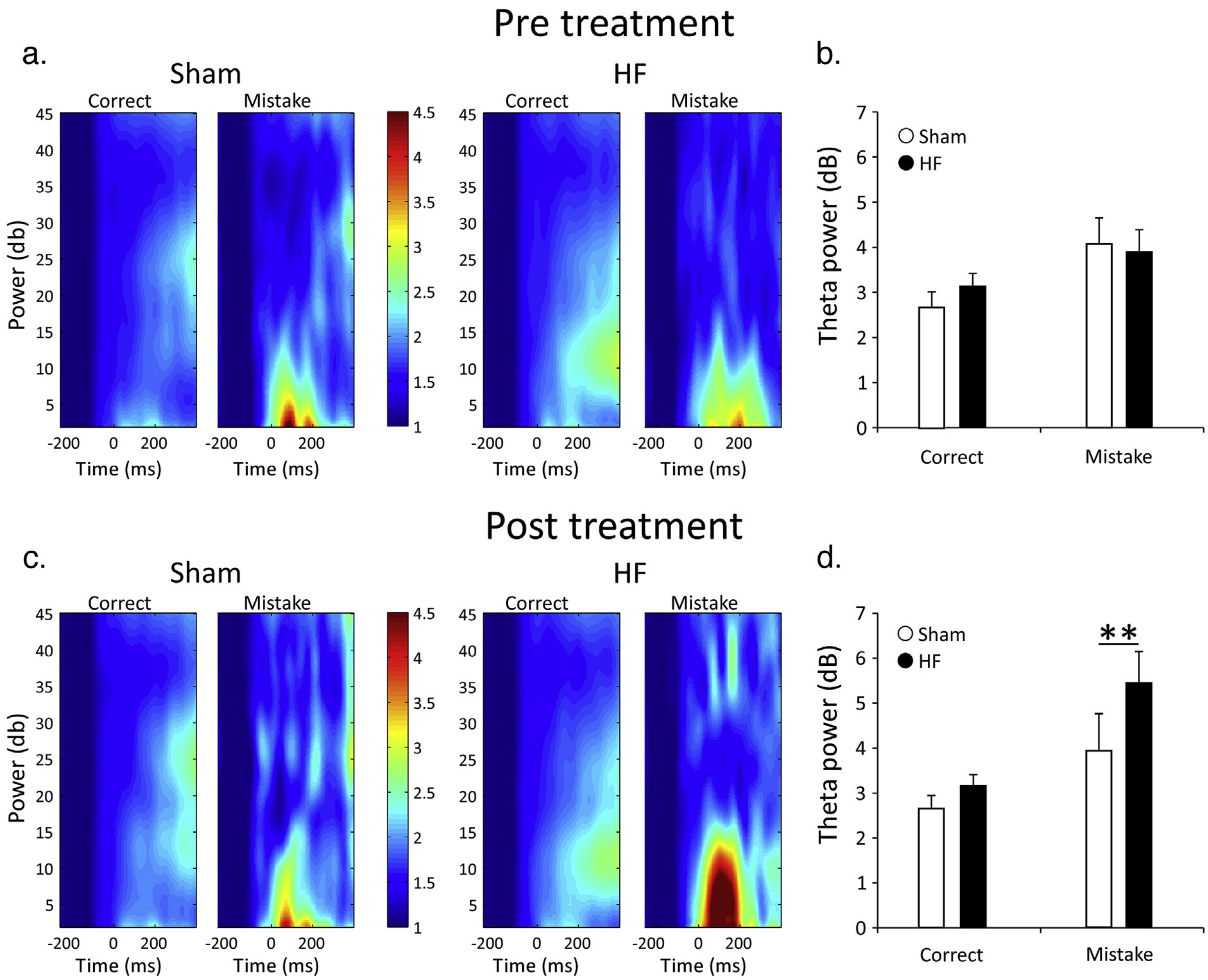

Fig. 3. Treatment effect on theta power during the Stroop task. Panels a and **c** present wavelet expression of pre- and post-treatment activity, respectively. Time point 0 represents motor response. **Panels b** and **d** present mean + SEM theta power following correct and mistake responses, pre- and post-treatment, respectively, as detailed in the text. **p < 0.01.

enhancement of dACC activity may be a primary mechanism of action of CBT for OCD, and it is therefore possible that administration of the provocation-DTMS protocol to participants undergoing CBT may produce a synergetic effect and will further improve treatment outcome.

Limitations

We note several limitations of the current study. First, the study was considered as a pilot study and the sample size is relatively small. As such, further studies should be conducted in order to

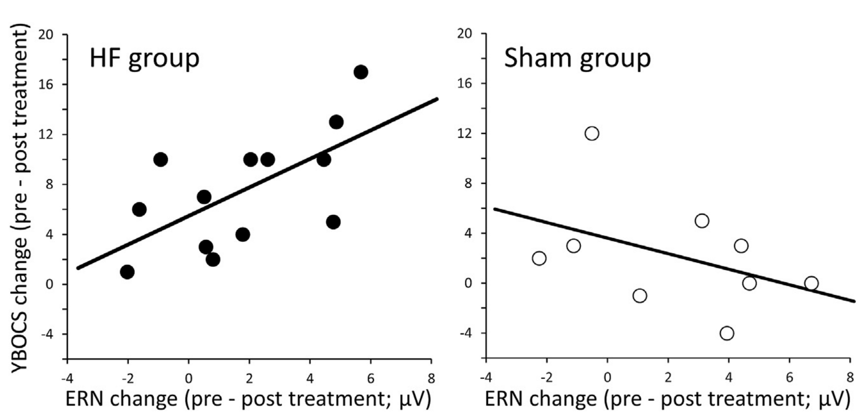

Fig. 4. Correlation between the clinical and the electrophysiological changes. Correlation between changes in YBOCS scores and ERN amplitudes (Pre-minus post-treatment) are presented for the HF and sham groups. Analysis revealed a significant positive correlation between the two measurements only in the HF group (r = 0.63, p < 0.01).

Please cite this article in press as: Carmi L, et al., Clinical and electrophysiological outcomes of deep TMS over the medial prefrontal and anterior cingulate cortices in OCD patients, Brain Stimulation (2017), http://dx.doi.org/10.1016/j.brs.2017.09.004

establish this intervention for the treatment of OCD. Second, the effect of provocation was not controlled, and relevant brain activity was not recorded during the provocation. Furthermore, the extent to which the ACC and the mPFC were adequately stimulated needs to be further investigated. Consequently, the above discussion in this matter should be regarded as speculative. Finally, the total number of pulses (over the 5 weeks of treatment) that was administered, was different between the LF group (22,500 pulses) and the HF group (50,000 pulses), which may stand as an alternative explanation for the superior efficacy of the HF treatment.

Conclusion

This study indicates that HF DTMS over the mPFC-ACC, when applied following provocation of OCD symptoms, is safe, tolerable and effective in reducing OCD symptoms. Larger studies should determine whether this promising technique may become an established treatment for OCD, while considering the option of an additional maintenance phase, as done for the treatment of major depression [53].

Financial disclosure

Dr. Zangen is a co-inventor of the TMS H-coils and serves as consultant for, and has financial interests in, Brainsway. All other authors report no biomedical financial interests or potential conflicts of interest.

ClinicalTrials.gov

Tolerability, Safety and Efficacy of the HAC-Coil Deep Transcranial Magnetic Stimulation in Medication Resistance Obsessive Compulsive Disorder (OCD) Subjects. NCT01343732.

Acknowledgements

The study was partially supported by Brainsway, which produces the deep TMS H-coil systems.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.brs.2017.09.004.

References

[1] Ruscio A, Stein D, Chiu W, Kessler R. The epidemiology of obsessive-compulsive disorder in the national comorbidity survey replication. Mol Psychiatry 2010;15(1):53–63.
[2] Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: global burden of disease study. Lancet 1997;349(9063):1436–42.
[3] Öst L-G, Havnen A, Hansen B, Kvale G. Cognitive behavioral treatments of obsessive–compulsive disorder. A systematic review and meta-analysis of studies published 1993–2014. Clin Psychol Rev 2015;40:156–69.
[4] Hollander E. Obsessive-compulsive disorder: the hidden epidemic. J Clin Psychiatry 1997;58:3–6.
[5] Leckman JF, Denys D, Simpson HB, Mataix-Cols D, Hollander E, Saxena S, et al. Obsessive–compulsive disorder: a review of the diagnostic criteria and possible subtypes and dimensional specifiers for DSM-V. Taehan Chikkwa Uisa Hyophoe Chi 2010;27(6):507–27.
[6] Mataix-Cols D, do Rosario-Campos MC, Leckman JF. A multidimensional model of obsessive-compulsive disorder. Am J Psychiatry 2005;162(2):228–38.
[7] O'Neill J, Feusner JD. Cognitive-behavioral therapy for obsessive–compulsive disorder: access to treatment, prediction of long-term outcome with neuroimaging. Psychol Res Behav Manag 2015;8:211.
[8] Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. Annu Rev Neurosci 2005;28:377–401.
[9] Bonato C, Miniussi C, Rossini P. Transcranial magnetic stimulation and cortical evoked potentials: a TMS/EEG co-registration study. Clin Neurophysiol 2006;117(8):1699–707.
[10] Wassermann EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. Clin Neurophysiol 2001;112(8):1367–77.
[11] Trevizol AP, Shiozawa P, Cook IA, Sato IA, Kaku CB, Guimarães FB, et al. Transcranial magnetic stimulation for obsessive-compulsive disorder: an updated systematic review and meta-analysis. J ECT 2016;32(4):262–6.
[12] Bear RE, Fitzgerald P, Rosenfeld JV, Bittar RG. Neurosurgery for obsessive-compulsive disorder: contemporary approaches. J Clin Neurosci 2010;17(1):1–5.
[13] Ahmari SE, Dougherty DD. Dissecting OCD circuits: from animal models to targeted treatments. Depress Anxiety 2015;32(8):550–62.
[14] Posner J, Marsh R, Maia TV, Peterson BS, Gruber A, Simpson HB. Reduced functional connectivity within the limbic cortico-striato-thalamo-cortical loop in unmedicated adults with obsessive-compulsive disorder. Hum Brain Mapp 2014;35(6):2852–60.
[15] Coles ME, Heimberg RG, Frost RO, Steketee G. Not just right experiences and obsessive–compulsive features: experimental and self-monitoring perspectives. Behav Res Ther 2005;43(2):153–67.
[16] Gehring WJ, Goss B, Coles MG, Meyer DE, Donchin E. A neural system for error detection and compensation. Psychol Sci 1993;4(6):385–90.
[17] Maia TV, Cooney RE, Peterson BS. The neural bases of obsessive–compulsive disorder in children and adults. Dev Psychopathol 2008;20(04):1251–83.
[18] Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9(1):357–81.
[19] Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet 1985;325(8437):1106–7.
[20] Speer AM, Kimbrell TA, Wassermann EM, Repella JD, Willis MW, Herscovitch P, et al. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. Biol Psychiatry 2000;48(12):1133–41.
[21] Lehéricy S, Ducros M, De Moortele V, Francois C, Thivard L, Poupon C, et al. Diffusion tensor fiber tracking shows distinct corticostriatal circuits in humans. Ann Neurol 2004;55(4):522–9.
[22] Yin HH, Knowlton BJ. The role of the basal ganglia in habit formation. Nat Rev Neurosci 2006;7(6):464–76.
[23] Fitzgerald KD, Welsh RC, Gehring WJ, Abelson JL, Himle JA, Liberzon I, et al. Error-related hyperactivity of the anterior cingulate cortex in obsessive-compulsive disorder. Biol Psychiatry 2005;57(3):287–94. http://dx.doi.org/10.1016/j.biopsych.2004.10.038.
[24] Herrmann MJ, Rommler J, Ehlis AC, Heidrich A, Fallgatter AJ. Source localization (LORETA) of the error-related-negativity (ERN/Ne) and positivity (Pe). Brain Res Cogn Brain Res 2004;20(2):294–9. http://dx.doi.org/10.1016/j.cogbrainres.2004.02.013.
[25] Ghisi M, Chiri LR, Marchetti I, Sanavio E, Sica C. In search of specificity:"Not just right experiences" and obsessive–compulsive symptoms in non-clinical and clinical Italian individuals. J Anxiety Disord 2010;24(8):879–86.
[26] Yeung N, Botvinick MM, Cohen JD. The neural basis of error detection: conflict monitoring and the error-related negativity. Psychol Rev 2004;111(4):931.
[27] Tzur G, Berger A. When things look wrong: theta activity in rule violation. Neuropsychologia 2007;45(13):3122–6. http://dx.doi.org/10.1016/j.neuropsychologia.2007.05.004.
[28] Hajcak G, Simons RF. Error-related brain activity in obsessive–compulsive undergraduates. Psychiatry Res 2002;110(1):63–72.
[29] Hajcak G, Moser JS, Yeung N, Simons RF. On the ERN and the significance of errors. Psychophysiology 2005;42(2):151–60.
[30] Chamberlain SR, Blackwell AD, Fineberg NA, Robbins TW, Sahakian BJ. The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. Neurosci Biobehav Rev 2005;29(3):399–419.
[31] Saxena S, Brody AL, Ho ML, Alborzian S, Ho MK, Maidment KM, et al. Cerebral metabolism in major depression and obsessive-compulsive disorder occurring separately and concurrently. Biol Psychiatry 2001;50(3):159–70.
[32] Luu P, Tucker DM, Derryberry D, Reed M, Poulsen C. Electrophysiological responses to errors and feedback in the process of action regulation. Psychol Sci 2003;14(1):47–53.
[33] Gehring WJ, Himle J, Nisenson LG. Action-monitoring dysfunction in obsessive-compulsive disorder. Psychol Sci 2000;11(1):1–6.
[34] Fitzgerald KD, Stern ER, Angstadt M, Nicholson-Muth KC, Maynor MR, Welsh RC, et al. Altered function and connectivity of the medial frontal cortex in pediatric obsessive-compulsive disorder. Biol Psychiatry 2010;68(11):1039–47.
[35] Cavanagh JF, Shackman AJ. Frontal midline theta reflects anxiety and cognitive control: meta-analytic evidence. J Physiol Paris 2015;109(1):3–15.
[36] Modirrousta M, Meek BP, Sareen J, Enns MW. Impaired trial-by-trial adjustment of cognitive control in obsessive compulsive disorder improves after deep repetitive transcranial magnetic stimulation. BMC Neurosci 2015;16(1):63.
[37] Tendler A, Barnea Ygael N, Roth Y, Zangen A. Deep transcranial magnetic stimulation (dTMS)–beyond depression. Expert Rev Med Devices 2016;13(10):987–1000.

[38] Modirrousta M, Shams E, Katz C, Mansouri B, Moussavi Z, Sareen J, et al. The efficacy of deep repetitive transcranial magnetic stimulation over the medial prefrontal cortex in obsessive compulsive disorder: results from an open-label study. Depress Anxiety 2015;32(6):445–50.
[39] Dinur-Klein L, Dannon P, Hadar A, Rosenberg O, Roth Y, Kotler M, et al. Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: a prospective, randomized controlled trial. Biol Psychiatry 2014;76(9):742–9.
[40] Naqvi NH, Rudrauf D, Damasio H, Bechara A. Damage to the insula disrupts addiction to cigarette smoking. Science 2007;315(5811):531–4.
[41] Gersner R, Kravetz E, Feil J, Pell G, Zangen A. Long-term effects of repetitive transcranial magnetic stimulation on markers for neuroplasticity: differential outcomes in anesthetized and awake animals. J Neurosci 2011;31(20):7521–6.
[42] Pallanti S, Hollander E, Bienstock C, Koran L, Leckman J, Marazziti D, et al. Treatment non-response in OCD: methodological issues and operational definitions. Int J Neuropsychopharmacol 2002;5(2):181–91.
[43] Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown obsessive compulsive scale: I. development, use, and reliability. Arch Gen Psychiatry 1989;46(11):1006–11.
[44] Amorim P. Mini International Neuropsychiatric Interview (MINI): validation of a short structured diagnostic psychiatric interview. Rev Bras Psiquiatr 2000;22(3):106–15.
[45] Raven JC. Progressive matrices: a perceptual test of intelligence. London: HK Lewis; 1938.
[46] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23(1):56–62.
[47] Guy W. Clinical global impression scale. ECDEU Assess Man Psychopharmacol-Revised Volume DHEW Publ No ADM 1976;76(338):218–22.
[48] Isserles M, Shalev AY, Roth Y, Peri T, Kutz I, Zlotnick E, et al. Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder–a pilot study. Brain Stimul 2013;6(3):377–83.
[49] Dudai Y. The neurobiology of consolidations, or, how stable is the engram? Annu Rev Psychol 2004;55:51–86.
[50] Dudai Y. Reconsolidation: the advantage of being refocused. Curr Opin Neurobiol 2006;16(2):174–8.
[51] Rauch SL, Savage CR, Alpert NM, Fischman AJ, Jenike MA. The functional neuroanatomy of anxiety: a study of three disorders using positron emission tomography and symptom provocation. Biol Psychiatry 1997;42(6):446–52.
[52] Saxena S, Rauch SL. Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. Psychiatr Clin North Am 2000;23(3):563–86.
[53] Levkovitz Y, Isserles M, Padberg F, Lisanby SH, Bystritsky A, Xia G, et al. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World Psychiatry 2015;14(1):64–73.
[54] Golden CJ. Stroop Color and Word Test: a manual for clinical and experimental uses. Chicago: Stoelting; 1978. p. 1–46.
[55] Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014;125(11):2150–206.
[56] Berlim MT, Neufeld NH, Van den Eynde F. Repetitive transcranial magnetic stimulation (rTMS) for obsessive–compulsive disorder (OCD): an exploratory meta-analysis of randomized and sham-controlled trials. J Psychiatr Res 2013;47(8):999–1006.
[57] Nakao T, Okada K, Kanba S. Neurobiological model of obsessive–compulsive disorder: evidence from recent neuropsychological and neuroimaging findings. Psychiatry Clin Neurosci 2014;68(8):587–605.
[58] Pell GS, Roth Y, Zangen A. Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: influence of timing and geometrical parameters and underlying mechanisms. Prog Neurobiol 2011;93(1):59–98.
[59] Gomes PVO, Brasil-Neto JP, Allam N. Rodrigues de Souza E. A randomized, double-blind trial of repetitive transcranial magnetic stimulation in obsessive-compulsive disorder with three-month follow-up. J Neuropsychiatry Clin Neurosci 2012;24(4):437–43.
[60] Hawken ER, Dilkov D, Kaludiev E, Simek S, Zhang F, Milev R. Transcranial magnetic stimulation of the supplementary motor area in the treatment of obsessive-compulsive disorder: a multi-site study. Int J Mol Sci 2016;17(3):420.
[61] Mantovani A, Simpson HB, Fallon BA, Rossi S, Lisanby SH. Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive–compulsive disorder. Int J Neuropsychopharmacol 2010;13(2):217–27.
[62] Dunlop K, Woodside B, Olmsted M, Colton P, Giacobbe P, Downar J. Reductions in cortico-striatal hyperconnectivity accompany successful treatment of obsessive-compulsive disorder with dorsomedial prefrontal rTMS. Neuropsychopharmacology 2015.
[63] Badawy AA, El Sawy H, El Hay MA. Efficacy of repetitive transcranial magnetic stimulation in the management of obsessive compulsive disorder. Egypt J Neurol Psychiatry Neurosurg 2010;47:393–7.
[64] Haghighi M, Shayganfard M, Jahangard L, Ahmadpanah M, Bajoghli H, Pirdehghan A, et al. Repetitive Transcranial Magnetic Stimulation (rTMS) improves symptoms and reduces clinical illness in patients suffering from OCD–Results from a single-blind, randomized clinical trial with sham cross-over condition. J Psychiatr Res 2015;68:238–44.
[65] Ma X, Huang Y, Liao L, Jin Y. A randomized double-blinded sham-controlled trial of a electroencephalogram-guided transcranial magnetic stimulation for obsessive-compulsive disorder. Chin Med J 2014;127(4).
[66] Seo H-J, Jung Y-E, Lim HK, Um Y-H, Lee CU, Chae J-H. Adjunctive low-frequency repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex in patients with treatment-resistant obsessive-compulsive disorder: a randomized controlled trial. Clin Psychopharmacol Neurosci 2016;14(2):153.
[67] Ruffini C, Locatelli M, Lucca A, Benedetti F, Insacco C, Smeraldi E. Augmentation effect of repetitive transcranial magnetic stimulation over the orbitofrontal cortex in drug-resistant obsessive-compulsive disorder patients: a controlled investigation. Prim Care Companion J Clin Psychiatry 2009;11(5):226.
[68] Alonso P, Pujol J, Cardoner N, Benlloch L, Deus J, Menchón JM, et al. Right prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a double-blind, placebo-controlled study. Am J Psychiatry 2001;158(7):1143–5.
[69] Mansur CG, Myczkowki ML, de Barros Cabral S, Sartorelli MdCB, Bellini BB, Dias ÁM, et al. Placebo effect after prefrontal magnetic stimulation in the treatment of resistant obsessive-compulsive disorder: a randomized controlled trial. Int J Neuropsychopharmacol 2011;14(10):1389–97.
[70] Nauczyciel C, Le Jeune F, Naudet F, Douabin S, Esquevin A, Vérin M, et al. Repetitive transcranial magnetic stimulation over the orbitofrontal cortex for obsessive-compulsive disorder: a double-blind, crossover study. Transl Psychiatry 2014;4(9):e436.
[71] Pelissolo A, Harika-Germaneau G, Rachid F, Gaudeau-Bosma C, Tanguy M-L, BenAdhira R, et al. Repetitive transcranial magnetic stimulation to supplementary motor area in refractory obsessive-compulsive disorder treatment: a sham-controlled trial. Int J Neuropsychopharmacol 2016;19(8).pyw025.
[72] Prasko J, Paskova B, Záleský R, Novak T, Kopecek M, Bares M, et al. The effect of repetitive transcranial magnetic stimulation (rTMS) on symptoms in obsessive compulsive disorder. A randomized, double blind, sham controlled study. Neuro Endocrinol Lett 2006;27(3):327–32.
[73] Sachdev PS, Loo CK, Mitchell PB, McFarquhar TF, Malhi GS. Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: a double-blind controlled investigation. Psychol Med 2007;37(11):1645–9.
[74] Sarkhel S, Sinha VK, Praharaj SK. Adjunctive high-frequency right prefrontal repetitive transcranial magnetic stimulation (rTMS) was not effective in obsessive–compulsive disorder but improved secondary depression. J Anxiety Disord 2010;24(5):535–9.
[75] Taylor SF, Stern ER, Gehring WJ. Neural systems for error monitoring: recent findings and theoretical perspectives. Neuroscientist 2007;13(2):160–72. http://dx.doi.org/10.1177/1073858406298184.
[76] Luu P, Tucker DM, Makeig S. Frontal midline theta and the error-related negativity: neurophysiological mechanisms of action regulation. Clin Neurophysiol 2004;115(8):1821–35.
[77] Stern ER, Liu Y, Gehring WJ, Lister JJ, Yin G, Zhang J, et al. Chronic medication does not affect hyperactive error responses in obsessive-compulsive disorder. Psychophysiology 2010;47(5):913–20.
[78] Saxena S, Gorbis E, O'Neill J, Baker S, Mandelkern MA, Maidment KM, et al. Rapid effects of brief intensive cognitive-behavioral therapy on brain glucose metabolism in obsessive-compulsive disorder. Mol Psychiatry 2009;14(2):197–205.
[79] Nakao T, Nakagawa A, Yoshiura T, Nakatani E, Nabeyama M, Yoshizato C, et al. Brain activation of patients with obsessive-compulsive disorder during neuropsychological and symptom provocation tasks before and after symptom improvement: a functional magnetic resonance imaging study. Biol Psychiatry 2005;57(8):901–10.

Please cite this article in press as: Carmi L, et al., Clinical and electrophysiological outcomes of deep TMS over the medial prefrontal and anterior cingulate cortices in OCD patients, Brain Stimulation (2017), http://dx.doi.org/10.1016/j.brs.2017.09.004