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Original Article

ORIGINAL ARTICLE

An attempt to identify reproducible high-density EEG markers of PTSD during sleep

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Abstract

Study Objectives: We examined electroencephalogram (EEG) spectral power to study abnormalities in regional brain activity in post-traumatic stress disorder (PTSD) during sleep. We aimed to identify sleep EEG markers of PTSD that were reproducible across nights and subsamples of our study population.

Methods: Seventy-eight combat-exposed veteran men with (*n* = 31) and without (*n* = 47) PTSD completed two consecutive nights of high-density EEG recordings in a laboratory. We performed spectral-topographical EEG analyses on data from both nights. To assess reproducibility, we used the first 47 consecutive participants (18 with PTSD) for initial discovery and the remaining 31 participants (13 with PTSD) for replication.

Results: In the discovery analysis, compared with non-PTSD participants, PTSD participants exhibited (1) reduced delta power (1–4 Hz) in the centro-parietal regions during nonrapid eye movement (NREM) sleep and (2) elevated high-frequency power, most prominent in the gamma band (30–40 Hz), in the antero-frontal regions during both NREM and rapid eye movement (REM) sleep. These findings were consistent across the two study nights, with reproducible trends in the replication analysis. We found no significant group differences in theta power (4–8 Hz) during REM sleep and sigma power (12–15 Hz) during N2 sleep.

Conclusions: The reduced centro-parietal NREM delta power, indicating reduced sleep depth, and the elevated antero-frontal NREM and REM gamma powers, indicating heightened central arousal, are potential objective sleep markers of PTSD. If independently validated, these putative EEG markers may offer new targets for the development of sleep-specific PTSD diagnostics and interventions.

Statement of Significance

The limited number of studies that have analyzed electroencephalogram (EEG) features to assess sleep in post-traumatic stress disorder (PTSD) have used data from only one or two electrodes during a single night of recording. In this study, we considerably expanded upon such analyses by seeking to identify sleep markers of PTSD that are reproducible across nights and study subsamples using high-density EEG and spectral-topographical analyses. Our findings suggest that reduced delta power during nonrapid eye movement sleep, indicating diminished depth of sleep, and increased gamma power throughout sleep, indicating high arousal, may be two characteristic features of PTSD. These putative EEG markers may serve as objective diagnostic indicators of this pervasive disorder as well as moderators of treatment outcomes.

Key words: post-traumatic stress disorder; sleep; high-density EEG; power spectrum; topography; delta activity; gamma activity; sleep depth; hyperarousal

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Introduction

Sleep disturbances are well-recognized symptoms of post-traumatic stress disorder (PTSD). Commonly reported complaints include difficulty of falling asleep or maintaining sleep, as well as recurrent nightmares [1], suggesting that sleep and arousal are profoundly dysregulated in PTSD. Polysomnography (PSG) studies also suggest that a variety of sleep architectures and sleep patterns are altered in PTSD [2–4]. For instance, one meta-analysis of such studies found that, compared with healthy sleepers, adults with PTSD show increased light sleep, reduced slow wave sleep, and increased rapid eye movement (REM) density [2]. However, despite the preponderance of such sleep disturbances, reliable markers of PTSD during sleep have yet to be identified. The discovery of such markers could have several important clinical implications. First, it could assist in the development of objective diagnostic tests of this pervasive disorder and deepen our understanding of its underlying sleep neuropathophysiology. Second, it could inform the development of sleep-focused, evidence-based interventions, leading to the design of pharmacological interventions or localized brain stimulation protocols to normalize specific patterns of brain activity during sleep in PTSD.

The quantification of sleep electroencephalogram (EEG) signals through power spectral analysis offers a way to study frequency-specific neural activities reflective of sleep functions and brain states. For example, low-frequency power in the delta range (1–4 Hz) during non-REM (NREM) sleep is considered an index of sleep homeostasis or sleep depth [5, 6], whereas high-frequency power in the beta (15–30 Hz) and gamma (30–40 Hz) ranges is thought to reflect central arousal during sleep [7–9]. To date, only a handful of studies have examined EEG spectral features to assess sleep in PTSD [3, 10–15], and these studies have focused on features derived from only one or two EEG locations, limiting their ability to detect regional changes in brain activity during sleep. In addition, although these studies suggest detectable differences in certain EEG features between PTSD and non-PTSD subjects, the nature and magnitude of the differences are inconsistent across studies. One reason for the divergent findings may be that these studies used data from only a single night of recording, without separate examination and consideration of night-to-night variability within subjects. For any EEG feature to be clinically useful in the diagnosis and personalized management of PTSD, it should be consistent across nights regardless of the inherent internight variability in EEG recordings and must be discriminative of individuals with and without PTSD.

The goal of the present study was to identify EEG markers of PTSD during sleep that are reproducible. To this end, we collected and analyzed 64-channel high-density EEG (hd-EEG) recordings from 78 combat-exposed veteran men with (*n* = 31) and without (*n* = 47) PTSD during two consecutive nights. We performed spectral-topographical analyses focusing on EEG activities considered to be functionally relevant to sleep, analyzing data from both nights to identify differences between the groups that were consistent across nights. To assess the reproducibility of our findings across subsamples of our study population, we first restricted our analyses to a subsample consisting of the first 47 consecutive subjects (18 with PTSD) for the initial identification of changes in PTSD and then examined whether we could reproduce the findings in the remaining 31 subjects (13 with PTSD).

Methods

Participants

All participants provided written informed consent in accordance with the protocol approved by the University of Pittsburgh Institutional Review Board (Pittsburgh, PA) and the United States (U.S.) Army Medical Research and Development Command Human Research Protection Office (Ft. Detrick, MD).

We recruited 85 combat-exposed veterans between the ages of 18 and 50 years who either met the diagnostic criteria for PTSD (*n* = 37, 31 men and 6 women) or did not (*n* = 48, 47 men and 1 women). We noticed that there were 6 women in the PTSD group but only 1 woman in the non-PTSD group. Because sex is a known confound in sleep studies [3, 16], we excluded all 7 women from the analysis to eliminate the potential effects of an imbalance in the sex ratio between groups. The remaining 78 veteran men, 31 with PTSD (mean age = 31.3 years, *SD* = 4.7 years) and 47 without PTSD (mean age = 32.8 years, *SD* = 6.2 years), comprised the set of participants used in this study.

All participants were free of any medication known to affect sleep or wakefulness for at least 2 weeks prior to study enrollment. The exclusion criteria were as follows: current diagnosis and/or untreated, severe depression; history of psychotic or bipolar disorder; substance or alcohol abuse within the past 3 months; significant or unstable acute or chronic medical conditions; current postconcussive symptoms or rehabilitation treatment for traumatic brain injury; and current sleep disorders other than insomnia or nightmares. Because alcohol consumption is common in the military population, we did not exclude participants who had a past history of alcohol use disorder (AUD).

Clinical assessments of sleep included the Pittsburgh Sleep Quality Index (PSQI) [17] and the Insomnia Severity Index (ISI) [18]. We assessed the presence and severity of mood, anxiety, psychosis, alcohol use, and substance use disorders using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders IV Axis I Disorders [19]. We determined the presence and severity of PTSD using the Clinician Administered PTSD Scale (CAPS) [20] and the presence of sleep disorders using a structured clinical interview developed at the University of Pittsburgh [21]. We obtained self-reported measures of depression using the Patient Health Questionnaire-9 (PHQ-9) [22].

To assess habitual sleep patterns, we asked participants to complete a sleep diary for 10 consecutive days prior to arrival at the laboratory. We instructed participants to limit their caffeine intake to no more than 2 cups of coffee (or the equivalent) per day and no more than 2 alcoholic drinks per day or 14 drinks per 2 week period prior to the sleep laboratory visit. We monitored daily intake of caffeine and alcohol in the 10-day sleep diaries.

All participants spent 2 consecutive nights and days in the sleep laboratory. On Night 1, they arrived at 20:00 and were fitted with a 64-channel hd-EEG montage (HydroCel Geodesic Sensor Net [without sponge inserts], Electrical Geodesics Inc., Eugene, OR). The Geodesic Sensor Net features a low-profile electrode pedestal designed to support both comfort and signal quality in sleep studies. We provided the participants with a gauze-like padding (Spandage Tubular Elastic Retainer Net, Medi-Tech International Corp., Brooklyn, NY) to further improve comfort and help alleviate the pressure of the cap. Some participants chose to use this as a “sock” by placing it over the cap to hold it in place for comfort. For others, we cut the material into small pieces and placed them between the chin and chinstrap, between the nasion and nasion tube, or both. We allowed participants to sleep undisturbed from 23:00 until 07:00 and recorded EEG data throughout the entire night of sleep. On the morning of the next day (Day 1), we removed the hd-EEG montage from the participants and asked them to perform multiple sessions of tests to assess daytime alertness and cognitive functions. At 21:00, we refitted the participants with the hd-EEG montage. We repeated the same procedures on Night 2 and Day 2 until the participants were discharged at 20:00 on the second day.

At the first in-person visit, we informed each participant of the detailed aims, procedures, risks, and risk-management strategies of the study so that the content and purpose of each assessment were transparent. During each visit, we provided each participant the opportunity to share any questions or concerns.

Hd-EEG recordings and preprocessing

We recorded 64-channel hd-EEG data (including 4-channel electrooculogram [EOG] data) and bipolar submentalis electromyogram (EMG) data at a sampling rate of 250 Hz. We referenced the EEG data to the linked mastoids and scored sleep stages in 30 s epochs according to the criteria of the American Academy of Sleep Medicine [23]. We processed data off-line using custom scripts written in MATLAB (The MathWorks Inc., Natick, MA), and, to eliminate unwanted frequencies, set digital filters as follows: EEGs at 0.5–50 Hz and EMGs at 10–70 Hz, with a 60 Hz notch filter. After filtering, we segmented the EEG data into 5 s epochs. To mitigate the impact of muscle artifacts, we removed all 5 s epochs that contained transient high-frequency activity from the recordings obtained at each EEG channel (one channel at a time) using a previously validated algorithm [24]. To mitigate the impact of ocular artifacts during REM sleep, first we identified eye-movement events by detecting sharp opposite-phase deflections in the EOG channels using the algorithm developed by Doman et al [25]. Next, we removed all 5 s epochs from each of the EEG channels whenever the epoch contained an eye-movement event [26]. To mitigate artifacts due to poor electrode contact or electrode movement (possibly resulting from body/head movement) for each EEG channel on a channel-by-channel basis, we removed 5 s epochs during which the signals were unreasonably large (i.e., the power between 4 and 50 Hz of the 5 s epoch exceeded six times the median for the whole night, for the channel). Overall, for the non-PTSD group, we rejected 9.2% (*SD* = 2.8%) of Night 1 data and 10.4% (*SD* = 3.8%) of Night 2 data; for the PTSD group, we rejected 10.1% (*SD* = 2.9%) of Night 1 data and 10.7% (*SD* = 2.9%) of Night 2 data. The differences in rejection rate between the groups were not statistically significant ($p > .220$).

EEG spectral analysis

We estimated spectral power density using artifact-free 5 s epochs for each electrode for each sleep stage based on a multitaper approach [27]. Specifically, we used discrete prolate spheroidal sequence tapers ($n = 4$) to obtain the spectral estimates. We focused our analyses on four sleep EEG activities considered to play essential roles in sleep functions: (1) delta activity (1–4 Hz) during NREM sleep, which is considered as an index of sleep homeostasis or sleep depth [5, 6], (2) theta activity (4–8 Hz) during REM sleep, which is suggested to be involved in emotional memory consolidation [28], (3) sigma activity (12–15 Hz) during stage N2 sleep, which is a putative measure of sleep spindles and is linked with learning and memory consolidation [29] as well as sleep protection [30], and (4) high-frequency activities in the beta-1 (15–20 Hz), beta-2 (20–30 Hz), and gamma (30–40 Hz) bands during NREM and REM sleep, which are considered as indicators of central arousal [7–9]. We therefore computed the average spectral power density for these frequency bands and sleep stages of interest, which resulted in nine combinations (i.e., NREM delta, REM theta, N2 sigma, NREM beta-1, NREM beta-2, NREM gamma, REM beta-1, REM beta-2, and REM gamma). We computed the nine power features for the whole night as well as for different sleep cycles using log-transformed power values.

Age correction

Age is well-recognized as a confounding variable in sleep studies [31–33]. Because our PTSD and non-PTSD groups were not strictly age-matched, we used a regression approach [34, 35] to control for potential age-related effects. Briefly, we performed univariate regression analyses to determine associations between age and each measure of sleep architecture and EEG spectral power. When an association was significant ($p < .05$), we corrected for age by subtracting the product of age and its regression coefficient from the raw value of the measure. Note that we used only non-PTSD participants to determine the regression coefficients, as determining the coefficients based on the PTSD group might result in removing disease-related changes [34]. We computed the regression coefficients using a robust regression method based on iteratively reweighted least squares [36]. We corrected for age prior to statistical analyses.

Statistical analyses

We used the Wilcoxon rank-sum test to assess group differences in clinical characteristics, sleep diaries, and sleep architecture measures. For sleep EEG power measures, we used the same test to initially assess group differences on an electrode-by-electrode basis. To account for multiple comparisons across electrodes, we first identified clusters of neighboring electrodes, where each electrode in the cluster passed the initial statistical threshold ($p < .05$), and then tested whether the number of the electrodes in the cluster was statistically greater than the number expected from chance based on a permutation approach [37]. Briefly, we created 10,000 permuted data sets by randomly shuffling the label of each participant in the two groups. For each permutation, we identified electrodes with $p < .05$, formed clusters of neighboring electrodes, and selected the cluster with the largest number of electrodes. Using the selected cluster for each permutation, we formed a distribution of the largest number of electrodes of the 10,000 pseudo clusters and, using this distribution, determined whether the cluster in the study data being tested met statistical significance ($p < .05$). In addition, to account for multiple comparisons across the nine EEG power features of interest, we corrected the *p*-values of the clusters using the Bonferroni correction. To examine group differences during different NREM–REM sleep cycles, we used two-way repeated-measures analysis of variance (rANOVA) with Group as the between-subject factor and Sleep Cycle as the within-subject factor. We considered p-values less than .05 as statistically significant. As a measure complementary to the p-value, we computed the effect size using a robust version of Cohen's d constructed by replacing the population mean with a 20% trimmed mean and the population standard deviation with the square root of a 20% winsorized variance [38].

Evaluation of reproducibility

An important aspect of this study is that we assessed the reproducibility of the findings by partitioning the entire sample into two subsamples—one for initial discovery and another for replication. However, evaluating reproducibility is not straightforward, because no single indicator can sufficiently describe whether a replication is a success [39]. In this study, we evaluated reproducibility by determining whether (1) the replication analysis showed a statistically significant effect ($p < .05$) in the same direction as the initial finding, (2) the effect size of the replication analysis fell within the 95% confidence interval (CI) of the initial finding, and (3) the analysis combining the discovery and replication data showed a statistically significant effect ($p < .05$) [39, 40]. We used a bootstrap approach with 10,000 replicates to determine the 95% CI of the effect sizes [41].

Results

Partitioning of data set

We partitioned our 78 participants into two subsamples: (1) a subsample including the first 47 consecutive participants (~60% of the total, consisting of 18 PTSD and 29 non-PTSD veterans) for initial identification of sleep abnormalities in PTSD (denoted as the discovery analysis) and (2) a subsample including the remaining 31 consecutive participants (~40% of the total, consisting of 13 PTSD and 18 non-PTSD veterans) for replication of the findings (denoted as the replication analysis).

Discovery analysis

Participant characteristics and sleep diaries

Table 1 shows the clinical characteristics and sleep diary measures for the subsample of participants included in the discovery analysis. The average age was 29.9 years (SD = 4.1 years) for the PTSD group (n = 18) and 33.5 years (SD = 7.3 years) for the non-PTSD group (n = 29). The difference in age did not reach statistical significance (p = .118). As expected, the PTSD group scored higher than the non-PTSD group on the CAPS, PHQ-9, ISI, and PSQI (all p's < .001). Eleven out of the 18 PTSD participants and 8 out of the 29 non-PTSD participants had a past history of AUD (absent within at least the past 3 months).

Participants completed the sleep diary for an average of 5.9 days (SD = 1.9 days) before they arrived at the sleep laboratory. Over this period, the PTSD group reported a mean time-in-bed of 428.3 min (SD = 100.0 min), which was not significantly different from that of the non-PTSD group (470.1 min, SD = 55.5 min; p = .328). However, compared with the non-PTSD group, the PTSD group reported significantly longer mean sleep latency (p < .001), shorter mean total sleep time (p = .011), and lower mean sleep efficiency (p = .017).

Table 1. Clinical characteristics and sleep diary variables (discovery analysis)

	PTSD (n = 18)	Non-PTSD (n = 29)	Group comparison
Variable	Mean (SD)	Mean (SD)	P[a]
Age (y)	29.9 (4.1)	33.5 (7.3)	.118
CAPS	52.6 (15.9)	10.6 (7.8)	<.001*
Intrusion	11.9 (4.7)	0.4 (1.3)	<.001*
Avoidance	18.4 (8.6)	2.4 (4.1)	<.001*
Hyperarousal	18.7 (7.9)	4.7 (4.3)	<.001*
PHQ-9	8.7 (5.0)	1.6 (2.6)	<.001*
ISI	12.7 (4.6)	3.9 (4.1)	<.001*
PSQI	9.3 (2.7)	4.1 (2.7)	<.001*
AUD history[b] (n)	11	8	–
SUD[c] history (n)	3	1	–
Sleep diary[d]			
Time in bed (min)	428.3 (100.0)	470.1 (55.5)	.328
Total sleep time (min)	395.9 (77.1)	450.5 (55.2)	.011*
Sleep efficiency (%)	93.4 (10.8)	95.9 (3.5)	.017*
Sleep latency (min)	21.9 (11.7)	9.6 (5.8)	<.001*
WASO (min)	6.9 (7.1)	3.2 (3.1)	.158

[a] Wilcoxon rank-sum test.

[b] Absent within at least the past 3 months.

[c] Assessed for sedatives-hypnotic-anxiolytic, cannabis, stimulants, opioids, cocaine, hall./pcp, and poly drugs.

[d] PTSD, n = 17. * values indicate p < .05.

AUD = alcohol use disorder; CAPS = Clinician Administered PTSD Scale; ISI = Insomnia Severity Index; PHQ-9 = Patient Health Questionnaire-9; PSQI = Pittsburgh Sleep Quality Index; SUD = substance use disorder; WASO = wakefulness after sleep onset.

Sleep architecture measures

Table 2 summarizes the objective sleep architecture measures from the two consecutive nights of laboratory sleep. The percentage of N3 sleep was significantly lower in the PTSD group than in the non-PTSD group during Night 1 (p = .004) and Night 2 (p = .021). Several sleep architecture measures, including sleep latency, total sleep time, sleep efficiency, wakefulness after sleep onset, number of awakenings per sleep hour, and N2 sleep percentage, exhibited significant group differences during Night 2 (p < .05) but not during Night 1.

Topographical analysis of sleep EEG power

We next examined topographical differences in sleep EEG power between the PTSD and non-PTSD groups for specific combinations of sleep stages and frequency bands of interest (NREM delta, REM theta, and N2 sigma, as well as NREM and REM high-frequency bands, including beta-1, beta-2, and gamma). Figure 1 illustrates the effect-size results. Black dots in the topographical maps indicate electrodes that passed the initial statistical threshold (uncorrected p < .05), whereas the white dots indicate electrodes that belong to a statistically significant cluster (p < .05) after accounting for multiple comparisons across electrodes.

NREM delta power: Compared with the non-PTSD group, the PTSD group exhibited reduced NREM delta power over the centro-parietal regions during both nights (Figure 1, top row, columns 1 and 4). The cluster-size test, which accounts for multiple comparisons across electrodes, showed that the centro-parietal cluster of electrodes approached significance for both Night 1 (N = 14 electrodes, p = .057, mean robust Cohen's d = –0.73)

Table 2. Sleep architecture measures of the PTSD and non-PTSD groups during the two consecutive nights of laboratory sleep (discovery analysis)

	PTSD ($n = 18$)	Non-PTSD ($n = 29$)	Group comparison[a]	
Measure	Mean (*SD*)	Mean (*SD*)	Effect size[b]	*P*[c]
Sleep latency (min)				
Night 1	16.6 (18.8)	13.8 (15.2)	0.09	.346
Night 2	12.5 (11.1)	7.4 (6.6)	0.68	.042*
Total sleep time (min)				
Night 1	408.7 (36.1)	405.7 (38.8)	−0.09	.735
Night 2	405.9 (31.7)	429.6 (34.8)	−1.77	<.001*
Sleep efficiency (%)				
Night 1	85.1 (7.5)	84.5 (8.1)	−0.09	.735
Night 2	84.6 (6.6)	89.5 (7.3)	−1.77	<.001*
WASO (min)				
Night 1	54.2 (28.8)	60.4 (35.3)	0.00	.751
Night 2	60.9 (31.5)	42.9 (34.2)	2.23	.002*
No. of awakenings per sleep hour				
Night 1	5.3 (2.0)	5.5 (2.3)	0.15	.638
Night 2	5.5 (1.9)	4.7 (1.8)	0.84	.022*
Stage N1 (%)				
Night 1	12.0 (5.4)	12.1 (6.5)	0.26	.424
Night 2	10.1 (4.1)	9.5 (5.4)	0.38	.090
Stage N2 (%)				
Night 1	58.0 (7.2)	55.9 (6.9)	0.56	.090
Night 2	56.3 (6.4)	53.5 (6.6)	0.79	.026*
Stage N3 (%)				
Night 1	8.6 (6.3)	13.2 (7.4)	−0.96	.004*
Night 2	10.6 (6.0)	14.4 (7.7)	−0.71	.021*
REM (%)				
Night 1	21.6 (6.3)	18.9 (5.6)	0.46	.208
Night 2	23.0 (5.1)	22.6 (5.9)	−0.10	.686*
REM density (counts/min)				
Night 1	5.3 (2.8)	5.4 (3.5)	0.02	.991
Night 2	5.9 (3.5)	5.9 (4.0)	−0.03	.852*

[a] Adjusted for age when age was significantly associated with the measure.

[b] Robust Cohen's *d*.

[c] Wilcoxon rank-sum test.

* values indicate $p < .05$.

WASO = wakefulness after sleep onset.

and Night 2 ($N = 12$ electrodes, $p = .063$, mean robust Cohen's $d = -0.66$).

REM theta and N2 sigma powers: We found no significant group difference in REM theta power or N2 sigma power for either night (Figure 1, top row, columns 2, 3, 5, and 6).

NREM and REM high-frequency powers: The high-frequency powers in the beta-1, beta-2, and gamma bands during NREM and REM sleep were generally higher in the PTSD group than in the non-PTSD group over the antero-frontal regions (Figure 1, bottom two rows). The effects were most prominent in the gamma frequency band and consistent across nights. For gamma power during NREM sleep, the antero-frontal cluster of electrodes was statistically significant for Night 2 ($N = 25$ electrodes, $p = .032$, mean robust Cohen's $d = 0.78$); the effect for Night 1, although similar, was not significant for the electrode cluster ($N = 3$ electrodes, $p = .116$, mean robust Cohen's $d = 0.69$). For gamma power during REM sleep, the antero-frontal cluster of electrodes was statistically significant for Night 1 ($N = 17$ electrodes, $p = .044$, mean robust Cohen's $d = 0.81$) and approached significance for Night 2 ($N = 11$ electrodes, $p = .061$, mean robust Cohen's $d = 0.79$). For beta-1 and beta-2 powers during NREM and REM sleep, we did not find significant clusters of electrodes. The only cluster of electrodes that approached significance was for beta-2 power during REM sleep for Night 1 ($N = 10$ electrodes, $p = .073$, mean robust Cohen's $d = 0.75$).

None of the electrode clusters survived further Bonferroni correction for multiple comparisons across frequency bands and sleep stages of interest ($p = .05/9 = .006$).

Replication analysis

The main findings of the discovery analysis above were that, compared with the non-PTSD group, the PTSD group had (1) reduced NREM delta power over the centro-parietal regions and (2) increased NREM and REM gamma power over the antero-frontal regions. In the replication analysis, our aim was to examine whether we could reproduce these findings in the reserved subsample of participants (13 PTSD and 18 non-PTSD). To this end, based on the topographical maps in Figure 1, we selected a centro-parietal ROI for assessing delta power and an antero-frontal ROI for assessing gamma power. Figure 2 illustrates the ROIs and the ROI-based group differences for the discovery analysis.

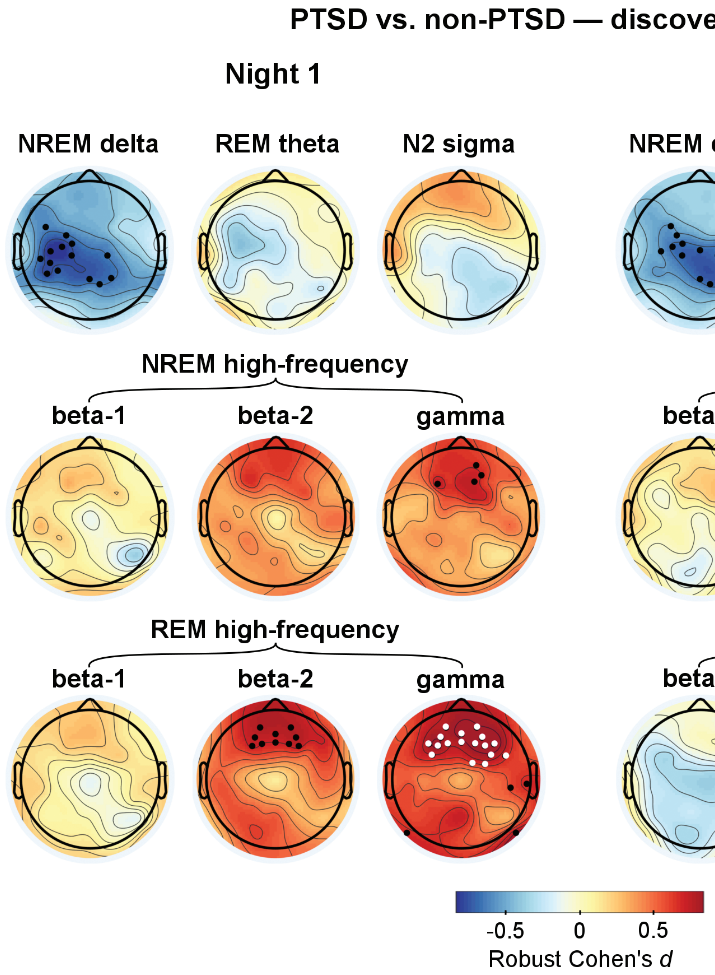

Figure 1. Topographical differences between the PTSD (n = 18) and non-PTSD (n = 29) groups in delta power (1–4 Hz) during nonrapid eye movement (NREM) sleep, theta power (4–8 Hz) during rapid eye movement (REM) sleep, sigma power (12–15 Hz) during stage N2 sleep, and high-frequency power in the beta-1 (15–20 Hz), beta-2 (20–30 Hz), and gamma (30–40 Hz) bands during NREM and REM sleep, for the discovery analysis. The maps show the individual-electrode effect size (a robust version of Cohen's *d*) for comparisons between PTSD and non-PTSD subjects in terms of log power. Blue areas show a decrease in EEG power in PTSD subjects relative to non-PTSD subjects (PTSD < non-PTSD), whereas red areas show an increase (PTSD > non-PTSD). Black dots indicate electrodes with uncorrected p-values less than .05. White dots indicate electrodes that belong to a statistically significant cluster (p < .05) after accounting for multiple comparisons across electrodes.

Table 3 summarizes the p-values and effect sizes for the ROI-based delta and gamma powers for the discovery and replication analyses, allowing us to evaluate the extent to which the original findings were reproduced in the replication analysis. Although the replication analysis did not show significant p-values (Table 3, column 3), the effect sizes were in the same direction and fell within the 95% CI of the initial findings (Table 3, columns 5–7). In addition, the analysis combining the discovery and replication data showed significant or nearly significant effects (Table 3, last two columns). These results indicate a reproducible trend of our original findings. Figure 3 shows a side-by-side comparison of the topographical maps from the discovery and replication analyses, which allows a visual assessment of reproducibility.

We report the participant characteristics, sleep diaries, and sleep architecture measures for the replication analysis in Supplementary Tables S1 and S2. We provide the replication results for all analyzed frequencies in Supplementary Figure S1. It is worth noting that we performed an age correction prior to statistical analyses for sleep features that were correlated with age (see Methods). We found that this affected the significance of the NREM delta findings but not that of the NREM and REM gamma findings. Supplementary Table S3 shows the correlations between sleep features and age among all non-PTSD participants. Supplementary Table S4 shows the uncorrected results for the ROI-based analyses.

Relationship between sleep EEG power and PTSD symptom severity

As an exploratory analysis, we computed the correlations of NREM delta as well as NREM and REM gamma powers with the CAPS total and subscale scores for all PTSD participants (n = 31). We computed the NREM delta power for the centro-parietal ROI and the NREM and REM gamma powers for the antero-frontal ROI. Table 4 and Figure 4 summarize the results. We observed a trend of negative correlation between NREM delta power and the CAPS hyperarousal score (CAPS-D) for both Night 1 (Spearman's rho = −0.30, uncorrected p = .097) and Night 2 (Spearman's rho = −0.42, uncorrected p = .019). We observed no other significant correlation.

Delta and gamma powers across sleep cycles

To explore the extent to which group differences might also be captured across sleep cycles, we evaluated EEG delta and

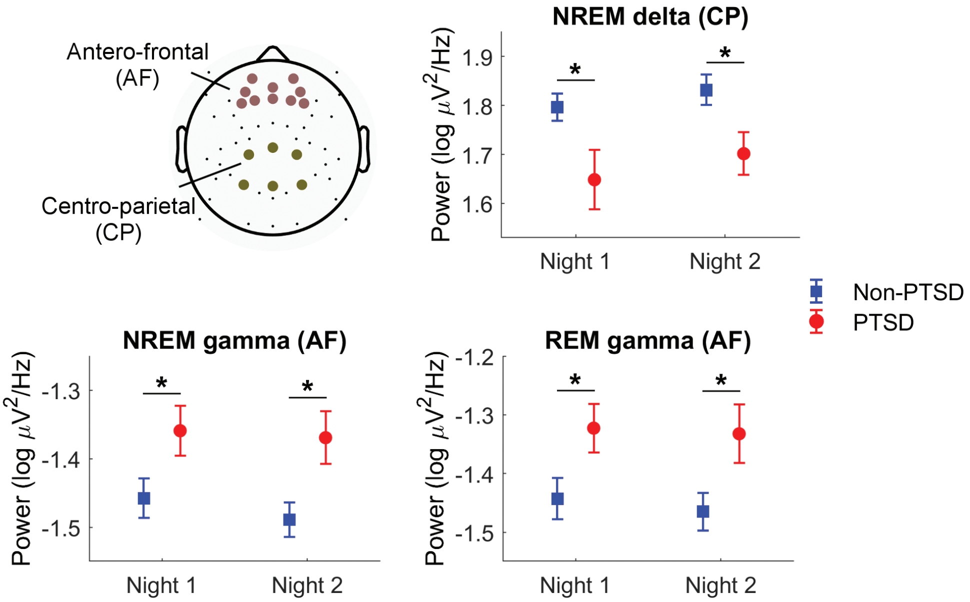

Figure 2. Group differences in delta power (1–4 Hz) during nonrapid eye movement (NREM) sleep and gamma power (30–40 Hz) during NREM and rapid eye movement (REM) sleep for the selected regions of interest (ROIs), for the discovery analysis (18 PTSD and 29 non-PTSD). We selected the ROIs based on the topographical maps in Figure 1, with a centro-parietal (CP) ROI and an antero-frontal (AF) ROI selected to show differences in NREM delta power and NREM and REM gamma power, respectively. We computed ROI-based powers by averaging electrodes within the ROIs. The plotted values are the group means of the ROI-based powers. Error bars indicate standard errors of the mean. Asterisks indicate significant group differences at $p < .05$.

Table 3. Summary of ROI-based *p*-values and effect sizes for evaluating reproducibility

Sleep EEG measure	*P* Discovery[a]	Replication[b]	Replication $p < .05$ (Yes/No)	Effect size (95% CI) Discovery	Replication	Replication effect size within discovery 95% CI (Yes/No)	Combined[c] *p*-value	Combined effect size (95% CI)
NREM delta								
Night 1	.035*	.435	No	−0.70 (−1.53, −0.05)	−0.35 (−1.32, 0.57)	Yes	.040*	−0.51 (−1.04, −0.03)
Night 2	.031*	.238	No	−0.69 (−1.44, −0.02)	−0.44 (−1.34, 0.40)	Yes	.030*	−0.46 (−1.04, −0.03)
NREM gamma								
Night 1	.039*	.222	No	0.75 (0.11, 1.50)	0.48 (−0.36, 1.55)	Yes	.025*	0.55 (0.12, 1.00)
Night 2	.010*	.057	No	0.86 (0.21, 1.91)	0.74 (0.08, 1.81)	Yes	.002*	0.74 (0.31, 1.27)
REM gamma								
Night 1	.013*	.307	No	0.84 (0.29, 1.62)	0.55 (−0.49, 1.65)	Yes	.038*	0.52 (0.03, 0.98)
Night 2	.028*	.535	No	0.79 (0.20, 1.48)	0.39 (−0.51, 1.59)	Yes	.067	0.47 (−0.02, 0.89)

[a] 18 PTSD, 29 non-PTSD.
[b] 13 PTSD, 18 non-PTSD.
[c] 31 PTSD, 47 non-PTSD.
CI = confidence interval; NREM = nonrapid eye movement; REM = rapid eye movement; ROI = region of interest.
NREM delta power for the centro-parietal ROI in Figure 2. NREM and REM gamma power for the antero-frontal ROI in Figure 2. * values indicate $p < .05$.

gamma powers across consecutive sleep cycles for all participants who had at least 3 sleep cycles (31 PTSD and 46 non-PTSD). Figure 5 illustrates the time courses of delta power (from the centro-parietal ROI in Figure 2) and gamma power (from the antero-frontal ROI in Figure 2) across the first 3 consecutive NREM–REM sleep cycles. For delta power during NREM sleep, a two-way rANOVA with Group (PTSD and non-PTSD) as the between-subject factor and sleep cycle (1, 2, and 3) as the within-subject factor revealed a nearly significant group effect for Night 1 ($F_{1,75} = 3.7$, $p = .058$) and a significant Group effect for Night 2 ($F_{1,75} = 6.6$, $p = .012$), but no significant Group × Sleep Cycle interaction ($p > .162$). Similarly, we identified Group effects that were significant or approached significance for gamma power during NREM (Night 1: $F_{1,75} = 4.5$, $p = .036$; Night 2: $F_{1,75} = 10.9$, $p = .002$) and REM sleep (Night 1: $F_{1,75} = 4.2$, $p = .045$; Night 2: $F_{1,75} = 3.7$, $p = .059$), but no significant Group × Sleep Cycle interaction ($p > .133$). The lack of Group × Sleep Cycle interaction indicates that the group differences in the NREM delta as well as the NREM and REM gamma powers were persistent across the first three sleep cycles.

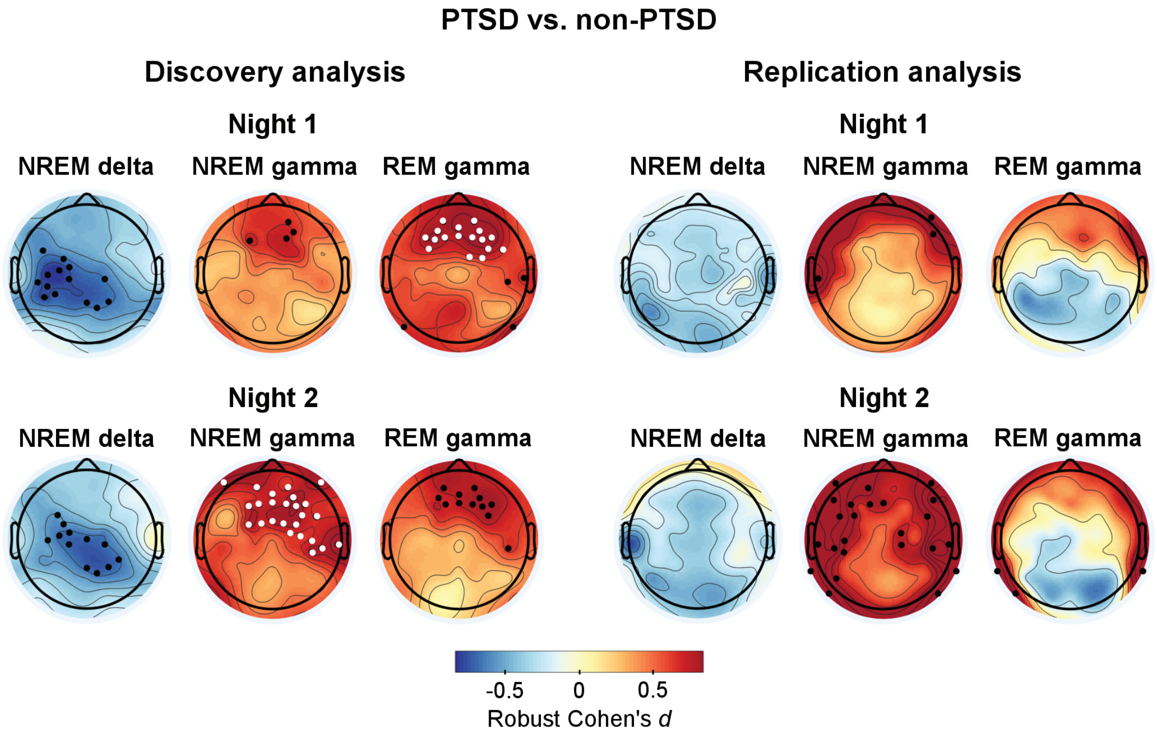

Figure 3. A side-by-side comparison of the results from the discovery analysis (18 PTSD and 29 non-PTSD) and the replication analysis (13 PTSD and 18 non-PTSD). The topographical maps show the individual electrode effect size (a robust version of Cohen's *d*) for comparisons between the PTSD and non-PTSD groups in terms of log power. Black dots indicate electrodes with uncorrected *p*-values less than .05. White dots indicate electrodes that belong to a statistically significant cluster ($p < .05$) after accounting for multiple comparisons across electrodes.

Table 4. Correlations (Spearman's rho) between sleep EEG measures and CAPS total and subscale scores among all PTSD participants ($n = 31$)

	Total CAPS	Intrusion (CAPS-B)	Avoidance (CAPS-C)	Hyperarousal (CAPS-D)
NREM delta				
Night 1	−0.21	−0.01	−0.10	−0.30
Night 2	−0.23	0.00	−0.10	−0.42*
NREM gamma				
Night 1	0.11	0.24	0.07	0.02
Night 2	−0.01	0.10	0.02	−0.14
REM gamma				
Night 1	0.06	0.25	0.11	−0.14
Night 2	0.06	0.16	0.11	−0.06

CAPS = Clinician Administered PTSD Scale; NREM = nonrapid eye movement; REM = rapid eye movement.
NREM delta power from the centro-parietal region of interest (ROI). NREM/REM gamma powers from the antero-frontal ROI. * value indicates significant correlation at $p < .05$.

Discussion

This study aimed to identify sleep EEG spectral features that are altered in PTSD. By performing hd-EEG recordings on two consecutive nights, we found evidence of lower NREM delta power over the centro-parietal regions and higher NREM and REM gamma power over the antero-frontal regions in PTSD subjects compared with non-PTSD subjects. Importantly, these findings were consistent across nights and their trend was reproducible across subsamples of our study population. The identified alternations in sleep EEG activities point to candidate neural mechanisms that may contribute to sleep disturbances that characterize PTSD.

PTSD is associated with a decrease in NREM delta power

The reduced delta power during NREM sleep in PTSD is consistent with several prior reports [3, 10, 11]. Delta power has been considered as an indicator of sleep depth [6]. In healthy individuals, high delta power during NREM sleep has been associated with better performance on memory, learning, and attention tasks in the morning [42, 43], suggesting that delta activity may reflect some restorative functions of sleep. Hence, the delta power reduction in PTSD identified here may reflect the fact that sleep in PTSD subjects is less restorative than the same amount of sleep in healthy subjects. Furthermore, a leading theory has postulated that delta activity is involved in downscaling synaptic strengths to restore the plasticity of the brain network [44]. Reduced delta activity during NREM sleep in PTSD may contribute to the neuropathophysiology of the disorder. This study cannot determine whether this reduced delta power is a marker of vulnerability to PTSD following trauma exposure or a result of chronic PTSD. Nevertheless, the findings raise the possibility that sleep enhancement strategies, such as auditory stimulation [45] or transcranial electrical stimulation [46] that targets delta activity during sleep, may have beneficial impacts on sleep quality and daytime symptoms of PTSD.

Delta activity is also an established marker of sleep homeostasis [5], with the delta power during initial sleep (i.e., the first sleep cycle) reflecting the level of sleep pressure accumulated

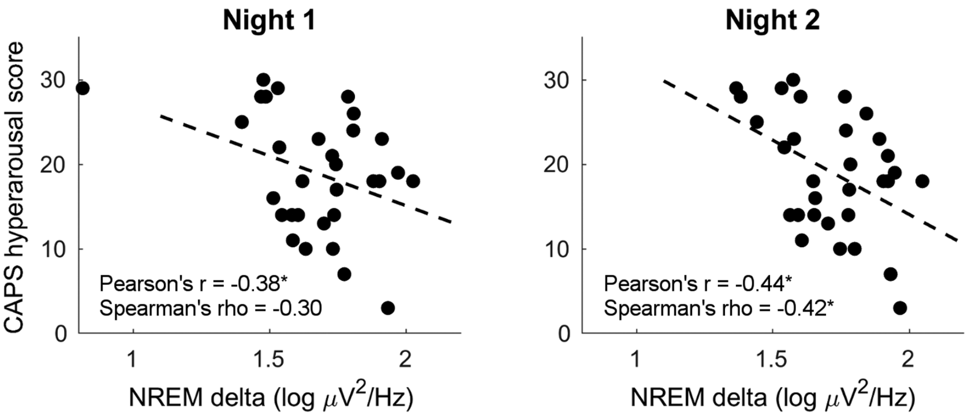

Figure 4. Scatterplots showing the correlation between delta power (1–4 Hz) during nonrapid eye movement (NREM) sleep and the Clinician Administered PTSD Scale (CAPS) hyperarousal score among all PTSD participants (*n* = 31). The delta power was measured from the centro-parietal region of interest in Figure 2. Asterisks indicate significant correlations at $p < .05$.

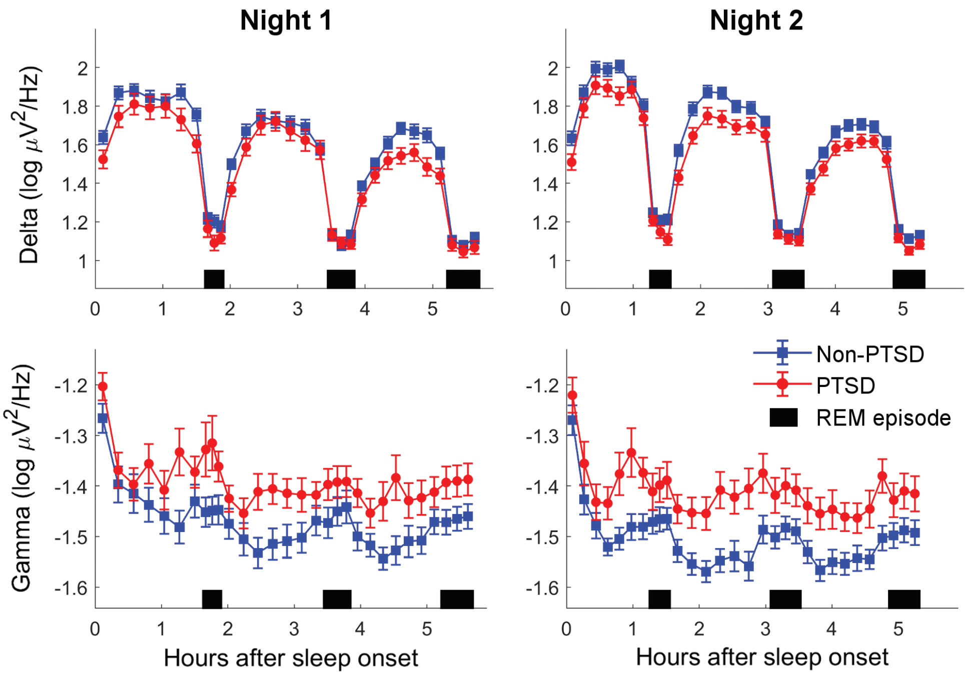

Figure 5. Time course of delta power (1–4 Hz) (upper panels) and gamma power (30–40 Hz) (lower panels) in PTSD (*n* = 31) and non-PTSD (*n* = 46) participants across the first 3 nonrapid eye movement (NREM)–rapid eye movement (REM) sleep cycles. Individual NREM and REM sleep episodes were subdivided into 7 and 3 time bins, respectively, of equal size. The data were aligned with respect to sleep onset and plotted against the mean timing of NREM and REM episodes averaged across participants. Error bars indicate standard errors of the mean.

during prior wakefulness [47]. According to this view, the observed reduction of delta power in PTSD may indicate that homeostatic sleep pressure was lower in PTSD subjects than in non-PTSD subjects. However, our data do not support this explanation, as the PTSD group reported less total sleep time than the non-PTSD group prior to the laboratory visit (Table 1), suggesting that PTSD subjects had higher sleep pressure in the laboratory. In addition, the group differences in delta power persisted across sleep cycles and were not specific to the first sleep cycle. Taken together, our findings suggest that the homeostatic regulation of delta activity is disrupted in PTSD. Such a disruption may contribute to PTSD hyperarousal symptoms, which we found to be negatively related to NREM delta power (Figure 4).

Interestingly, although delta activity is mostly generated in the frontal regions [48], we found that the group differences in delta power were greatest over the centro-parietal regions (Figure 1). Although it is unclear what cortical sources were responsible for these differences, the posterior topography is consistent with a recent study that showed an association between local decreases in NREM and REM delta activity in the posterior cortical regions and reports of dream experiences [49].

PTSD is associated with an increase in NREM and REM gamma power

High-frequency beta and gamma activities have been proposed as putative markers of central arousal during sleep in research on insomnia [7–9]. Although it has long been postulated that increased beta and gamma activities during both NREM and REM sleep could serve as an index of the "persistent symptoms of hyperarousal" that characterize PTSD [10], the handful of existing studies have yet to demonstrate evidence for this hypothesis [3, 10, 12–14]. This could partly be attributed to the limited use of EEG derivations (i.e., 1 or 2 central channels) in these prior studies. By using hd-EEG recordings and performing topographical analysis, we were able to examine regional brain activity in greater detail and, thereby, identify a characteristic frontal increase of gamma activity in PTSD subjects. Thus, studies that use only a few central channels may fail to detect such a change.

Increases in gamma activity during sleep have also been found in insomnia, schizophrenia, and depression [9, 50]. However, the scalp distributions of these increases were unclear given the lack of evidence from hd-EEG recordings. Recently, a small-sample-size pilot study of insomnia using hd-EEG recordings found that increases in gamma power during NREM sleep occurred over a widespread area [51], unlike the more restricted frontal topography we observed in PTSD. It is unclear whether the topography of increases in gamma power during sleep in frontal channels is unique to PTSD. Importantly, a study that combined functional magnetic resonance imaging and EEG sleep recordings demonstrated that, in healthy subjects, an overnight dissipation of amygdala activity in response to previous emotional experiences was specifically correlated with a reduction of prefrontal gamma power during REM sleep [52]. This suggests the possibility that the abnormally high level of gamma activity over the frontal regions in PTSD during sleep reflects amygdala dysregulation, which is conceptualized as a core neuropathology of PTSD [53].

Although high-frequency EEG activity, particularly within the gamma band, is prone to muscle artifacts, several lines of evidence suggest that the gamma effects observed here primarily originated in the brain. First, the gamma activity for both the PTSD and non-PTSD groups exhibited the greatest power over the midline frontal regions (Supplementary Figure S2). If scalp measures of gamma activity were muscle artifacts propagated from nonscalp regions, we would expect the power to be greatest over peripheral regions. Second, we found no significant group differences in submentalis EMG activity during REM sleep on both nights and during NREM sleep on Night 2 (Supplementary Figure S3). Third, although EMG activity was higher in PTSD subjects than in non-PTSD subjects during NREM sleep on Night 1 (Supplementary Figure S4, top-left panel), the group difference in NREM gamma power remained even after statistically controlling for EMG-related effects (Supplementary Figure S4).

No group differences in REM theta power and N2 sigma power

We examined REM theta power because theta waves during REM sleep have been associated with emotional memory consolidation [28], a function that has been postulated to be affected in PTSD [52]. In addition, a previous study reported that REM theta power was lower in trauma-exposed participants who had developed PTSD when compared with those who had not [15]. Contrary to this previous study but consistent with two others [10, 14], we found no significant group differences in REM theta power. Our results suggest that theta power during REM sleep may not be a stable feature that reliably distinguishes between PTSD and non-PTSD subjects.

Sigma power in stage N2 sleep is an indicator of the activity level of sleep spindles, which have been associated with sleep protection mechanisms as individuals who generate more spindles exhibit higher tolerance for disruptive stimuli [30]. We examined N2 sigma power, given that a common complaint of PTSD subjects is the difficulty of maintaining sleep [1]. However, it is unclear whether sleep spindles and sleep protection mechanisms are affected in PTSD, as N2 sigma power did not significantly differ between the two groups. Although this finding is consistent with two existing studies [10, 14], further investigations of the architecture of sleep spindles, such as their density, amplitude, duration, and frequency, will be necessary to elucidate potential changes of sleep spindles in PTSD.

Group differences in sleep architecture measures

Prior PSG studies of sleep architecture in PTSD have yielded inconsistent results. Whereas some studies have found sleep architecture measures among PTSD subjects to be worse than those among healthy controls [2–4], others have not [54, 55]. Our findings on sleep architecture also varied greatly across nights and across subsamples of our study population. For instance, for the participants used in the discovery analysis, we found significantly longer sleep latency, lower sleep efficiency, and more wakefulness after sleep onset in the PTSD group than in the non-PTSD group for Night 2 but not for Night 1 (Table 2). The inconsistency across nights may be explained by first-night effects [56]. For example, changes in bedtime routines due to a new sleep laboratory environment and, possibly, laboratory-dependent emotional states of apprehension or safety, may have affected sleep recordings and the resulting features. Although healthy individuals typically experience worse sleep on their first night in a sleep laboratory than on subsequent nights, several studies of insomniacs [57–59] and one study of PTSD subjects [60] have suggested that the laboratory environment may influence sleep quality positively in these patients. Interestingly, in the replication analysis, we essentially observed no significant differences between groups for any of the two nights of the study (Supplemental Table S2). Compared with our sleep EEG spectral features, which were generally consistent across the two study nights, the sleep architecture measures may be more sensitive to the testing environment or other potential confounding factors.

Strengths and limitations

Our study has several important strengths. In contrast to prior studies, which were all based on data from a single night, we analyzed data from two nights to identify neural correlates of PTSD that are stable across nights. In addition, our study is the first PTSD sleep study to use hd-EEG recordings, which provide enhanced spatial resolution. Moreover, we evaluated the reproducibility of our findings by performing a replication analysis using additional samples.

The limitations of this study include the potential lack of generalizability of our findings to the overall PTSD population. We used a sample consisting of young, combat-exposed male veterans who were free of medications and without comorbid disorders of sleep, mood, or substance abuse. Although such a sample allowed us to gain information about sleep in PTSD with few, if any, confounding factors, the extent to which the EEG markers identified here are robust for PTSD subjects with comorbid disorders needs to be directly evaluated in independent samples. Our study was also limited to combat-exposed men. In addition, we note that none of the EEG results from the topographical analysis survived Bonferroni corrections for multiple testing across the nine combinations of frequency bands and sleep stages of interest. Nevertheless, our findings in the delta and gamma frequency bands are unlikely to be due to chance, as they exhibited a reproducible trend across nights and subsamples.

Another potential limitation is that although we had excluded subjects with alcohol abuse within at least the previous 3 months, we had not excluded subjects with a past history of AUD, which comprised over 60% of the PTSD group. Heavy drinking is common among Service members and veterans and, more generally, in individuals with PTSD [61]. Had we excluded subjects with a past history of AUD, the study population would have been much smaller, and the data less generalizable. Instead, we instructed subjects to consume no more than 2 alcoholic drinks per day for 2 weeks prior to the sleep laboratory visit, and excluded subjects who failed to comply. However, alcoholism may affect sleep for extended periods of time following cessation of drinking [62]. Nevertheless, it remains unclear how a past history of AUD affects sleep EEG in combat-exposed veterans. To determine whether AUD history was a significant factor in our analyses of sleep EEG power features, we tested the ROI-based delta and gamma powers using a two-way ANOVA with Group (PTSD and non-PTSD) and AUD history (with and without a past history of AUD) as between-subject factors. We found that AUD history was not a significant factor on either night in the discovery and replication analyses ($p > .05$). We also examined topographical differences in delta and gamma powers between the PTSD and non-PTSD groups using only subjects without a past history of AUD ($n = 12$ for PTSD, $n = 37$ for non-PTSD) and found a similar pattern of results, namely, reduced NREM delta power over the posterior regions and increased NREM and REM gamma powers over the frontal regions in PTSD subjects (Supplementary Figure S5). These results indicate that our main findings in delta and gamma powers were not due to the high prevalence of AUD history in PTSD subjects.

Conclusions

In summary, the results from this study demonstrate that PTSD is characterized by reduced centro-parietal delta activity during NREM sleep and increased antero-frontal gamma activity during both NREM and REM sleep. The decreases in delta activity suggest a deficit in restorative sleep, whereas the increases in gamma activity suggest heightened central arousal. Our findings also have clinical implications, as the EEG features we identified could potentially serve as objective markers of PTSD. In addition to further validation in independent studies of PTSD subjects with comorbid sleep, psychiatric, or medical conditions, these features should also be investigated as potential predictors of treatment response, daytime performance on cognitive readiness tasks, and longitudinal changes of improvement or deterioration of symptoms. The results of such studies could guide the development of sleep-focused, evidence-based interventions for PTSD.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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