Beta spectral power during sleep is associated with impaired recall of extinguished fear

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Abstract

Background: The failure to retain memory for extinguished fear plays a major role in the maintenance of post-traumatic stress disorder (PTSD), with successful extinction recall necessary for symptom reduction. Disturbed sleep, a hallmark symptom of PTSD, impairs fear extinction recall. However, our understanding of the electrophysiological mechanisms underpinning sleep's role in extinction retention remain underdetermined.
Methods: We reanalyzed data from two existing datasets examining the relationship between the microarchitecture of sleep and extinction recall in healthy controls (Study 1, n = 46) and a pilot study in individuals with PTSD (Study 2, n = 12). In both studies, participants underwent a fear conditioning and extinction protocol over the course of two days, with polysomnography sleep recording occurring between conditioning and extinction. Twenty-four hours after extinction learning, participants underwent extinction recall. Power spectral density (PSD) was computed for NREM and REM sleep during both pre- and post-extinction learning.
Results: Increased PSD in frequencies spanning the canonical beta band during pre-extinction learning sleep were associated with worse extinction recall in healthy participants (r = .41, p = .004). Beta PSD was shown to be highly stable across three nights of sleep (NREM intraclass correlation (ICC) = 0.93; REM ICC = 0.94). Individuals with PTSD were found to have increased beta PSD compared to healthy controls (NREM: p = .038; REM: p = .007), and beta PSD correlated with extinction recall in the PTSD group at a similar magnitude to controls (r = .39).
Conclusions: The present findings suggest that beta band PSD may be a trait-like feature of the sleep EEG that is heightened in PTSD and associated with impaired fear extinction recall. Thus, beta PSD during sleep may reflect a trait marker for vulnerability to PTSD, specifically implicated in difficulties recalling extinguished fear.

Keywords: Memory, fear conditioning, extinction, PTSD, sleep, beta power

Introduction

Post-traumatic stress disorder (PTSD) is an emotional disorder characterized by a hyperarousal syndrome that impacts both daytime functioning and sleep (American Psychiatric Association, 2013). PTSD has been described as a disorder of emotional learning and memory that can be modeled experimentally using Pavlovian aversive conditioning paradigms (Milad & Quirk, 2012; Pace-Schott et al., 2015). In these paradigms, aversive stimuli (e.g., finger shocks or air puffs to the throat) are paired with neutral stimuli (e.g., colored lights), generating a conditioned fear response that can be measured using psychophysiological measures such as skin conductance or the blink-startle response. This learning process parallels the fear learning in PTSD, whereby neutral situations, locations or objects become associated with an aversive outcome (i.e., the index trauma). Fearful responses to non-threatening stimuli can be overcome by a process of extinction learning, whereby individuals are repeatedly presented with conditioned stimuli in the absence of the aversive outcome. Memory for learned extinction attenuates fear responses (Pace-Schott et al., 2015) and is necessary for PTSD symptom reduction (Foa et al., 2019).

Sleep disturbances are considered a hallmark feature of PTSD (Germain, 2013) present in approximately 70% of patients (Ohayon & Shapiro, 2000). Sleep quality in PTSD is often highly variable from night to night (Straus et al., 2015). Meta-analytic evidence suggests that those with PTSD exhibit reduced total sleep time, decreased sleep efficiency, increased time spent in light non-rapid eye movement sleep (i.e., NREM stage 1), reduced time spent in slow wave sleep, and increased rapid eye movement (REM) density (Kobayashi et al., 2007; Zhang et al., 2019).

A growing body of research has linked sleep to extinction memory processes. The retention of extinction memories has been linked to the sleep that occurs both following (Bottary et al., 2020; Pace-Schott et al., 2015) and prior (Straus et al., 2017) to extinction learning. Evidence for the former has come from studies of healthy, good sleeping participants, suggesting a role of post-extinction REM duration and quality being associated with fear extinction retention (Bottary et al., 2020; Pace-Schott et al., 2014; Schenker et al., 2021; Spoormaker et al., 2010, 2012). Furthermore, cueing fear memories during NREM sleep also promotes fear extinction retention (Hauner et al., 2013; He et al., 2015). Additionally, sleep disturbances *prior* to extinction learning can disrupt later recall of extinguished fear. Using a total sleep deprivation design, sleep deprivation prior to extinction learning impairs the retention of extinction memory without impairing the initial acquisition of extinction (Straus et al., 2017). Notably, sleep deprivation *after* extinction learning did not lead to any impairment in subsequent extinction retention (Straus et al., 2017). This line of work suggests that sleep prior to extinction learning may be important in preparing the brain for the consolidation of new learning.

Theta (~4-7Hz) oscillatory power during REM sleep has been linked to emotional memory processing during sleep in some studies (Kim et al., 2019; Marquis et al., 2017; Nishida et al., 2009; Schäfer et al., 2020; Sopp et al., 2017), though this association has not been found (Davidson et al., 2021). Theta power has been shown to be elevated in trauma-exposed individuals who were resilient to, compared to those diagnosed with, PTSD (Cowdin et al., 2014; though see Denis et al., 2021). Similarly, electroencephalographic spectral power in in the beta frequency range (~20-30Hz) during sleep has also been shown

to be elevated in PTSD compared to those without PTSD (de Boer et al., 2020; Germain et al., 2006; Wang et al., 2020; Woodward et al., 2000), and has been theorized as a marker of hyperarousal (Hall et al., 2007; Krystal et al., 2002; Perlis et al., 2001; Riedner et al., 2016; Spiegelhalder et al., 2012). In contrast however, beta power during sleep has also been associated with reduced risk of PTSD development (Mellman et al., 2007) and reduced symptomatology in healthy participants and those with PTSD (Denis et al., 2021). The role of beta power in the consolidation of extinction memories is yet to be investigated. Thus, it remains unclear if and when elevated sleep beta power is harmful or helpful to the processing of traumatic experiences.

Taken together, these literatures provide converging evidence for a critical role of sleep in fear extinction retention, and that sleep disturbances in PTSD may play a key role in the difficulty for these individuals to retain memories of extinguished fear and thus maintain disordered symptoms. Although many studies have linked alterations in sleep spectral power with PTSD symptomatology, spectral power correlates of fear extinction recall in PTSD remain unknown. The goal of this report was to examine whether sleep oscillatory activity that is altered in PTSD, such as theta and beta spectral power, impact the basic fear memory processes that are implicated in PTSD development, such as the retention of extinction memories.

Given recent evidence for the importance of the sleep period prior to extinction learning for extinction memory retention, in this report we first examined associations between pre-extinction learning sleep spectral power and extinction recall in an existing dataset of healthy controls (Straus et al., 2017). As a secondary analysis, we also examined associations with *post*-extinction learning sleep spectral power, on the basis of other work showing sleep macroarchitecture correlations (Bottary et al., 2020; Pace-Schott et al., 2014; Schenker et al., 2021; Spoormaker et al., 2010, 2012). This approach allowed us to examine, for the first time, the relative contributions of pre- and post-extinction learning sleep spectral power for extinction recall. Finally, utilizing a second pilot dataset (Straus et al., 2018) we examined whether similar associations were present in a sample of individuals with PTSD.

We predicted that across all participants, greater theta-band spectral activity during REM sleep would be associated with better extinction recall, given previous links between extinction recall and REM architecture, and between REM theta power and emotional memory in general. We also predicted that greater beta-band spectral activity during sleep would be associated with poorer subsequent recall of extinguished fear. As beta power may be an indicator of disturbed sleep, we anticipated these associations would be stronger for pre-extinction compared to post-extinction learning sleep, on the basis that experimental sleep disturbance only appears to impact extinction recall when pre-extinction learning sleep is disrupted (Straus et al., 2017). Finally, we expected that the pilot group of individuals with PTSD (Straus et al., 2018) would show decreased theta and increased beta activity during NREM and REM sleep compared to a group of healthy good sleepers, and that associations between beta power and extinction recall would also exist in the PTSD group.

Study 1

Methods

Note that this study was a reanalysis of a previously published dataset (Marshall et al., 2014; Straus et al., 2017) of healthy controls. All analyses reported here were novel. The University of California, San Diego's Human Research Protections Program approved the study.

Participants

Seventy-three healthy adults were enrolled in the study. Of those, 2 participants with incomplete datasets were removed, leaving a total of 71 participants in the final analysis. Following written informed consent, participants underwent a screening for sleep disorders, drug use, psychiatric, and medical disorders via structured clinical interview and laboratory testing. Inclusion criteria for participants were: 1) aged 18-39 years old; 2) regular sleep-wake schedule including 7-9 hours in bed with a bedtime of 10pm-midnight and a wake time of 6-8am; 3) no current medical or psychiatric diagnoses; 4) no personal history of any Axis 1 diagnosis or family history of mood or psychotic disorders; and 5) exhibited a consistent blink-startle response at screening (over 75% discernible responses to twelve 105dB 40ms startle pulses). Female participants completed the experimental sessions in the early follicular phase of the menstrual cycle.

Procedure

Participants maintained a regular sleep-wake schedule, matching their self-reported habitual schedule, at home for seven days. Adherence was monitored via actigraphy, voicemail call-ins, and sleep diaries. Participants then spent 4 consecutive days and nights in the sleep laboratory (**Figure 1A**), where they underwent a fear potentiated startle (FPS) procedure (see below). Following an adaptation night of sleep in the laboratory, the FPS consisted of three sessions: fear acquisition (day 1); fear extinction learning (day 2); and fear extinction recall (day 3, the focus of the present analysis). All testing took place in the evening, 10-12 hours after participant's habitual final awakening time. All testing took place in the same context. Participants were randomized to one of three conditions: 1) a normal sleep condition consisting of a full night of sleep on all experimental nights (n = 21); 2) 36 hours of total sleep deprivation after extinction learning ("post-extinction deprivation", n = 25) or 3) 36 hours of total sleep deprivation before extinction learning ("pre-extinction deprivation"; n = 25). Data from groups 1 and 2 were focused on for this analysis. Participants were not allowed to leave the laboratory during the study period, engage in strenuous exercise, and were not permitted to consume alcohol, caffeine, or other stimulants beginning 48 hours before entering the laboratory. Sleep was monitored using polysomnography (PSG) including electroencephalography (EEG), electrooculography (EOG), and chin electromyography (EMG). To screen for unreported sleep apnea and periodic leg movements during sleep, additional monitors were added on the adaptation night.

Fear potentiated startle

Each session began with six startle pulses (108db, 30ms acoustic startle probes) presented in the absence of any other stimuli in order for participants to acclimate startle responses. The fear acquisition session on day 1 consisted of 1) eight 6-second long presentations of a blue circle (CS+), following by a 500 ms electric shock (US) in 75% of blue circle trials; 2) eight 6-second presentations of a red circle serving as a second CS+, also followed by a 500

ms electric shock US in 75% of trials; 3) sixteen 6-second presentations of a yellow circle serving as a non-reinforced conditioned stimulus (CS-), never followed by a shock; and 4) 16 presentations of the startle pulse in the absence of any stimuli (noise only; NA). The first half of the acquisition session consisted of only blue CS+ trials, and the second half consisted of only red CS+ trials. Startle pulses were presented 4 seconds following CS+ or CS- onset. Stimulus presentation was randomized within each CS+ acquisition block (blue vs red) and with the constraint of the two trials of each type (CS+, CS-, and NA) per block. On day 2, participants underwent extinction learning, consisting of 16 presentations of each stimulus type (blue CS+, yellow CS-, blank screen) in a block randomized order as in the acquisition session. No shocks were presented during this session. On day 3, participants completed extinction recall. This session was identical to the fear acquisition session except no shocks were delivered.

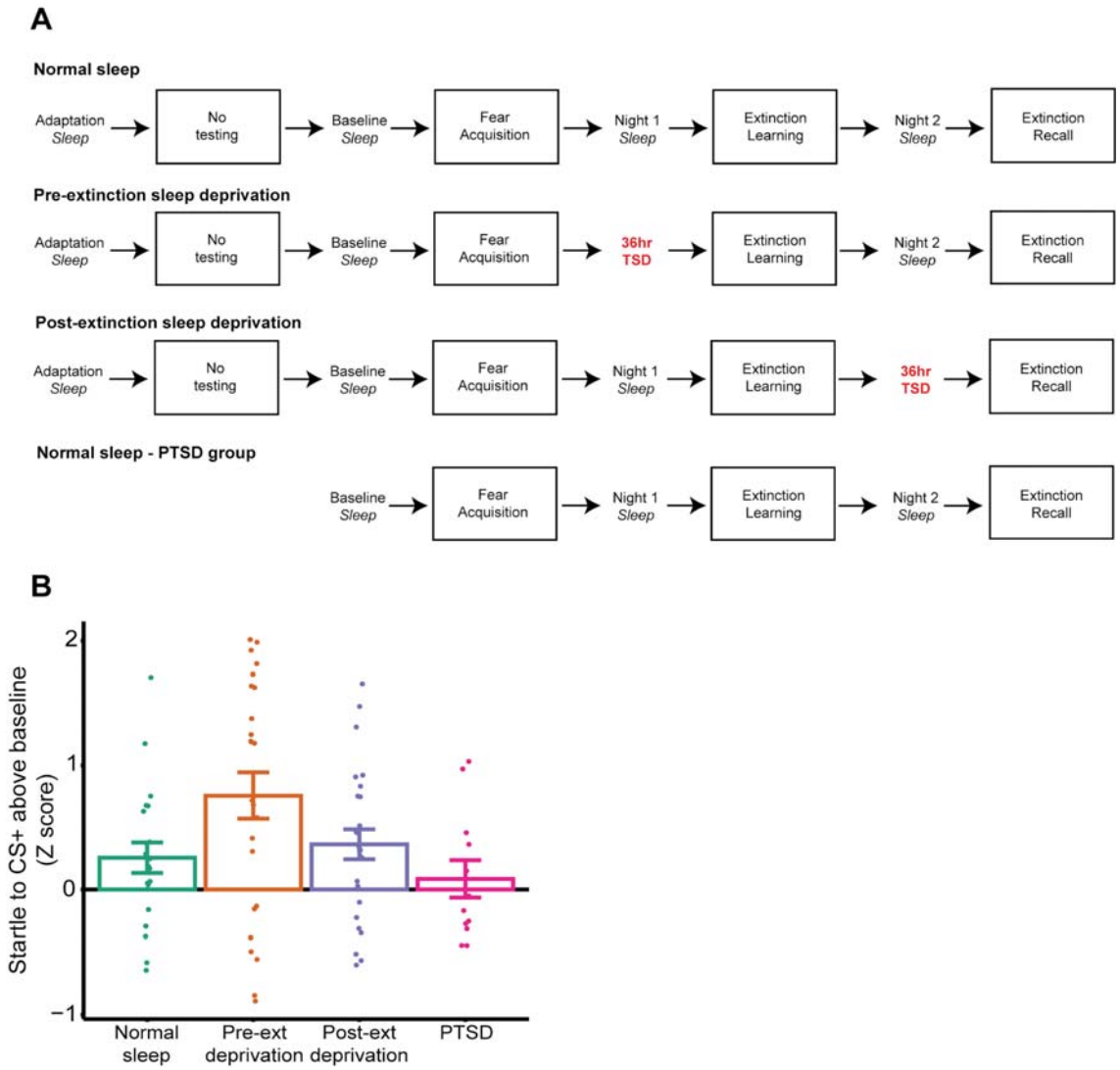

Figure 1. Experimental design and behavioral results. **A** - Study timeline for each group. **B** - Fear extinction recall, displayed as the startle response to CS+ above baseline (Z score). Note that the PTSD sample performed a different fear potentiated startle protocol. Error bars indicate the between-subject standard error.

Fear extinction recall analysis

Eyeblink electromyogram (EMG) responses were recorded and used to index startle responses. EMG data were recorded at sampling rate of 1000Hz, band-pass filtered (100-1000Hz), rectified and then smoothed with a five-point rolling average. Blink responses were examined on a trial-by-trial basis -100 - 200ms around the pulse. Only responses that peaked within 100ms of the pulse were scored as a startle response.

Initial data reduction involved averaging responses to CS+ and CS- trials within each session into blocks of two trials each. Blank screen trials within a session were averaged to acquire a baseline startle response. This baseline was then subtracted from the respective CS+ and CS- block within each session, creating scores representing potentiated startle above baseline for each CS type within each block. Note phases of the acquisition and recall sessions that contained blue or red CS+ were analyzed separately. To reduce between-subjects variability created by individual differences in startle magnitude overall, each individual participant's blocks were standardized into Z-scores such that all scores represented departure from each individual's mean level of potentiated startle across the entire experiment. Fear extinction recall was quantified as the initial fear response to the blue CS+ (first 4 recall session CS+ Z-scores) averaged together during the extinction recall session on day 3.

Polysomnography

Polysomnography (PSG) recordings consisted of six electroencephalogram (EEG) channels (electrode positions F3, F4, C3, C4, O1, O2) referenced to contralateral mastoids (M1, M2), 2 electrooculogram (EOG) channels, and 2 submental EMG channels. Signals were recorded at 200 Hz, and subsequently exported with a 0.3-35 Hz band pass filter (plus 60 Hz notch filter) for sleep scoring. All nights of sleep were scored in accordance with American Academy of Sleep Medicine guidelines (Iber et al., 2007).

Power spectral density

First, artificial epochs of PSG data were detected using an automated algorithm. For each frontal (F3, F4) and central (C3, C4) channel we calculated per-epoch summary metrics of three Hjorth parameters (signal activity, mobility, and complexity; Hjorth, 1970). Any epochs where at least 1 channel was > 3 standard deviations from the mean on any of the three Hjorth parameters was marked as an artifact and removed from subsequent analysis (Purcell et al., 2017). Artifact detection was performed twice (in case of extreme outlying epochs), and performed separately for each sleep stage (given the inherent differences in the EEG signal between sleep stages). The power spectral density (PSD) was estimated at each frontal (F3, F4) and central (C3, C4) electrode for all artifact-free sleep, separately for NREM (N2 + N3) and REM. PSD was estimated using Welch's method with 5s windows and 50% overlap. To minimize the typical 1/f scaling of the EEG power spectrum, estimates were obtained from the temporal derivative of the EEG time series (Cox et al., 2017; Denis et al., 2021). Given that signal amplitude is at least partly driven by individual difference factors such as skull thickness and gyral folding (Cox & Fell, 2020), we then normalized, within participant, each electrode's power spectrum by dividing power at each frequency by that

electrode's average power (Cunningham et al., 2021; Denis et al., 2021). PSD estimates from the two frontal channels were averaged together to get an average estimate of frontal spectral activity, and PSD estimates from the two central channels were averaged together to obtain an average of central activity. PSD estimates from 0-30 Hz were subjected to further statistical analysis.

Statistical analysis

Our primary analysis examined the relationship between PSD on Night 1 (i.e. prior to extinction learning), and the recall of extinguished fear on Day 3. We focused on this night due to previous reports using this dataset showing that sleep deprivation prior to extinction impaired later recall (Straus et al., 2017). Given that markers of sleep spectral power may relate to sleep disturbances, we reasoned that sleep on the pre-extinction learning night may be the most important for subsequent extinction recall. As a secondary analysis, we performed the same analysis using the Night 2 (i.e. post-extinction learning, pre-extinction recall) PSD estimates, again correlating them with extinction recall on Day 3.

Statistical analysis of PSD estimates were primarily performed using cluster-based permutation testing, implemented in the FieldTrip toolbox for MATLAB (Oostenveld et al., 2011). This approach allowed us to take the full power spectrum into account (and thus preserve its continuous nature), while simultaneously controlling for multiple comparisons. This approach was used to test for the presence of correlations between PSD and fear extinction recall (using the *ft_statfun_correlationT* function) with the following parameters: 10,000 iterations, a *clusteralpha* of 0.05 with the default *maxsum* method to determine cluster significance, and a significance threshold of 0.05. PSD in the range of 0-30 Hz was included in the analysis (e.g. Denis et al., 2021). Separate tests were performed for NREM and REM sleep. To better visualize significant correlations, scatterplots were also created. For these, PSD at each frequency that formed part of a significant cluster was averaged together to provide a single value for the purpose of visualization in the scatterplot. We report on PSD estimates from averaged central channels, though we note that primary results were largely unchanged when using PSD estimates from averaged frontal channels.

Results

Extinction recall across the groups are shown in **Figure 1B**. Note that group differences in extinction recall in the healthy control sample have been previously reported elsewhere (Straus et al, 2017), but we re-summarize them here. Extinction recall was significantly impaired in the pre-extinction sleep deprivation group compared to the normal sleep group (t (44) = -2.15, $p < .04$, $d = 0.65$). The post-extinction sleep deprivation group did not differ in extinction recall compared to the normal sleep group (t (44) = -0.53, ns, $d = 0.16$).

We next turned to the relationship between sleep spectral power and extinction recall. We first examined how sleep spectral power in participants who *did* sleep following fear acquisition and prior to extinction learning was associated with subsequent recall of extinguished fear (i.e. the pre-extinction sleep deprivation group was excluded from this analysis). During NREM sleep, a significant positive correlation cluster was found for frequencies in the beta band (16.99-23.63 Hz; $t_{cluster} = 101.19$, $p = .013$), indicating that greater beta PSD during NREM sleep was associated with *worse* recall of extinguished fear (**Figure 2A**). This translated to a cluster-averaged correlation of $r = .41$, $p = .004$ (**Figure**

2B). With regards to REM sleep, a near identical pattern emerged. For REM sleep during the post-acquisition night, a significant correlation cluster was found for beta band frequencies ranging from 19.34-25.97 Hz ($t_{cluster}$ = 92.63, p = .014; **Figure 2C),** with a cluster-averaged correlation coefficient of r = .41, p = .004; **Figure 2D**).

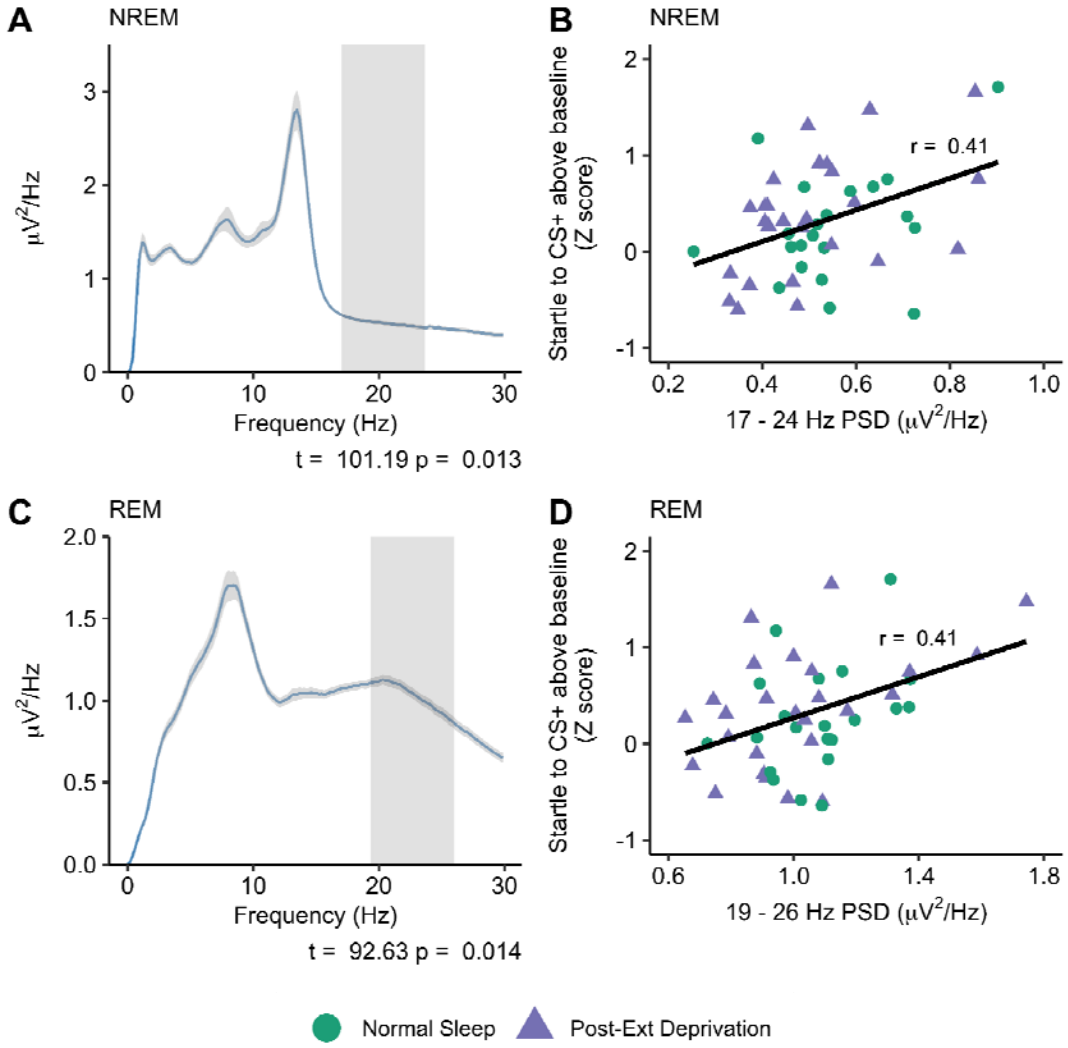

Figure 2. Beta power during pre-extinction learning sleep is associated with impaired extinction recall. **A** - NREM power spectrum. Frequencies showing a significant correlation with extinction recall (cluster-corrected) are highlighted in gray. Shaded area around the line indicates the between-subject standard error. **B** - Scatterplot illustrating the relationship between cluster-averaged NREM PSD and fear extinction recall. **C** - REM power spectrum. Frequencies showing a significant correlation with extinction recall (cluster-corrected) are highlighted in gray. Shaded area around the line indicates the between-subject standard error. **D** - Scatterplot illustrating the relationship between cluster-averaged REM PSD and fear extinction recall.

As a secondary analysis, we ran additional correlations between beta-band spectral power during the *post*-extinction night and subsequent extinction recall. This analysis was conducted separately in the normal sleep condition and the pre-extinction learning deprivation group, as the latter group was recovering from sleep deprivation which may have impacted the macro- and micro-architecture of the sleep period. In the normal sleep group, the correlation between beta-band PSD and extinction recall was in the same direction, but

not statistically significant (NREM: $r = .34$, $p = .132$; REM = $r = .42$, $p = .060$), potentially due to the reduced statistical power. In the pre-extinction learning sleep deprivation group, the correlation between beta power and extinction recall was not statistically significant, and showed either no (REM post-extinction night: $r = .09$, $p = .667$) or a non-significant *negative* relationship (NREM post-extinction night: $r = -.30$, $p = .148$).

Taken together, these results suggest that heightened beta power during both NREM and REM sleep are associated with a worse ability to successfully recall extinguished fear, and high levels of beta power during sleep can exert a similar negative effect on extinction recall as sleep deprivation. Notably, the effects of sleep on extinction recall were significant only during the night pre-, as opposed to post-, extinction recall.

Given this distinction, we were curious as to whether beta PSD estimates were stable across nights, which would suggest it to be a trait-like feature of the sleep EEG. Using the normal sleep group, we were able to investigate the stability of sleep beta activity across the three experimental nights (Baseline, Night 1, Night 2; both sleep deprivation groups were excluded from this analysis). There was no significant difference in beta power between the three nights for either NREM (F (2, 40) = 0.68, $p = .512$, $np^2 = .033$) or REM (F (2, 40) = 1.88, $p = .166$, $np^2 = .086$) sleep (**Figure 3A-B**). Next, intraclass correlation coefficients (ICC) were used to quantify the level of similarity of an individual's beta power across the three nights. ICCs were found to be very high (NREM ICC = 0.93 [95% CI: 0.87, 0.97]; REM ICC = 0.94 [0.89, 0.97]), indicating a high agreement in beta PSD across nights (see **Figure 3C-D** for illustrative examples). These results show that estimates of beta spectral power were highly consistent across the three nights of sleep.

Interim discussion

Our primary finding from Study 1 was that beta-band spectral power during pre-extinction learning sleep is associated with inhibited fear extinction recall. This finding in healthy controls has important implications for psychiatric conditions such as PTSD. These individuals have been shown to exhibit higher spectral power in the beta range compared to healthy controls (Wang et al., 2020), and also have been documented to have difficulty recalling extinguished fear (Milad et al., 2009). To our knowledge, no previous research has tried to link these two processes. To investigate this possibility, we examined sleep spectral power and associations with extinction recall in an existing sample of individuals with PTSD (Straus et al., 2018).

Study 2

Methods

Note that this study was a reanalysis of a previously published dataset (Straus et al., 2018) of individuals with PTSD. All analyses reported here were novel. The VA Internal Review Board as well as the University of California, San Diego's Human Research Protections Program approved the study.

Participants

Study 2 participants were 15 Veterans with a primary diagnosis of PTSD. Of these, two participants who did not complete the full protocol, and one participant with unsuitable EEG data (high levels of noise) were removed, leaving a total of 12 participants. The following inclusion criteria were applied: 1) no history of mania and/or psychosis; 2) no history of a substance use disorder in the 6 months prior to the study; 3) no untreated sleep disorders other than insomnia and nightmares; 4) no change in type and/or dosage of psychotropic medication in the preceding two months; 5) no history of severe TBI; 6) no color blindness; and 7) exhibited a consistent startle response at screening (over 75% discernable responses to twelve 105dB 40ms startle pulses).

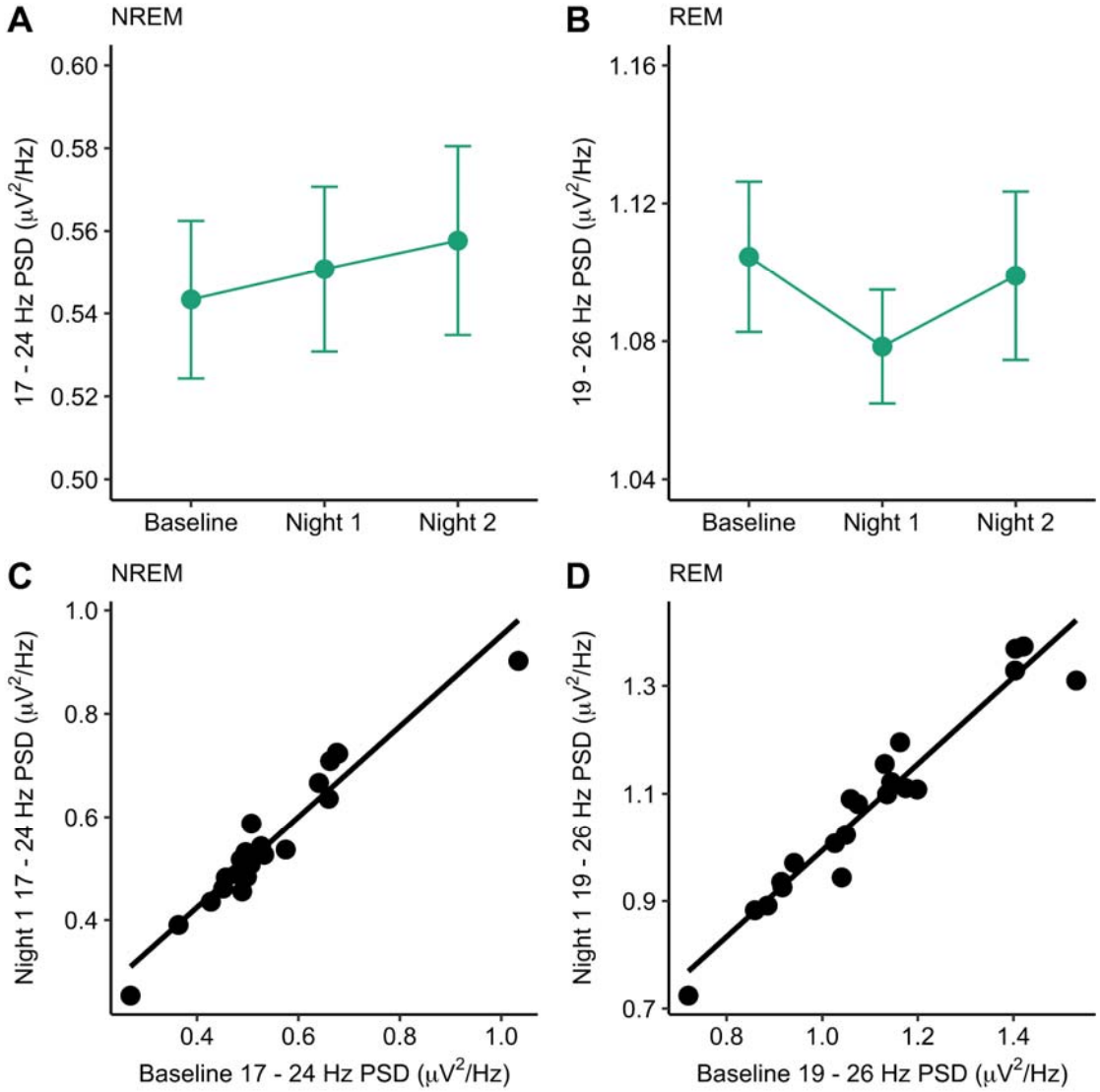

Figure 3. Beta power during sleep is trait-like. **A** - Beta power during NREM sleep across three nights in the normal sleep group. **B** - Beta power during REM sleep across three nights in the normal sleep group. **C** - Correlation between NREM beta power during the baseline night and during night 1 (pre-extinction learning). **D** - Correlation between REM beta power during the baseline night and during night 1 (pre-extinction learning). Error bars indicate the within-subject standard error.

<u>Procedure</u>

Participants first underwent baseline sleep monitoring at home, during which sleep was monitored via actigraphy and sleep diaries. Participants then spent three consecutive nights in the laboratory with PSG monitored sleep (**Figure 1A**). The first night served as an adaptation night, which was also used to screen for unreported sleep apnea and periodic leg movements. This was followed by the same study timeline as the normal sleep condition in Study 1 (**Figure 1A**). There were no sleep deprivation conditions in Study 2.

Fear potentiated startle

Fear acquisition started with the same six trial acclimation period as Study 1. Following acclimation, participants were exposed to: 1) eight 6-second long presentations of a blue circle (CS+), paired with an air puff (US) to the throat in 75% of trials; 2) eight 6-second long presentations of a yellow circle that was never paired with an air puff (CS-); and 3) 8 presentations of the startle pulse in the absence of any stimuli. Stimulus presentation was block randomized with the constraint of two trials of each type per block. On day 2, participants underwent extinction learning, consisting of 16 presentations each of CS+, CS-, blank screen along with startle pulses but without any air puffs being delivered. On day 3, participants performed the extinction recall session. This session followed the exact same procedure as initial fear acquisition, except no air puffs were delivered.

Statistical analysis

Methods regarding the analysis of fear extinction recall, polysomnography, and calculation of PSD estimates were identical to Study 1. To test for group differences in spectral power between the healthy controls from Study 1 (groups 1 and 2 only) and the PTSD group, the same cluster-based permutation framework was followed except the *ft_statfun_indepsamplesT* function was used to compare two between-subjects groups. Again, PSD estimates at frequencies spanning 0-30Hz were included in the analysis. Because our analysis of healthy controls in Study 1 only found significant associations between beta PSD and extinction retention during the pre-extinction learning night, we focused our analyses of the PTSD group solely on pre-extinction learning sleep.

Results

The PTSD sample did not differ significantly in terms of extinction recall from the normal sleep group (t (24.6) = 0.88, p = .39, d = 0.31), and showed significantly better extinction recall compared to the pre-extinction sleep deprivation group (t (34.1) = 2.80, p = .008, d = 0.89; **Figure 1B**), though we note the differences in FPS procedure between the healthy control and patient study (see Methods).

We next assessed group-level differences between healthy controls and the PTSD group. Replicating previous research, we found significant clusters of higher PSD in the beta frequency range in PTSD relative to controls during both NREM (15.82-21.48Hz; $t_{cluster}$ = 81.13, p = .038; **Figure 4A**) and REM (17.58-23.83Hz; $t_{cluster}$ = 105.15, p = .007; **Figure 4B**) sleep. In addition to these beta-band clusters, cluster-based permutation testing also revealed significantly lower high theta/low alpha REM PSD in PTSD (7.03-10.94Hz; $t_{cluster}$ = 68.03, p = .030) and a trend for reduced low frequency PSD during NREM sleep (0.59-2.73Hz; $t_{cluster}$ = 32.26, p = .096). Finally, we correlated cluster-averaged beta power (i.e. beta-band frequencies which significantly differed between the groups) with fear extinction

recall. For the NREM cluster, a positive correlation with a magnitude similar to the healthy controls was observed (PTSD: r = .39, p = .214; Healthy controls: r = .37, p = .011; **Figure 4C**). The lack of statistical significance in the PTSD group may be attributed to the small sample size. We did not observe a correlation between beta power during REM sleep and extinction recall in the PTSD sample (r = .12 p = .704; Healthy controls: r = .37, p = .011; **Figure 4D**).

Finally, we examined whether PSD estimates in the frequency band associated with impaired extinction recall is also a stable, trait-like measure in PTSD. As with healthy controls, beta spectral power was found to be highly stable across all three nights in PTSD (NREM: ICC = .92 [95%CI: .78, .98], REM: ICC = .94 [.87, .97]). In summary, this provides the first, albeit highly preliminary, evidence that beta frequency activity during sleep, characteristic of PTSD sleep, is indeed associated with the often documented deficit in fear extinction recall seen in this group. This finding will of course have to be replicated in larger samples.

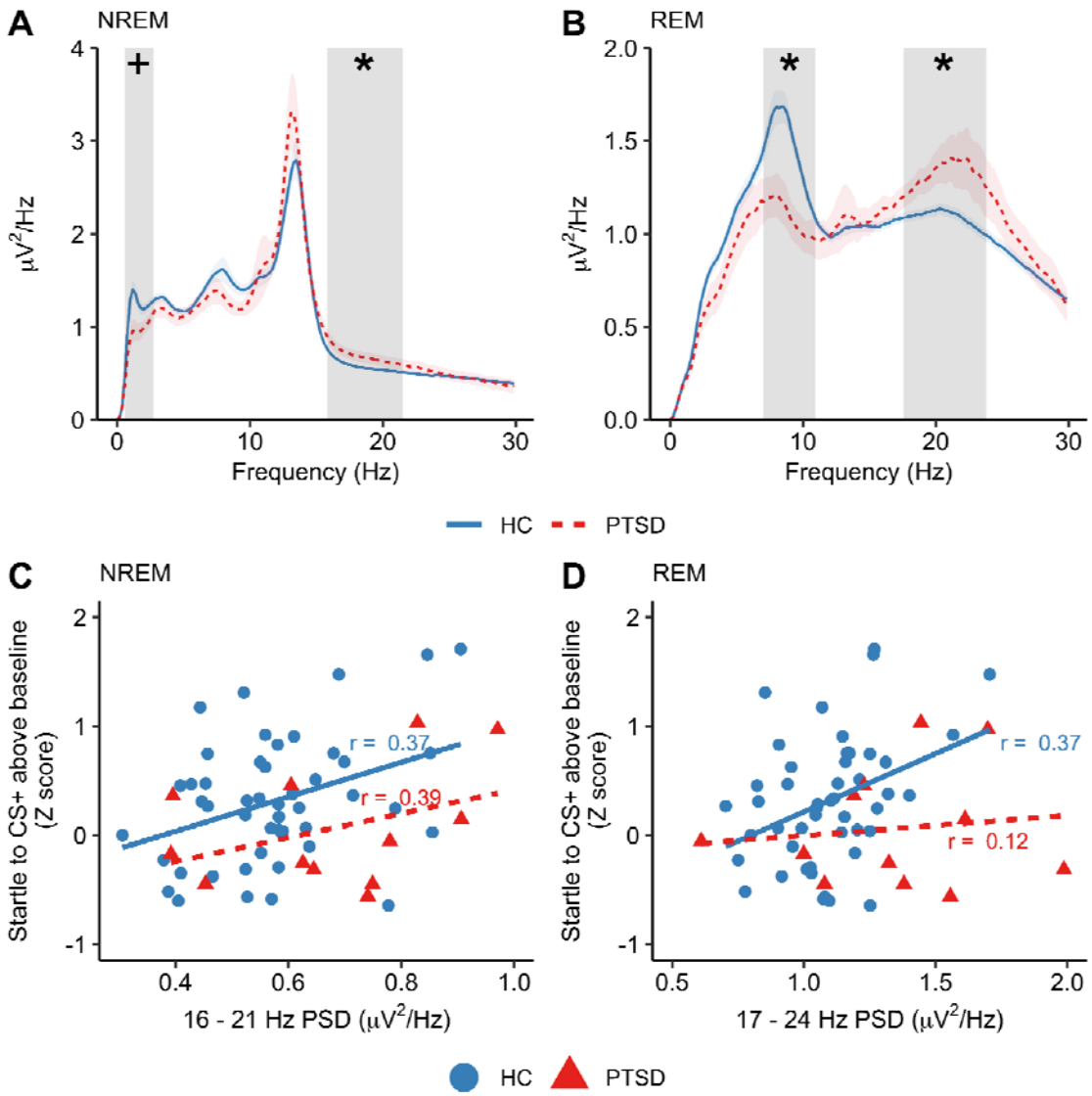

Figure 4. Spectral power differences in PTSD. **A** - NREM power spectrum. Significant group differences between healthy controls and PTSD highlighted in gray. Shaded areas around the line indicate the between-subject standard error. **B** - REM power spectrum. Significant group differences between healthy controls and PTSD highlighted in gray. Shaded areas around the line indicate the between-subject standard error. **C** - Correlation between NREM beta and extinction recall in healthy controls (solid blue line) and PTSD (dashed red line). **D** - Correlation between REM beta and extinction recall in healthy controls and PTSD. * = $p < .05$, + = $p < .10$.

Discussion

The current study, a reanalysis of existing datasets, investigated the association between sleep spectral power and the ability to recall extinguished fear. In Study 1, a sample of healthy individuals, we found that increased beta spectral power during pre-extinction learning sleep was associated with poorer extinction recall. This association was significant for both NREM and REM sleep, and was significant only during sleep prior to extinction learning. This finding mirrors that of prior work using sleep deprivation, which found an impairment in extinction recall when total sleep deprivation preceded, rather than followed, initial extinction learning (Straus et al., 2017). Pre-encoding sleep loss has been linked to attenuated functioning in memory-related brain structures, such as the hippocampus (Poh & Chee, 2017; Prince & Abel, 2013; Yoo et al., 2007), as well as impaired consolidation, even following subsequent periods of recovery sleep (Yoo et al., 2007). In a fear conditioning task, neuroimaging work has shown a failure to activate both fear and extinction processing-related brain regions following either sleep restriction or total sleep deprivation (Seo et al., 2021). Similarly, beta power during sleep has also been suggested as a proxy of disturbed sleep, and is related to increased autonomic arousal and the disturbance of both NREM and REM sleep (Kuo et al., 2016). As such, it is possible that sleep disturbance, indexed here as heightened beta spectral power, led to changes in the neural substrates of extinction learning, which in turn led to poor consolidation of the fear extinction process.

A second major finding of the current study was that beta power was highly consistent across nights, in both healthy individuals and individuals with PTSD. This fits with previous work that has shown the sleep EEG (and specific EEG features such as sleep spindles) to be highly stable and trait-like within subjects (Buckelmüller et al., 2006; Cox et al., 2017, 2018; De Gennaro et al., 2005; Purcell et al., 2017; Werth et al., 1997). Twin studies have shown that sleep spectral power is highly heritable (Ambrosius et al., 2008; De Gennaro et al., 2008; Purcell et al., 2017), with beta-band power exhibiting the highest heritability estimates of the canonical sleep EEG frequency bands (Ambrosius et al., 2008). Higher beta power during sleep (relative to healthy controls) has been documented in a number of psychopathologies, including PTSD (de Boer et al., 2020; Germain et al., 2006; Woodward et al., 2000). Notably, when individuals with PTSD are compared to trauma-exposed, non-PTSD participants, higher beta power is not always observed (Cohen et al., 2013; Denis et al., 2021; Mellman et al., 2007). Rather than a biomarker of psychopathology, it may be the case that beta power estimates reflect a trait marker of heritable vulnerability to the development of psychopathology, which then may be magnified by trauma exposure.

As well as finding beta spectral power to be heightened in PTSD relative to healthy controls, we also found that the association between pre-extinction learning NREM beta power was associated with poorer extinction memory at a magnitude similar to healthy controls. We therefore speculate that beta spectral power may be a stable sleep biomarker that confers vulnerability to impaired consolidation of fear extinction. While this result is both novel and

intriguing, we stress that these results should be considered preliminary due to the small sample size, and so must be replicated in larger samples. While the relationship between NREM beta power and extinction recall showed a similar strength of association in both healthy participants and PTSD, this was not the case for REM sleep, where the correlation was smaller in PTSD. This could reflect a functional dissociation in NREM vs REM sleep microarchitecture following a trauma, especially given that numerous alterations in REM architecture and physiology have been observed in PTSD (Pace-Schott et al., 2015). Furthermore, work in other clinical groups such as insomnia has observed opposing relationships between REM sleep and fear extinction recall between PTSD and controls (Bottary et al., 2020).

We found novel evidence that beta band spectral power during sleep impairs fear extinction recall. However, the mechanistic basis and origins of the beta rhythm in the sleep EEG remains poorly understood. It is often stated that beta band activity is a marker of cortical hyperarousal, a claim stemming largely from studies in insomnia patients who have frequently been observed to have heightened power in the beta band (Zhao et al., 2021). A link with hyperarousal is not always found however. For example, following a mindfulness-based intervention for chronic insomnia, NREM beta band power increased from baseline to follow up, and higher beta power was significantly associated with fewer insomnia symptoms (Goldstein et al., 2019). In a large sample of PTSD patients and trauma-exposed controls, beta power levels were associated with fewer symptoms of subjective hyperarousal, fewer nightmares, and improved emotion regulation (Denis et al., 2021). Notably, experienced meditators also show an increase in high-frequency activity during NREM sleep (Ferrarelli et al., 2013), and mindfulness meditation enables increased physiological arousal concurrent with relaxation and well-being (Britton et al., 2014). As such, it has been proposed that while beta activity during sleep may index heightened arousal, the nature of this hyperarousal may either be adaptive or maladaptive (Goldstein et al., 2019).

Limitations

A limitation of the present study was that the association between beta power and extinction recall is purely correlational, and as such causal inferences cannot be conclusively made from these data alone. In a genetic mouse model of impaired fear extinction, large differences in the sleep EEG spectral power can be seen compared to extinction-competent mice, including heightened activity in beta-band frequencies (Fritz et al., 2021). Acoustic and electrical stimulation methods can be used to enhance frequency-specific sleep oscillations that have been shown to either promote (Ngo et al., 2013) or impair (Marshall et al., 2011) memory consolidation. While we are not aware of any attempts to directly increase beta rhythm activity via stimulation, closed-loop stimulation of theta (~5Hz) oscillations during REM sleep promote large, event-related increases in beta power (Harrington et al., 2020). Applying stimulation protocols to the current experimental paradigm would determine whether causal enhancements of beta activity leads to worse fear extinction recall. A second limitation is that we did not collect any measures of insomnia symptom severity, meaning we were unable to investigate whether beta spectral power was linked to any symptoms of hyperarousal seen in insomnia.

Conclusions

Sleep disturbances are extremely common in PTSD, and contribute to its onset and maintenance. We found evidence of a highly stable, trait-like feature of the sleep EEG, beta oscillatory power, to be associated with subsequent ability to recall extinguished fear in healthy controls and individuals with PTSD. Given the importance of extinction recall for the treatment of PTSD symptoms, this work provides an important new contribution to our understanding of the electrophysiological underpinnings of a key mechanism of PTSD maintenance.

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Disclosures

The authors have no conflicts of interest to disclose.

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