Sleep as a window to treat affective disorders

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Sleep disturbances represent a core symptom in affective disorders. While healthy sleep patterns help to regulate emotions and consolidate memories, disturbed sleep participates in the genesis and maintenance of mental illnesses. As the electrophysiological mechanisms underlying restorative sleep start to be uncovered, exciting opportunities for direct applications arise. Here we discuss the first evidence on manipulation of emotional processing and memories during sleep. In particular, we examine the advantage of targeted memory reactivation procedures, especially when phase-locked to slow oscillations dynamics, in achieving such manipulations. Extrapolating from this knowledge, we propose sleep-based interventions that could provide new therapeutic avenues for the treatment of maladaptive emotional memories, as in phobias, addictions or PTSD.

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Sleep is important for emotional housekeeping

Sleep hosts a myriad of processes that are essential for physical and mental functions [1]. In particular, sleep plays a crucial role in emotion regulation [2••]. Sleep quality is highly correlated with next day mood [3] (Figure 1a), while sleep loss consistently results in more negative appraisals [4] (Figure 1b), stronger subjective and physiological responses to threatening stimuli (Figure 1c), attentional bias toward negative stimuli and diminished ability to understand other people's feelings and to show empathy [2••]. This relationship is bidirectional since emotional events can also influence subsequent sleep patterns, leading to more or less adaptive emotion regulation [5] (Figure 2).

Given the major role of sleep in emotional appraisal and regulation, it is not surprising to find that virtually all affective disorders are accompanied by sleep disturbances [6,7]. In fact, insomnia has been recently highlighted as a significant predictor for a wide range of psychopathologies, including depression, anxiety, and psychosis [8]. With an approximate 25–30% life-time prevalence, mental disorders represent one of the most prevailing and global health issues [9], and this incidence can be expected to increase in the near future [10]. Furthermore, current treatments are typically expensive in time, energy and resources, resulting in a low mental health facilities use rate [11,12].

In this context, it is urgent to understand the unique role of sleep in affective disorders, to uncover new avenues for mental health care.

Physiological underpinnings of sleep's role in emotional regulation

Many sleep-related processes could explain the impact of sleep on emotional state. At the systems level, coordinated endocrine and autonomic changes, occurring particularly during deep NREM sleep [13], favor molecular biosynthesis and other basic processes that support host defense responses [14,15], glucose metabolism and other cell metabolism functions [16,17]. Such processes are crucial for general health and for handling stress – including emotional stress – on the system.

Some of these maintenance processes specifically regard the nervous system. For instance, findings in rodents suggest that sleep supports global synaptic downscaling [18] and the clearance of neurotoxic waste substances from intercellular space [19]. Such processes may influence mood and emotional regulation through global effects on neural processing. Accordingly, extended wakefulness and sleep deprivation have been shown to lead to adverse changes in neural function, including loss of long-range functional connectivity [20], excessive neural excitability [21] and loss of inhibitory control from cortical onto subcortical emotional centers, associated to enhanced emotional reactivity [22–24] (Figure 1c–d).

Another way in which sleep may contribute to emotional housekeeping is through reprocessing of emotional memories. Indeed, a large body of evidence supports a role of sleep in memory reactivation and consolidation [25,26]. While the exact neural underpinnings of these off-line processes need to be confirmed, substantial evidence

Figure 1
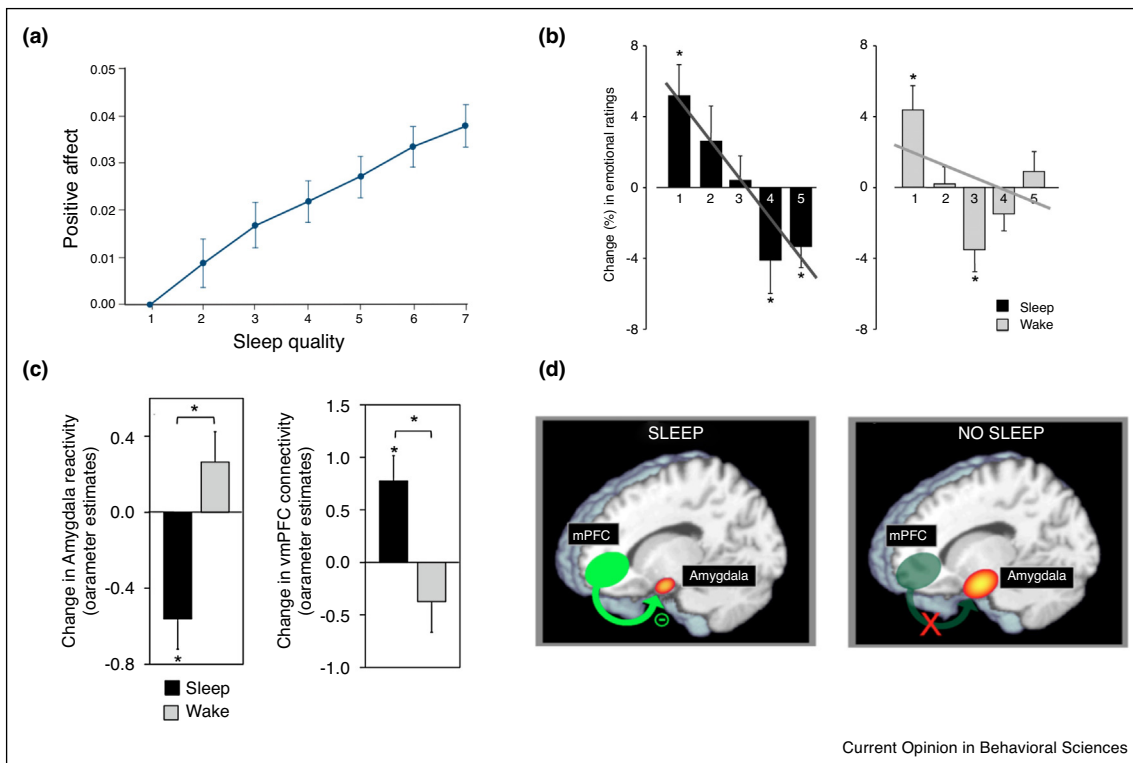
Effects of sleep on emotional processing. **(a)** Effect sizes of subjective sleep quality (as reported on awakening) on average positive affect during the day (reproduced with permission from Ref. [3]). **(b)** Sleep decreases emotional rating of stimuli: after sleep (in black) the rating of the most Intense emotional stimuli (4s, 5s) significantly decreases, which is not the case after a wake period of the same duration (in grey) (reproduced with permission from Ref. [24]). **(c)** Amygdala reactivity is decreased by sleep and increased by wake (left graph), while amygdala-ventromedial prefrontal cortex (vmPFC) connectivity is increased by sleep and decreased by wake (right graph) (reproduced with permission from Ref. [24]), **(d)** suggesting that sleep restores fronto-cortical inhibition on lower order emotional centers (reproduced with permission from Ref. [23]).

points to reactivation of neural memory traces during NREM sleep. Reactivation over distributed areas is coordinated by slow oscillations (SO; 0.5–1.5 Hz) [27•,28•,29], in which thalamic spindles (12−15 Hz) and hippocampal sharp-wave ripples [30] appear hierarchically nested (Figure 3a). Besides the hippocampus and (neo)cortex, memory reactivations can involve amygdala and ventral striatum, for memories with aversive and rewarding components, respectively [31•].

In contrast, the replay of previously encoded information could not convincingly be demonstrated in rodent's REM sleep (at least not using pairwise firing-rate correlation methods [31•]). It should herein be noted that the transient nature and limited amount of REM sleep in rodents complicate such investigations. Even if REM sleep is not associated to high-fidelity memory reactivations, this does not preclude a role of REM sleep in memory processing. A recent study showed that attenuating REM sleep theta rhythm by optogenetically silencing medial septum g-aminobutyric acid–releasing neurons, erased subsequent novel object place recognition and impaired

fear-conditioned contextual memory [35••]. Interestingly, stress during encoding, as indexed by cortisol levels, seems to modulate REM sleep theta and in turn emotional memory consolidation in humans [40•]. As such, convincing evidence ties REM sleep-related (emotional) memory processes to theta activity [32,33], possibly in association with ponto-geniculo-occipital (PGO) waves [34].

Although the research literature on memory consolidation is extensive, not much is known about the mechanisms participating specifically in emotional memory consolidation. Acute emotional stressors seem to cause both an increase in slow wave sleep, and a flattening of the REM sleep distribution across the night (Figure 2c,d) [5]. The slow wave sleep increase is associated to a decrease in memories' emotional tone across sleep (Figure 2e) and thus appears to constitute an adaptive response. Investigations focusing on the role of REM sleep in emotional memory consolidation have provided mixed results so far [2••]. Using split-night paradigms to distinguish the effects of NREM versus REM sleep, some studies

Figure 2
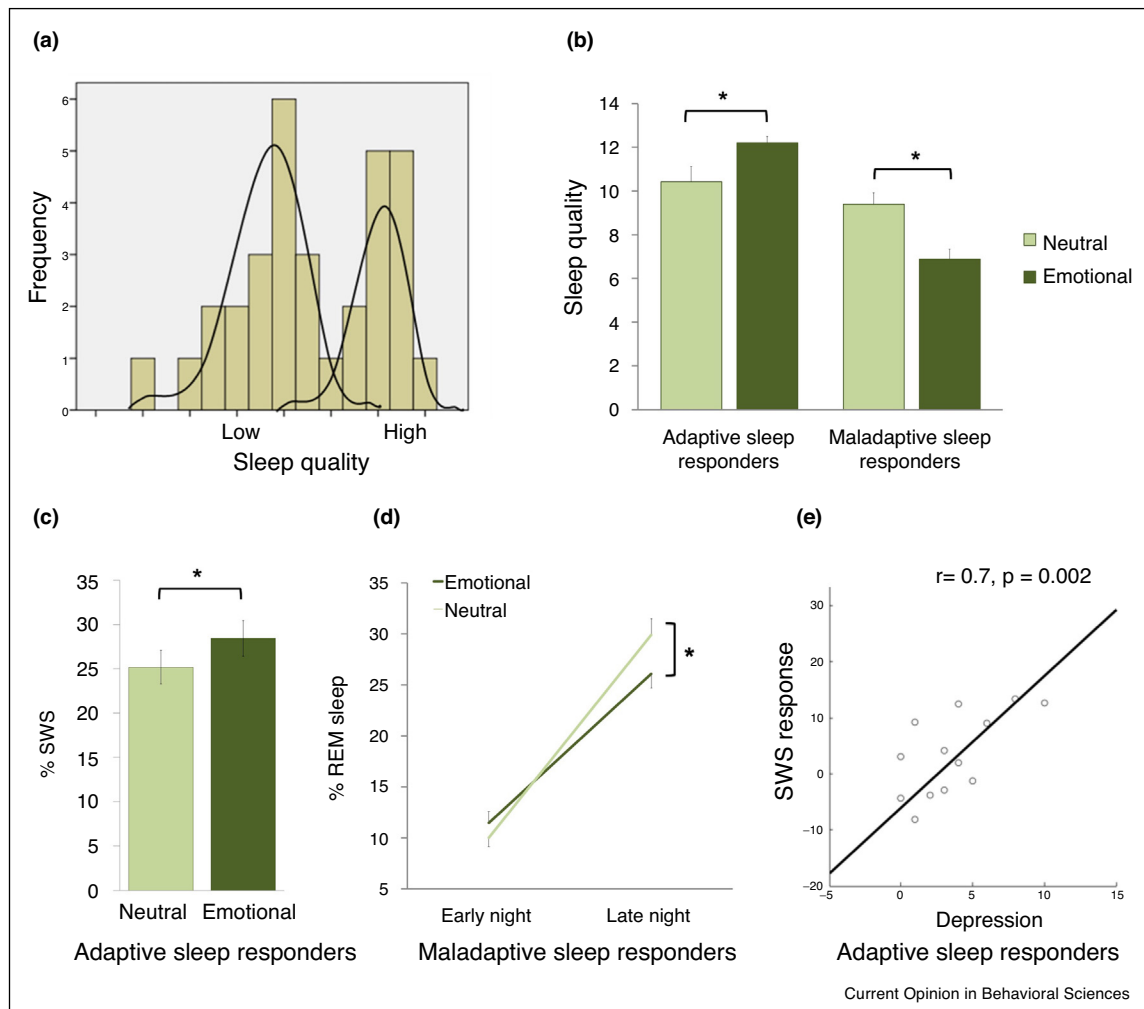
Effects of emotional distress on sleep. **(a)** Sleep quality scores after an emotionally distressing experience show a bimodal distribution. **(b)** After an emotional event, adaptive sleep responders report better sleep, while maladaptive sleep responders report worse sleep; there is no difference between the groups after a neutral event. **(c)** Adaptive sleep responders increase SWS% after an emotional experience. **(d)** Maladaptive sleep responders show a flattened distribution of REM sleep across the night after an emotional event. **(e)** Depression induced by the emotional experience strongly correlates with SWS activity in the second part of the night in adaptive sleep responders. *$p < 0.05$. Adapted and reproduced under the Creative Commons Licence Agreement from Ref. [5].

highlight the role of REM sleep in emotional memory consolidation [36,37], while other studies cannot replicate this advantage [38,39]. Circumstantial evidence suggests that NREM and REM sleep might play interactive and complementary roles in the processing of emotional memories [41,42], but few studies thus far have directly addressed this hypothesis.

TMR to bias memory consolidation
Causal support for sleep-related processing of individual memories comes from experiments in which such processing was influenced by presenting sensory memory cues during sleep, a procedure referred to as Targeted Memory Reactivation (TMR) [43,44••]. A seminal study in rats

showed that TMR biases sleep-related information processing toward the cued memory representation [45]. Several studies in humans have now shown that TMR during sleep can elicit neural responses related to learning content [46,47•]. The effects of TMR on memory performance have, however, been somewhat variable, with some studies reporting enhanced post-sleep recall of cued items [48–51], some reporting no behavioral effect of cueing [52–56], and some negative findings remaining unpublished (including two studies from our lab). These discrepancies might be explained by the substantial variations in paradigms, memory types and sensory cues [57]. However, given the limited sample sizes in many of these studies, type I and II errors could also play a role.

Figure 3
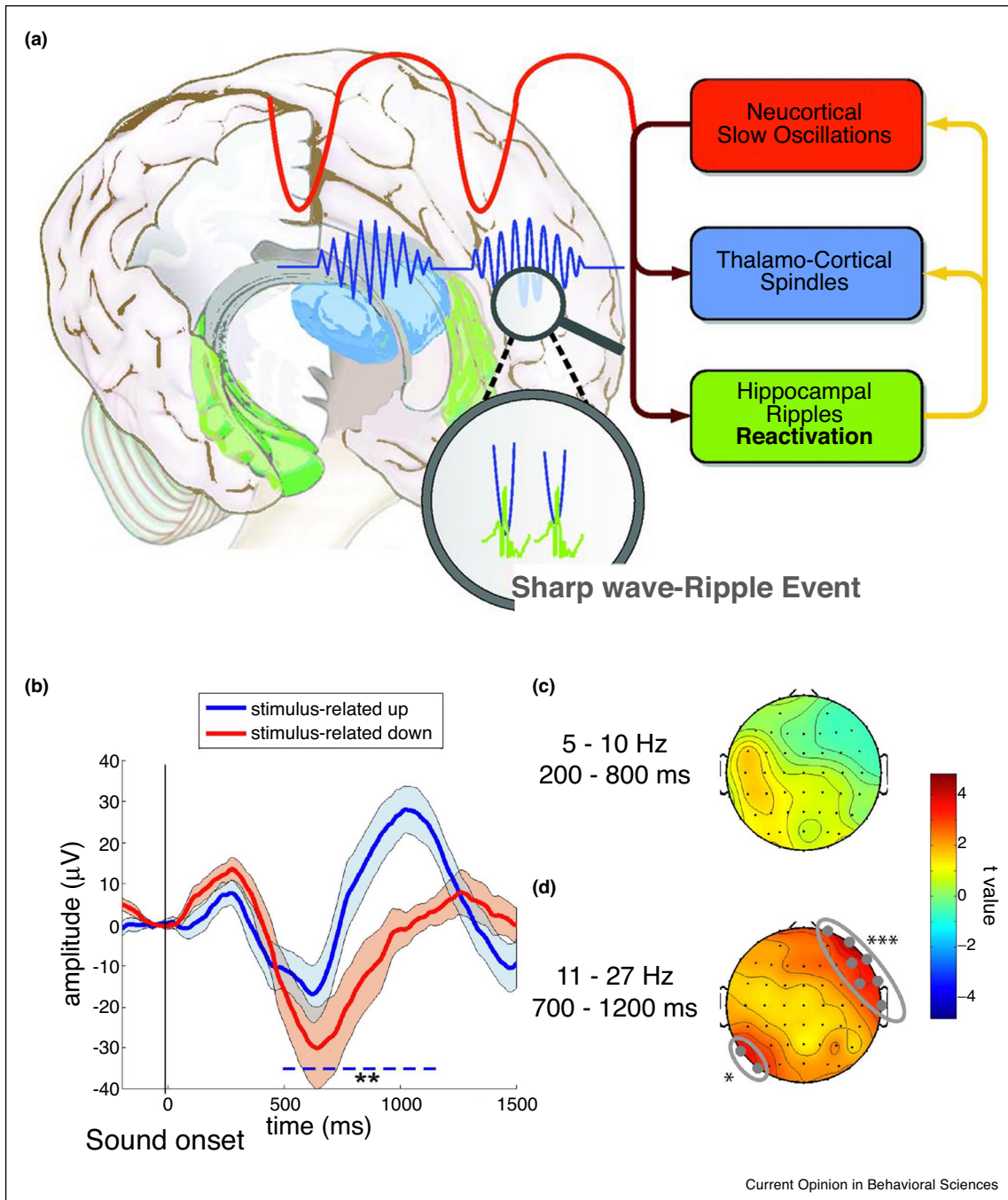
(a) Coupling of sleep oscillatory dynamics across hippocampus, thalamus and cortex. Spindles (in blue) are nested in the SO depolarizing upphase (in red) while sharp-wave ripples events (in green) occur in the troughs of spindles. Adapted and reproduced with permission from Ref. [25]. (b) Slow oscillation phase-dependent stimulus processing. Differential stimulus-evoked waveforms for up (blue) and down (red) state-presented sound stimuli for frontal channel Fz. (c) Early stimulus-evoked theta power did not differ reliably between up- and down-targeted stimuli. (d) Late spindle/beta power was higher for uptargeted sounds than for downtargeted stimuli across the entire scalp, reaching significance in a right fronto-temporal area (electrodes Fp2, F8, FC6, T8, AF8, F6 and FT8), and a left parietal region (P7 and PO7). Reliable differences are indicated with: $*p < 0.025$; $**p < 0.01$; $***p < 0.001$. Reproduced under the Creative Commons Licence Agreement from Ref. [52].

Of note, most TMR studies thus far target reactivation of neutral memories during NREM sleep; a few studies on TMR of neutral memories during REM sleep report it to be ineffective [58–60]. Similarly, evidence for a benefit of TMR on emotional memories is limited: TMR of declarative memories during NREM sleep led to a post-sleep memory retrieval benefit of emotional items but not neutral ones [60], a benefit for emotional and neutral items alike [61], or no effect [54,62,63]. In one of these studies, TMR during N2 or REM sleep did alter stimuli's emotional tone, as reflected in reduction post-sleep arousal ratings for both aversive and neutral stimuli, in the absence of a memory performance benefit [62].

Cueing emotional memories during REM sleep has only been done in three studies in humans so far, which failed to show specific retrieval benefits for emotional items [60,62,64]. One of these studies did, however, report increased response bias (i.e. increase of both correct and false recognition) for cued items as compared to not cued ones, irrespective of emotional valence [64]. Another study found decreased arousal ratings for both emotional and neutral stimuli, without effects on memory performance, similar to cueing in NREM sleep [62]. The last study did not find any benefit after cueing emotional nor neutral items [60].

In the specific context of fear conditioning, TMR has also produced inconsistent findings. An elegant study in rodents used artificial patterns of olfactory bulb stimulation as conditioned stimuli in a fear conditioning procedure [65]. Imposed post-training replay during NREM sleep enhanced subsequent memory strength, whereas the identical replay during wake induced extinction. Two other rodent studies assessed fear conditioning using sensory stimuli. In one of these, cueing with the conditioned stimulus during NREM, but not REM sleep, impaired subsequent fear memory [66], while in the other cueing during REM sleep led to increased fear memory, with a marginal increase for cueing during wake ([67]; of note, this study used mild ear shock as conditioned stimulus, which might by itself be aversive). In humans, re-presenting conditioned stimuli during NREM sleep was reported to favor extinction of fear memory, as compared to no cueing [68], but to a similar extent as during wake [69].

Phase-targeted TMR
A possible reason why TMR interventions lack stronger results might reside in the fact that memory cues are randomly presented throughout the sleep period. Indeed, it has been shown that cues evoke different responses depending on their temporal association with NREM sleep's prevailing oscillatory population dynamics [44••], and especially relatively to the phase of SOs [52,70••,71]. This may be understood considering that SOs in the EEG reflect fluctuations in underlying cortico-

thalamic networks between periods of enhanced activity, plasticity and connectivity (during SO positive half-waves) and periods of synchronized neuronal hyperpolarization (during SO negative half-waves) [52,70••,71] (Figure 4e).

As introduced earlier, the reprocessing of memories during sleep, leading to memory consolidation, is believed to be driven by SOs orchestrating hippocampo-cortical interactions [29] (Figure 3a). In particular, the SO upslope constitutes a sensitive window during which sharp-wave ripples and spindles are starting to develop, and the instantiation of a full blown pattern might be most successfully amplified [28•] or modified by external inputs [72]. Auditory stimuli presented during NREM sleep can evoke high-amplitude K-complex- or slow oscillation-like responses, with increased spindle and higher frequency activity grouped in the positive deflection [52,73,74]. Importantly, this effect is maximal when sound onset is targeted to the positive going zero-crossing of ongoing SOs ('stimulus-related up' condition), as compared to the negative going SO zero-crossing ('stimulus-related down' condition) [52] (Figure 3b–d; see Figure 4d for schematic illustration of the terminology). Accordingly, externally boosting SO and spindles, using the aforementioned auditory stimulation procedures, improves memory performance for material studied before sleep, as compared to sham stimulation, confirming their role in memory consolidation [75].

Given the aforementioned evidence, combining phase-locked stimulation with TMR paradigms seems to be the next step toward optimizing memory consolidation interventions. Indeed, if the sound stimulus evoking the SO upslope response is a memory cue, or otherwise meaningful, the evoked processing capacity might be geared to the pertaining stimulus, activating related content. Studies assessing this notion are only now starting to emerge. In one of these, participants were re-exposed to previously studied foreign vocabulary. Studied items were presented during SO up-slopes, down-slopes or not at all, in a within subject design. While a benefit of TMR was observed for upcued items compared to not cued ones, there was no significant effect of the crucial up-versus down-cueing manipulation [76]. Using a similar foreign vocabulary task, another study applied a more accurate SO phase targeting procedure, based on EEG signal modeling (Figure 4a–d): sleep-reactivation stimuli were targeted either to the positive or negative going SO zero-crossing (0° or 180°), with also a sham-up and a sham-down condition, in a between subjects design [44••,70••]. Results showed significant memory enhancement for upcued items and significant forgetting for downcued items, as compared to no cueing. Moreover, auditory stimuli locked to positive SO zero-crossings (0°) boosted SO dynamics beyond evoked K-complexes, inducing long SO trains that effectively increase the amount of deep

Figure 4
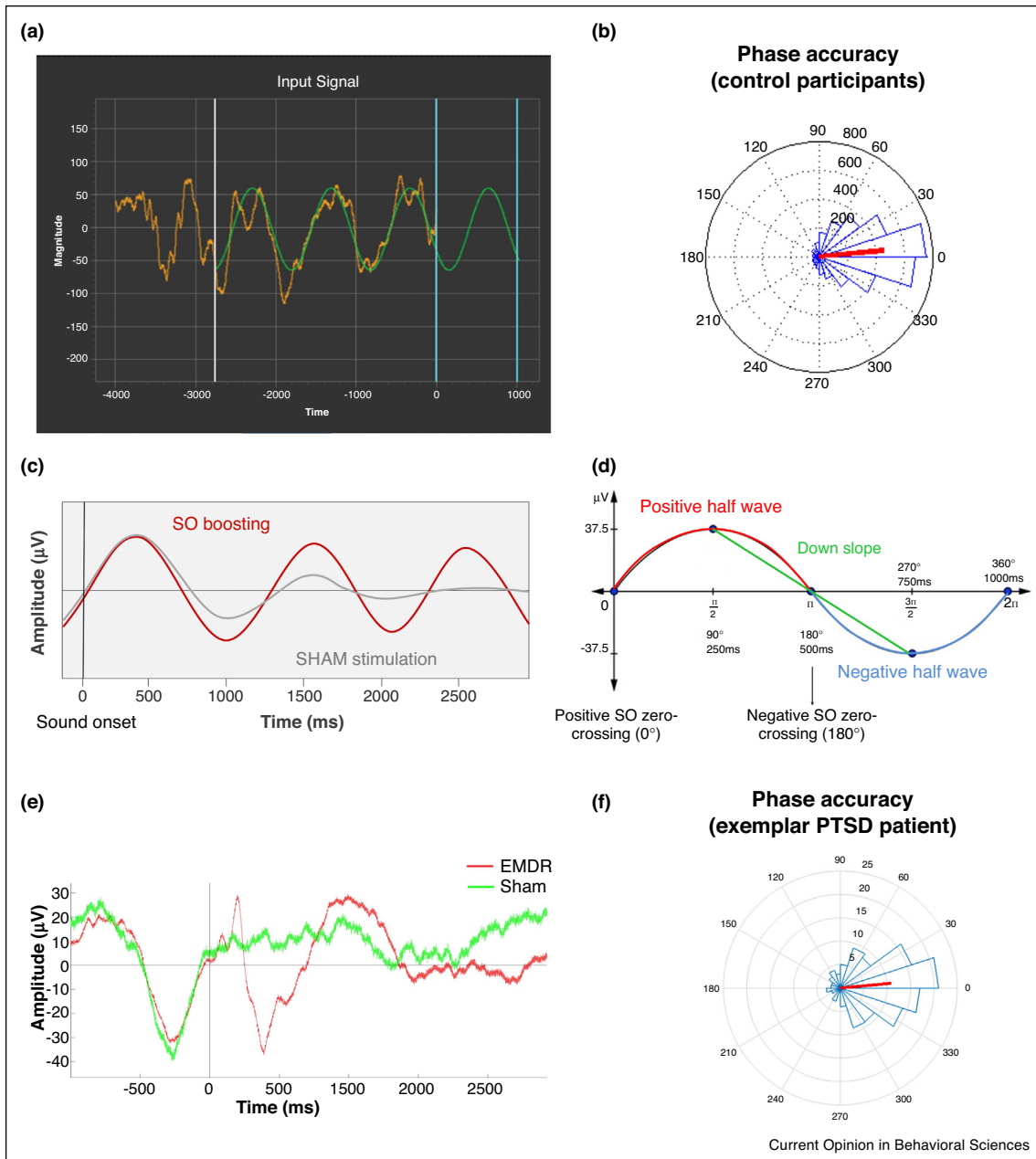
Details of the closed-loop neurostimulation method used in our lab. **(a)** Slow oscillations from the incoming EEG signal for channel Fz (in orange) are modelled in real-time using sine fitting (in green) and used to make predictions about the phase of future oscillations (between the two blue lines). **(b)** Phase targeting accuracy (targeting 0°) in young healthy subjects, for a total of 4281 predictions. Mean phase error was $5.71° \pm 50.74°$ (SD). **(c)** Auditory stimuli targeted at phase 0° of SO tend to evoke long trains of SO (in red), relatively to no stimulation (in grey). **(d)** Schematic illustration on terminology regarding features of EEG slow oscillations. In particular, the 0° phase corresponds to the positive SO zero-crossing (half-way up slope), and down slope refers to the negative going slope (in green) with 180° phase at the negative SO zero-crossing. **(e)** Representative ERP data (channel Fz) for a single PTSD patient from our ongoing study [89]. Auditory cueing during sleep was done using EMDR clicks (red trace; $n = 100$), which is contrasted to a sham condition (i.e. silence; green trace, $n = 36$). Cues were presented at 0 ms, phase-locked to the positive SO zero-crossing (0°). Presenting EMDR clicks elicited a boosting of slow oscillations, as compared to the sham condition. **(f)** Accuracy of SO targeting in the same PTSD patient, combined for EMDR and sham cues during N2 and N3 (136 predictions). Mean phase error was $5.23° \pm 56.0°$ (SD), suggesting that similar phase targeting accuracy and SO boosting performance can be reached in a population with disturbed sleep as in young healthy subjects (cf. panel **(b)**). Panels **(e)** and **(f)** courtesy of van der Heijden and van Marle [89].

sleep across the night. This global sleep deepening was confirmed in a second, independent study (paper in preparation).

These clear results contrast with previous studies and underline the importance of high precision in SO phase targeting. Since cueing can either provoke consolidation or forgetting depending on the targeted SO phase, any phase inaccuracy can dilute the effects. Therefore, the precision and general performance of automated oscillatory phase targeting procedures have to be excellent to be effective. A few methods have thus far been proposed to model human SO dynamics, with variable precision [52,70**,77], and more advanced closed-loop neural manipulations are being developed [78]. Crucial factors to achieving high performance are signal modeling – allowing adaptation to the high temporal variance of electrophysiological signals (introduced in Ref. [52]) – and minimizing lag in the closed hardware-software loop — during which the physiological signal can deviate from the model. Another point that could explain these better results regards the use of single sound stimuli rather than repeated, rhythmic ones. A single, precisely timed stimulus induces a train of SOs and spindles with their own intrinsic dynamics (Figure 3b–d, Figure 4c) that may be disturbed by subsequent stimulations [79]. Accordingly, silent periods after cueing seem necessary for efficient memory consolidation [56,80,81•].

Given the instrumental role of SOs in orchestrating memory reprocessing, future TMR studies should consider carefully how their cues align with on-going oscillatory activity. In addition, while phase-locked stimulation has mostly been performed on SOs during NREM sleep periods, it is in theory possible to apply the same technique to other types of oscillations. For instance, the rhythmic slow activity or slow theta dynamic of ~3 Hz, which occurs in the human hippocampus during REM sleep and waking, has been shown to synchronize across brain regions and may serve similar activity coordinating functions to SOs in NREM sleep [33]. Closed-loop neuro-manipulations could play a unique role in uncovering the fundamental role of these oscillations in information processing, and in exploring new avenues for sleep and memory interventions.

Toward new treatment strategies for sleep and affective disorders

Besides their scientific relevance, findings on sleep and memory manipulation have instigated exciting potential applications, especially with regard to affective disorders. It might be for instance possible to modify derailed trauma memories in PTSD, extinguish maladaptive stimulus reward association in addiction, or alter fear associations in phobias. Moreover, acting on sleep quality to relieve sleep impairments could by itself be effective, by re-engaging the normal functions of sleep in emotional housekeeping.

Indeed, treating co-morbid insomnia seems to improve affective symptoms in depressive patients [82]. However, so far non-pharmacological treatment options for insomnia are limited, moderately effective and resource intensive, while pharmacological treatments have not demonstrated long-term efficacy and are accompanied by side effects including disturbed sleep architecture and risk of addiction. A new, low-cost, non-invasive treatment that could safely be used by patients in the home environment would, therefore, be of considerable societal interest. Current efforts regarding sleep enhancement include vestibular stimulation through gentle rocking [83,84], transcranial electrical stimulation or transcranial magnetic stimulation (TMS) [85], but closed-loop neurostimulation of the SO dynamic seems the most promising approach, given its portability and ease of use [86].

With regard to the possibility of modifying maladaptive memories, evidence is still scarce. A first study in rodents, applying intracranial rewarding stimulation anytime a specific place cell fired during sleep, was able to ascribe an emotional valence to the corresponding spatial location and thus influence the animal's goal-directed behavior during subsequent wake [87]. In humans, using aversive conditioning to reduce addictive smoking gave encouraging results: pairing a highly aversive odor with cigarette smoke smell during NREM 2 reduced cigarette smoking by approximately 30% in the following week [88]. Using closed-loop neurostimulation, our group is currently conducting a study aimed at modifying trauma memories in PTSD [89]. Despite limited efficacy, the first choice treatment of PTSD is eye movement desensitization and reprocessing (EMDR) therapy, during which traumatic memories get reactivated and subsequently re-encoded with lower fear. Hoping to improve its efficacy, we present auditory cues from the EMDR session during the following night, time-locked to SOs' positive zero-crossing. This should facilitate the consolidation of the newly acquired EMDR memories, while stabilizing and deepening sleep. Preliminary findings show that SO modeling and oscillatory phase targeting is accurate despite the reduced SO power in these patients [90**] and result in similar stimulus-evoked responses as in healthy subjects (Figure 4e–f).

While evidence is as yet limited, it can be envisaged that the sleep state might present with possibilities for therapeutic intervention that are not available during wake. For instance, during sleep the prefrontal cortex is less active and information processing less goal-directed than during wake. This is reflected in sleep mentation (dreams), which can feature inconsistencies and bizarre components without generating a notable conflict response. These conditions might favor acceptance of

external influences and facilitate associations and insights [91], creating ideal circumstances to modify existing memories.

To conclude, auditory closed-loop sleep manipulations offer unique possibilities to investigate the function of neural activity components, but also new avenues toward non-invasive, low-cost approaches to the treatment of sleep, affective and memory disorders [43,44••]. Developments in the field are progressing fast, in particular with regard to emotional memory research. These developments will likely contribute to fundamental knowledge on the nature of sleep-emotional memory interactions and pave the way to new sleep-based approaches to diagnose, treat and even prevent affective disorders.

Conflict of interest statement

CRediT authorship contribution statement

Lucia M Talamini: Conceptualization, Visualization, Writing - review & editing, Supervision. **Elsa Juan:** Conceptualization, Visualization, Writing - original draft, Investigation.

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