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# Combining Trauma Script Exposure With rTMS to Reduce Symptoms of Post-Traumatic Stress Disorder: Randomized Controlled Trial

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## ABSTRACT

**Background:** Innovative therapeutic interventions for post-traumatic stress disorder (PTSD) are required. We opted to facilitate fear extinction by combining trauma script exposure with repetitive transcranial magnetic stimulation (rTMS) to reduce symptoms of PTSD.

**Objective:** The efficacy and safety of 10 Hz rTMS of the right dorsolateral prefrontal cortex simultaneously with exposure to personal traumatic narrative were studied in patients with PTSD.

**Materials and Methods:** This trial was a single-center randomized controlled trial (NCT02584894). Patients were randomly assigned 1:1 to receive eight daily sessions of 110% of motor threshold high frequency (HF) 10 Hz rTMS (110% HF rTMS) or 70% low frequency (LF) 1 Hz rTMS (70% LF rTMS) with trauma script exposure in both groups. Severity of PTSD, depression, and anxiety were assessed before and after study treatment (one month, three months) by an assessor masked to the trial group assignment. The primary outcome was the severity of PTSD assessed by the Clinician Administered PTSD Scale (CAPS). We used mixed linear regression models for statistical comparisons.

**Results:** Thirty-eight patients (65.8% females) were randomly assigned to 110% HF rTMS ( $n = 18$ ,  $31.3 \pm 10.0$  years, 13 females) or 70% LF rTMS ( $n = 20$ ,  $33.5 \pm 11.1$  years, 12 females). From baseline to three months, mean CAPS scores decreased by 51% in the 110% HF rTMS group (from  $83.7 \pm 14.4$  to  $41.8 \pm 31.9$ ) and by 36.9% in the 70% LF rTMS group (from  $81.8 \pm 15.6$  to  $51.6 \pm 23.7$ ), but with no significant difference in improvement (time by treatment interaction  $-3.61$  [95% confidence interval (CI),  $-9.70$  to  $2.47$ ];  $p = 0.24$ ; effect size 0.53). One serious adverse event occurred during the study (psychogenic nonepileptic seizure).

**Conclusion:** We found no evidence of difference in clinical improvement or remission rates between the 110% HF and 70% LF stimulation. These findings may reflect the importance of exposure procedure and that larger number of participants is needed.

**Keywords:** enhancement therapy, exposure therapy, neuromodulation, PTSD, repeated transcranial magnetic stimulation, traumatic stress

**Conflict of Interest:** Wissam El-Hage reports personal fees from Air Liquide, ELSAI, Janssen, Lundbeck, Nordic Pharma, Otsuka, UCB, Roche, and Chugai. He received research grants from the Fondation de France, and from the French National Hospital Program for Clinical Research (PHRC), unrelated to the submitted work. No potential conflict of interest was reported by the other authors.

## INTRODUCTION

Post-traumatic stress disorder (PTSD) is a common trauma-related disorder, with a cross-national lifetime prevalence of 3.9% (1). Trauma-focused therapies are highly recommended interventions, with the most support for cognitive- and exposure-based approaches (2,3,4). However, most patients with PTSD suffer residual symptoms following pharmacologic and/or psychotherapeutic treatments (5,6). Potentiation therapies represent significant interest among treatment-resistant patients, in particular combining neuromodulatory techniques with adjunctive psychotherapies (7). For instance, the addition of repetitive transcranial magnetic stimulation (rTMS) to cognitive processing therapy (CPT) compared to sham with CPT produced significantly greater PTSD symptom reduction early in treatment and was sustained up to six

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months posttreatment (8). However, a systematic review on the use of neuromodulation strategies for PTSD demonstrated considerable variation across trials regarding stimulation parameters, symptomatic response, and the role of adjunctive psychotherapy (7). Thus, the development of new research-based evidence in the treatment of PTSD is still required.

PTSD is a disorder of neural circuitry that commonly involves the fear network including the ventral medial and dorsolateral prefrontal cortex (DLPFC), amygdala (basolateral and central nuclei), and hippocampus (9,10). The prefrontal cortex can modulate the response of fear through inhibitory effects on amygdala. Nevertheless, PTSD is associated with hyperactivation of the amygdala and impaired cortical ability to inhibit its activity (9,11,12), resulting in a lack of emotional regulation and difficulties of fear extinction responsible for sensitivity to threat and state of hypervigilance (13). Neuromodulatory techniques such as rTMS can modulate dysfunctional brain circuits in PTSD patients and induce causal change in fronto-limbic activity and in clinical symptoms (14). Hence, rTMS has shown its efficacy in treatment-resistant depression, anxiety disorders, and obsessive-compulsive disorder (15). rTMS is routinely applied over the right DLPFC, a central node in this network, but has demonstrated minimal efficacy when applied alone in PTSD treatment (7,16). Novel treatments in PTSD are expected to strengthen the balance between DLPFC (cognitive control) and medial prefrontal cortex and amygdala (affective processing) networks to improve overall functioning for patients (17). Patients suffering from PTSD often show excessive amygdala and reduced DLPFC functioning (9,18). We hypothesized that high frequency (HF) rTMS applied on the DLPFC would strengthen its function, impair the “fear network” in order to enhance the top-down function of the prefrontal cortex (DLPFC), while reducing the emotional responses of the amygdala.

Several studies have shown the effectiveness of exposure therapy to traumatic narrative in the process of desensitization involved in the extinction phenomenon of fear (19,20). The potentiation of exposure therapy with rTMS could lead to better treatment efficiency of PTSD through a variety of factors, while reduced therapy time could lead to better access to treatment. Moreover, the noninvasive nature of the treatment allows for a wide use of this technique. To our knowledge, there are only preliminary data on neurostimulation potentiation of exposure therapy in PTSD (21,22). Previous studies reported that repeated exposure to a traumatic script combined to rTMS could be effective to cure or/and help patients with PTSD symptoms, but using different study designs and with unclear results (21,23–25). Two studies found significant improvement in PTSD symptoms in the low frequency (LF) rTMS (1 Hz) group (21,24), while one study indicated improvement in PTSD and comorbid depressive symptoms in the HF rTMS (10 Hz) of the right DLPFC. We have opted here to study the addition of rTMS to trauma script exposure to reduce symptoms of PTSD.

Evidence suggests a state of sympathetic nervous system overactivity in PTSD (26,27), PTSD patients having higher resting heart rates (HRs) and blood pressure, and decreased heart rate variability (HRV) (28). In a study of PTSD twin pairs, reduced HRV was demonstrated in the twins that had PTSD (29). In their review, Gillie and Thayer showed that low resting HRV is associated with poorer performance on tasks that require cognitive control

processes (30). Moreover, findings suggest that individual differences in HRV may also index the extent to which individuals are subject to reexperiencing symptoms such as intrusive thoughts and memories.

## OBJECTIVES

The main objective of this study was to evaluate the efficacy and safety of rTMS in improving PTSD total severity score at 110% HF stimulation targeted at the right DLPFC simultaneously with exposure to personal traumatic narrative, in comparison with 70% LF stimulation of the right DLPFC simultaneously with exposure to personal traumatic narrative (control group).

Secondary objectives of this study were to evaluate the efficacy of rTMS on PTSD symptom clusters, anxiety and depressive symptoms, reactivity of the autonomic nervous system as well as cognitive function at 110% HF stimulation targeted at the right DLPFC simultaneously with exposure to traumatic narrative, in comparison to 70% LF stimulation under the same conditions. We expected to demonstrate a positive effect of treatment on clinical, physiological, and cognitive measures. PTSD is indeed associated with detrimental impact of negative emotion on cognitive function (31). We hypothesized that efficient treatment would normalize functional brain abnormalities (prefrontal hypoactivation) and result in a better cognitive performance in those cognitive tasks (attention, executive function, processing speed, and working memory).

## MATERIALS AND METHODS

### Ethics Approval

This study was approved by the French National Agency (ANSM 2015-A01179-40) and an independent national research ethics committee (CPP 2015-R28). The project was registered on the ClinicalTrials.gov website (NCT02584894) and was supervised by a clinical investigations monitoring committee (Inserm CIC1415). All of the patients signed informed-consent forms before enrolling in the trial.

### Study Design

We conducted a single-center randomized controlled trial in two parallel groups with follow-up at one and three months after completion of the treatment.

### Randomization

Participants were randomly assigned to a 110% HF or 70% LF rTMS condition. Treatment allocation was performed in a 1:1 ratio as per a computer-generated randomization schedule (SAS-based). Randomization was stratified on the use of selective-serotonin reuptake inhibitors (SSRI) at inclusion. The sequence was generated by a biostatistician independent from the recruitment using permuted blocks of varying sizes. Randomization was centralized via an online procedure using Ennov Clinical®, an online central randomization procedure via e-CRF. To ensure allocation concealment, randomization procedure was possible after the participant has been recruited into the trial, namely after the consent and all eligibility criteria met.

### Blinding

Patients and evaluators were blind to the treatment allocated (rTMS frequency), throughout the study. The rater was an experienced neuropsychologist or psychiatrist blinded to the treatment status and with no contact with the treatment team. Only trained intervention providers (nurse, psychologist) who administered the rTMS were not blind to the patient allocation group.

### Participants

All patients suffering from PTSD were first assessed by a psychiatrist. Patients were included if they have the ability to provide written informed consent and have a principal diagnosis of PTSD for more than three months, according to the DSM-IV, as confirmed by the Mini-International Neuropsychiatric Interview (MINI) (32). A score of 40 or higher was required at the PTSD Checklist for DSM-5 (PCL-5) (33). We included patients aged 18–65 years, with unchanged treatment for at least four weeks prior to entry into the study. All the patients were naïve from trauma-focused psychotherapy.

Noninclusion criteria comprised people with hearing impairments, braces or cochlear implants, those with identified neurological pathologies, patients with psychoactive substance addictions at the time of the study, as well as acute or chronic delusional conditions. Patients with any acute medical condition were not included because such conditions could affect treatment response.

### rTMS Procedure

rTMS was administered in a quite dedicated treatment room at the hospital using a MagPro R30 stimulator (MagVenture, A/S, Denmark) with a Cool-B65 A/P coil. Ear protection was offered when requested. Participants were seated in a comfortable treatment chair with neck rest for use with vacuum pillow to ensure stable positioning of the head. Prior to the initial rTMS session, the resting motor threshold (rMT) was determined as the lowest setting at which  $\geq 5$  out of 10 stimuli resulted in any observable movement of the contralateral index finger. Stimulation was then applied at 110% of the rMT. Coil positioning was determined by the 10–20 EEG system, such that F4 corresponds to the right DLPFC. Stimulation was performed on workdays for more than two weeks with a total of eight sessions. Any missed sessions were added at the end of the treatment course.

An automatic rTMS procedure was scripted in the machine software. In the 110% rMT HF 10 Hz rTMS (110% HF rTMS) was applied in 60 trains of 5-sec duration with 20-sec intertrain intervals, resulting in 3000 pulses per session. The control group had the same settings except for the frequency and the stimulation intensity. We applied 70% LF 1 Hz rTMS (70% LF rTMS) in 60 trains of 5-sec duration with 20-sec intertrain intervals, totaling 300 pulses per session. For both 110% HF and 70% LF rTMS treatments, the rTMS coil was placed at a 45° angle to the head.

At inclusion, participants were asked to describe in writing their main traumatic event during an approximate 30-min script preparation session, addressing in detail the traumatic experience that caused the PTSD. The subject described the traumatic experience in writing on a standard script preparation form. The investigator reviewed the script and requested additional details as necessary. During all the rTMS sessions, 110% HF and 70% LF, participants read their personal traumatic script throughout the session as well as receiving rTMS stimulation. Each session lasted for at least

45 min. We asked patients to report any side effect after each treatment session. In the event of poor study adherence, the patient was invited to discuss it with the study investigator. The rTMS intervention was fully described following the TIDieR list (Supplemental Material 1) (34).

### Outcome Measures

Follow-up visits were performed at one and three months after completion of the treatment protocol. The primary outcome was PTSD severity assessed by the Clinician Administered PTSD Scale (CAPS) (35) measured at baseline, one, and three months after completion of treatment. A decrease in the score at the end of the follow-up was considered as an improvement. The secondary outcomes were changes in the scores of the PTSD Checklist (PCL-5) (33), different dimensions of PTSD as measured by the CAPS and PCL-5, Hamilton Anxiety Rating Scale (HAM-A) (36), and Hamilton Depression Rating Scale (HAM-D) (37).

Cognitive function was evaluated using the trail-making test A (attention test), trail-making test B (executive function test) (38), the emotional Stroop (interference test) (39), and the Wechsler Adult Intelligence Scale (processing speed and working memory indexes) (40).

We included some physiological measures as an indication of self-regulatory capacity (HR, HRV, skin conductance [SC], and respiratory rate [RR]) and to assess the autonomic changes in PTSD. Physiological assessment was performed before and three months after completion of the treatment protocol using the ADInstruments system (PowerLab 8/35, AD Instruments Pty, Bella Vista, Australia). Measures were collected for ten minutes, after a five-minute resting period in seated position. It included HR, HRV, SC, and RR at rest through a pressure cuff. All physiological data analyses were performed on Matlab (MathWorks Inc, Natick, MA, USA) (41–45).

### Sample Size

Considering a 10-point intergroup difference in CAPS score three months after completion of the treatment with a standard deviation of 19 points, a two-sided 5% type I error rate, an 80% power and a correlation coefficient of 0.50 (due to repeated measures of CAPS per patient), the required sample size was 60.

### Statistical Analysis

Categorical variables were described with the use of numbers and percentages, and continuous variables with the use of means and standard deviations or medians and interquartile ranges. Changes over time on the different scores between baseline, one, and three months after completion of treatment were compared between the two groups using mixed linear models. In such models, treatment effects are represented as interaction effects (time  $\times$  treatment group), which corresponds to the difference between the 110% HF rTMS and 70% LF rTMS groups in mean change from baseline to three months after completion of treatment. No imputation of missing data was performed. Variation of physiological assessment between baseline and 90 days were analyzed using Wilcoxon's nonparametric tests. Data were analyzed with SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.3.1.

## RESULTS

### Subjects

Due to the difficulties encountered in recruiting study participants within the planned recruitment period, the study was terminated after only 38 participants had been randomized. These 38 patients were randomly assigned to two groups: 110% HF rTMS with trauma script exposure ( $n = 18$ ) and 70% LF rTMS with trauma script exposure ( $n = 20$ ) (Fig. 1). Table 1 summarizes their baseline clinical characteristics. Groups were comparable on psychiatric disorders using the MINI.

### Adherence to the Intervention

Most participants completed the study. Compliance with rTMS intervention was high (94.4% in the HF rTMS group and 90% in the LF rTMS group). The eight sessions took place within the two-week planned duration period for all but one participant for whom the eight sessions took place over a 16-day period. One patient in the 110% HF rTMS group did not complete all eight sessions; this patient was lost to follow-up after five sessions. Two patients in the 70% LF rTMS group did not complete all eight sessions; one received only one session and had a serious adverse event that prevented from continuing the planned sessions and the other received only seven sessions and did not receive the last session for an unknown reason.

### Safety

One serious adverse event occurred during the study (psychogenic nonepileptic seizure). Headache occurred in two patients from the 110% HF rTMS group, and required a treatment. Other adverse events were observed in both groups: diarrhea, nausea, vomiting, and increase in suicidal thoughts. An anxiety attack

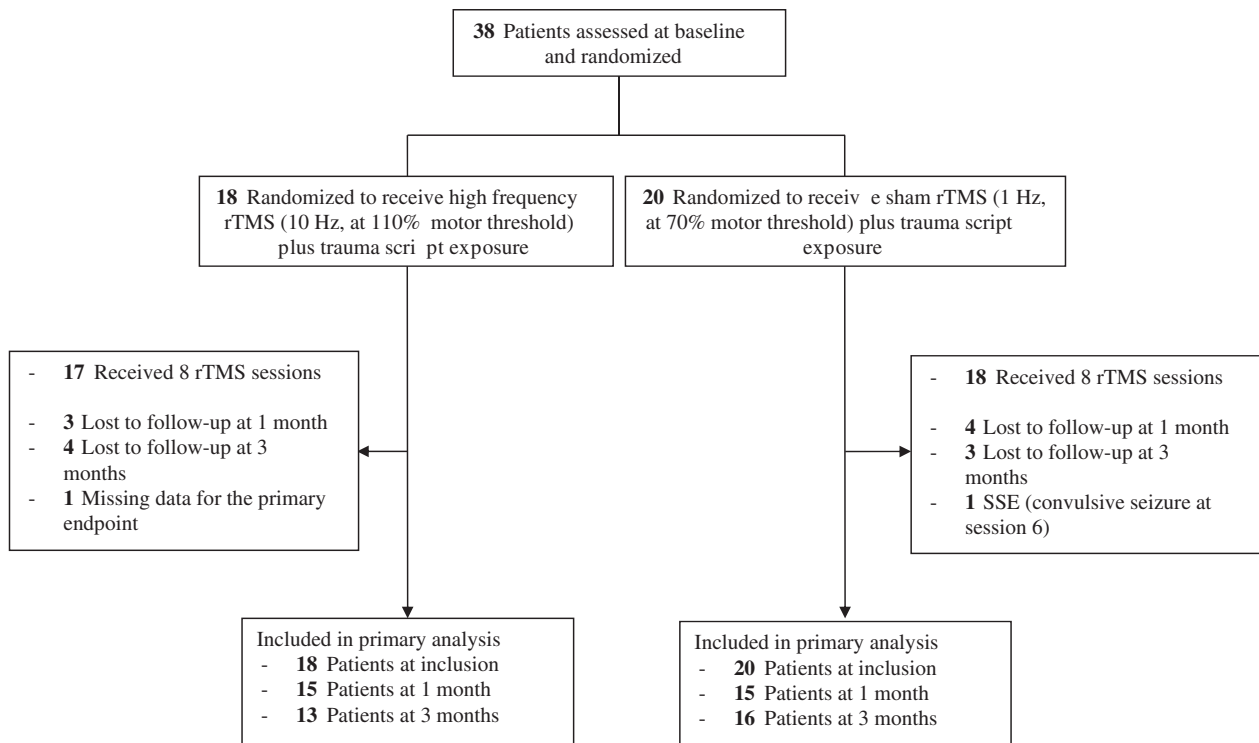
occurred in one patient from the 70% LF rTMS group, and was associated with an increase in suicidal thoughts. All these adverse events were classified as not related to the study protocol.

### Outcomes

From baseline to three months, mean CAPS scores decreased from  $83.7 \pm 14.4$  to  $41.8 \pm 31.9$  in the HF rTMS group, and from  $81.8 \pm 15.6$  to  $51.6 \pm 23.7$  in the LF rTMS group. Thus, a 51.0% reduction in CAPS scores was observed in the HF rTMS group, compared with a reduction of 36.9% in the LF rTMS group (Fig. 2), but with no significant between-group difference in improvement (time by treatment interaction  $-3.61$  [95% confidence interval (CI),  $-9.70$  to  $2.47$ ];  $p = 0.24$ ; effect size 0.53). Between-group mean difference in CAPS change in the model adjusted for SSRI uptake at inclusion (stratification variable for randomization) was also nonsignificant ( $-3.76$  [95% CI,  $-9.84$  to  $2.31$ ],  $p = 0.22$ ). The CAPS posttreatment PTSD diagnosis decreased in both groups with no significant between-group difference at three months: 7/13 patients (53.8%) were in remission in the HF rTMS group and 4/16 (25.0%) in the LF rTMS group ( $p = 0.23$ ).

We observed the same pattern of response using the self-report measure of PTSD symptoms (PCL-5). From baseline to three months, mean PCL-5 scores decreased from  $53.4 \pm 9.2$  to  $30.9 \pm 21.0$  in the 110% HF rTMS group, and from  $54.1 \pm 10.4$  to  $37.5 \pm 18.7$  in the 70% LF rTMS group, namely a 42.1% reduction in the HF rTMS group vs. a reduction of 30.7% in the LF group ( $-2.01$  [95% CI,  $-6.00$  to  $1.96$ ],  $p = 0.32$ ).

In addition, from baseline to three months, mean HAM-D scores decreased from  $18.8 \pm 4.9$  to  $9.9 \pm 8.2$  in the HF rTMS group, and from  $16.4 \pm 5.7$  to  $11.9 \pm 8.2$  in the LF rTMS group. Mean HAM-A scores decreased from  $24.1 \pm 7.7$  to  $14.4 \pm 12.2$  in the HF rTMS group, and from  $21.4 \pm 8.4$  to  $17.8 \pm 12.3$  in the LF rTMS group.



**Figure 1.** Flowchart of participants through the study. rTMS, repetitive transcranial magnetic stimulation; SSE, serious side effects.

**Table 1.** Baseline Characteristics of Participants.

	Group rTMS 10 Hz (n = 18)	Group rTMS 1 Hz (n = 20)
Age, years	31.3 ± 10.0 31.9 [21.7; 35.6]	33.5 ± 11.1 34.9 [22.3; 38.4]
Sex female	13 (72.2)	12 (60.0)
Body mass index, kg/m <sup>2</sup>	22.6 ± 4.4 22.5 [18.4; 25.0]	24.6 ± 4.7 23.9 [21.5; 25.5]
Number of schooling years	14.0 ± 2.1 13.0 [13.0; 15.0]	13.0 ± 2.1 13.0 [12.0; 14.0]
In couple	8 (44.4)	11 (55.0)
In professional activity	12 (66.7)	8 (40.0)
Number of traumatic events	3.6 ± 2.2 3.0 [2.0; 5.0]	3.8 ± 2.7 2.5 [2.0; 6.5]
Type of traumatic events		
Transport accidents	3 (16.7)	0 (0)
Physical assaults	7 (38.9)	3 (15.0)
Weapon assaults	1 (5.6)	4 (20.0)
Sexual assaults	5 (27.8)	10 (50.0)
Combat or exposure to a war zone	2 (11.1)	2 (10.0)
Illness or injury threatening survival	0 (0)	1 (5.0)
Age at the time of trauma, years	21.0 ± 8.7 19.5 [15.0; 27.0]	19.9 ± 11.1 17.5 [12.0; 27.0]
Age at onset of symptoms, years	21.6 ± 8.1 20.0 [15.0; 27.0]	23.6 ± 9.9 20.0 [15.5; 34.0]
On selective-serotonin reuptake inhibitors	11 (61.1)	11 (55.0)
CAPS total score, at inclusion	83.7 ± 14.4 85.0 [70.0; 94.0]	81.8 ± 15.6 82.0 [72.5; 91.0]
PCL-5 total score, at inclusion	53.4 ± 9.2 53.5 [48.0; 60.0]	54.1 ± 10.4 53.5 [46.5; 63.5]
MINI		
PTSD	18 (100.0)	20 (100.0)
Current depressive episode	8 (44.4)	8 (40.0)
Current suicidal thoughts	2 (11.1)	8 (40.0)
HAM-D score	18.8 ± 4.9 18.0 [15.0; 24.0]	16.4 ± 5.7 15.0 [11.5; 20.5]
HAM-A score	24.1 ± 7.7 22.0 [19.0; 29.0]	21.4 ± 8.4 20.5 [17.0; 25.5]

CAPS, Clinician Administered PTSD Scale according to DSM-IV; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; MINI, Mini-International Neuropsychiatric Interview; PCL-5, PTSD Checklist according to DSM-5; PTSD, post-traumatic stress disorder; Qualitative variables, *n* (%); Quantitative variables, mean ± standard deviation, median [1st quartile; 3rd quartile].

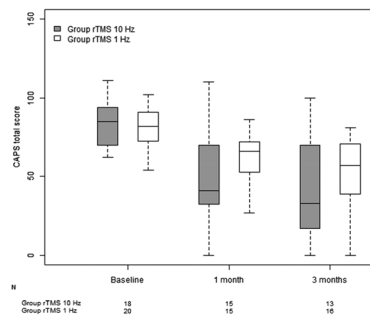
There was no significant time by treatment interaction found on the Hamilton Rating Scale for Anxiety (−1.65 [95% CI, −4.12 to 0.82], *p* = 0.19) and the Hamilton Rating Scale for Depression (−1.40 [95% CI, −3.11 to 0.31], *p* = 0.11).

In the Stroop task, there was no between-group difference to identify the color of negative than neutral items and in reaction times for negative and neutral items. There was no significant interaction between group and time (−2.40 [95% CI, −6.69 to 1.88], *p* = 0.27). The groups did not differ neither before nor after treatment on scores of attention (trail-making test A), executive function (trail-making test B) (−0.76 [95% CI, −7.80 to 6.27], *p* = 0.83), processing speed (1.13 [95% CI, −0.94 to 3.21], *p* = 0.28), and working memory (−0.53 [95% CI, −2.34 to 1.27], *p* = 0.55) of the Wechsler Adult Intelligence Scale.

Physiological parameters were tested. HR was not significantly different before and after treatment in both groups (*p* = 0.72). There was no significant modification of the HRV measures (*p* = 0.46). SC magnitude and RR did not differ between groups and over time (Supplemental Material 2).

## DISCUSSION

The present study investigated whether combining 110% HF rTMS with trauma script exposure is superior to 70% LF rTMS with trauma script exposure in terms of improvement of PTSD symptoms. After completion of eight-sessions trial, the total CAPS and PCL-5 scores improved in both groups and, although non-statistically significant, improvement seems to be larger in the 110% HF group across all measures. Similar results were observed for the other secondary outcomes, namely on PTSD, depression and anxiety symptoms, and cognitive and physiological outcomes. At three months posttreatment, PTSD diagnosis decreased in both groups: half (53.8%) of the patients achieved remission in the 110% HF rTMS group and a quarter in the 70% LF rTMS group. The consensus responder criteria consists of a 30% or greater reduction in the CAPS total severity score (46,47). Clinical improvement was important and clinically relevant in both groups (>30% improvement), even though not significant between groups.



CAPS total score	Group rTMS 10 Hz + exposure	Group rTMS 1 Hz + exposure
Baseline	83.7 ± 14.4, 85.0 [70.0; 94.0]	81.8 ± 15.6, 82.0 [72.5; 91.0]
1 month	50.5 ± 32.8, 41.0 [32.0; 71.0]	60.1 ± 19.3, 66.0 [51.0; 73.0]
3 months	41.8 ± 31.9, 33.0 [17.0; 70.0]	51.6 ± 23.7, 57.0 [39.0; 70.5]

*Mean ± Standard Deviation, Median [1<sup>st</sup> quartile; 3<sup>rd</sup> quartile]*

**Figure 2.** Effects of rTMS intervention over time.

In this randomized, double-blind study, we chose to combine exposure to personal traumatic script with rTMS. The applied treatment combining exposure to the trauma scenario and rTMS (110% HF, 70% LF) improved symptoms of PTSD, anxiety, and depression in both groups. However, we found no significant difference between the groups one and three months after treatment. The absence of significant between-group differences could have different explanations. First, we can suppose a potential lack of power of our trial as we failed to recruit the planned sample size ( $n = 60$ ). Second, we can assume that both stimulation protocols (110% HF and 70% LF rTMS) were active delivering differentiated therapeutic benefit, as both groups showed important clinical improvement. Third, this is a randomized clinical study vs. control group (70% LF rTMS), which cannot be considered as sham condition. Fourth, the therapeutic effect may be largely attributable to the trauma script exposure.

The choice of the control condition (70% LF rTMS) is not ideal as it cannot be considered as sham condition. We had indeed no sham coil at the starting date of this study. Thus, we had to find an alternative for a placebo rTMS fulfilling a number of criteria (48): the same position as the active coil over the scalp, the same subjective somatic scalp sensation and the same acoustic artifacts during stimulation, but with no physiological effect on the targeted cortical region. Thus, the stimulation was applied at the same position with a stimulus intensity of 70% to avoid affecting the cortical circuitry. The stimulus intensity is based on individually determined rMT, commonly between 110% and 120% rMT (49). Todd et al. investigated the effect of ten minutes of intermittent rTMS on motor cortical excitability in normal subjects at low (2 Hz) and high frequencies (6 Hz) (50). They compared three low intensities of stimulation (70, 80, and 90% of active MT) and sham stimulation. They demonstrated that rTMS stimulation at 70% of active MT and sham stimulation did not induce a significant group effect on motor-evoked potential magnitude. They concluded that it is likely that this intensity of stimulation is not sufficient to affect the cortical circuitry important for motor-evoked potential generation.

Participants in our study were naïve from trauma-focused psychotherapy, actively recalled their traumatic event and showed a substantial decrease in PTSD symptoms. The duration of the trauma script exposure in our study was probably long enough to cause therapeutic benefits. Indeed, previous study showed that

30-minute imaginal exposure sessions are as effective as 60-minute exposure sessions, and that within-session habituation may not be a necessary condition for successful treatment of PTSD (51). Thus, the clinical improvement observed in both groups could be attributed to the exposure procedure, which was repeated eight times in participants naïve from exposure-based treatment.

Even though the DLPFC is a target of choice in many brain stimulation studies, particularly when it comes to applying rTMS, other frontal brain regions are of interest in PTSD. Indeed, other frontal regions showed hypoactivity in PTSD and have been implicated in the extinction impairment, such as the medial prefrontal cortex (25). Thus, other targets for brain stimulation need to be explored to offer alternative therapies for PTSD using rTMS.

Also, we might reasonably question the effectiveness of rTMS as the best neuromodulation technique. On one hand, other neuromodulation options are now available, such as transcranial direct current stimulation (tDCS) or deep brain stimulation (DBS): tDCS is a form of noninvasive brain stimulation that changes the likelihood of neuronal firing through modulation of neural resting membranes (52), while DBS involves implanting an electrode that delivers electrical pulses repeatedly (7,53). Novakovic et al. assumed that stimulation of other regions than DLPFC can be useful such as stimulation of the amygdala (53). Moreover, DBS has other positive aspects as it can be administered wherever the person is, and it is adjustable without further surgery. However, acceptability of DBS as an invasive form of neurostimulation remains problematic (54). On the other hand, rTMS is a noninvasive and innovative technique that can have many therapeutic effects, especially when it comes to treating depression, anxiety disorders, and PTSD. It allows, through stimulation, the modification of the excitability of neurons that could influence emotional regulation.

Finally, previous research has highlighted different neuroactivation patterns between patients suffering from PTSD, for example, related to the presence of dissociative symptoms. Patients suffering from PTSD and dissociative symptoms demonstrated different brain activations during traumatic script-driven symptom provocation paradigm (55) and a greater activation of neural networks involved in representing bodily states in dissociated PTSD subjects than in non-PTSD control subjects (56). The presence of dissociative symptoms may therefore have interfered with neuromodulation benefits. Further studies should take into account the presence of dissociative symptoms, and thus compare the effectiveness of rTMS in dissociated PTSD subjects compared to nondissociated PTSD subjects and non-PTSD control subjects.

Concerning physiological measures, most of the studies assessed the autonomic changes in PTSD in response to fear-related stimuli. However, we did not want to increase the emotional burden of patients' participation to the study and we wanted to capture the basal overactivation of the sympathetic nervous system. Unfortunately, we found no significant changes in these at rest physiological measures in our study. This reflects participants' reactivity level at rest but does not presume the reactivity to threat-related stimuli. Regarding the neuropsychological consequences, the tests assigned to the patients did not reveal any significant difference either. Replication of this study with larger number of participants could bring precious pieces of information about the lack of significant results to this study.

## LIMITATIONS

First, the main limitation of this study is its small sample size, even though our sample is larger than in previous studies. Larger studies are still needed to choose the best treatment strategy, between LF and HF rTMS, duration of treatment periods, method of exposure, combination therapy with neuromodulation, target site, and laterality. Second, we used here a simple trauma script exposure that should not be thought of as a therapy. A standard exposure-based therapy for PTSD would probably demonstrate significantly higher effectiveness than trauma script exposure. Third, this trial evaluated the efficacy and safety of 110% HF rTMS against 70% LF rTMS, both conditions can be considered as active with a missing genuine “sham” condition. Fourth, this study used the 10–20 system for TMS positioning, which is applicable at low cost but less reliable than navigation-guided rTMS as we cannot exclude positioning errors due to possible interindividual differences. Fifth, we included only 8 treatment sessions while previous studies included more often 10 sessions over a two-week period, with a large variability between 1 and 30 sessions (23). We have prioritized, as regards the practical implications, feasibility and effectiveness, but we cannot exclude that higher number of sessions is more beneficial. Finally, further studies should also allow evaluating the effectiveness of the neuromodulation on comorbidities of PTSD (depression and anxiety).

## CONCLUSION

In conclusion, this study showed that the traumatic script reactivation procedure is effective, since we obtained important improvement of symptoms in both groups. Clinical improvement was larger in the 110% HF rTMS compared to the 70% LF rTMS, even though with no significant difference on PTSD symptoms. The absence of significant group differences is most probably explained by potential lack of power of our trial and by the absence of sham condition. These results are consistent with the literature indicating that effective reactivation of traumatic memory is a good strategy to improve PTSD symptoms. Combining trauma script exposure with rTMS to reduce symptoms of PTSD is still a promising strategy, which we failed to demonstrate given the lower-than-expected sample size of the study. This strategy needs to be evaluated with a larger sample of patients using rTMS or with other neuromodulation techniques.

## Authorship Statements

Drs. Wissam El-Hage, Agnès Caille, Marc Legrand, and David Clarys designed and conducted the study, including patient recruitment, data collection, and data analysis. Drs. Sarah Thierrée and Marie Raulin-Biot prepared the manuscript draft with important intellectual input from Drs. Wissam El-Hage, Agnès Caille, Amelie Le Gouge, Andrei-Cristian Tudorache, and Bruno Brizard. Fondation de l'Avenir provided funding for the study. Dr. Amelie Le Gouge provided statistical support in analyzing the data with input from Drs. Alexis Vancappel, Bruno Brizard, and Agnès Caille. Drs. Agnès Caille and Amelie Le Gouge had complete access to the study data. All authors approved the final manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article.

## COMMENT

Testing whether the combination of non-invasive neuromodulation together with therapy, or a therapeutic-like process, is effective is of high relevance to the field. The current paper adds to this literature by testing the application of transcranial magnetic stimulation, either applying (1) 10Hz at 110% of resting motor threshold for 3000 pulses or (2) 1Hz at 70% of resting motor threshold for 300 pulses, while participants read personal traumatic scripts during eight stimulation sessions. Although stimulated groups did not differ significantly, likely due to low power, there was a clear reduction in PTSD symptom severity from baseline to three months post intervention that was numerically greatest for individuals who received 10Hz stimulation. Generally, this line of research will allow greater insight into the context-dependency of brain stimulation with the ultimate goal to improve treatment outcomes for mental disorders.

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