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Effectiveness of Deep Transcranial Magnetic Stimulation Combined with a Brief Exposure Procedure in Post-Traumatic Stress Disorder – A Pilot Study

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ABSTRACT

Background: Post-traumatic stress disorder (PTSD) is a debilitating anxiety disorder induced by traumatic experiences. To date, psychotherapy and drug treatment achieve only partial success, indicating need for further development of treatment strategies.
Recent research has found that impaired acquired fear extinction capability serves as an important factor at the pathogenesis of the disorder. Medial prefrontal cortex (mPFC) hypo-activity has been implicated in this extinction impairment, providing insight as to why some trauma exposed individuals will develop PTSD.
Objective: To test whether fear extinction can be facilitated and therapeutic effect achieved by repeated mPFC deep transcranial magnetic stimulation (DTMS) of PTSD patients resistant to standard treatment.
Methods: In a double-blind study, 30 PTSD patients were enrolled and randomly assigned into 3 treatment groups: **A**) DTMS after brief exposure to the traumatic event with the script-driven imagery procedure; **B**) DTMS after brief exposure to a non-traumatic event; **C**) sham stimulation after brief exposure to the traumatic event.
Results: Significant improvement was demonstrated in the intrusive component of the CAPS scale in patients administered DTMS after exposure to the traumatic event script, while patients in the control groups showed no significant improvement. Similar trend was demonstrated in the Total-CAPS score as in the other rating scales. A significant reduction in the HR response to the traumatic script was evident in group **A,** further supporting the above results.
Conclusions: Combining brief script-driven exposure with DTMS can induce therapeutic effects in PTSD patients. A wide multi-center study is suggested to substantiate these findings.
Trial registration: ClinicalTrials.gov identifier: NCT00517400.

Introduction

Post-traumatic stress disorder (PTSD) is a serious consequence occurring in large numbers of trauma survivors. With a 3.5% estimated 12 month prevalence and about a third of those affected presenting a severe form of the condition; this disorder poses a significant therapeutic challenge [1,2].

Symptoms of PTSD include three distinct clusters: 1) intrusive re-experiencing of the traumatic event in the form of nightmares or flashbacks, with an exaggerated response to cues; 2) persistent avoidance of stimuli associated with the trauma and emotional numbness; 3) symptoms of hyper-arousal like exaggerated startle response, anger outbursts, sleeping problems and sustained preparedness for an instant alarm response [3].

Current mainstay of treatment for PTSD relies on psychopharmacological and trauma-focused psychological interventions. These interventions are effective but some patients fail to respond [4,5]. There have been recent studies which aim to facilitate

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exposure based psychological treatments applying means such as virtual reality or the partial NMDA agonist D-cycloserine [6].

The broadly accepted neurobiological model for PTSD considers it as a stress-induced fear circuitry disorder [7]. The ability to achieve and preserve extinction of the acquired fear response is severed due to functional impairment in the medial prefrontal cortex (mPFC) control over the amygdala. This model has been corroborated by numerous animal and human studies [7–13] although challenged by some [14] (see discussion). Medial PFC hypo-activation is inversely correlated with amygdalar hyper-activation in PTSD patients versus trauma exposed controls [10,12]. mPFC activation was also found to be negatively correlated with PTSD symptom severity while successful treatment has been associated with increased mPFC activation [7]. One possible way to try and amend this mPFC hypo-activation is Transcranial Magnetic Stimulation (TMS).

TMS enables non-invasive modulation of brain activity. In October 2008 the FDA approved TMS for the treatment of Major depression, following a pivotal study by O'Reardon et al. [15]. While in depression TMS has been widely utilized in clinical studies for almost two decades and recently also in regular clinics, very few studies of TMS in PTSD patients were published thus far. In a sham-controlled study, Cohen et al. demonstrated that 10 daily treatments of TMS of the right prefrontal cortex at 10 Hz, but not at 1 Hz, had therapeutic effects on PTSD patients, and that core symptoms (re-experiencing, avoidance) markedly improved [16]. In another sham-controlled trial [17], 30 patients were randomly allocated to receive 10 sessions of 20 Hz sham, right or left dorsolateral PFC TMS. Both active conditions induced a significant decrease in PTSD symptoms with a more pronounced effect in the right stimulation group. PTSD symptom improvements were long lasting and the effects found still significant at the 3-months follow-up. A recently published study by Watts et al. [18] indicated that 1 Hz right dorsolateral PFC stimulation can induce improvements in core PTSD and depressive symptoms. One study is noteworthy as the only published study that combined TMS with exposure in treating PTSD thus far. In this preliminary cross-over study on 9 PTSD patients, Osuch et al. studied the effect of 20 sessions of 1 Hz right dorsolateral prefrontal active versus sham TMS combined with exposure therapy. Statistically significant differences were not found in any of the behavioral measures, but the CAPS hyper-arousal score showed mild to moderate improvement with exposure combined with TMS. No effect was found with exposure combined with sham TMS [19]. The patients were instructed to talk about their traumatic events during the stimulation and the rational was to use low frequency stimulation to diminish presumed right frontal hyperactivity previously found in patients with PTSD. The authors commented that this finding seems inconsistent in PTSD patients and indeed was not found in their patients. They conclude that higher TMS frequencies (10–20 Hz) might prove preferable.

Deep TMS (DTMS), utilizing the special architecture of the H-Coils, allows stimulation of deeper cortical areas then standard TMS coils. H-coils can safely induce an effective field at a depth of approximately 3–4 cm below the skull compared to 1 cm with the standard figure-8 TMS coil [20–22]. Clinical studies in unipolar (e.g. [23,24]) and bipolar [25] depressive patients, as well as in schizophrenic patients [26] further indicated on the safety and effectiveness of DTMS utilizing the H-coil.

The present study was designed to evaluate the potential effectiveness of DTMS in the treatment of refractory PTSD patients, and to test whether recall of the traumatic memory just prior to the stimulation can affect the clinical outcomes. We tested the hypothesis that high frequency (excitatory) stimulation of the mPFC could facilitate extinction of the fear response to the traumatic memory elicited via exposure procedure just prior to stimulation. The rational to administer the extinction procedure shortly after the reactivation of the fear memory, during its reconsolidation window derives from numerous studies (see Quirk et al. [27] for review). Facilitated extinction induced by mPFC TMS applied immediately after the traumatic recall would in turn convert the original fear memory to a safety memory and improve core PTSD symptoms, specifically the intrusion component. We used the script-driven imagery procedure to elicit the fear response prior to stimulation and not as a therapeutic intervention. This "ultra-brief-exposure" procedure was proved before as a potent mean of eliciting fear response and assessing treatment outcome in PTSD patients [28–30].

Methods and materials

The study was approved by the Institutional Review Board (IRB) and was conducted at the Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem, Israel. The study was registered in the NIH clinical trials registry (NCT00517400). Active enrollment of 30 PTSD patients took place from March 2008 through March 2011, with candidates recruited via newspaper ads and referrals from collaborations with medical faculties and personnel. These volunteers signed informed consent forms before study entry and were free to withdraw at any time without prejudice.

Study overview

The screening procedure included a structured psychiatric interview, a medical interview and a physical and mental examination to determine suitability according to the Inclusion and Exclusion criteria. Main criteria included: PTSD diagnosis; treatment failure with an antidepressant medication and or trauma-focused psychotherapy; no other active DSM-IV-TR axis I or major axis II disorder except depression, and absence of known TMS contraindications. Patients receiving psychoactive medications were enrolled after at least 4 weeks of stable regimen. During the study no change was made in the psychoactive medications and only limited use of hypnotic or anxiolytic medication (up to 2 mg/day of clonazepam or equivalent) was allowed for treatment-emergent insomnia or anxiety.

Consenting candidates signed a detailed informed consent form, completed baseline symptom assessments and filled a structured form describing 3 events in their life: a positive experience, a neutral one, and the traumatic experience that caused the PTSD. These forms were then used to write and record audio scripts about 30 s long that were played to the patients just prior to the magnetic stimulation. The script was written using the second person, present tense as described before [28,30].

Patients were randomly allocated to one of 3 treatment groups:

A) "EXP-STIM"– receiving DTMS after script-driven imagery of the traumatic experience immediately followed by script-driven imagery of a neutral event.
B) "NOEX-STIM"– receiving DTMS after script-driven imagery of a positive experience immediately followed by script-driven imagery of a neutral event.
C) "EXP-SHAM"– receiving sham-DTMS after script-driven imagery of the traumatic experience immediately followed by script-driven imagery of a neutral event.

Three treatment sessions were administered weekly for 4 weeks (12 sessions in total). Patients allocated to the control groups that did not reach response criteria ($\geq$50% improvement in CAPS score) were offered an open cross-over treatment according to traumatic

exposure – active stimulation group protocol after completing the 5th week assessments and un-blinding.

Evaluations conducted

A trained psychiatrist performed weekly psychiatric status examinations, administered the DTMS treatments and monitored the patients for any adverse effects or subjective complaints. All symptoms scales and assessments were done by a blinded experienced rater or self-rated by the patients. The assessments included: the Clinician-Administered PTSD Scale-II (CAPS, a widely used tool considered the gold standard in PTSD assessment [31]); the PTSD Symptom Scale—Self Report version (PSS-SR, Foa et al. [32]); the Hamilton Depression Rating Scale 24 items (HDRS-24); and the self-graded Beck Depression Inventory II (BDI). The CAPS was performed at baseline, before randomization into the study, to confirm PTSD diagnosis and to test baseline symptom severity, at the 5th week to assess primary outcome and at weeks 7 and 13 (2 weeks and 2 months follow-up visits). The other rating scales were administered at baseline, weekly thereafter-at the beginning of each treatment week, at the end of the treatment phase at week 5 and at the follow-up visits. The CAPS was not administered weekly due to its length and burdensome nature.

During the script-driven imagery procedure, heart rate (HR) and skin conductance (SC) were recorded as an objective measure of the physiological response to the cued traumatic re-experiencing along the treatment sessions [30].

Materials

DTMS device

The DTMS stimuli were delivered using a Magstim Rapid^2 stimulator (Magstim, UK) with the novel H-coil (Brainsway Inc., Jerusalem, Israel), an extracorporeal device positioned on the patient's scalp (see Figure S1). For theoretical considerations see Roth et al., [21,33]. The H-Coil used in this study is designed to stimulate deep prefrontal brain regions and was placed to induce electromagnetic fields in the mPFC. The effective part of the coil, in contact with the patient's scalp, includes 14 strips of 7–12 cm long wire. The frame of the inner rim of the coil is flexible in order to allow optimal fit to individual skull's shape. Placebo stimulation is performed with a sham coil placed in the same helmet encasing the active TMS coil. The sham coil produces a similar acoustic artifact and scalp sensation as the active coil. An electronic system controls which of the two coils is connected to the stimulator in a certain session. The sham coil induces only a negligible electric field inside the brain itself due to a very rapid reduction of the field as a function of distance insured by the non-tangential orientation of the sham coil relative to the scalp and by elements producing significant field cancellation. Field maps induced in a phantom brain by these coils are presented in supplementary Figure S2.

Physiological measurements

A modular instrument system was used to record patients' HR and SC before, during and after each script and imagery period (Coulbourn instruments, PA, USA). The analog signals were sampled at 120 Hz per channel, digitized and then recorded by a lap-top computer for further analysis.

Procedure

Treatment sessions took place 3 times a week for 4 weeks in a temperature and humidity controlled room. Motor threshold (MT) was established for each patient in a similar way to that described before [23]. Prior each stimulation session, the script-driven imagery procedure, about 4 min long, was performed. Firstly, 30 s of recorded instructions were played explaining the nature of the procedure and asking the patient to refrain from moving. A silence period of 60 s followed, which was used to measure psychophysiological baseline. Next, came up a traumatic or positive (control) script followed by an imagery period and a 30 s break. Lastly came up a neutral script followed by an imagery period. Patients were instructed to listen carefully to the scripts, each about 30 s long, and then imagine the event portrayed for 30 s (until a beep sounds). The rational for the neutral script was to control excessive patient anxiety that might be evoked by the traumatic script. The patients listened to the recorded audio scripts through high quality earphones connected to a lap-top computer. The scripts were played using Microsoft media player. Heart rate and skin conductance were measured during the procedure to assess the patient's response to the traumatic exposure along the treatment. Consecutive to the script procedure the DTMS coil was placed over the PFC and active or sham stimulation of the mPFC commenced. Each stimulation session consisted of 42, 20 Hz trains of 2 s each, with 20 s inter-train interval (1680 pulses). The intensity of pulses was set to 120% of the measured MT. These stimulation parameters were used by our group in previous studies on clinically depressed patients [23,24] and were found safe and effective. Each treatment session lasted about 20 min, 4 min dedicated to the script-driven imagery procedure and 15.5 min for the stimulation. Patients received 3 treatment sessions per week for 4 weeks.

Data analysis

Data analysis was performed with SAS v9.1 (SAS institute, Cary NC, USA). Continuous variables are presented with their mean and standard error values and compared between the treatment groups with repeated measures analysis of variance model. Pre-planned comparisons of means were performed by contrast *t*-tests. Discrete data are presented by a count and compared between the treatment groups with a Fisher's exact test. The HR response to the traumatic or positive script was derived subtracting average HR value of a 30 s baseline period from the average HR value of the consecutive script. In order to reduce variance, average response was calculated for each week. All statistical tests were two sided and tested at a 5% level of significance.

Results

30 adult patients suffering from resistant PTSD and fulfilling inclusion and exclusion criteria were enrolled in the study. Baseline demographic and clinical characteristics are summarized in Table 1. There were no significant differences in baseline data between the 3 treatment groups. Analysis of outcome measures took place on 26 patients who received at least 8 treatment sessions. Flow of patients in the study, reasons for dropout and time points are specified in the consort diagram (supplementary Figure S3).

Safety and tolerability

Overall, the treatment was easy to tolerate and most patients suffered no side-effects, nor complained of any significant discomfort. Few patients complained of mild headaches, typically during the first few treatments and mostly self-limited or (rarely) necessitating common analgesics. Three patients withdrew consent during the treatment. One patient complained of increased anxiety and withdrew consent after the 4th treatment, one left after the second treatment due to unease during treatment (both were in the

Table 1
Baseline demographic and clinical characteristics.

	Group A ($n = 9$)	Group B ($n = 8$)	Group C ($n = 9$)	P
Age	49 ± 12.5	40.5 ± 9.8	40.4 ± 10.5	0.17
PTSD duration [Y]	18 ± 18.5	17.6 ± 13.8	11.9 ± 12.1	0.62
Baseline CAPS	88 ± 16.4	85.8 ± 15.4	86.1 ± 27.7	0.97
Baseline HDRS	26 ± 8.9	29 ± 6.7	30.3 ± 9.2	0.6
Gender F/M	2/7	3/5	1/8	0.45
Mil./Terror trauma Y/N	7/2	4/4	4/5	0.37
SSRI Y/N	4/5	2/6	5/4	0.54
BZ Y/N	2/7	1/7	2/7	1
AP Y/N	0/9	0/8	2/7	0.31
Failed treatments-pharm	2.0 ± 1.1	1.6 ± 2.4	2.7 ± 2	0.53
Failed treatments-psychol	1.2 ± 0.4	1.1 ± 0.4	1.4 ± 0.7	0.46

Values are presented ± SD, groups were compared by one way ANOVA for continuous variables and by the Fisher exact test for categorical variables. (Mil. = military; SSRI = serotonin selective reuptake inhibitors; BZ = benzodiazepine; AP = antipsychotic; Pharm = pharmacotherapy; Psychol = psychological treatment). Groups A,B and C for traumatic exposure − active stimulation, sham exposure − active stimulation and traumatic exposure − sham stimulation respectively.

EXP-STIM group). The third patient to withdraw consent did so after the 4th treatment due to feeling uncomfortable with the treatment and the study requirements. This patient was in the EXP-SHAM group. One patient from the EXP-STIM group suffered from a short tonic-clonic generalized seizure toward the end of his 8th treatment session. The seizure was self-limited and the patient did not require any treatment. The patient did not receive any further treatments in the study. In a single patient, the designated stimulation intensity could not be reached due to an exceptionally low pain threshold. This patient, allocated to EXP-STIM group was removed from the analysis.

Treatment outcomes

The primary outcome measure was the CAPS, measured after 4 treatment weeks. Mean CAPS score improved from 88(±5.5) at baseline to 61(±8.8) [mean ± SE] in the EXP-STIM group ($N = 9$), from 86(±5.4) to 76(±10.9) in the NOEXP-STIM group ($N = 8$) and from 86(±9.2) to 76(±10.7) in the EXP-SHAM group ($N = 9$) (see Fig. 1A and Table 2). Repeated measures ANOVA (performed for the baseline and 5th week data) on the CAPS of all groups did not indicate significant group*time interaction ($P = 0.12$), however, pre-planned comparisons showed the improvements in CAPS score to be significant only in the EXP-STIM group (P-values of 0.0003, 0.164 and 0.122 for the EXP-STIM, NOEX-STIM & EXP-SHAM groups respectively). For the intrusion component of the CAPS, group*time interaction was found significant ($F_{2,23} = 3.75$, $P = 0.039$) and pre-planned contrasts found the improvements to be significant only for the EXP-STIM group (P-values of <0.0001, 0.117 and 0.265 for the EXP-STIM, NOEX-STIM & EXP-SHAM groups respectively; Fig. 1 B and Table 3). For the two other CAPS domains (avoidance/numbness and arousal), group*time effect was not significant but pre-planned contrasts again found the improvements to be significant only for the EXP-STIM group (Fig. 1 C–D).

Response criteria defined as an improvement of 50% or more relative to the baseline Total-CAPS score [34] were achieved in 4/9 patients (44%) in the EXP-STIM group, in 1/8 patients (12.5%) in the NOEXP-STIM group and in none of the 9 patients (0%) in the EXP-SHAM group ($P = 0.055$, Fisher's exact test).

Mean CAPS change during the treatment within each group and between group comparisons are shown in Tables 2 (Total-CAPS) and 3 (Intrusion-CAPS). Data are presented for the intention to treat patients (ITT, $N = 30$), treatment criterion ($N = 26$) and the completers ($N = 25$).

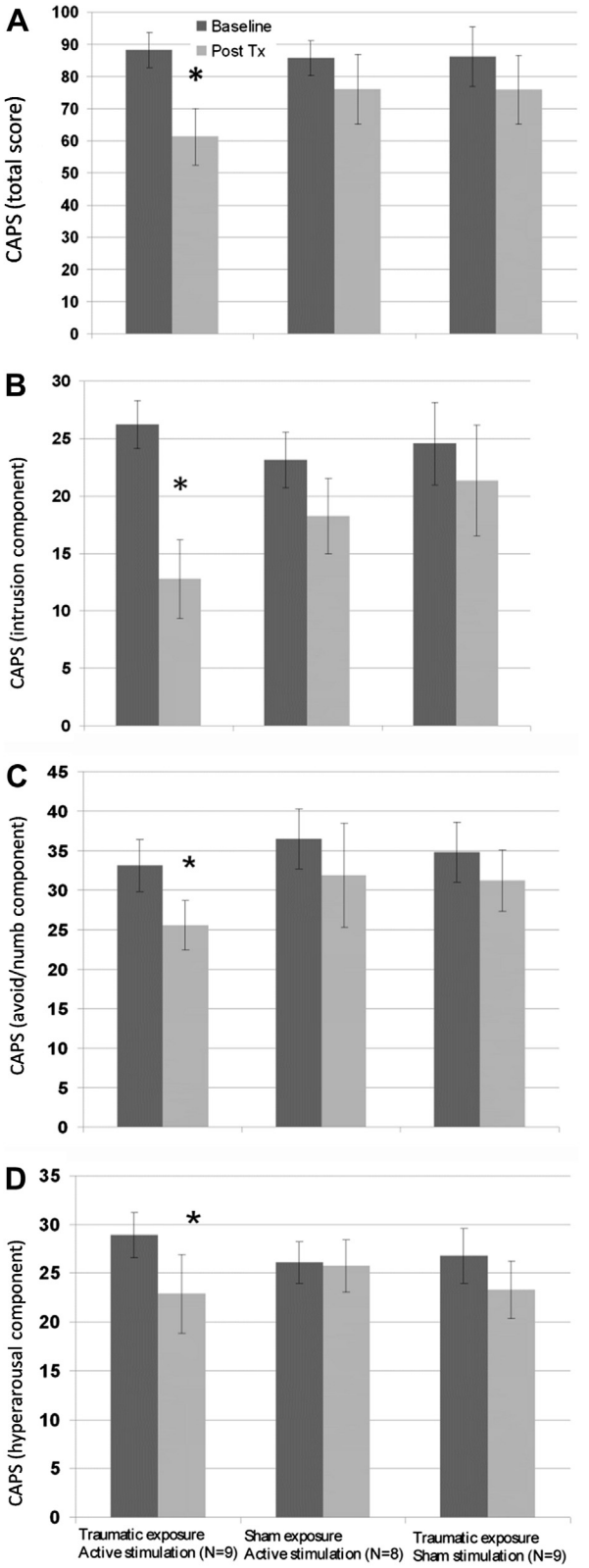

Figure 1. CAPS severity score at baseline and post treatment in the first (blinded) phase. Panel A depicts Total-CAPS score, while Panels B, C and D show the intrusion, avoidance/numbing and hyper-arousal components, respectively. Values are presented as mean ± standard errors. *$P < 0.05$, relative to baseline.

Secondary outcome measures included PSS-SR, HDRS-24 and BDI which were assessed weekly. Although group*time effects were

Table 2
The mean ± SE Total-CAPS change during the treatment within each group and between group comparisons.

	ITT ($N = 30$)	Treatment criterion ($N = 26$)	Completers ($N = 25$)
Improvement (EXP-STIM)	24.3 ± 7.4	27 ± 7.7	28 ± 8.7
Improvement (NOEX-STIM)	7.9 ± 4.8	9.9 ± 5.9	9.9 ± 5.9
Improvement (EXP-SHAM)	9.1 ± 5.1	10.3 ± 5.5	10.3 ± 5.5
rANOVA *P* value (group*time interaction)	0.11	0.12	0.12
EXP-STIM vs NOEX-STIM (Fisher's PLSD)	0.06	0.08	0.08
EXP-STIM vs EXP-SHAM (Fisher's PLSD)	0.08	0.08	0.08

Data are presented for the intention to treat patients (ITT, $N = 30$), treatment criterion ($N = 26$) and the completers ($N = 25$). The values used for comparisons between groups were the changes during the treatment.

found insignificant for all these measures, pre-planned contrasts demonstrated the improvements to be significant only for the EXP-STIM group, in accordance with the above findings (Fig. 2).

Cross-over phase

Ten patients crossed-over to the open phase (4 of the NOEXP-STIM group and 6 of the EXP-SHAM group). Their average Total-CAPS score improved from 87 (±7.5) to 73 (±9.4). Applying repeated ANOVA on their scores measured from baseline via the end of the blinded phase to the end of the cross-over phase, revealed a significant time effect ($F_{2,18} = 6.1$, $P = 0.0096$). While after treatment in the first phase the improvement in mean CAPS score for these patients from the control groups was not significant ($P = 0.25$), after the cross-over phase (i.e. treatment according to the protocol of the EXP-STIM group) a significant improvement was indeed observed ($P = 0.037$, Fisher's PLSD).

Constancy of the therapeutic effect was evaluated in the EXP-STIM group as in the cross-over group by follow-up visits 2 weeks and two months post treatment. The beneficial effect was well preserved in both groups: CAPS scores of 61(±8.8), 56(±8.4) and 62(±9.5) at end of treatment, 2 weeks and 2 months follow-up visits respectively in the EXP-STIM group; CAPS score of 73(±9.4), 73(±8.9) and 64(±9.7) at end of treatment, 2 weeks and 2 months follow-up visits respectively in the cross-over group. Similarly, all the secondary scales supported this preserved effect (data not shown).

Psychophysiological data

Heart rate responses to the brief script-driven imaginal traumatic exposure demonstrated a significant attenuation throughout the treatment in the EXP-STIM group (Fig. 3). This effect was not apparent in the EXP-SHAM group that received traumatic exposure (as in the EXP-STIM group) followed by sham, instead of active stimulation. Repeated ANOVA revealed a significant group*time interaction ($F_{4,64} = 2.63$, $P = 0.042$).

A robust correlation was found in both groups receiving the traumatic exposure, between the change in the heart rate response to the traumatic script (first week relative to the fourth week) and the change in the CAPS score ($r = 0.69$, $P = 0.039$ in the EXP-STIM group and $r = 0.81$, $P = 0.006$ in the EXP-SHAM group). This correlation further corroborates the relation between the psychophysiological data and the clinical phenomenology.

Unfortunately the skin conductance data were of too poor quality to allow proper analysis.

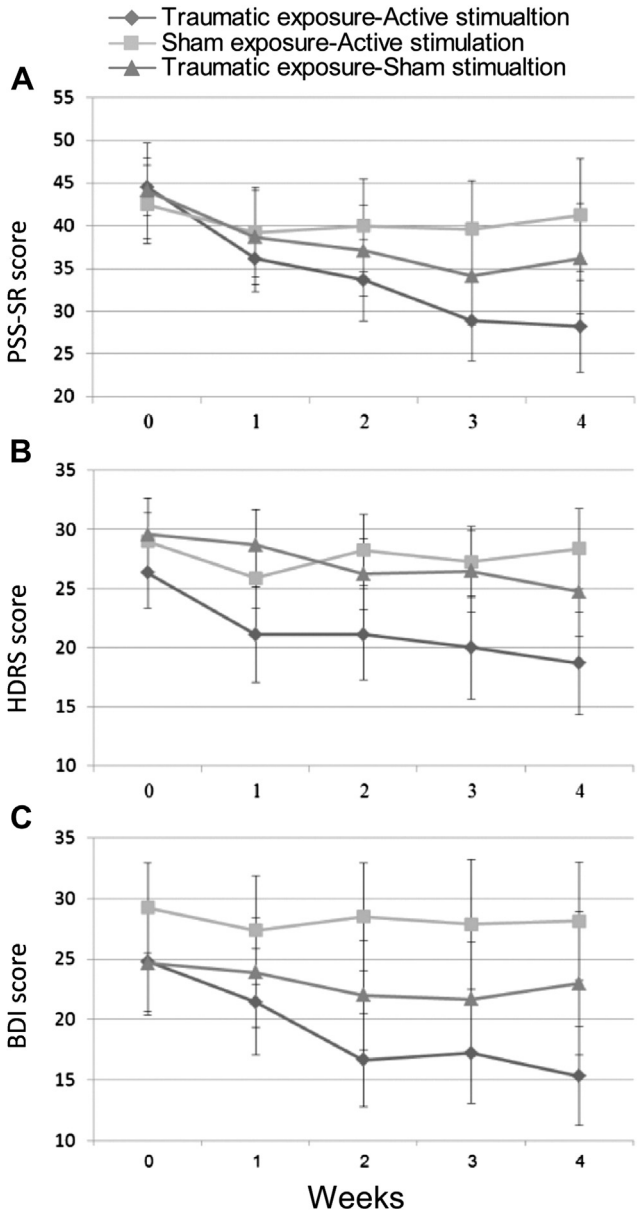

Figure 2. Secondary outcome measures. PTSD Symptom Scale—Self Report (PSS-SR, panel A), Hamilton Depression Rating Scale 24 items (HDRS-24, panel B) and Beck Depression Inventory (BDI, panel C) severity scores are presented at baseline and post each treatment week. Values are presented as mean ± standard errors, $N = 9, 8, 9$ in the EXP-STIM, NOEX-STIM & EXP-SHAM groups, respectively.

Table 3
The mean ± SE Intrusion-CAPS change during the treatment within each group and between group comparisons.

	ITT ($N = 30$)	Treatment criterion ($N = 26$)	Completers ($N = 25$)
Improvement (EXP-STIM)	12.1 ± 3.3	13.4 ± 3.4	13.6 ± 3.8
Improvement (NOEX-STIM)	3.9 ± 1.9	4.9 ± 2.3	4.9 ± 2.3
Improvement (EXP-SHAM)	2.8 ± 2.5	3.2 ± 2.7	3.2 ± 2.7
rANOVA *P* value (group*time interaction)	0.04	0.04	0.05
EXP-STIM vs NOEX-STIM (Fisher's PLSD)	0.04	0.05	0.06
EXP-STIM vs EXP-SHAM (Fisher's PLSD)	0.02	0.02	0.02

Data are presented for the intention to treat patients (ITT, $N = 30$), treatment criterion ($N = 26$) and the completers ($N = 25$). The values used for comparisons between groups were the changes during the treatment.

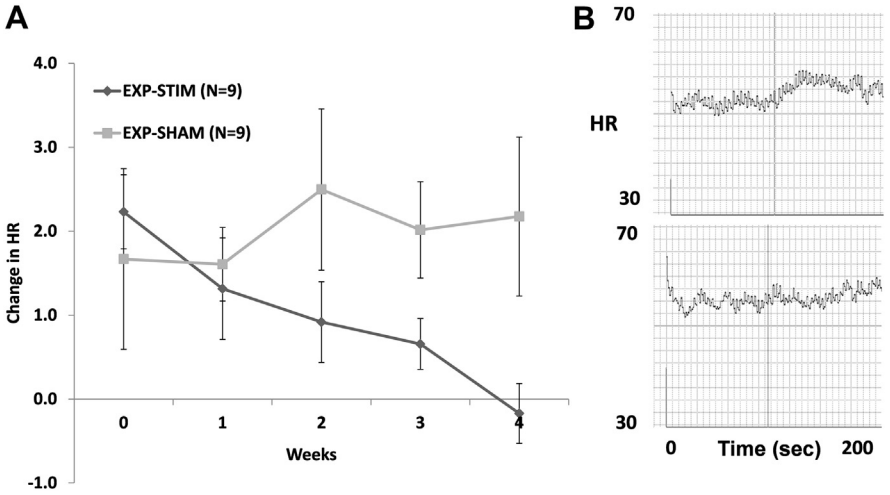

Figure 3. Heart rate (HR) data. Panel A shows the mean baseline and average weekly responses in both groups receiving exposure to traumatic experience: with active stimulation (group A) and with sham stimulation (group C) (vertical lines denote standard error). Panel B shows HR response to the traumatic exposure before and in the lower panel after a successful treatment (example of raw data from one patient in group A. Vertical lines mark the beginning of an 80 s script & imagery period, 210 s record shown).

Discussion

The present study indicates that high frequency DTMS stimulation of the mPFC following a brief exposure procedure to the traumatic experience can be effective in treating resistant PTSD patients. While in Major Depression, a significant body of research studies led to TMS inclusion as a biological treatment alternative to pharmacotherapy, only few TMS studies were published in PTSD thus far. Moreover, to the best of our knowledge, apart from a small preliminary report by Osuch et al. [19], this is the first study to combine exposure and TMS in PTSD patients, although this approach was recently suggested based on studies in animal models [10].

Based on the rational provided by extensive human and animal research, the current study aimed to examine the hypothesis that repeated high frequency stimulation of the mPFC, a key region in PTSD, would enable the extinction of the fear response and hence aid the patients in alleviating or even eliminating their symptoms. The treatment effect found, mainly in the CAPS-Intrusive scores, was both clinically and statistically significant. This effect was corroborated by a consistent trend demonstrated in the Total-CAPS as in the secondary measure scales both for PTSD and for depressive symptoms. Moreover, further support for the above findings was provided by the psychophysiological data. Heart rate responses to the traumatic exposure demonstrated a significant attenuation throughout the treatment, only when exposure was followed by active stimulation. A strong correlation was found between the changes in the heart rate response to the traumatic recall and the improvement in the CAPS score. Using a physiological measure like the heart rate response to personal traumatic cues might provide an objective way to monitor patients' response to the treatment.

The beneficial effect of the treatment was apparent in the cross-over open group ($N = 10$) as well. The effects were well preserved for both the blinded and the open cross-over groups 2 weeks and 2 months post treatment. Apart from one short, self-limited seizure leaving no sequel there were no serious adverse events in the study.

Importantly, our results converge with those of a very recent animal study by Baek et al. [35]. In this rat study, the effect of 10 Hz TMS, 5 min before versus during and right after the conditioned stimulus (CS) presentation was assessed. While TMS administered before the CS did not affect the freezing time, TMS during and right after the CS resulted in significantly less freezing behavior than in the sham group. This enhancement of fear extinction remained after 24 h without further stimulation. While the design and the results of this animal study are in line with our study, there are several aspects discriminating our study from the previous human study by Osuch et al. [19]. In the Osuch et al. study ($n = 9$), the stimulation was applied to the right dorsolateral PFC at low frequency while in our study stimulation was applied to the bilateral mPFC at high frequency. Indeed, Osuch et al. concluded by suggesting high frequency as a potentially more effective alternative. In addition, Osuch et al. used a very different exposure procedure, instructing patients to talk about various stressful events. Their target symptoms were in the intrusive domain, however, the effect found was in the hyper-arousal domain. They compared within subjects and not between groups and used a cross-over design that is problematic since patients might notice the difference between active and sham TMS when they experience both.

There are limitations in the present study. Despite the initial clinical severity (see Table 1), treatment effects were large. However, the small size of each group and the lack of a fourth control group receiving sham stimulation following sham exposure might have prevented part of the outcome measures from reaching statistical significance.

While the rational for the study is firmly supported by a vast body of human and animal research (see above and Introduction), an important study by Koenigs and Grafman [14] challenges the broadly accepted theory that the mPFC exerts inhibition over the amygdala and that a defect in this inhibition accounts for the pathogenesis of PTSD. In their study of brain-injured and trauma exposed combat veterans, they found that contrary to the prediction of the top-down inhibition model, mPFC damage **reduced** the likelihood of developing PTSD symptoms. Regarding this theoretical challenge we would like to argue that: firstly, although traumatic brain-injured patients can express PTSD-like symptoms, this clinical condition is likely to differ significantly from PTSD without brain injury [36]; secondly, brain modulation achieved by magnetic stimulation is different in nature from the effect of brain injury and the potential compensatory mechanisms following injury.

In conclusion, this study indicates that ultra-brief exposure sessions followed by non-invasive DTMS of the mPFC is safe and can be an effective treatment for PTSD, even when resistant to standard therapies. Obviously, a multi-center study involving a larger group of patients is required and planned to substantiate and expand these promising findings.

Acknowledgments

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.brs.2012.07.008.

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