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van der Heijden, Anna C.; van der Werf, Ysbrand D.; van den Heuvel, Odile A.; Talamini, Lucia M.; van Marle, Hein J.F.

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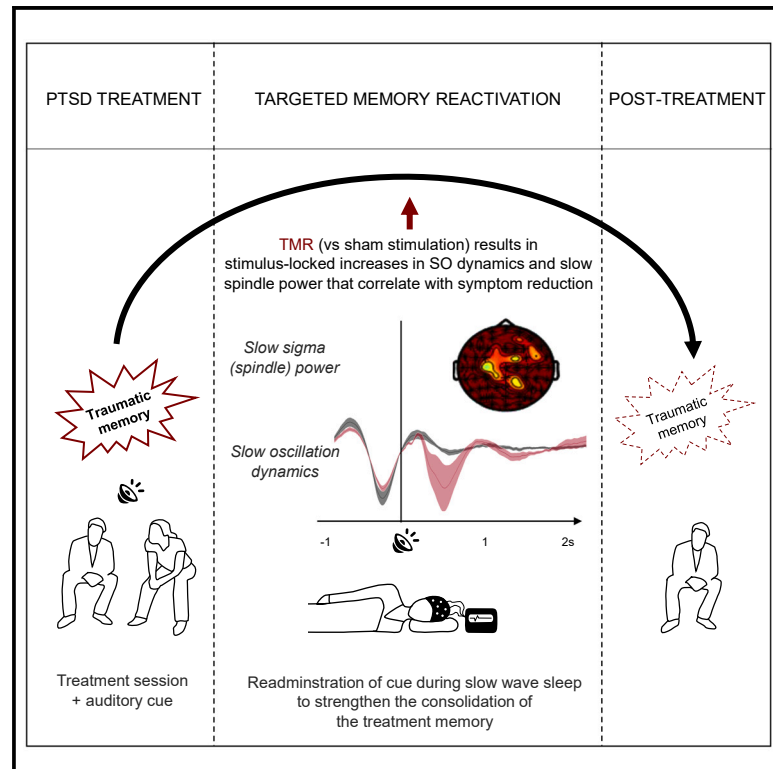
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Targeted memory reactivation to augment treatment in post-traumatic stress disorder

Graphical abstract



Authors

Anna C. van der Heijden,
Ysbrand D. van der Werf,
Odile A. van den Heuvel,
Lucia M. Talamini, Hein J.F. van Marle

Correspondence

h.j.vanmarle@amsterdamumc.nl

In brief

Targeted memory reactivation (TMR) is a novel way to strengthen memories during sleep. Van der Heijden et al. apply TMR during post-treatment sleep in patients with PTSD. Findings suggest that TMR potentiates the consolidation of treatment memories, yielding proof of principle that TMR may be a viable future treatment augmentation strategy for PTSD.

Highlights

- Targeted memory reactivation (TMR) is technically feasible and safe in PTSD sleep
- TMR potentiated slow oscillation (SO) dynamics and increased SO and spindle power
- TMR-induced changes in sleep physiology correlated with PTSD symptom reduction
- TMR reduced avoidance during script-driven imagery of the targeted memory



Article

Targeted memory reactivation to augment treatment in post-traumatic stress disorder

Anna C. van der Heijden,^{1,2,3,4} Ysbrand D. van der Werf,^{1,5} Odile A. van den Heuvel,^{1,2,5} Lucia M. Talamini,^{4,6,9} and Hein J.F. van Marle^{2,3,7,8,9,10,*}

¹Amsterdam UMC, Vrije Universiteit Amsterdam, Department Anatomy & Neuroscience, Boelelaan 1081 HV Amsterdam, the Netherlands

²Amsterdam UMC, Vrije Universiteit Amsterdam, Psychiatry, Oldenaller 1081 HJ Amsterdam, the Netherlands

³Amsterdam Neuroscience, Mood Anxiety Psychosis Stress Sleep, Boelelaan 1081 HV Amsterdam, the Netherlands

⁴University of Amsterdam, Department of Psychology, Brain & Cognition, Nieuwe Achtergracht 1018 WS Amsterdam, the Netherlands

⁵Amsterdam Neuroscience, Compulsivity Impulsivity and Attention, Boelelaan 1081 HV Amsterdam, the Netherlands

⁶University of Amsterdam, Amsterdam Brain and Cognition, Nieuwe Achtergracht 1001 NK Amsterdam, the Netherlands

⁷GGZ inGeest Mental Health Care, Oldenaller 1081 HJ Amsterdam, the Netherlands

⁸ARQ National Psychotrauma Center, Nienoord 1112 XE Diemen, the Netherlands

⁹These authors contributed equally

¹⁰Lead contact

*Correspondence: h.j.vanmarle@amsterdamumc.nl

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SUMMARY

Post-traumatic stress disorder (PTSD) is a psychiatric disorder with traumatic memories at its core. Post-treatment sleep may offer a unique time window to increase therapeutic efficacy through consolidation of therapeutically modified traumatic memories. Targeted memory reactivation (TMR) enhances memory consolidation by presenting reminder cues (e.g., sounds associated with a memory) during sleep. Here, we applied TMR in PTSD patients to strengthen therapeutic memories during sleep after one treatment session with eye movement desensitization and reprocessing (EMDR). PTSD patients received either slow oscillation (SO) phase-targeted TMR, using modeling-based closed-loop neurostimulation (M-CLNS) with EMDR clicks as a reactivation cue ($n = 17$), or sham stimulation ($n = 16$). Effects of TMR on sleep were assessed through high-density polysomnography. Effects on treatment outcome were assessed through subjective, autonomic, and fMRI responses to script-driven imagery (SDI) of the targeted traumatic memory and overall PTSD symptom level. Compared to sham stimulation, TMR led to stimulus-locked increases in SO and spindle dynamics, which correlated positively with PTSD symptom reduction in the TMR group. Given the role of SOs and spindles in memory consolidation, these findings suggest that TMR may have strengthened the consolidation of the EMDR-treatment memory. Clinically, TMR vs. sham stimulation resulted in a larger reduction of avoidance level during SDI. TMR did not disturb sleep or trigger nightmares. Together, these data provide first proof of principle that TMR may be a safe and viable future treatment augmentation strategy for PTSD. The required follow-up studies may implement multi-night TMR or TMR during REM sleep to further establish the clinical effect of TMR for traumatic memories.

INTRODUCTION

Post-traumatic stress disorder (PTSD) is a highly disabling psychiatric disorder with a lifetime prevalence of 7%–12%, depending on the population studied.^{1–3} At the core of the disorder are intrusive memories about the traumatic event that result in key symptoms such as nightmares and dissociative flashbacks.⁴ Additional symptoms include hypervigilance, hyperarousal, diverse mood and cognitive problems, sleep problems, and avoidance of triggers related to the traumatic event. With patients being generally unable to work, and with annual costs associated with PTSD rising to €9 billion in Europe alone,⁵ PTSD constitutes a major personal and societal burden. Currently, up to half of patients do not respond sufficiently^{6–8} to first-choice, exposure-based psychotherapy, such as imaginal exposure or eye movement desensitization and

reprocessing (EMDR).^{9,10} Furthermore, due to the emotionally demanding nature of these treatments, drop-out rates are high.¹¹ Pharmacotherapy effects in PTSD are unfortunately small.¹² Thus, new treatment strategies are needed.

Sleep represents a unique time window to enhance therapeutic interventions for PTSD.¹³ During psychotherapy, traumatic memories are revisited and subsequently re-encoded with lower levels of fear and arousal. During EMDR, for example, sensory and working memory tasks leave little processing capacity to re-experience the normally occurring fear, resulting in the memory being re-encoded in a more neutral form.^{14,15} In line with the memory function of sleep,^{16,17} these therapeutically altered memories likely need to be stored into long-term memory networks during sleep to solidify the treatment effect.^{18,19} This process, referred to as memory consolidation, stabilizes the memory and further reduces its affective charge.^{20,21} According to a



large body of evidence, the neuronal underpinnings of memory consolidation involve reactivation of hippocampo-neocortical memory representations during slow-wave sleep (SWS). During this neuronal replay, hippocampal sharp-wave ripples synchronize with thalamo-cortical spindles and cortical slow oscillations (SOs), promoting information transfer and integration of the memory trace into existing memory networks.^{22,23}

New developments in memory research show that memory reprocessing during sleep can be influenced in order to boost memory consolidation.^{24–27} Specifically, in a process referred to as targeted memory reactivation (TMR), sensory cues (such as sounds and scents) that are linked to the memory at encoding are presented again during SWS, resulting in improved memory post-sleep.^{28–31} Although the precise underlying neural mechanisms remain unclear, TMR is thought to selectively bias ongoing neuronal replay toward the memory representations linked to the reactivation cue, facilitating their hippocampo-cortical transfer.^{32–34} TMR has been shown to augment performance in a wide variety of memory tasks^{35–38} with small to moderate effect sizes.³⁹ However, only a handful of studies have applied TMR in an attempt to alter fear memories in healthy subjects or phobia-related memories in patients, and they have shown mixed results.^{40–46} A recent advance concerns phase-targeted TMR. Here, cue presentation is time locked to the depolarizing and plasticity-promoting positive deflections of cortical SOs (hereafter referred to as SO upwaves) in order to maximize the impact on spontaneous memory reactivations and hippocampo-cortical transfer.^{25,31,47,48} Here, we applied (phase-targeted) TMR for the first time in PTSD patients in an attempt to increase therapeutic efficacy of standard PTSD treatment. All participating patients were treated in the evening with a single session of EMDR, including a standard distracting auditory stimulus to tax working memory (Figure 1). Following a randomized, controlled, between-subjects design, the EMDR click was then re-administered as a context cue of the positive treatment outcome in half of patients ($n = 17$, TMR group). EMDR clicks were administered time locked to SO upwaves using a new, modeling-based closed-loop neurostimulation (M-CLNS) method that tracks and predicts the electroencephalogram (EEG) signal.^{25,49} This flexible method is expected to adapt to the atypical EEG signature of PTSD sleep, enabling accurate phase targeting despite the severe (slow-wave) sleep disturbance in this population.^{50,51} In the sham control group ($n = 16$), the same M-CLNS method left markers in the EEG recording, but no sounds were presented. To avoid potentially strengthening a negative treatment outcome, TMR was only administered if patients showed a reduction of ≥ 2 points on the subjective units of distress (SUDs) scale during EMDR treatment (which was the case for all patients). Patients were recruited from several mental health care institutions in the Netherlands while they were on a waiting list for treatment. Inclusion was based on diagnostic criteria of PTSD, as assessed with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5).^{52,53} Exclusion criteria included several clinical, sleep-related, and MRI-related criteria (see STAR Methods). We hypothesized that, as a result of facilitated consolidation of the EMDR treatment memory, TMR (as compared to sham stimulation) would result in a bigger reduction in subjective and autonomic responses related to the targeted traumatic memory (as measured during script-driven imagery [SDI] task^{54,55}), as well

as a bigger reduction in overall PTSD symptom severity. Symptom severity was measured with the CAPS-5 W (week version) and the self-administered PTSD checklist for DSM-5 (PCL-5).^{52,53,56,57} High-density EEG was obtained during the TMR night to assess phase targeting accuracy and to study the neural underpinnings of TMR. Based on previous experiments in healthy subjects,^{58,59} we expected phase-locked TMR to induce SOs and spindles. Given their role in memory consolidation,¹⁷ we expected these dynamics to positively correlate with clinical TMR effects. The pre- and post-intervention SDI sessions took place during functional MRI to track (TMR-enhanced) neural reorganization of the targeted memories. In line with stronger system-level consolidation,²³ we expected the TMR group to show a stronger reduction in both hippocampus and amygdala activation and a stronger reduction in functional coupling between hippocampus (as seed region) and the amygdala and ventromedial prefrontal cortex (vmPFC) (as designated neocortical memory representation area).^{60,61} Given the challenges and potential risks of applying TMR in pathological sleep, considerable attention was given to assessing the feasibility and safety of TMR application in PTSD.

RESULTS

Feasibility and safety of TMR

TMR was applied during N2 and N3 sleep for 3 h after first onset of N3 sleep (referred to as the cued period). On average, 187 EMDR clicks (± 75) were administered per participant in the TMR condition, precisely at the start of the SO upwave (average phase at stimulus onset: $1.86^\circ \pm 50^\circ$) (Figure 2A). Polysomnographic recordings of the intervention night indicated that TMR did not affect sleep macroarchitecture, including sleep efficiency and continuity, during either the cued period or the whole night (Table S1). Furthermore, sleep diary reports showed that TMR did not affect subjective sleep quality, nor did patients in the TMR group report more nightmares during the intervention night. Upon awakening after the TMR session, none of the patients reported having heard the auditory stimulation.

TMR effects on therapeutic efficacy

No baseline differences in clinical factors and factors possibly impacting TMR success were found between groups (Table 1). The effect of TMR was primarily assessed through SDI of the targeted traumatic memory before and after the TMR or sham intervention. During SDI, patients listened for 30 s to a personalized auditory script of their traumatic event and then imagined themselves for 30 s back in the event, including all sensory sensations. Preceded by a baseline (30 s) and ending with a “letting go” (60 s) phase, this cycle was repeated 3 times (Figure 1). Next, patients rated their subjective experience on the Responses to Script-Driven Imagery Scale (RSDI⁶²) covering the following three dimensions: re-experiencing, avoidance, and dissociation. To test whether TMR augmented EMDR treatment outcome, we performed 2 × 3 factorial ANOVAs with group (TMR vs. sham) as the between-subjects factor and time (pre, post, follow-up) as the within-subjects factor, followed by post-hoc *t* tests (Figure 3). The combined groups reported a decrease in re-experiencing and avoidance from pre- to post-intervention (main effect of time, respectively: $F(1.58, 48.85) = 52.80$, $p < 0.001$; $F(1.67, 51.83) = 15.64$,

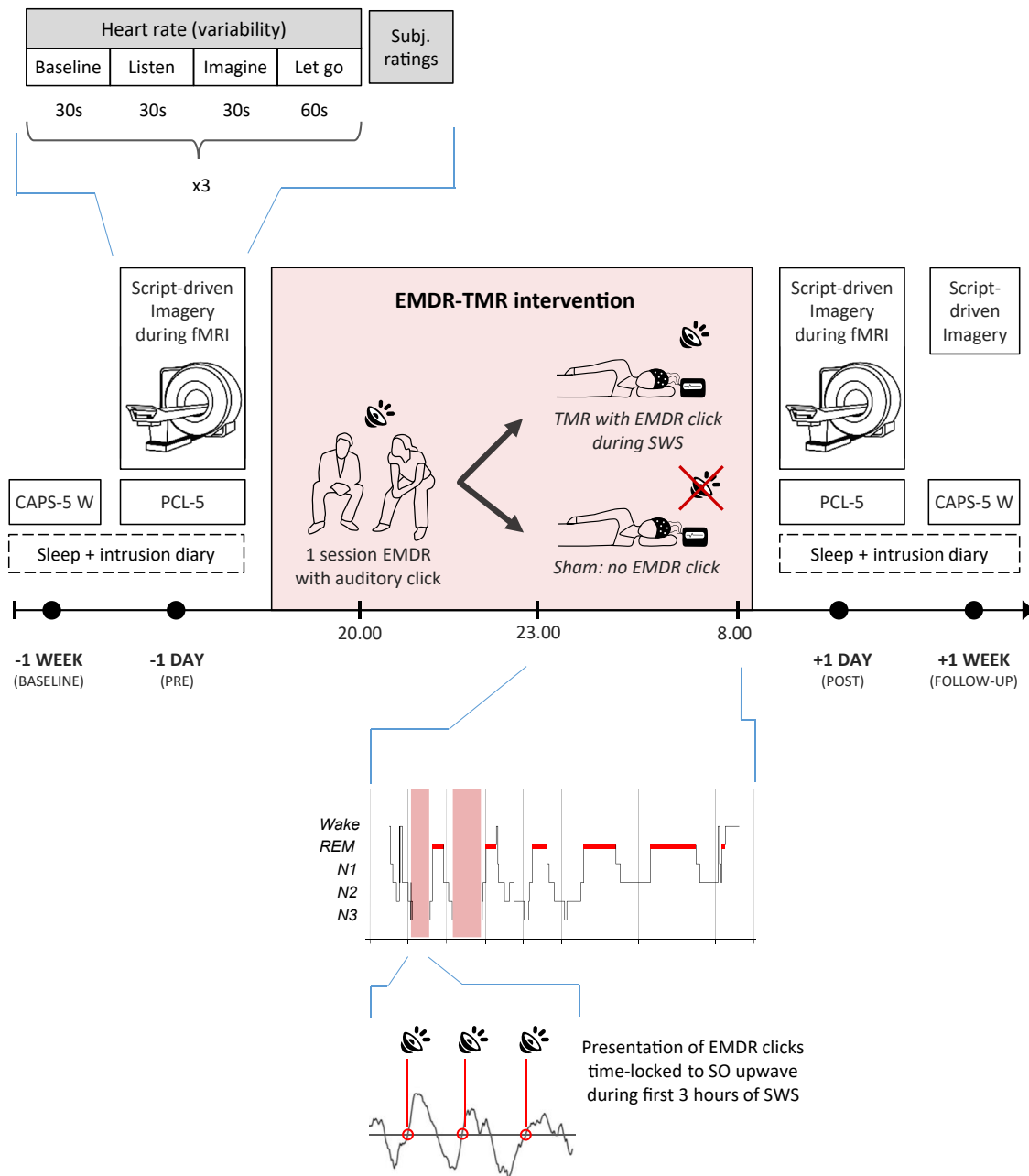


Figure 1. Schematic overview of experimental design and outcome parameters

PTSD patients were treated in the evening with a single session of eye movement desensitization and reprocessing (EMDR) including standard auditory clicks (middle). During the following polysomnographically monitored night, patients received either targeted memory reactivation (TMR) using the EMDR click as a reactivation cue or sham stimulation (no sound presentation). TMR was administered for 3 h after first onset of slow-wave sleep (SWS), with presentation of clicks precisely time locked to slow oscillation (SO) upwaves using a closed-loop neurostimulation method (lower part of figure).⁴⁹ Subjective, autonomic (heart rate and heart rate variability), and neural (bold) responses to script-driven imagery (SDI) of the targeted traumatic memory were obtained 1 day before (pre) and 1 day after (post) the intervention under functional MRI (left and right). Subjective and autonomic measures to SDI were again obtained 1 week after intervention (follow-up). See upper left part of figure for graphical depiction of SDI task. During the TMR night, high-density EEG was recorded. Overall PTSD symptom severity was measured 1 week before (baseline) and 1 week after intervention (follow-up) using the Clinician-Administered PTSD Scale for DSM-5, week version (CAPS-5 W), and at moments coinciding with SDI using the PTSD checklist for DSM-5 (PCL-5). Patients kept a daily sleep and intrusion diary from 3 days before intervention to 1 week post-intervention.

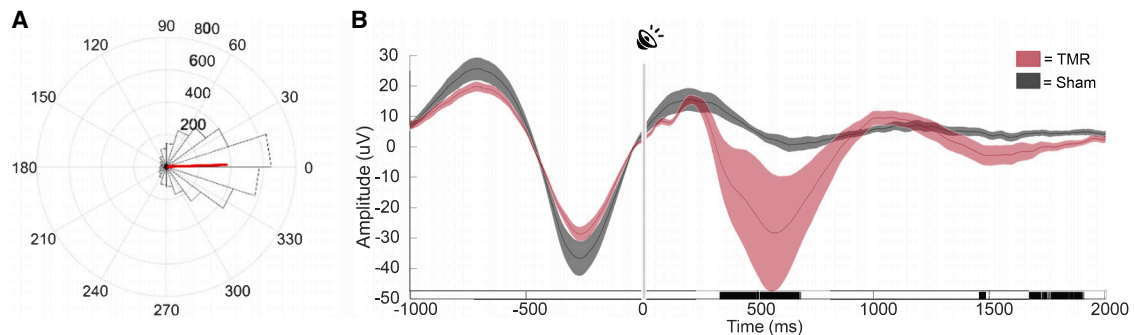


Figure 2. Phase accuracy of TMR and event-related potential (ERP)

(A) Phase accuracy of modeling-based closed-loop neurostimulation (M-CLNS) procedure, with the red line indicating that TMR cues were delivered at an average phase angle of 1.86° with respect to the SO upwave. (B) After cue presentation (0 ms), the TMR group showed an amplification and prolongation of the SO dynamic, leading to significant differences with the sham group ($p < 0.05$, black lines in x axis).

$p < 0.001$). More specifically, across groups both re-experiencing and avoidance reduced from pre to post (re-experiencing: $t(32) = 7.56$, $p < 0.001$; avoidance: $t(32) = 3.38$, $p = 0.002$) and pre to follow-up (re-experiencing: $t(32) = 8.33$, $p < 0.001$; avoidance: $t(32) = 2.33$, $p = 0.025$). In addition, we found a group \times time interaction for avoidance ($F(1.67, 51.83) = 4.30$, $p = 0.024$), with patients in the TMR group showing a larger reduction than the sham group in avoidance from pre to post ($t(31) = -2.57$, $p = 0.015$) and from pre to follow-up ($t(26.937) = -2.113$, $p = 0.044$). While the TMR group showed higher avoidance at baseline ($t(31) = -2.26$, $p = 0.03$), this additive effect of TMR on avoidance within the TMR group showed a (trend-level) positive correlation with the number of EMDR clicks during sleep ($r = 0.42$, $p = 0.095$), possibly indicating TMR specificity of the effect. Other measures—including PTSD symptom severity (CAPS-5 W, Figure 2D; PCL-5, Figure S2); autonomic responses during SDI (Figure S1); number of daily intrusions of the targeted memory and associated level of distress (Figure S2); and sleep diary measures, including number of nightmares (Figure S3)—generally showed a reduction from pre- to post-intervention but no additive effect of TMR. Notably, TMR did not worsen any PTSD symptoms, including sleep-related symptoms, such as nightmares and insomnia.

TMR effects on the sleep EEG

Event-related potential

To study the brain response evoked by TMR, event-related potentials (ERPs) were compared between the TMR and sham group at the frontal Fz derivation, where SO dynamics are particularly pronounced. After cue presentation, the TMR group showed an amplification of the SO dynamic, leading to significant differences with the sham group ($p < 0.05$) from 334 to 681 ms, from 1,455 to 1,484 ms, and at various time points between $\pm 1,668$ and 1,904 ms post-cue (Figure 2B). These findings show that TMR amplified and prolonged the ongoing SO dynamic.

Time-frequency analyses

Effects of TMR on oscillatory brain activity were assessed through time-frequency analyses (TFAs) on the frontal Fz and centroparietal CPz derivations, as preferred locations for expression of SOs and slow spindles (Fz) and fast spindles

(CPz). Both frontally and centroparietally, TMR induced two significantly different clusters compared to sham stimulation: an early cluster showing increased low frequency, followed by a later increase in sigma-beta power (Figure 4). The low-frequency cluster coincided with the early, negative deflection in the ERP response, likely reflecting the low-frequency content of the SO. The sigma-beta increase aligned with the induced SO upwave-like positivity in the ERP (1,000–1,200 ms after cue presentation) and thus likely reflects increased spindle and higher-frequency activity known to accompany SO upwaves. TMR thus seems to potentiate precisely those oscillatory frequency bands that are strongly linked to sleep-dependent memory consolidation. Analysis through spectropomaps showed that both the low frequency and sigma-beta increase by TMR were significant for nearly all electrodes, indicating a widespread TMR effect across the brain (Figure 4, upper part).

EEG-TMR response is associated with PTSD symptom improvement

To evaluate whether the TMR-induced changes in sleep physiology were associated with changes in PTSD symptomatology, we extracted from our findings index measures for SO and spindle enhancement. The SO indexes were the minimum and maximum ERP amplitudes between 0 and 2000 ms; slow and fast spindles were indexed as power averaged over all data points in the significant TFA sigma-beta cluster, between 11 and 13.25 Hz at Fz and between 13.25 and 15.75 Hz at CPz. These indexes were correlated to the pre- to post-intervention change in various PTSD severity measures. Both the minimum and maximum ERP amplitudes within the TMR group correlated with the reduction in PTSD severity indexed by the CAPS-5 W severity score (minimum amplitude $r_s = -0.575$, $p = 0.020$; maximum amplitude $r_s = 0.523$, $p = 0.038$). This indicates that the SO amplification, reflected in a deeper SO trough and a higher peak, corresponded with more alleviation of PTSD severity. In addition, the increased frontal slow sigma (11–13.25 Hz) power within the TMR group was associated with reduced PTSD intrusions measured with the PCL-5, subscale intrusions ($r = .535$, $p = 0.027$). There were no significant correlations with RSDI measures or number of EMDR clicks ($p > 0.10$). In addition, the reported correlations were not

Table 1. Sample characteristics

	TMR M (SD)	Sham M (SD)	<i>p</i>
Demographics			
Patients (females/males)	17 (10/7)	16 (10/6)	0.829 ^a
Age	42.47 (9.81)	41.25 (8.93)	0.712
Education level (Mdn)	7.00	6.50	0.631 ^b
Baseline scores			
CAPS-5 – week	34.76 (9.13)	37.38 (11.97)	0.485
CAPS-5 – month	38.41 (7.39)	38.88 (10.30)	0.882
Sleep quality (PSQI)	11.00 (2.98)	10.50 (3.09)	0.204 ^b
Efficacy of EMDR-session (decrease in SUD scores)	6.81 (2.90)	6.82 (1.78)	0.683 ^b
Beck Anxiety Inventory (BAI)	40.69 (7.27)	43.13 (9.02)	0.407
Beck Depression Inventory II (BDI)	21.63 (8.26)	23.56 (11.7)	0.592

Sociodemographic characteristics and baseline PTSD symptom scores and sleep quality are shown. CAPS-5, Clinician-Administered PTSD Scale; Mdn, median; PSQI, Pittsburgh Sleep Quality Index; SUD, subunits of distress (in relation to the treated memory).

^a χ^2 test.
^bMann-Whitney U test.

significant within the sham group (CAPS-5 W severity score [ERP minimum amplitude, $r_s = -0.062$, $p = 0.820$; ERP maximum amplitude, $r_s = 0.307$, $p = 0.272$]; PCL-5 severity score [frontal slow sigma power, $r_s = 0.016$, $p = 0.952$]).

TMR effects on fMRI correlates of trauma memory recall

At pre- and post-intervention, the SDI was performed during fMRI to visualize the hypothesized enhanced system-level consolidation as a result of TMR. Based on their documented role in memory consolidation, we performed a region of interest (ROI) analysis focusing on bilateral amygdala, hippocampus, and ventromedial PFC. Beta values representing the imagine vs. baseline condition were extracted for these regions and analyzed with SPSS using a 2 (TMR vs. sham) \times 2 (pre vs. post) ANOVA (Figure S4). In addition, exploratory whole-brain analysis was performed in statistical parametric mapping (SPM) (Table S2). To visualize consolidation-related changes in functional coupling between the hippocampus as seed region and the two other ROIs, we additionally performed a generalized form of context-dependent, psychophysiological interaction analysis (gPPI).⁶³ Here, analyses were done in SPSS based on extracted beta values of the ROIs using the same 2 \times 2 ANOVA. Activation-based analyses (ROI and whole brain) showed that our ROIs, together with several other regions, were involved in the task. In both the activation-based and connectivity-based analyses, we did not find evidence of enhanced system-level consolidation as a result of TMR (interaction effect) or treatment in general (main effect of time) (Figure S4; Table S2).

DISCUSSION

In this study, we applied TMR for the first time in patients with PTSD in an attempt to strengthen the consolidation of EMDR treatment memories and thereby increase therapeutic efficiency. We, first of all, showed that it was technically feasible and safe to apply SO phase-targeted TMR in (severely disturbed) PTSD

sleep. Moreover, TMR (vs. sham stimulation) resulted in a larger reduction of avoidance in relation to the targeted traumatic memory during scripted imagery, which correlated at trend level with the number of TMR cues during sleep. During sleep, TMR amplified and prolonged the SO dynamic and caused stimulus-locked power increases in the frequency ranges of SOs and sleep spindles. Importantly, within the TMR group, these induced changes in sleep physiology correlated with PTSD symptom reduction.

Patients in the TMR group showed a reduced tendency to avoid the targeted traumatic memory during SDI the next day. Avoidance is a key symptom of PTSD. Reducing avoidance is one of the main targets of exposure-based treatments for PTSD, as traumatic memories need to be successfully accessed in order for the associated level of fear and arousal to reduce.^{64,65} As such, the enhanced reduction in avoidance observed here can precede improvements in, for example, the level of re-experiencing during scripted recall. Of note, while the CAPS-5-based severity of avoidance did not differ between groups at baseline, there was a baseline difference in avoidance level during SDI (TMR > sham) and no difference in avoidance level between groups post-intervention. This somewhat complicates the interpretation of the observed interaction, as alternative explanations concerning, for example, a bigger opportunity in the TMR group to improve, cannot be ruled out. A floor effect in the sham group seems unlikely, as almost none of the patients in this group rated their avoidance at 0 either before or after intervention. The observed correlation with the number of reactivation cues during sleep may suggest that the extra reduction in avoidance was, in fact, TMR dependent, although the trend-level significance of the correlation leaves room for other factors mediating the reduction of avoidance in both groups.

TMR directly impacted memory-related sleep physiology. Both SOs and spindles are key oscillations in the neural process of memory consolidation.^{66,67} Hippocampo-cortical reorganization of newly acquired memories appears to rely on conjunct

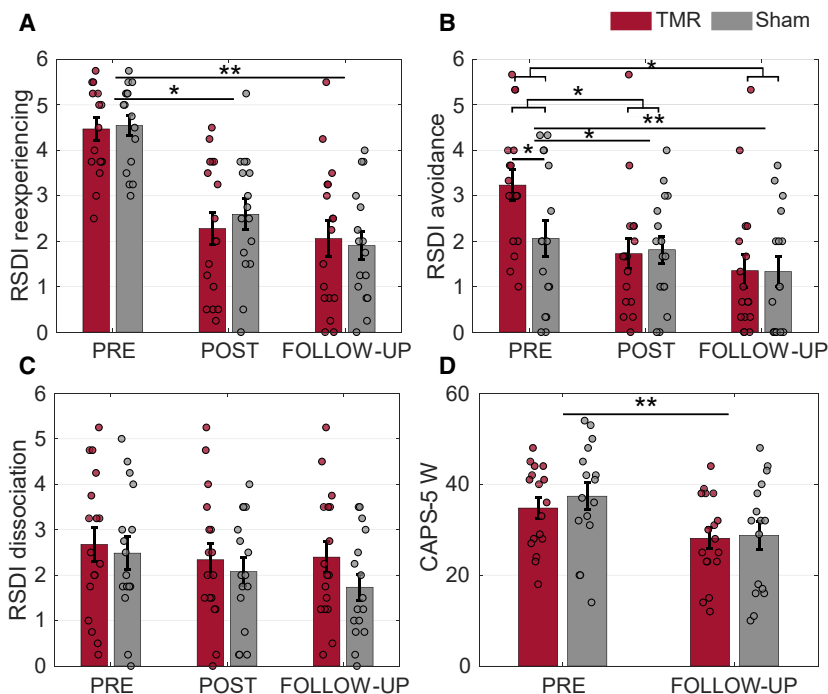


Figure 3. Effects of TMR on subjective ratings of the targeted traumatic memory and overall PTSD symptom severity

Subjective ratings of re-experiencing (A), avoidance (B), and dissociation (C) in response to SDI of the targeted traumatic memory and overall PTSD symptom severity, as assessed with the CAPS-5 W, for the TMR and sham group 1 day before (pre), 1 day after (post), and 1 week after intervention (follow-up). Error bars represent the standard error. See also Figures S1–S3.

* $p < 0.05$; ** $p < 0.001$; CAPS-5 W, clinician-administered PTSD symptom scale for DSM-5 (week version); RSDI, responses to script-driven imagery.

reactivation of hippocampal and (neo)cortical components of the memory, reflected in the coupling of hippocampal sharp-wave ripple events and thalamo-cortical spindles, time locked with the plasticity-promoting, depolarizing upwave of neocortical SOs.^{67–69} This intricate coupling of local and global oscillatory dynamics is thought to result in the memory trace being integrated into pre-existing cortical memory networks, thereby stabilizing it and reducing its affective charge.^{20,21} Although the precise neuronal mechanisms underlying TMR are not clear, memory cueing during sleep is thought to selectively bias ongoing hippocampo-cortical replay toward the associated memory representation, prioritizing its consolidation.^{32,34,70} Existing TMR studies measuring intracranial^{71,72} or scalp^{73–75} EEG indeed show that the reported memory benefits by TMR are associated with (TMR-induced) increases in SO and spindle activity. Accordingly, TMR effects are generally largest when reactivation cues are time locked to SO upwaves,^{31,45,58,59,76–78} which is known to boost SO dynamics. In line with these studies, we now show in PTSD patients that presenting a treatment reminder cue phase locked to SO upwaves during post-treatment sleep specifically enhanced the SO dynamic and increased power in SO- and spindle-related frequency bands. The increase in sigma power temporally aligned with the SO upwave in the ERP, thus likely representing consolidation-promoting spindle activity. Importantly, index measures for SO enhancement (ERP amplitudes of SO peaks and troughs) and spindle enhancement (frontal slow sigma power) correlated positively with the pre- to post-intervention reduction in PTSD symptoms in the TMR group. Together, these findings suggest that TMR strengthened the system-level consolidation of the EMDR treatment memory, further reducing PTSD symptoms. This interpretation warrants caution, since we did not find a significant group difference between TMR and sham stimulation for most clinical outcome measures.

one of these studies, in patients with nightmare disorder, a sound was linked to the positively altered nightmare scenario at the end of an imagery rehearsal therapy (IRT) session.⁸¹ The subsequent re-administration of the sound at home, for 2 weeks during rapid eye movement (REM) sleep following a short IRT session in the evening, resulted in less frequent nightmares and more positive dream emotions in the TMR group compared to a group that was not exposed to the sound during the initial IRT session. The majority of successful TMR studies thus far have applied TMR during non-REM (NREM) sleep.³⁹ Conversely, in this study, TMR was applied during REM sleep, considering that the consolidation of emotional memories might benefit preferentially from REM sleep.^{16,83} In addition, TMR was applied nightly for 2 weeks, using an ambulatory EEG-recording and stimulation device.⁸¹ In two other recent studies, TMR cues were associated with the positive outcome of exposure-based psychotherapy for spider phobia⁸⁰ and social anxiety.⁸² In patients with spider phobia, TMR was applied during NREM sleep (daytime nap),⁸⁰ while patients in the social anxiety study received TMR for 1 week at home during REM sleep.⁸² No additive clinical effect of TMR was observed in either case. The spider phobia study reported ceiling effects of the psychotherapeutic treatment itself. Interestingly, in this study, TMR also increased frontal (slow) and parietal (fast) spindle activity; however, this did not correlate to symptom improvement. Importantly, in line with the aforementioned studies, we show that it is feasible and safe to apply TMR in pathological sleep. PTSD sleep is characterized by severe sleep disturbances, such as frequent insomnia, nightmares, and a marked shortage of SWS and SO power in general.^{50,51} Despite this, we were able to target SOs and showed that TMR did not cause awakenings, disrupt sleep architecture, or trigger nightmares. In addition, no adverse events were reported, and no increases in any of the clinical outcome measures were found after

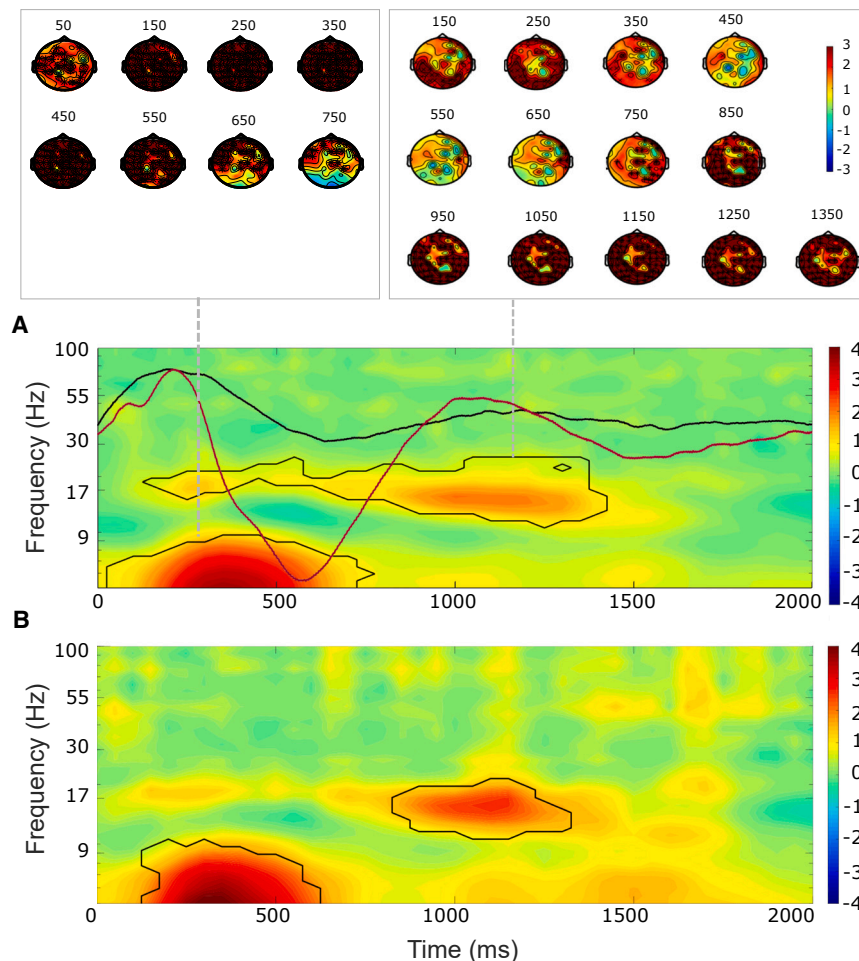


Figure 4. Effects of TMR on sleep physiology

Time-frequency response after stimulus onset (0 ms) for frontal channel Fz (A) and centroparietal channel CPz (B). Significant clusters are outlined. Warm colors indicate higher power in the TMR compared to the sham group. Widespread spatial effects of TMR are demonstrated by topoplots for both the low frequency (left upper part) and sigma-beta frequency clusters (right upper part). Significant electrodes are indicated by “*” and “x,” representing p levels of 0.01 and 0.05, respectively. For Fz, the event-related potential (ERP) has been plotted over the time-frequency response to show alignment of the ERP with power changes over time (A).

at present it is more safe to attribute the observed effects to TMR and/or SO boosting. Beyond memory enhancement, the type of TMR/SO boosting adopted here was found to globally increase sleep depth in healthy subjects (unpublished data). If this translates to patients with PTSD, TMR/SO boosting may prove to be a useful treatment augmentation strategy in PTSD aimed at fostering the general restorative functions of deep sleep, such as the clearance of neurotoxic waste,⁸⁸ promotion of cellular growth and recovery, and a wide range of immunological processes.^{89,90}

We did not observe group-level differences for most clinical outcome measures, either related to the targeted mem-

TMR. This suggests it is safe to apply TMR in PTSD to strengthen the consolidation of therapeutically altered memories. Despite modest clinical effects so far, our study and other clinical TMR studies using similar strategies seem to generate momentum rather than caution toward future attempts to alleviate pathological memories by TMR. Importantly, these attempts could include testing the efficacy and safety of alternative TMR strategies,¹³ such as targeting the traumatic memory directly to facilitate “healthy” consolidation⁸⁴ or attempting to counter-condition trauma-associated cues during sleep.⁴⁵

Presenting the EMDR click at the start of the SO upwave resulted in a clear amplification and prolongation of the targeted SO. This type of SO boosting by EEG-guided acoustic stimulation has been shown by itself to strengthen slow-wave-dependent memory consolidation in healthy subjects.^{16,58,85–87} Therefore, our observed effects could be (partly) due to SO boosting rather than reactivation of a specific memory with an associated TMR cue. Confident distinction of TMR effects from SO stimulation effects would require an additional control group that receives a treatment-unrelated sound during sleep. The demanding nature of our study, including multiple lab visits, high-density EEG with M-CLNS, and two fMRI sessions, in combination with the limited taxability of PTSD patients, made it challenging to recruit the necessary patients. Nevertheless,

memory or overall PTSD symptom severity. There may be several reasons for this. First, EMDR treatment alone resulted in a marked improvement on most outcome measures, leaving little room for an additive improvement by TMR. This may be related to the high level of training and experience of the EMDR therapists involved. Setting an upper learning threshold to avoid ceiling effects poses both ethical and practical problems in the context of psychiatric treatments. Pre-selection of a relatively treatment-resistant patient group, however, may result in larger TMR effects. Second, subjective ratings of targeted memories, as assessed here with RSDI, have been shown to be a challenging outcome measure in TMR research.³⁹ Furthermore, the limited spread in the seven-point Likert scale of the RSDI may have impeded detection of subtle TMR effects. As an alternative measure of outcome, future studies may consider the index trauma memory interview,^{91,92} which uses a 0–100 visual analog scale to assess the memory. Third, our chosen time interval of testing 1 day post-intervention may have been too short to assess system-level consolidation effects with fMRI, as the underlying neural reorganization can develop over longer time periods of up to a year.^{93,94} In addition, the activation and connectivity patterns during SDI were relatively heterogeneous across patients, possibly reflecting the varying levels of engagement and avoidance during the task. Further to this point, the

individually highly different memories of our PTSD patients were likely more widely distributed across cortical memory networks than the task-related memories examined in most TMR studies.²⁸ Together, these circumstances may have obscured subtle fMRI effects by TMR. Finally, the majority of TMR studies thus far have targeted new, experimentally acquired, relatively simple memories. Our study represents the first attempt to manipulate the consolidation of highly complex PTSD memories that were established in a naturalistic way, months to years before the start of the experiment. PTSD memories are often linked to other traumatic memories and complex emotional states, such as feelings of guilt and shame. The possible collateral reactivation of such associated memories and emotional states during TMR is beyond the experimenter's control.¹³ This poses a translational challenge that can only be overcome by further experimentation into the (many) different experimental factors that may determine TMR success in pathological memories.

Several limitations of our study deserve mention. First, while the sample size of 33 patients is comparable to most TMR studies in healthy subjects,³⁹ it is considered small for fMRI studies or clinical trials. A larger sample size might have enabled us to detect the presumably subtle TMR effects over and beyond an active treatment, particularly concerning the highly variable fMRI responses during SDI. Second, we did not include a wake control group. Therefore, strictly speaking, we cannot claim sleep specificity of the observed effects. Keeping PTSD patients awake in a full-night design is, however, not advisable given the risk of increasing symptoms. Using a nap design is also problematic, since patients are unlikely to fall asleep during the day following a highly arousing, exposure-based treatment session.

There were multiple strengths of the study. We used a new and advanced M-CLNS setup to deliver phase-targeted TMR. The importance of phase targeting is increasingly recognized in TMR research.^{25,59} Indeed, recent findings from healthy subjects in our laboratory showed memory enhancement when TMR sounds were presented time locked to SO upwaves, while time locking cues to the hyperpolarizing downwaves of SOs resulted in a reduction of memory performance.³¹ Phase-targeted TMR therefore seems a viable option to test whether TMR can strengthen a positive treatment outcome in patients, while avoiding the risk of accidentally negating it. Furthermore, we applied a broad array of measures to assess the effects of TMR, from neural to behavioral levels of organization, considering not only effects of TMR on traumatic memories but also potential disturbing effects on sleep.

More research is required to warrant clinical application of TMR in PTSD. A first step in future research efforts could be to test TMR in a multi-session design aimed at cumulatively augmenting the positive outcome of multiple treatment sessions in PTSD. This experiment becomes more feasible with the recent development of ambulatory EEG devices that permit closed-loop neurostimulation (CLNS) and phase-targeted TMR in home or clinical treatment settings.⁹⁵ The practical advantages of such a setup would additionally allow for the inclusion of extra control groups and larger samples. Another promising avenue for future research may be studying TMR during both SWS and REM. Combining both sleep stages in a single design could

determine the optimal sleep phase for targeting traumatic memories, and could enable the study of whether SWS- and REM-TMR might have complementary effects on the respective consolidation and emotional depotentiation of traumatic memories.⁹⁶ Note that phase-targeted TMR is considerably more challenging during REM sleep, although first attempts to target REM-related theta oscillations (4–8 Hz) are currently underway.⁹⁷

In summary, this first attempt to apply TMR in PTSD shows that re-administering a treatment reminder cue during post-treatment sleep potentiated the sleep physiology underlying memory consolidation, possibly resulting in the prioritized processing of treatment memories and subsequent PTSD symptom reduction. Clinically, TMR resulted in a larger reduction in avoidance during script-driven trauma imagery. Together with the observation that TMR did not disturb sleep or trigger nightmares, these data bare first proof of principle that strengthening treatment memories by TMR may be a viable and safe future treatment augmentation strategy for PTSD. With pharmacological research not having produced many new treatment options for PTSD in recent decades, sleep-based interventions like these are both promising and needed. Based on our findings, follow-up studies can delineate the conditions with regard to multi-session TMR and target sleep phase to unlock the full clinical potential of TMR and open up sleep as a new treatment window for PTSD.

STAR★METHODS

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SUPPLEMENTAL INFORMATION

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AUTHOR CONTRIBUTIONS

Conceptualization, H.J.F.v.M.; experimental design, A.C.v.d.H., L.M.T., Y.D.v.d.W., O.A.v.d.H., and H.J.F.v.M.; data acquisition, A.C.v.d.H. and H.J.F.v.M.; data analysis, A.C.v.d.H.; writing – original draft, A.C.v.d.H. and H.J.F.v.M.; writing – review and editing, L.M.T., Y.D.v.d.W., O.A.v.d.H., and H.J.F.v.M.; supervision, L.M.T., Y.D.v.d.W., O.A.v.d.H., and H.J.F.v.M.; funding acquisition, H.J.F.v.M.

DECLARATION OF INTERESTS

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
Castor Electronic Data Capture System	https://www.castoredc.com	RRID: SCR_022150
EEGLAB toolbox	http://sccn.ucsd.edu/eeglab/index.html	RRID: SCR_007292
E-prime 2.0	http://www.pstnet.com/eprime.cfm	RRID: SCR_009567
EventIDE software	https://www.okazolab.com	N/A
FieldTrip toolbox	https://www.fieldtriptoolbox.org	RRID: SCR_004849
fMRIPrep	https://fmriprep.org	RRID: SCR_016216
gPPI toolbox	https://www.nitrc.org/projects/gppi	N/A
Hera toolbox	https://github.com/can-lab/hera	N/A
MATLAB	http://www.mathworks.com/products/matlab/	RRID: SCR_001622
MarsBaR region of interest toolbox for SPM	http://marsbar.sourceforge.net/	RRID: SCR_009605
MRIQC	https://mriqc.readthedocs.io/en/latest/	RRID: SCR_022942
SPM	https://github.com/spm	RRID: SCR_007037
SPSS	https://www.ibm.com/products/spss-statistics	RRID: SCR_002865
Other		
Modeling-based closed loop neuro-stimulation	International patent application WO2018156021	N/A

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, H.J.F. van Marle, h.j.vanmarle@amsterdamumc.nl.

Materials availability

This study did not generate new unique materials.

Data and code availability

- The data that support the findings of this study are available from the corresponding author upon reasonable request.
- This paper does not report original code, apart from the modelling-based closed-loop neurostimulation (M-CLNS), which is patented under International patent application WO2018156021 of University of Amsterdam and Okazolab Ltd.
- Any additional information required to reanalyze the data reported in this paper is available from the [lead contact](#) upon reasonable request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

A total of thirty-three PTSD patients participated in this study (TMR group: 17, 7 males; Sham group: 16, 6 males). Patients were recruited from several mental health institutions in The Netherlands (GGZ inGeest, ARQ National Psychotrauma centre and Psytrek), while being on the waiting list for full PTSD treatment. Inclusion criteria were the following: (1) PTSD diagnosis, as assessed with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5, previous month edition^{52,53} and (2) age between 18 and 65. Exclusion criteria were the following: (1) impossibility to isolate a traumatic memory for treatment or dissociative complaints in response to re-activation of the traumatic memory, (2) presence of bipolar disorder, psychotic disorder, moderate to severe alcohol disorder or substance use disorder, assessed using the MINI International Neuropsychiatric Interview,^{98,99} (3) use of benzodiazepines or other sleep medication in the week before the study started until the end of the study period and use of other psychotropic medication in general (unless on a stable dosage for at least 6 weeks), (4) use of alcohol during the measurement days and use of recreational drugs throughout the study period, (5) active suicide ideation, (6) current or history of neurological disorder or recent history of major head trauma with loss of consciousness, (7) any contraindications for MRI, such as metal implants or claustrophobia and (8) irregular sleep/wake rhythm (e.g., night shifts, jetlag), a sleep window outside 22:00 and 10:00, sleepwalking or presence of REM sleep

behavior disorder. There were no exclusion criteria related to sleep macro- or micro-architecture. Prior to participating, all participants provided written informed consent. All study procedures were approved by the Medical Ethical Committee of the VU University Medical Center.

METHOD DETAILS

General procedure

Seven days pre-intervention, baseline PTSD symptom severity was assessed using the CAPS-5 (previous week edition) and the self-administered PTSD checklist for DSM-5 (PCL-5).^{52,53,56,57} In addition, patients selected their most distressing traumatic memory as target for the Script-Driven Imagery (SDI)-procedure and EMDR-session. One day pre-intervention (PRE), patients underwent an (f) MRI session during script-driven recall and imagery to assess the pre-intervention subjective, autonomic and neural responses related to the targeted traumatic memory. In addition, PTSD symptom severity was assessed using PCL-5. The evening of the next day (intervention night), all patients received a single EMDR-session including standard auditory clicks. During the following polysomnographically-monitored night, patients were randomized to receive either TMR using the EMDR clicks (TMR group) or sham stimulation (no sound presentation, Sham group). Both the following morning (POST) and one week later (FOLLOW-UP, in the morning), patients underwent SDI again to assess post-intervention outcome measures (at FOLLOW-UP outside the MRI scanner). In addition, PTSD symptom severity was assessed again by CAPS-5 (only at FOLLOW-UP) and PCL-5. In addition, patients kept a daily sleep- and intrusion diary three days pre-intervention and seven days post-intervention. See [Figure 1](#) for a schematic overview of experimental procedures.

Script-driven imagery procedure

The Script-Driven recall and Imagery task (SDI) was performed during MR-scanning. The SDI is a well-validated symptom provocation task for PTSD.^{54,55,100,101} For SDI, personalized auditory scripts of the targeted traumatic memory were constructed according to standard procedures.¹⁰¹ The scripts were read aloud by a (male) voice in a neutral tone. The SDI consisted of four phases: baseline (30s), listening to the trauma-script (30s), imagining oneself in the traumatic event described in the script, including all sensory sensations (30s), and letting go of the image (60s). The four phases were repeated three times. After SDI, patients rated their subjective experience during SDI using the Responses to Script-Driven-Imagery scale (RSDI)^{62,102}. The RSDI is a 13-item questionnaire that assesses the level of re-experiencing (e.g., emotionality and vividness), avoidance and dissociation in response to the trauma-script. Patients rated each question on a 7-point Likert scale, ranging from 0 (not at all) to 6 (very much). E-prime software was used for stimulus presentation and registering responses to the RSDI.¹⁰³ To assess the autonomic response to the targeted traumatic memory, pulse oximetry (integrated in the MRI scanner) was recorded continuously during SDI. Heart rate (HR) and heart rate variability (HRV) were calculated after manual trial rejection, using in-house software.¹⁰⁴ To define HRV, the root-mean-square (RMSSD) of successive differences between heartbeats was calculated. HR and HRV were averaged across the imagine blocks of the SDI and baseline-corrected by subtracting the averaged values during the baseline blocks.

EMDR

On the intervention night, all patients received a single session of EMDR (eye-movement desensitization and reprocessing) at the sleep laboratory from a certified therapist. EMDR is a first-choice treatment for PTSD.¹⁰⁵ Based on standard EMDR procedures, patients were asked to recall their traumatic memory (the same as used in SDI) while simultaneously listening to binaurally presented auditory clicks (presented at 75 dB, at a fixed distance from the head, using EventIDE software (Okazolab Ltd, London, United Kingdom) and making therapist-directed lateral eye movements. The clicks are part of standard EMDR therapy. At the beginning and end of the EMDR-session, patients reported their general level of distress in relation to the treated memory (subjective units of distress, SUD) using a 10-point rating scale. To avoid potentially strengthening a negative treatment outcome,¹⁰⁶ TMR was only administered if patients showed a pre-to-post EMDR reduction of ≥ 2 points on the SUD scale (which was the case for all patients).

Polysomnography

During the intervention night, sleep was continuously recorded through high-density electroencephalography (EEG), using a 64-channel WaveGuardTM cap (ANT, Enschede, The Netherlands) and Refa amplifier (TMSi, Oldenzaal, The Netherlands). Electro-oculography (EOG) and chin electromyography (EMG) were also recorded. All signals were sampled at 512 Hz. A scheduled bedtime was used (23.00 lights-off, 8.00 lights on). In preparation for the recording, impedances of all channels were kept below 10 k Ω .

TMR

TMR, or sham stimulation, were administered during N2 and N3 sleep for a total duration of 3 h after the first onset of N3 sleep ("cued period"), or after 30 min of uninterrupted N2 sleep after sleep onset in case no N3 sleep was observed. During the cued period, the occurrence of these sleep stages was detected by the experimenter who turned the algorithm on and off accordingly. TMR or sham cues were presented phase-locked to the positive zero-crossing of slow oscillations (SOs) (0°) using a modelling-based closed-loop neurostimulation (CLNS) method,^{31,107} see below. TMR cues consisted of a single EMDR click and were presented at 50 dB via identical speakers as used during EMDR at a fixed distance from the patient's head. In case of repeated arousals in response to the TMR

cue, as detected in the EEG, the computer volume level was lowered by 10%. In the Sham group, the sound was turned off while running the TMR protocol, so that time markers of phase-locked sham stimulation in the EEG were registered, but no cues were delivered.

Modelling-based closed-loop neurostimulation

A modelling-based closed-loop neurostimulation (M-CLNS) algorithm was applied to target SOs (0.5–1.5 Hz) at 0° phase.^{25,31,58} A copy of the Fpz-M1 signal was transferred from the recording computer to the stimulation computer for real-time analysis. The data was received into a buffer holding the most recent 10s of data. The CLNS algorithm then performed a non-linear sine fitting procedure on the most recent 1 s of unfiltered EEG signal and checked the following criteria for stimulus release at each iteration: (1) the fitted sine was in a predefined frequency range of interest (0.5–1.5 Hz), (2) the fitting error was below threshold of 0.3, (3) the predicted target phase occurred within a narrow time between 24 to 34 ms into the future. If all criteria were met, the TMR cue was released to coincide with the upcoming predicted target phase. An interstimulus interval of 4 s was applied. The realtime phase prediction algorithm was implemented in EventIDE software (Okazolab Ltd, London, United Kingdom). To assess the accuracy of the cue presentation in relation to the slow oscillation target phase (0°), circular statistics were computed using the CircStat toolbox for MATLAB.¹⁰⁸

PTSD symptom severity

PTSD diagnosis and symptom severity were assessed by CAPS-5,^{52,53} administered by a trained psychiatrist blind to experimental condition. CAPS-5 is a structured diagnostic interview, in which the interviewer rates the severity of DSM-5 PTSD symptoms on a scale from 0 (absent) to 4 (extreme), using information on both frequency and intensity of the symptoms. A previous month edition of the CAPS-5 was used to establish PTSD diagnosis (including dissociative subtype). A previous week edition was used to assess severity of PTSD symptoms pre- and post-intervention. PTSD symptom severity was additionally assessed using the PCL-5, in which patients rate the severity of their PTSD symptoms at that moment on a 5-point Likert scale, ranging from 0 (not at all) to 4 (extremely).^{56,57}

PTSD intrusions & sleep-related outcomes

To assess both sleep and intrusions of the targeted traumatic memory daily, patients kept a combined sleep and intrusion diary for three days before TMR-intervention and for one week after. The sleep diary consisted of an adapted version of the Consensus Sleep Diary (CSD),¹⁰⁹ in which participants kept track of standard sleep-related measures (sleep latency, subjective sleep quality, number of awakenings) plus two additional questions on the number of nightmares, specifically related to the targeted traumatic memory and in general. In the intrusion diary patients reported the total number of intrusions related to the targeted traumatic memory the previous day, as well as the associated (average) level of subjective distress (the 5 questions of the Re-experiencing subscale of the RSDI). Pre-intervention and post-intervention scores were calculated by averaging diary output over the three days prior and seven days following intervention respectively.

Baseline measures

Baseline sleep profiles were assessed using the Pittsburgh Sleep Quality Index.¹¹⁰ The presence of sleep disorders was assessed with the SLEEP-50 questionnaire.¹¹¹ Baseline level of depressive and anxiety-disorder related complaints were assessed with the Beck Depression Inventory II (BDI)¹¹² and Beck Anxiety Inventory (BAI)¹¹³ respectively. Also, the history of PTSD treatment (including medication) was assessed at baseline using a standardized questionnaire.

QUANTIFICATION AND STATISTICAL ANALYSIS

Statistical analysis of clinical results

To test the additive effect of TMR on subjective and autonomic responses in relation to the targeted traumatic memory, RSDI-subscale scores and HR and HRV were analyzed using 2x3 factorial ANOVAs with Group (TMR vs. Sham) as between subjects factor and Time (PRE vs. POST vs. FOLLOW-UP) as within subjects factor. Post-hoc testing was performed using the appropriate T-tests. Results related to autonomic results are reported in the main text and in [Figure S1](#). To test the additive effect of TMR on overall PTSD symptom severity, PCL-5 scores were analyzed with the same 2x3 factorial ANOVAs, and CAPS-5 scores with 2x2 factorial ANOVAs (Time: only PRE vs. POST). Sleep and intrusion diary output were analyzed with similar 2x2 factorial ANOVAs. Results related to PCL and intrusion diary are reported in the main text and in [Figure S2](#), and results related to sleep diary in main text and in [Figure S3](#). Within the TMR group, Spearman's correlations were calculated between (pre- to post-intervention difference scores of) RSDI avoidance and number of TMR cues during cued period, as assumptions of parametrical tests were violated. For all tests, alpha was set at $p < 0.05$.

EEG – Preprocessing

Preprocessing of the data entailed re-referencing to the average of the mastoids, high-pass (0.1 Hz) and notch filtering (48–52 Hz), and artefact rejection. All preprocessing steps were done using the EEGLAB toolbox.¹¹⁴

EEG – Sleep macro architecture

To test the effect of TMR on sleep on macro architecture measures during the intervention night, these measures were compared between groups using independent t-tests, or a Mann-Whitney-U test in case of non-parametric distributions. Sleep macro architecture measures included minutes and percentages of wake, N1, N2, N3 and REM. REM latency, wake after sleep onset (WASO), total sleep time, sleep efficiency, sleep latency, number of awakenings and arousals, number of sleep stage shifts from N2 to wake, N3 to wake, REM to wake, total number of sleep stage shifts, sleep fragmentation index¹¹⁵ and nightmares. Sleep scoring was performed according to AASM guidelines using REMlogic software (NATUS) by a trained clinical neurophysiologist blind to the experimental condition. Results are reported in the main text and in [Table S1](#).

EEG – Event related potentials (ERPs)

To compare the slow oscillation (SO) dynamic during the intervention night between the TMR and Sham group, the average EEG amplitude was measured over the interval from 1s pre- until 2s post-cue presentation. Given the frontal origin of slow oscillations^{116,117} and the phase targeting of TMR cues to a frontal derivation, event related potentials (ERPs) were studied for channel Fz. ERP statistics were performed using the EEGLAB toolbox¹¹⁴ and a FieldTrip plugin.¹¹⁸ To correct for multiple comparisons, a false discovery rate (FDR) of $p < 0.05$ was used. One extreme outlier was removed from the TMR group, resulting in a final sample size of 32 (TMR $n = 16$, Sham $n = 16$). Extreme outliers were defined as three times the interquartile range (IQR). Specifically, we subtracted three times the IQR from the first quartile (Q1) to define lower extreme outliers and added three times the IQR to the third quartile (Q3) to define upper extreme outliers.

EEG – Time frequency analyses

To compare spectral power in a short time window around cue presentation between the TMR and Sham group, time frequency analyses (TFAs) were performed. A family of complex Morlet wavelets was used to decompose all multi-channel epoched time series into time-frequency representations, according to the method of Cox et al.,⁵⁸ using a frequency range of 5–100 Hz and a 3 s time window (from 1s pre-cue until 2s post-cue). The time frequency representations were compared between the TMR and Sham group at $\alpha = 0.01$, using Monte-Carlo permutation-based statistics with cluster correction. To examine the spread of the TMR effect across the brain, spectrotopomaps, including all 64 electrodes, were created per significant group-level cluster. To capture potential differences in slow and fast sigma power, two derivations were analyzed, reflecting the preferred location for EEG expression of slow and fast spindles, respectively. Slow sigma power (11–13.25 Hz) was evaluated at the frontal derivation Fz, whereas fast sigma power (13.25–15.75 Hz) was evaluated centroparietally at channel CPz. These derivations were based on previous reports describing the frequency related dominance on these locations.¹¹⁹ All TFA analyses, including the spectrotopomaps, were created using EEGLAB¹¹⁴ and FieldTrip.¹¹⁸

fMRI – Image acquisition

For the SDI, 205 whole brain T2 weighted gradient EPI BOLD-fMRI images were acquired with a Philips Achieva DS 3T MR-scanner equipped with a 32-channel head coil (TE/TR: 3/2.334 s, $3 \times 3 \times 3$ mm voxels, flip angle: 76°, FoV: 240 × 240 × 138 mm). High resolution structural T1-weighted images were additionally acquired (TE/TR: 3.8/8.3 s, $1 \times 1 \times 1$ mm voxels, flip angle: 8°, FoV: 240 × 188 × 220).

fMRI – Image analysis

Image processing was performed in SPM12 (Wellcome Department of Imaging Neuroscience, University College London, UK) implemented in MATLAB 2020b (Natick, MA, USA) and statistical analyses were performed both in SPSS and SPM12. Quality control was performed using MRIQC.¹²⁰ Preprocessing was performed using fMRIprep v20.2.1¹²¹ followed by spatial smoothing within SPM12. First-level contrasts, consisting of the Imagine vs. Baseline condition of the SDI, were calculated using a high-pass filter with a 128s cutoff period and six head-motion parameters calculated in SPM. The Imagine and Baseline condition were modeled separately as boxcar regressors and convolved with the canonical HRF. Contrast parameter images generated at the single subject level (Imagine vs. Baseline) were submitted to second level group analysis. Given their role in (emotional) system-level memory consolidation,^{16,60} the amygdala, hippocampus and vmPFC were used as regions of interest (ROIs). Mean parameter estimates of these ROIs were extracted (using anatomical AAL-based masks for amygdala and hippocampus and a 10 mm sphere around MNI coordinate $x, y, z = 0, 40, -8$ for vmPFC¹²²) using MarsBaR,⁶³ and entered into an 2X2 ANOVA in SPSS with Group (TMR vs. Sham) as between subject factor and Time (PRE vs. POST) as within-subject factor. Alpha was set at $p < 0.05$. For exploratory whole brain analyses, statistical parametric maps were created within SPM12 using a flexible factorial ANOVA with the same factors. The statistical threshold was set at $p < 0.05$, family-wise-error (FWE) rate corrected. Results are reported in main text, [Figure S4](#) and [Table S2](#).

fMRI – Functional connectivity analysis

To assess the effect of TMR on functional connectivity patterns during the SDI, a generalized form of context-dependent, psychophysiological interaction analysis (gPPI)⁶³ was performed in SPM12 with our ROIs using the hippocampus as a seed-region (as defined by AAL-based anatomical mask). For each subject the physiological activity of the seed region was computed as the mean time series of all voxels within the hippocampus seed.¹²³ The following psychological/task vectors were included in the

gPPI analysis: Listening vs. baseline, Imagining vs. baseline and Letting go vs. baseline. A whole-brain analysis (single-subject level) was performed using the general linear model in SPM12 with the three PPI regressors, three task regressors, six motion parameters and the mean time course in the seed region. Contrast parameter images generated at the single subject level (Imagine vs. Baseline) were submitted to second level group analysis. A similar ROI-analysis was performed in SPSS as for the activity-based analysis. Results are reported in main text and [Figure S4](#).