Sleep as a window to target traumatic memories

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ABSTRACT

Post-traumatic stress disorder (PTSD) is a severe psychiatric disorder in which traumatic memories result in flashbacks and nightmares. With one-third of patients not responding to standard exposure-based psychotherapy, new treatment strategies are needed. Sleep offers a unique time window to enhance therapeutic efficacy. Traumatic memories that are neutralized in therapy need to be stored back into memory (consolidated) during sleep to solidify the treatment effect. New basic research shows that memory consolidation can be enhanced by presenting sounds or scents that were linked to the memory at encoding, again during sleep. This procedure, termed targeted memory reactivation (TMR), has, despite its clinical potential, not been tested in (PTSD) patients. In this narrative review, we explore the potential of TMR as a new sleep-based treatment for PTSD. First we provide the necessary background on the memory and sleep principles underlying PTSD as well as the present applications and conditional factors of TMR. Then, we will discuss the outstanding questions and most promising experimental avenues when testing TMR to treat traumatic memories.

1. Introduction

Post-traumatic stress disorder (PTSD) is a psychiatric illness that may develop after experiencing a traumatic event (Kessler et al., 1995). In general, over 75 % of people encounters traumatic events in the course of their lives (de Vries and Olff, 2009). Although most trauma-exposed individuals prove resilient, a significant portion develops lasting and debilitating symptoms that meet criteria for PTSD diagnosis. This leads to a lifetime prevalence of PTSD of 1–12 %, depending on the population studied (Kessler et al., 2005; Shalev et al., 2017). Intrusive traumatic memories are at the core of the disorder, resulting in key symptoms such as involuntary memories, flashbacks and nightmares (Anon, 2013). Patients additionally suffer from hyperarousal, emotional dysregulation, hypervigilance and sleep problems and tend to excessively avoid all that triggers recall of the traumatic event. Current first-choice treatments, consisting of exposure-based psychotherapy, like imaginary exposure (IE) or eye movement desensitization and reprocessing (EMDR) (Bisson et al., 2013; Bisson and Olff, 2021), prove ineffective in one-third of

PTSD patients (Bradley et al., 2005). Furthermore, due to the emotionally demanding nature of the treatment, drop-out rates are high (Watts et al., 2014). Medication effects in PTSD are unfortunately small (Hoskins et al., 2021). This creates a need to develop novel treatment strategies. Sleep may represent a new route towards such treatments since it is deemed crucial in the treatment of traumatic memories (van Marle, 2015). During exposure-based treatment, traumatic memories get reactivated and subsequently re-encoded with lower fear and arousal. This treatment effect is then likely solidified during memory consolidation while asleep when the 'neutralized' memories get stabilized in existing memory networks (Lane et al., 2015). Over the last decade an exciting new technique has emerged to non-invasively enhance memory consolidation during sleep, known as targeted memory reactivation (TMR). This growing body of experimental work holds tremendous potential for psychiatric treatment, yet clinical applications of TMR do not yet exist. In this article, we explore how these basic findings on TMR can be translated into a treatment option for PTSD. In the first part, we will discuss the general principles of memory processing during sleep and

introduce TMR, including conditional factors and present applications. In the second part, we will discuss different ways to employ TMR to treat traumatic memories in PTSD, referencing each (experimental) option against existing data. Different methodological considerations that apply to the use of TMR in PTSD are additionally reviewed, as well as potential risks. Finally, other potential sleep-based treatments for PTSD are also considered.

2. Sleep, memory consolidation and TMR

2.1. Sleep's role in (emotional) memory consolidation

Sleep plays a pivotal role in memory processing, especially concerning memory consolidation, which serves to stabilize or even strengthen memories and protect them against interference and decay (Diekelmann and Born, 2010; Dudai et al., 2015; Ellenbogen et al., 2006). While memory encoding and retrieval are best served by a waking brain, memory consolidation may benefit from the relative (but not complete) paucity of sensory processing during sleep (comprising non-REM (NREM) stages N1–3 and REM sleep). According to system-level consolidation theory (Frankland and Bontempi, 2005), newly acquired memories are initially represented as hippocampo-cortical neural patterns. In these patterns, the different aspects of an episode, which are represented in widespread cortical areas, are interlinked via the hippocampus. As a function of time and especially during sleep, the memory then gradually gets reorganized to a hippocampus-independent representation, linked by extrahippocampal cortical connections (although see (Moscovitch et al., 2005)) for an alternative consolidation account with lasting hippocampus involvement for certain memories). At a neuronal level, this memory recoding involves reactivation (replay) of hippocampo-cortical firing patterns that likely represent the memory at encoding during deep sleep, also known as slow wave sleep (SWS) (Wilson and McNaughton, 1994). This type of memory reprocessing is thought to promote information integration into pre-existing memory networks, resulting in the stabilization, as well as the categorization and conceptualization of memory (Breton and Robertson, 2013; Dudai et al., 2015). Optimal hippocampo-cortical information transfer during NREM sleep is thought to depend on synchronization of thalamo-cortical sleep spindles (waxing and waning oscillations of 9–16 Hz) with the plasticity-promoting, depolarizing part of neocortical slow oscillations (SOs, traveling waves of 0.5–1 Hz linking cortical areas). Hippocampal sharp wave ripples (excitatory bursts of 70–110 Hz), thought to represent the reactivation

of memories, are in turn nested in the trough of the spindles (see Fig. 1) (Cox et al., 2014; Marshall et al., 2020; Rasch and Born, 2013). This specific coupling of global and local oscillatory dynamics, fostering communication between brain regions, is unique to NREM sleep, making this a key sleep stage to host memory consolidation. The consolidation of emotional memories, however, has been argued to involve REM sleep (Tempesta et al., 2018), although split-night paradigms testing this directly gave mixed results (Goldstein and Walker, 2014; Morgenthaler et al., 2014; Wagner et al., 2001). SWS has been implicated in emotional memory as well (Talamini et al., 2013). Aided by intrinsically low noradrenergic levels, reprocessing of emotional memories during REM sleep likely promotes integration in memory networks such that the factual core of the memory trace is preserved, while its affective charge is reduced (van der Helm and Walker, 2010). Experimental evidence of this emotional depotentiation function of REM sleep is scarce (Marshall et al., 2014; Nishida et al., 2009; van der Helm et al., 2011), but a recent series of experiments in patients with insomnia disorder indirectly supports the idea. Using neuroimaging, Wassing and colleagues showed that specifically discontinuous REM-sleep (with frequent stage transitions from REM to wake and light sleep) is related to a failure of overnight alleviation of emotional distress as reflected by continued amygdala reactivity (Wassing et al., 2019). Most likely, NREM and REM sleep act interactively and complementarily in the processing and long-term storage of emotional memories (Cairney et al., 2015). On a neuronal level, sleep after learning may additionally serve to globally renormalize synaptic strength and restore cellular homeostasis, requirements for effective memory consolidation (Tononi and Cirelli, 2014). Finally, apart from a direct memory function, (specifically NREM-) sleep also hosts a myriad of restorative functions such as the clearance of neurotoxic waste, that likely have a permissive function on memory processing (Plog and Nedergaard, 2018). Sleep is often severely disturbed in PTSD patients. Based on the described role of sleep in memory consolidation and emotional dissipation, PTSD sleep disturbances and possible resulting (aberrant) consolidation processes are increasingly considered a crucial factor in the pathogenesis and maintenance of the disorder. An excerpt of the pertaining literature, which has been reviewed more extensively by others (Pace-Schott et al., 2015; Richards et al., 2020, Spoormaker and Montgomery, 2008), is presented in BOX 1.

2.2. Sleep's role in the treatment of traumatic memories

Through its function in emotional memory consolidation, (adequate)
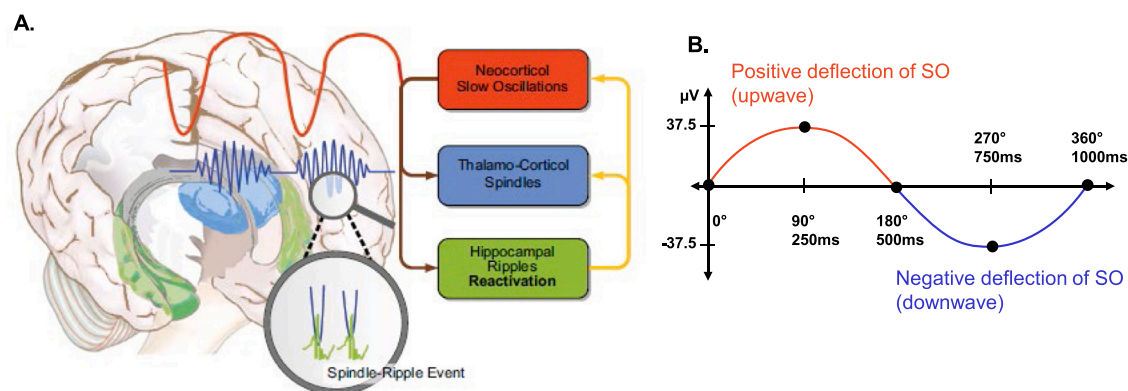
Fig. 1. A. Coupling of global and local oscillatory dynamics across hippocampus, thalamus and cortex fostering memory consolidation. Thalamo-cortical spindles (in blue) get synchronized with the slow oscillation (SO) depolarizing upwave (in red) while hippocampal sharp-wave ripples (in green) are nested in the troughs of spindles. B. Schematic illustration on terminology regarding features of EEG SOs. In particular, the depolarizing positive deflection of SOs (associated with increased cortical activity and preferable conditions for hippocampo-cortical information transfer) is referred to as SO upwave. The hyperpolarizing negative deflection of SOs (associated with decreased cortical activity and limited communication across brain regions) is referred to as SO downwave. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Adapted with permission and licensing from Rasch and Born (2013).

BOX 1
Sleep disturbances in PTSD and their possible role in PTSD pathogenesis.

Sleep disturbances are a hallmark symptom of PTSD with patients typically suffering from insomnia and nightmares, but also nocturnal panic attacks and sleep terrors (Lancel et al., 2021). Sleep studies in PTSD patients show both subjective and objective sleep problems, including reduced sleep efficiency and total sleep time, more time spent awake, less SWS and higher REM density (and in younger patients less REM-sleep) (Kobayashi et al., 2007; Zhang et al., 2019). A recent study implementing spectral analyses of the sleep EEG of PTSD patients showed reduced slow oscillatory power during NREM sleep, but increased slow oscillatory power during REM sleep, which correlated respectively to severity of insomnia and nightmares (de Boer et al., 2020). Moreover, increased spindle activity in PTSD has been associated with daytime intrusive symptoms (van der Heijden et al., 2021). Sleep disturbances both preceding and following a traumatic event have been shown to predict the development of PTSD. Specifically, in the early aftermath of trauma, both the level of discontinuous REM sleep (Mellman et al., 2002) and the extent of insomnia complaints (Koren et al., 2002) predicted subsequent development of PTSD symptoms. This suggests that sleep plays a decisive part in preventing memories of an aversive event to become traumatic. Furthermore, both sleep disturbances (Bryant et al., 2010) and nightmares (van Liempt et al., 2013) occurring prior to a traumatic event have also been shown to increase the risk of developing PTSD. Based on these findings, disturbed sleep is increasingly seen as a causal factor in the etiology and maintenance of PTSD as opposed to a mere symptom or consequence (Richards et al., 2020; Spoormaker and Montgomery, 2008). As a possible underlying mechanism, insomnia after trauma may disrupt normal sleep-related consolidation and emotional regulation of traumatic memories. The resultant nightmares and further increased insomnia may then induce a vicious cycle of poor sleep and inadequate or maladaptive memory processing, perpetuating PTSD symptoms (Pace-Schott, 2015, Talamini et al., 2013). Discontinuous REM sleep, in addition, resulting from the noradrenergic hyperactivation typical of PTSD, has been hypothesized to hamper the spontaneous consolidation of extinction memories. This may lead to a failure of the extinction memories to persist and generalize and PTSD memories to prevail (Pace-Schott et al., 2015). The described shortage of SWS could hamper growth and recovery processes, leading to reduced (emotional) well-being and feeling restored, maintaining the affective symptoms of PTSD. Both REM and NREM disturbances, when occurring during post-treatment sleep, could prevent the consolidation of new or updated (treatment) memories (van Marle, 2015). The sleep disturbances described here potentially affect the applicability of new behavioral strategies to manipulate memory processing during sleep, as will be discussed in Part 2.

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sleep seems particularly important for treating traumatic memories. The intrusive memories characterizing PTSD have been suggested to depend on the involvement of a perceptual memory system and to lack the appropriate integration in autobiographical, cortical memory networks (see Brewin, 2014 for extensive account of this notion). In addition, PTSD has been characterized by a general failure of prefrontal control over limbic regions, such as the amygdala and insula (Fenster et al., 2018). Together, this results in traumatic memories being poorly contextualized, fragmented memories, that, when triggered, are experienced as involuntary intrusions, accompanied by strong sensory impressions and with a strong sense of reliving in the present (Brewin, 2015). These features clearly set traumatic memories in PTSD apart from generally aversive or emotional memories tested in experimental studies (see 2.3). Traumatic memories in PTSD are typically treated with exposure-based psychotherapy, like IE and EMDR (Bisson et al., 2013). During these treatments, traumatic memories get revisited and then altered, in this way reducing the level of associated fear and arousal. During EMDR for example, working memory gets taxed by visual or auditory tasks after reactivation of the traumatic memory. This is thought to leave very little processing capacity to re-experience the normally occurring emotional and physical signs of fear, resulting in the memory being re-encoded in a more neutral form (van den Hout and Engelhard, 2012). From a theoretical point of view, the mechanism of action during exposure-based therapy could be based on two different memory mechanisms. During *memory extinction,* the absence of the feared (conditioned) outcome after repeated exposure to trauma reminders, results in a new so-called safety memory that competes with the (still existing) traumatic memory trace (Bouton, 2004; Myers and Davis, 2007, 2002). Conversely, in case of *memory reconsolidation*, the traumatic memory is thought to become labile after reactivation, such that its re-encoding under favorable therapeutic conditions results in an updated (neutralized) version of the original traumatic memory (Lee et al., 2017; Nader et al., 2000). Whether traumatic memories in a typical therapeutic session are being altered through extinction, reconsolidation or through both mechanisms is hard to discern (Kroes and Fernández, 2012). So far, the boundary conditions for both processes

have been studied mostly in experimental and not clinical settings. An important clinical discriminative factor is that extinction, as opposed to reconsolidation, leaves room for the original fear memory to return (e.g. through spontaneous recovery or renewal) (Dunsmoor et al., 2015). Crucial to the topic of this paper, however, is the notion that independent of the type of memory process during treatment, the resulting new or updated memory needs to be consolidated during post-treatment sleep to solidify the treatment effect (Lane et al., 2015). During this period the new memory gets integrated into long-term memory networks, stabilizing the memory and further reducing its affective charge (van der Helm and Walker, 2011). In addition, irrespective of newly formed therapeutic memories, healthy sleep by itself will promote the consolidation process of the traumatic memory. This results in the gradual decoupling of the affective tone of the memory from its factual content (Goldstein and Walker, 2014; van der Helm and Walker, 2010). Adequate post-treatment sleep therefore seems a prerequisite for any daytime therapy to succeed and trauma complaints to diminish. Both sleep and sleep interventions have nevertheless received little attention in PTSD therapeutics and research. Only a handful of studies have directly investigated the role of sleep in the treatment of PTSD. Two recent studies associate poor sleep quality with reduced responsiveness to trauma-focused therapy (Kartal et al., 2021; Sullan et al., 2021). Furthermore, Lommen and colleagues correlated subjective ratings of sleep quality and duration during treatment to clinical outcome and found a positive bidirectional relationship (Lommen et al., 2016). In another recent study objectively measuring sleep after a single treatment session, it was found that a higher percentage of SWS and lower REM density positively predicted treatment outcome (Kobayashi et al., 2016). Finally, treating insomnia in PTSD patients with cognitive behavioral therapy has been shown to simultaneously result in a reduction of PTSD complaints (Ho et al., 2016). With current PTSD treatments being ineffective in 33 % of cases, these findings propagate the use of sleep-based interventions targeting memory consolidation to not only solidify but potentially also amplify any daytime treatment effects.

2.3. Targeted memory reactivation (TMR) to bias consolidation

Recent literature in both animals and humans shows that memory reprocessing during sleep can be probed in order to bias memory consolidation. Specifically, in a process referred to as targeted memory reactivation (TMR), sensory cues that are linked to the memory at encoding, are presented again during sleep, resulting in improved memory post-sleep (Fig. 2) (Cellini and Capuozzo, 2018; Hu et al., 2020; Oudiette and Paller, 2013; Paller, 2017). Although the underlying neuronal mechanism is not yet clear, studies in animals and humans indicate that external memory cueing during sleep selectively biases ongoing hippocampo-cortical replay towards the memory representations that are linked to the reactivation cue at encoding (Bendor and Wilson, 2012; Wang et al., 2019). This facilitates the consolidation of the associated memory representations. Importantly, although the sleeping brain is partly blocked off from information-processing, it continues to process certain (e.g. auditory and olfactory) sensory input. In a study propelling the TMR field, Rasch and colleagues introduced a rose odour to participants learning object-location associations (Rasch et al., 2007). Re-administering the rose odour again during subsequent SWS led to increased memory performance on the visuospatial task the next day. This memory benefit was not observed when an odorless control scent was presented, or when the rose odour was administered during REM sleep or wake. Since then TMR has been shown to augment memory performance for a wide variety of memory tasks, such as vocabulary learning (Schreiner and Rasch, 2015), word recall (Fuentemilla et al., 2013), skill learning (Antony et al., 2012), and even counter-stereotype learning to reduce implicit social biases (Hu et al., 2015). A recent meta-analysis covering 91 TMR studies indicated a small to moderate effect size of TMR (Hedges' g=0.29) (Hu et al., 2020). The effect sizes of TMR may in general be modest given the fact that TMR is additive to the intrinsic function of sleep in supporting memory consolidation.

2.3.1. Conditional factors of TMR

Given the large divergence in methodological approaches to TMR, the authors of the meta-analysis delineate several experimental factors that seem to determine TMR success. First, TMR has been mostly studied and shown to be effective when cues were presented during NREM sleep as target sleep phase (SWS, Hedges' g=0.27, n = 70 studies; and N2, Hedges' g=0.32, n = 6 studies). Cueing during REM did not result in an overall memory benefit for the associated memories (Hedges' g=−0.06, n = 7 studies), although several individual studies did show positive TMR effects during REM (Batterink et al., 2017; Cai et al., 2009; Tamminen et al., 2017). Second, TMR effectiveness was shown to vary based on the type of memory that is manipulated. Across studies, TMR was able to augment spatial learning, associative learning, language acquisition, skill learning and cognitive bias modifications. In contrast, emotional memories, fearful memories and false memories, although studied much less frequently, did not seem susceptible to TMR. Third, TMR was shown to be effective only when the resulting memories were probed using recall and indirect behavioral performance (such as speed and accuracy or problem solving) as outcome measures. When findings were based on recognition, subjective ratings or skin conductance response (SCR), no effect of TMR was found. Finally, concerning sensory cue modality, TMR has been applied successfully using mainly auditory (verbal and nonverbal) or olfactory cues but visual and tactile cues have also been used successfully.

2.3.2. Phase-targeted TMR

One factor that is not taken into account in the meta-analysis of Hu and colleagues, but most likely plays a crucial role in TMR success, is the precise timing of the reactivation cue with respect to ongoing oscillatory dynamics (Talamini and Juan, 2020). Memory consolidation primarily happens during SWS, where the depolarizing positive deflections of SOs (hereafter referred to as *upwaves*) likely represent ideal conditions for plasticity and hippocampo-cortical information transfer (Niethard et al., 2018; Staresina et al., 2015) (Fig. 1B). In contrast, the hyperpolarizing negative deflections of SOs (*downwaves*) are associated with decreased cortical activity, limiting communication across brain regions necessary for system level consolidation. In theory, opposing effects of TMR can thus be expected when applied during up- and downwaves (Niethard et al., 2018; Steriade, 2003; Steriade et al., 1993). This has likely reduced effect sizes of existing TMR studies that generally presented the reactivation cue randomly, in a non-phase-locked fashion. An exception
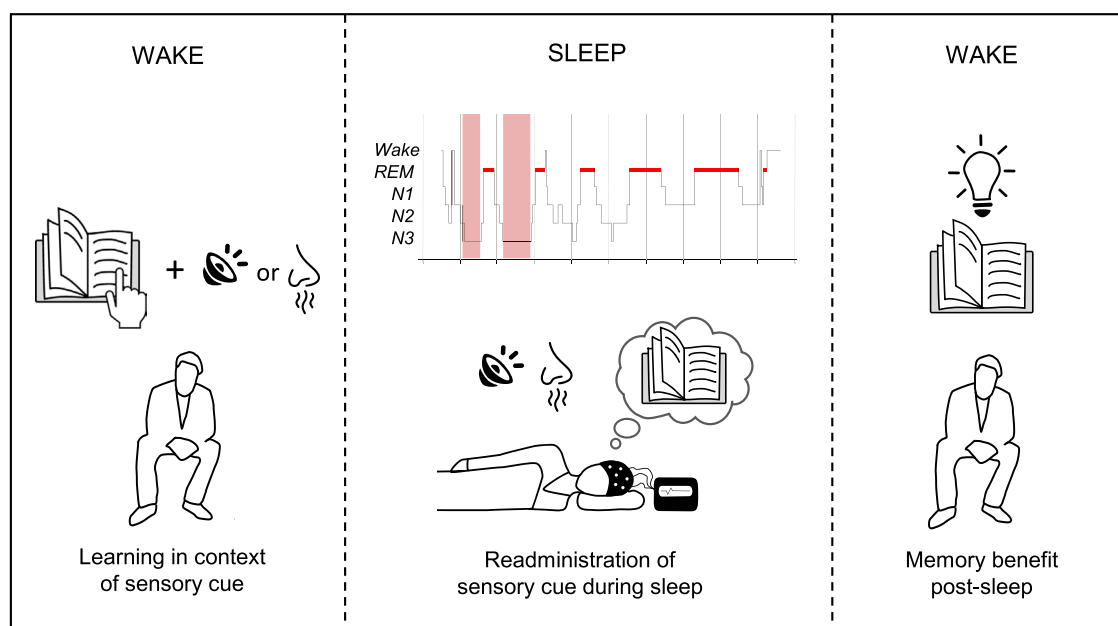
Fig. 2. Principles of targeted memory reactivation (TMR) as a means to bias memory consolidation. During pre-sleep learning, new memories are formed in the context of (or in association with) a certain sensory cue (e.g. smell or sound). Presenting the sensory cue again during subsequent (in this case N3) sleep, is thought to selectively bias ongoing hippocampo-cortical replay towards the memory representation that is linked to the cue at learning. This results in a post-sleep memory benefit of the reactivated (vs not-reactivated) memory. Depending on several experimental factors, such as the target sleep phase, type of memory task and cue modality, TMR paradigms generally show small to moderate effect sizes (Hu et al., 2020).

is a recent study in which newly learned Danish words were presented time-locked to either upwaves or downwaves (van Poppel and Talamini, 2019). This resulted in memory enhancement for words cued during upwaves and forgetting for words cued during downwaves, as compared to no cueing. Technically, phase-targeted TMR can be achieved by using a closed-loop neurostimulation (CLNS) method in which real-time analysis of the EEG signal informs timing of subsequent cue presentation (Talamini, 2017) (Fig. 3). As the TMR field advances, attempts are made to also target faster EEG oscillations, such as theta oscillations (4–8 Hz) occurring during REM sleep (Patriota et al., 2020).

2.3.3. TMR for emotional or fear memory

For the application of TMR in PTSD, existing TMR studies that aimed to manipulate emotional or fearful memories in healthy participants seem particularly relevant. Concerning emotional memory tasks, TMR has shown mixed results. Reactivating declarative emotional memories during NREM sleep has led to either a post-sleep memory retrieval benefit for emotional but not neutral items (Lehmann et al., 2016), a benefit for both emotional and neutral items (Groch et al., 2017), or no effect (Ashton, 2018; Cairney et al., 2014; Rihm and Rasch, 2015). Cueing emotional memories specifically during REM also failed to show specific retrieval benefits for emotional items (Lehmann et al., 2016; Rihm and Rasch, 2015). The few TMR studies on fear memory have mostly attempted to reactivate the conditioned fear response during SWS by re-exposing participants to either the auditory conditioned stimulus (CS+) itself (He et al., 2015) or an olfactory context cue that got associated with the fear memory (the association between the CS+ and the unconditioned stimulus (US) (Hauner et al., 2013a) (Table 1). Both studies reported an attenuated SCR (as indicative of reduced fear) after TMR as compared to various sleep-related control conditions. He and colleagues, however, found a similar effect when cues were administered during wake (He et al., 2015). Both authors interpret their effects as continued extinction learning during sleep. An alternative explanation would be facilitated system level consolidation of the associated fear memory directly, which could also result in a less aversive memory. The latter interpretation is supported by the functional MRI finding of reduced hippocampal involvement when the targeted memories are reactivated post-sleep (Hauner et al., 2013b). Reactivating conditioned fear (with auditory CS+ as cue) during REM sleep, resulted in reduced
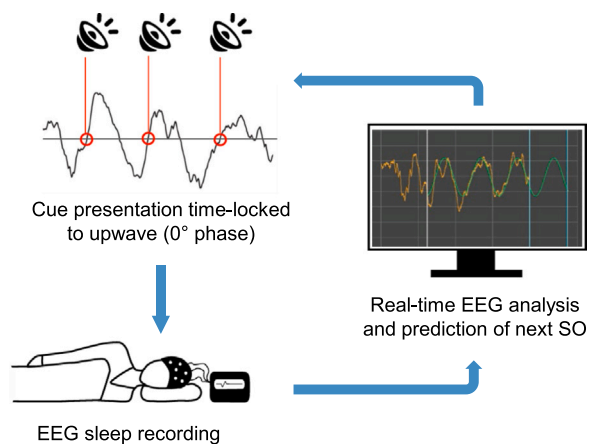

Fig. 3. Phase-targeted TMR using a closed-loop neurostimulation (CLNS) method. EEG is continuously recorded during sleep (lower part). Slow oscillations (SOs) from the incoming EEG signal for channel Fz (in orange) are modeled in real-time using sine fitting (in green) and used to make predictions about the phase of future oscillations (between the two blue lines) (right part). Based on these predictions sound presentation can be time-locked precisely to the 0° phase of the next SO, effectively targeting the favorable upwave part of SOs and avoiding reactivation in the downwave part. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

subjective (but not physiological) arousal ratings post-sleep (Rihm and Rasch, 2015). This finding supports the proposed role of REM sleep in the emotional depotentiation of affective memories (van der Helm and Walker, 2011), although a similar reduction of arousal was found when (neutral) CS- sounds were used as cue. In a final TMR study on fear memory, an auditory context cue was presented during the extinction (as opposed to the acquisition) phase of fear conditioning such that it got associated with the extinction (safety) memory (Ai et al., 2015). Readministering the sound during SWS resulted in an increased fear response (as compared to no sound or new sound). The reverse effect (reduced fear) was found for wake TMR. This counterintuitive result is interpreted as the original fear memory being reinstated during sleep, but not wake TMR. The detailed theoretical framework of fear and extinction learning provides an alternative context to interpret TMR results beyond the view that reactivation during sleep biases the neuronal replay underlying systems consolidation. An important emerging question is whether reactivation during sleep can induce new learning (Arzi et al., 2012; Diekelmann and Born, 2015).

2.3.4. TMR for pathological memories

To our knowledge, TMR has been applied only twice in an attempt to target true pathological memories in psychiatric disorders (Table 1). In a study by Groch and colleagues, children and adolescents with social anxiety disorder (SAD) and healthy controls learned associations between pictures showing ambiguous social scenes and acoustically presented positive and negative words (Groch et al., 2017). Half of the words were subsequently presented again during ensuing SWS. This led to a retention benefit for all cued associations (both valences) compared to non-cued ones, in both SAD patients and controls when tested the next morning. When tested again one week later, this retention benefit was no longer present. At this time, however, the SAD patients did report a decrease in pleasantness and arousal ratings of specifically the cued negative associations, which was not observed in healthy controls. The authors state that TMR further increased the existing negative memory bias in SAD by facilitating the gist extraction of negative content information (indexed by reduced pleasantness. In another study in spider phobia patients, TMR was combined with exposure-based treatment (Rihm and Rasch, 2015). At the end of a therapy session consisting of stepwise exposure to a real spider, a context odor was presented during the positive feedback round. This presumably resulted in the odor getting associated with feelings of therapy success and self-efficacy. Next, the odor was readministered during NREM sleep (daytime nap) to facilitate consolidation of the extinction memory and thus augment treatment effect. Control conditions consisted of the presentation of an odorless vehicle during sleep or participants staying awake. There was no effect of TMR on subjective, behavioral and physiological measures of phobia-related fear. This null-finding is likely explained through ceiling effects of the treatment itself, leaving little room for further improvement due to TMR. Alternatively, the cueing of the verbalized therapy success may have been too weak to enhance the consolidation of the actual extinction memory. Odor re-exposure did result in stimulus-locked increases in spindle activity, possibly representing enhanced neuronal replay and some form of transfer of the related memories.

3. TMR to treat traumatic memories in PTSD

As described above, PTSD can be considered a disorder of intrusive traumatic memories, which is typically treated with exposure-based treatment. Hence, memory reactivation strategies during (post-treatment) sleep may be especially suited to treat PTSD symptoms. In the second part of this review, we will discuss the different possible strategies to apply TMR to treat traumatic memories in PTSD with the ultimate goal to open up sleep as a new treatment window for PTSD (Paller, 2017; Talamini and Juan, 2020).

Table 1
Overview of TMR studies on fearful and pathological memories.

Paper	Cueing sleep stage	Type of memory	Outcome measure	Cue type	Sample and experimental conditions	Experiment	Main finding and interpretation
Ai et al. (2015)	SWS (nap)	Fear extinction	SCR	Auditory non-verbal	6 groups (n = 133, healthy adults, between-subject): Contextual extinction tone-SWS Control tone -SWS No tone-SWS Contextual extinction tone-wake Control tone-wake No tone-wake	Subjects underwent fear conditioning. During extinction learning, an auditory contextual cue presented such that it got associated to the extinction (safety) memory. Post-sleep SCR in response to CS+ presentation was evaluated and compared between readministration of the contextual extinction tone, presentation of a control tone or no tone presentation, during either SWS or wake (all between-subjects factors).	TMR during SWS resulted in an increased fear response, which is interpreted as the original fear memory being reinstated during sleep. Re-exposure to the TMR cue during wake resulted in an attenuated fear response.
Groch et al. (2017)	SWS (whole night)	Declarative memory	Memory performance + subjective ratings	Auditory verbal	2 groups (children and adolescents with social anxiety disorder, SAD (n = 13) and age-matched healthy children and adolescents (n = 13), between-subject): Readministration of half of the words during SWS (within-subject).	Subjects learned associations between pictures showing ambiguous social scenes and acoustically presented positive and negative words. Half of the words were subsequently readministered during SWS. Recall of picture–word associations and subjective ratings of pleasantness and arousal in response to the pictures were evaluated for cued and uncued stimuli directly after and one week post TMR (within-subjects factor), and compared between subjects with SAD and healthy controls (between-subjects factor).	TMR resulted in a retention benefit for both positive and negative memories in both groups the morning after cueing. One week later, this cueing benefit was no longer present, however, pleasantness and arousal ratings of specifically negative cued associations were reduced in subjects with SAD but not in healthy controls. This is interpreted as TMR further increasing the existing negative memory bias while at the same time reducing the affective tone of the associated memories.
Hauner et al. 2017	SWS (nap)	Fear conditioning	SCR, fMRI	Olfactory	2 groups (n = 15, healthy adults, within-subject): (target) Odor associated to fear memory - SWS (control) Odor associated to fear memory - not readministered during sleep Follow-up experiment (n = 15, healthy adults, between-subject): (target) Odor associated to fear memory - SWS (target) Odor associated to fear memory - wake	Subjects underwent fear conditioning (in an fMRI scanner) in the presence of two background odors that thus got associated with the fear memory. Only one odor (the target odor) was readministered during SWS (nap). Post-sleep SCR as well as fMRI whole brain activity in response to CS+ presentation were evaluated and compared between the target and control odor (within-subjects factor). In a follow-up experiment readministration of the target odor during SWS was compared to re-administration of the target odor during wake (between-subjects factor).	TMR during SWS resulted in an attenuated fear response together with a reduction in hippocampal activity and a reorganization of amygdala ensemble patterns. This is interpreted as continued extinction learning (of the now unreinforced CS+) during sleep as well as the accelerated consolidation of the unreinforced CS+, as indexed by reduced hippocampal dependency.
He et al. (2015)	SWS (first half of night)	Fear conditioning	SCR	Auditory non-verbal	6 groups (n = 96, healthy adults, between-subject): CS+ tone - SWS (for 3 min) CS+ tone - SWS (for 10 min) Control tone - SWS (for 10 min) No tone - SWS Follow-up experiment: CS+ tone - wake (for 10 min) No tone - wake	Subjects underwent fear conditioning. Post-sleep SCR in response to CS+ presentation was evaluated and compared between readministration of CS+ tone during SWS (either 3 min or 10 min), presentation of a control tone during SWS (10 min) and no sound presentation during SWS (between-subjects factor). Subjects were awakened after 4 h of sleep (around 3 a.m.) to perform the test. In a follow-up experiment, readministration of CS+ tone during wake (10 min) was compared to no sound presentation during wake.	TMR during both SWS and wake resulted in an attenuated fear response. This is interpreted as continued extinction learning (of the now unreinforced CS+) during sleep and wake alike.
Rihm et al. (2016)	SWS (nap)	Fear extinction in	SCR + subjective	Olfactory	3 groups (n = 54, patients with spider phobia, between-subject):	Spider-phobia patients underwent regular exposure therapy. At the end of the	TMR during N2 and N3 did not augment exposure therapy. This null-finding is explained

Table 1 (*continued*)

Paper	Cueing sleep stage	Type of memory	Outcome measure	Cue type	Sample and experimental conditions	Experiment	Main finding and interpretation
		treatment setting	ratings of spider fear		Contextual extinction odor - N2 and N3 Control odorless-vehicle - N2 and N3 No odor - wake	therapy session, patients verbalized their subjectively experienced therapy success in the presence of a background odor such that the odor got associated with feelings of therapy success and self-efficacy. Post-sleep SCR and subjective ratings of spider fear were evaluated and compared between readministration of the contextual extinction odor during N2 and N3, presentation of an odorless vehicle during N2 and N3 and no presentation of odor during wake (between-subjects factor).	through ceiling effects of the treatment itself, leaving little room for further increases due to TMR. TMR did result in stimulus-locked increases in (slow and fast) spindle activity, possibly representing enhanced neuronal replay and some form of transfer of the related memories.

Abbreviations: CS: Conditioned stimulus; fMRI: Functional magnetic resonance imaging; SCR = Skin conductance response; SWS: Slow wave sleep.

3.1. What memory to target?

A first fundamental question when employing TMR in PTSD, is what (version of the) memory to target. From a theoretical point of view, we see three ways to reduce symptom level in PTSD by applying TMR: 1.) Strengthen an adapted version of the traumatic memory trace after treatment; 2.) Weaken the traumatic memory trace by reinstating normal hippocampo-cortical consolidation; 3.) Weaken the traumatic memory trace directly by blocking its consolidation (Fig. 4).

3.1.1. Strengthen consolidation of treatment memory

The safest option to employ TMR in PTSD is to augment a positive treatment outcome. During successful exposure-based treatment, traumatic memories are being altered through extinction (or reconsolidation, see above, (Kroes and Fernández, 2012)). The resulting therapeutic memory, associated with less fear and arousal, needs to be consolidated to stabilize the memory and solidify the treatment effect (Lane et al., 2015; van Marle, 2015). TMR can be used to facilitate this process. Experimentally, an auditory or olfactory context cue can be presented during the therapy session, leading to an association between the cue and the updated or neutralized traumatic memory. During post-treatment sleep (whole night or nap) this association can be targeted by readministering the context cue, which is thought to result into the preferential reorganization of the therapeutic memory. A necessary precautionary measure in this set-up would be to refrain from TMR in case of a negative treatment outcome to prevent strengthening a reinforced traumatic memory. It should be noted that, in theory, the context cue could also get associated with other, more negative aspects of the therapeutic process. Especially the start of the session is typically accompanied with increased levels of fear and arousal. To circumvent this, the cue can be presented only at the end of the session or during a positive feedback round (like in the study of Rihm and colleagues (Rihm et al., 2016)). Based on traditional TMR studies targeting new learning however, one could argue that pairing the cue to the process of learning (in this case trauma memory extinction or alteration), will produce larger TMR effects. Another theoretical risk relates to the fact that traumatic memories in PTSD may arise from dysfunctional consolidation processes, resulting from severe sleep disturbances (see BOX 1). Therefore the effect of TMR, even if used to enhance the consolidation of therapeutic (neutralized) memories, cannot be fully predicted (see also discussion of second TMR strategy below). As discussed in 1.4, this use of TMR to strengthen the consolidation of positively altered fear memories, has been investigated in phobia patients (after exposure therapy) (Rihm et al., 2016) and in healthy participants (after the extinction phase of a fear conditioning paradigm) (Ai et al., 2015). The ongoing

TMR-TRAUMA study (van der Heijden et al., 2017) represents a first attempt to use the described approach to modify traumatic memories in PTSD patients. In this study, PTSD patients undergo a single EMDR treatment session, including a standard distracting auditory stimulus to tax working memory. During subsequent SWS, the same auditory stimulus is readministered as context cue (as opposed to no readministration) time-locked to SO upwaves using CLNS. This is hypothesized to enhance the consolidation of the treatment memory and thereby increase the effectiveness of the EMDR treatment. The main outcome measure in this study is subjective and physiological fear in relation to the targeted memory (as assessed in a script-driven imagery and recall task), as well as overall PTSD symptom level.

3.1.2. Weaken traumatic memory by reinstating normal consolidation

Under normal circumstances, the process of hippocampo-cortical consolidation is likely accompanied by a conceptualization and generalization of memories, which involves loss of contextual detail and a dampening of emotional tone. Healthy memory consolidation processes by themselves should then reduce the affective charge of a memory (Rasch and Born, 2013; Tempesta et al., 2018; van der Helm and Walker, 2010). TMR could in principle be employed to weaken the traumatic memory by enhancing its hippocampo-cortical consolidation directly. This approach would appear especially useful when targeting potentially traumatic memories in the direct aftermath of a traumatic event. Fostering the initial consolidation of the memory may speed up its integration in existing, semantic memory networks and its separation from the associated autonomic and visceral fear (Goldstein and Walker, 2014; van der Helm and Walker, 2011). Once traumatic memories are more established, their recurrent intrusive recall, often running a highly negative course, entails the risk of reactivating the full traumatic experience when using TMR during subsequent sleep. Experimentally, when employing TMR in this preventive way, an auditory or olfactory context cue could be presented during sleep that is intrinsically linked to the traumatic memory. This could be the smell of gasoline in a car accident memory or the sound of gunfire in a war memory. Ideally, TMR is then used shortly after the traumatic event, for instance in an emergency room or battlefield hospital with facilities for sleep monitoring and cue delivery. This, together with the personalized content of the context cue, can make the practical implementation of this strategy challenging. Furthermore, as discussed, 'normal' consolidation in PTSD may constitute a maladaptive form of consolidation. PTSD-related sleep disturbances, such as lack of SWS and heightened noradrenergic tone during REM-sleep, may give rise to the dysfunctional processing of traumatic memories (see BOX 1). Therefore, it cannot be excluded that using TMR in the described way may propagate a pathological form of
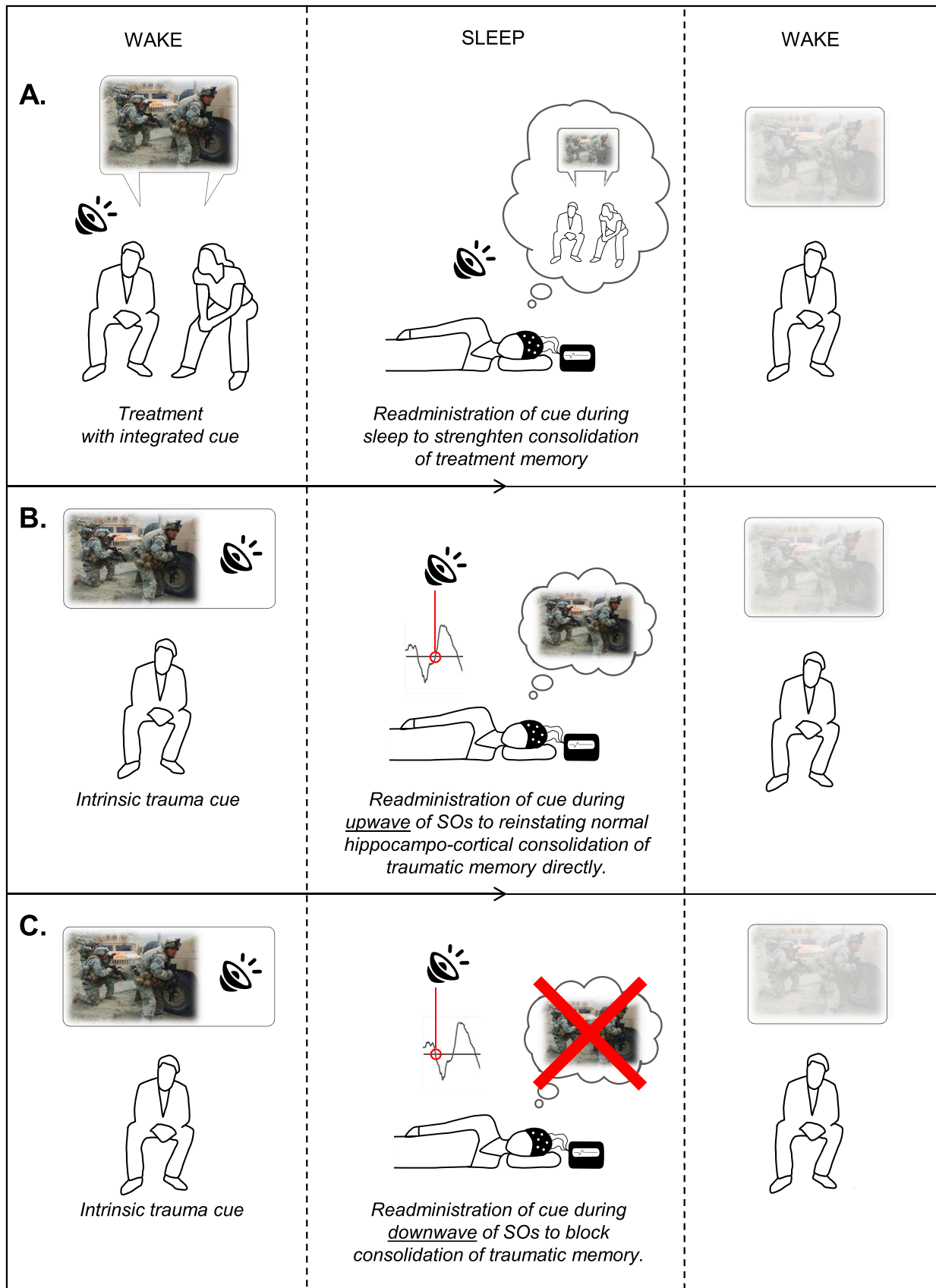
Fig. 4. Schematic illustration of three hypothetical strategies to treat traumatic memories in PTSD with TMR. See main text for background and description of associated practicalities and risks.

consolidation, leading to a strengthening rather than a weakening of the traumatic memory trace. This risk may be mitigated by additionally normalizing and stabilizing PTSD sleep, for instance by amplifying and prolonging SOs using acoustic stimulation (see 2.4). Another intuitive risk of reactivating traumatic memories directly, is that the reactivation cue gets processed as a trigger initiating nightmares. This may be true especially when applying memory reactivation during phasic REM sleep when sensory cues are known to get integrated into dream content (Solomonova and Carr, 2019; Wehrle et al., 2007). Together, these risks render the described option speculative. The two existing TMR studies that are closest to this set-up both target fear memories in healthy participants during SWS directly following fear acquisition (Hauner et al., 2013a; He et al., 2015). Using either the auditory CS+ as reactivation cue (He et al., 2015) or an olfactory context cue (Hauner et al., 2013a), they found that physiological levels of fear get reduced as a function of TMR. They explain their positive findings however, not through enhanced consolidation, but through continued extinction learning during sleep, which requires new learning by the sleeping brain (Diekelmann and Born, 2015).

3.1.3. Weaken traumatic memory by blocking consolidation

Finally, based on our own preliminary finding of induced forgetting of newly learned words when reactivated during downwaves (van Poppel and Talamini, 2019) one could argue that targeting traumatic memories during downwaves may block their consolidation. Again, this approach seems especially applicable in the first phase after trauma exposure, when the initial consolidation of potentially traumatic memories may be hampered in an attempt to prevent their long-term retention. Experimentally, patients could be exposed to intrinsically related sounds or smells, that are presented precisely time-locked to downwaves using a CLNS method. Based on limited data in healthy TMR paradigms, this approach is less likely as a first translational attempt of TMR in PTSD.

3.2. Methodological considerations

When experimentally translating TMR principles into a potential treatment for PTSD, several methodological considerations arise.

3.2.1. Phase-targeted TMR

A crucial choice relates to the use of phase-targeted TMR versus randomly administered reactivation cues during sleep. Based on the discussed finding of opposite effects of cueing during up- or downwaves (van Poppel and Talamini, 2019), we advocate the use of TMR in a phase-locked manner using CLNS. When attempting to augment a positive treatment outcome for example, cueing time-locked to upwaves would ensure bigger consolidation effects. Omitting cues during downwaves likewise keeps the positive treatment outcome from getting weakened. In addition, administering auditory stimuli time-locked to upwaves have been shown to amplify and prolong SOs (see 2.4) (Marshall et al., 2006; Ngo et al., 2013). Apart from facilitating memory consolidation directly, this also reduces the risk of awakenings during TMR. Phase-targeted TMR poses an technical challenge by requiring a closed-loop system (Cox et al., 2014). This clearly limits applicability in clinical or home settings, although closed-loop ambulatory EEG set-ups (using an EEG-headband wirelessly coupled to a tablet) are already being developed (Talamini, 2021).

3.2.2. Sleep phase

In the majority of (successful) TMR studies, also on emotional or fear learning, memories get reactivated during SWS. Experimentally, this has the advantage that SOs are relatively easy to target using CLNS (compared to faster brain rhythms). Presenting cues during the deepest sleep stage limits the risk of induced awakenings, but the reported shortage of SWS and reduced slow oscillatory power in PTSD patients (de Boer et al., 2020; He et al., 2015; Kobayashi et al., 2016) may limit

the number of available SOs to target. The next sleep phase to consider is REM. REM sleep seems a likely target phase, given the fact that emotional memories (including extinction memories) are thought to get reprocessed primarily during REM sleep. So far, only one study has attempted to manipulate fear memories in healthy participants during REM sleep (Rihm and Rasch, 2015). Using the CS as reactivation cue, they found reduced subjective arousal for fearful/CS+ (but also neutral/CS-) memories after TMR during REM. Targeting traumatic memories during REM poses several challenges. First, the relatively fast theta oscillations (4–8 Hz) that make up REM sleep, are more difficult to phase-target than SOs. Second, REM sleep is often fragmented in PTSD patients (Habukawa et al., 2007), likely resulting from increased noradrenergic tone during (REM) sleep (Mellman et al., 1995). Nightmares during REM additionally result in frequent awakenings, after which patients have difficulty falling back to sleep or fear to do so. Both phenomena reduce the amount of useable REM sleep to reactivate associated memories. Finally, TMR has also been applied phase-locked to the eye movements of REM sleep itself, which was shown to enhance memory performance in a complex logic task (Smith, 1990) REM density has been shown to be decreased in PTSD (Zhang et al., 2019).

3.2.3. Type of outcome measure

With respect to the type of memory task, Hu and colleagues showed weak or absent TMR effects when subjective ratings were used as outcome measure. This constitutes a problem for clinical applications of TMR, since a reduction in symptom level (as resulting from the reprocessing of maladaptive memories) is then often the desired outcome of TMR. Symptom level is generally assessed with clinical interviews or self-administered questionnaires. Alternatively, one can focus on the evaluation of the specific memory that is being targeted, for instance by using the script-driven imagery and recall task (Lanius et al., 2002, 2001). This gives the opportunity to add objective outcome measures, like heart rate or brain reactivity patterns (e.g. measured with functional MRI) in relation to the targeted memory. While SCR did not come forward as a reliable outcome measure across fear TMR studies (Hu et al., 2020), the use of SCR in fear studies targeting SWS (Hauner et al., 2013b; He et al., 2015) did render positive effects of TMR (as calculated from supplementary materials (Hu et al., 2020), Hedges' G= 1.64). Memory tasks that are reported to successfully detect TMR effects, like recall and indirect behavioral performance (e.g. accuracy or problem solving) (Hu et al., 2020), seem less suited to probe the emotionality of the long-existing, complex memories that make up PTSD.

3.2.4. Cue modality

Both auditory and olfactory reactivation cues have advantages as well as disadvantages when used in TMR for PTSD. The main advantage of auditory stimulation is the presentation speed that enables phased-targeted TMR. The upwave part of a SO lasts 500 ms, while sounds as short as 0.25 ms have been shown to be perceived during sleep (Novitski et al., 2007). Another advantage of auditory stimulation, especially when using TMR to strengthen the positive outcome of EMDR, is that an auditory, distracting stimulus is a common feature of the EMDR treatment protocol. This auditory stimulus can be used conveniently as reactivation cue during subsequent TMR. This is important since adding a sensory context cue to an existing treatment may by itself affect therapeutic outcome. The main limitation of using auditory reactivation cues concerns the risk of worsening already disturbed sleep by inducing light sleep and/or awakenings. Given the emotion regulatory and general restorative function of sleep, this could aggravate PTSD symptoms. This limitation can be overcome by lowering the volume of the auditory cue when presentation leads to visual arousals in the EEG. While EEG-studies in PTSD show increased wake time after sleep onset (Zhang et al., 2019), higher awakening thresholds have been reported in PTSD patients in response to disturbing environmental sounds (Dang-Vu et al.,

2010). To circumvent TMR cues becoming too soft to get processed, individual hearing thresholds can be determined pre-sleep. With respect to olfactory stimulation, the probability of arousals and awakening (Carskadon and Herz, 2004) is much lower, yet experimental procedures are more complicated. Having to sleep with a nasal mask can negatively affect sleep quality. Furthermore, olfactory stimulation is currently too slow for phase-targeted TMR. The direct connections of the olfactory bulb with limbic structures including the amygdala and hippocampus may pose an advantage of using olfactory cues to target emotional or traumatic memories.

3.2.5. General factors

Several other general considerations are important when testing TMR in PTSD. Patients generally experience severe symptoms that mark their daily lives. The risk of overtaxing vulnerable PTSD patients may limit the feasibility of some of the described methodologies. This especially concerns elaborate lab-based TMR protocols that include sleep-related control conditions of TMR (such as a wake condition or presentation of an unrelated cue).

3.3. Other risks and considerations

3.3.1. Too complex to target?

Reactivating traumatic memories during sleep in an attempt to alleviate PTSD symptoms represents a big leap in the field of TMR. So far, most TMR studies have attempted to manipulate the first-time consolidation of simple associative memories that have been acquired hours before in an experimental lab-setting. Traumatic memories in contrast, have been established in a naturalistic way, months and often even years in the past. In addition, even compared to other pathological fear memories, like in phobia, traumatic memories are considered complex. They are insufficiently integrated in autobiographical memory, strongly coupled to autonomic and perceptual markers and they can be linked to many other emotions besides fear, such as anger, guilt and shame (Brewin, 2015). Whether TMR is able to bias the ongoing consolidation of such complex memory traces is currently unknown. Also, because traumatic events often do not happen in isolation, different traumatic memories can be strongly linked and trigger each other. The possible collateral reactivation of such associated memories and emotional states during TMR are beyond the experimenter's control and may impact symptom levels. Finally, due to the many intrusive recollections during flashbacks and nightmares, the traumatic memory trace changes continuously. This makes it experimentally hard to control what version of the memory is reactivated when presenting associated cues. This challenge especially applies when attempting to target existing traumatic memories directly (options 3.1.2 and 3.1.3 in 3.1). These uncertainties make it hard to predict the effect of TMR on traumatic memories in PTSD.

3.3.2. Worsening symptoms

The most important risk when applying TMR in PTSD is that the traumatic memory trace gets strengthened and PTSD symptoms get aggravated. Of the few TMR studies on conditioned fear, one reported an increase in physiological fear after the extinction memory got reactivated during SWS (Ai et al., 2015). Two other TMR studies that directly targeted fear memories after fear acquisition found that TMR attenuated fear levels (Hauner et al., 2013a; He et al., 2015). An attempt to strengthen the consolidation of treatment memories in spider phobia patients, did not find an increase (or decrease) in physiological and behavioral fear after TMR (Rihm et al., 2016). Thus, existing studies do not seem to warrant nor exclude a safe use of TMR in PTSD.

3.4. Other sleep-based interventions to treat PTSD

Next to TMR, a number of other sleep-based interventions can be considered when trying to treat traumatic memories in PTSD. First,

studies in healthy participants show that SWS can be deepened (Cox et al., 2014) and memory performance can be enhanced by experimentally amplifying and prolonging slow waves (Marshall et al., 2006; Ngo et al., 2013; Papalambros et al., 2017). This is achieved by presenting short, non-arousing sounds time-locked to plasticity-promoting upwaves using CLNS (Cox et al., 2014). In the context of PTSD, this technique of sleep deepening may restore intrinsically disturbed SWS (de Boer et al., 2020; Zhang et al., 2019), as well as enhance the emotion regulation, memory consolidation and general restorative functions of sleep. Note that TMR, when using auditory cues time-locked to upwaves, may also result in SO boosting (van Poppel and Talamini, 2019). SOs specifically in posterior brain regions have been associated with decreased dream recall (Siclari et al., 2017). Boosting these posterior SOs using TMR may be a potential avenue in combatting nightmares in PTSD patients. However, caution is warranted since absence of dream recall does not equal absence of dreaming. The physiological stress during nightmares may still occur independent of verbal dream recall. Furthermore, certain forms of pre-sleep hypnosis have also been shown to increase SWS in highly-suggestible individuals (Cordi et al., 2020, 2014). In addition to SOs, theta oscillations can also be boosted during REM sleep (Patriota et al., 2020). Second, not sleep deepening, but sleep deprivation could be considered, on theoretical grounds, as a direct intervention after trauma exposure. This would be aimed at hampering the initial consolidation of the trauma-related memory. Support for this idea is limited and mostly based on trauma analogue paradigms in healthy participants. In one of these studies, Porcheret and colleagues reported fewer intrusions in participants that were sleep-deprived after watching a trauma film as opposed to participants that were allowed to sleep (Porcheret et al., 2015). Follow-up studies failed to replicate this or conversely showed that sleep reduced the number of intrusive recollections (Kleim et al., 2016; Porcheret et al., 2015; Sopp et al., 2019; Wilhelm et al., 2021). In PTSD, prospective studies have shown that sleep disturbances prior to, or following a traumatic event, predict the development of the disorder (Bryant et al., 2010; Koren et al., 2002; Mellman et al., 2002; van Liempt et al., 2013). Together, these observations highlight a protective role of (intact) sleep in the processing of aversive and potentially traumatic memories. This warrants caution with regard to sleep deprivation as a potential treatment strategy for PTSD. Ultimately, different interventions could be combined that enable a trauma-exposed individual to store all necessary information related to the event while downregulating the associated negative emotion and physiological arousal. As an example, deep sleep could be promoted by boosting SOs, while noradrenergic tone during REM sleep gets reduced pharmacologically. Finally, insomnia and sleep complaints in PTSD can be treated with cognitive behavioural therapy focused on insomnia (CBT-I) (Ho et al., 2016). Given the crucial role of healthy sleep in the consolidation of (extinction) memory and emotion regulation, CBT-I may concurrently reduce PTSD symptoms.

3.5. TMR in other psychiatric disorders?

Given the universal nature of the memory processes at play, these viewpoints and considerations concerning TMR can be readily extrapolated to other psychiatric disorders in which treatment typically centers on the updating and consolidation of maladaptive memories or associations. This is the case for virtually all anxiety and obsessive-compulsive disorders, as well as addiction. In theory, sensory cues could be integrated in exposure-based psychotherapies of these disorders and readministered during subsequent sleep to boost the consolidation of any positive treatment outcome. Maladaptive memory processing in depression is characterized by strong memory biases toward negative (interpretations of) experiences (Everaert et al., 2012). Changing these biases through cognitive behavioral therapy also involves new learning, which in theory could be augmented using TMR. Beyond psychiatry, TMR could be employed to aid physiotherapy in stroke patients by boosting (relearned) motor memory overnight (Paller,

2017). The recent adaptation of TMR for home use strongly increases the feasibility of new experimental studies testing TMR in clinical populations. Finally, TMR is one of the few experimental methods to manipulate and study the elusive process of memory consolidation. The use of TMR to treat psychiatric and neurological disorders could therefore elucidate the dysfunctional memory processes underlying them.

4. Conclusion

In this review, we explore different strategies to apply TMR to treat traumatic memories in PTSD. The majority of TMR studies so far target new, experimentally-acquired, relatively simple associative memories. In contrast, the traumatic memories that constitute PTSD are highly complex and have been established in a naturalistic way often months or years before. This poses a translational challenge, since the chronicity and complexity of PTSD memories are insufficiently modeled in TMR studies in healthy subjects, even when they target emotional or fear memories. Nevertheless, the potential benefits of TMR for PTSD seem to outweigh the possible risks, especially when attempting to strengthen a positively altered traumatic memory during post-treatment sleep. With pharmacological research not having produced many new treatment options for PTSD in the last decades, sleep-based interventions like TMR are both promising and needed. Future studies need to determine the criteria for successful TMR with regard to factors such as target sleep phase, cue modality and use of phase-targeting. We hope this review provides the necessary background for these experimental efforts to succeed and open up sleep as a new treatment window for traumatic and other pathological memories.

Declaration of Competing Interest

International patent application personal information from one of the co-authors removed for anonymity during the review process.

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