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Effects of oral temazepam on slow waves during non-rapid eye movement sleep in healthy young adults: a high-density EEG investigation

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Abstract

Slow waves are characteristic waveforms that occur during non-rapid eye movement (NREM) sleep that play an integral role in sleep quality and brain plasticity. Benzodiazepines are commonly used medications that alter slow waves, however, their effects may depend on the time of night and measure used to characterize slow waves. Prior investigations have utilized minimal scalp derivations to evaluate the effects of benzodiazepines on slow waves, and thus the topography of changes to slow waves induced by benzodiazepines has yet to be fully elucidated. This study used high-density electroencephalography (hdEEG) to evaluate the effects of oral temazepam on slow wave activity, incidence, and morphology during NREM sleep in 18 healthy adults relative to placebo. Temazepam was associated with significant decreases in slow wave activity and incidence, which were most prominent in the latter portions of the sleep period. However, temazepam was also associated with a decrease in the magnitude of high-amplitude slow waves and their slopes in the first NREM sleep episode, which was most prominent in frontal derivations. These findings suggest that benzodiazepines produce changes in slow waves throughout the night that vary depending on cortical topography and measures used to characterize

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Conflicts of Interest

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slow waves. Further research that explores the relationships between benzodiazepine-induced changes to slow waves and the functional effects of these waveforms is indicated.

Keywords

slow wave; sleep; temazepam; benzodiazepine; spectral analysis; EEG

1. Introduction

Slow waves are characteristic electroencephalographic waveforms that are a hallmark of non-rapid eye movement (NREM) sleep. These waveforms are thought to play several roles in the central nervous system (CNS), including promotion of sleep maintenance, quality, and restoration (Dijk, 2009). Correspondingly, alterations in slow waves have been described across a range of disorders associated with reduced sleep quality including major depressive disorder, idiopathic hypersomnia, and obstructive sleep apnea syndrome (Borbely et al., 1984; Hoffmann et al., 2000; Jones et al., 2014; Plante et al., 2012; Sforza et al., 2000). Slow waves are homeostatically regulated such that their highest activity is during early sleep, with decreasing activity as the night progresses (Borbely, 1982). Moreover, increased slow wave activity during sleep after extended wakefulness is a well-characterized physiological indicator of increased sleep pressure (Achermann et al., 1993; Borbely et al., 1981). Slow waves are also integral factors in cortical development and sleep-dependent memory consolidation (Rasch and Born, 2013; Ringli and Huber, 2011). Thus understanding the effects pharmacologic agents have on slow waves during NREM sleep is important for several spheres of research including those related to neuropsychiatric disorders, CNS plasticity, and sleep deprivation.

As a class, benzodiazepines are agents commonly utilized for a broad range of clinical applications including sedation, anxiolysis, muscle relaxation, and seizure management. These agents have prominent effects on the sleep electroencephalogram (EEG) during NREM sleep (Lancel, 1999). Using spectral analysis, they have been shown to reduce slow wave activity (SWA; activity ~1–4.5Hz) as well as activity in a broader low frequency band (~1–10Hz) during NREM sleep (Aeschbach et al., 1994a; Aeschbach et al., 1994b; Arbon et al., 2015; Borbély et al., 1985; Dijk et al., 1989). Moreover, these reductions in SWA are attenuated or not observed early in the night, and are more prominent in the latter portions of sleep (i.e., by the third NREM sleep cycle) (Achermann and Borbély, 1987; Aeschbach et al., 1994b; Borbély et al., 1985). However, one limitation of spectral analysis is that the technique is not able to distinguish the specific morphological change(s) in slow waves that account for alterations in spectral power (i.e., whether changes in SWA are due to reductions in the number of incident waves and/or amplitude of the waveform).

Using period amplitude analyses, which allows for the detection and subsequent morphological characterization of slow waves, benzodiazepines have been shown to decrease the amplitude of detected waves (Feinberg et al., 1977; Feinberg et al., 2000; Johnson et al., 1979; Wright et al., 1986). However, changes in the incidence of slow waves have been less consistent among studies, with both reductions (Feinberg et al., 1977; Feinberg et al., 2000; Johnson et al., 1979) and increases (Wright et al., 1986) demonstrated.

These discrepant results may be due to the reduction of high amplitude waves with a concurrent increase in waves of lower amplitude caused by these medications (Wright et al., 1986). Regardless, prior analyses that examined benzodiazepine effects using wave detection techniques have not evaluated changes in slow wave morphology and incidence across the night, nor have prior studies examined alterations to slow-wave slope, which is posited to be a more sensitive marker of sleep pressure (Riedner et al., 2007; Vyazovskiy et al., 2007).

An additional limitation of prior spectral and period amplitude analyses to examine the effects of benzodiazepines on slow waves has been the reliance on a limited number of EEG derivations (typically 1–2 central channels). Slow waves demonstrate a characteristic topography with increased activity in frontal derivations (Cajochen et al., 1999; Finelli et al., 2000; Tinguely et al., 2006; Werth et al., 1997). Because use of limited-EEG montages can fail to detect pertinent alterations in SWA between groups (Plante et al., 2012), this study sought to utilize high-density (hd) EEG to evaluate the topographic effects of temazepam, a non-selective benzodiazepine, on slow waves. Based on the previous literature, we hypothesized that administration of the drug would result in reductions in SWA in later sleep cycles, but not during the first part of the night, a reduction in amplitude and incidence of slow waves, and that both spectral and morphological changes would be more pronounced in frontal EEG derivations.

2. Methods

2.1. Participants

Participants were right-handed healthy volunteers recruited as part of a larger parent study that examined the effects of medications on sleep restriction. All participants provided written informed consent, and this study was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board. Inclusion criteria included age 18–35 years, body mass index (BMI) 19–32kg/m^2, a typical bedtime between 2100 and 0100 hours, and usual self-reported nightly sleep duration 6.5–8.5 hours. Initial evaluation included the Structured Clinical Interview for DSM-IV-TR Axis I disorders (First et al., 2002), urine drug screen, and urine pregnancy test (for female participants). Exclusion criteria included current or past psychiatric disorder, current or recent major neurologic or medical illness, pregnancy, use of central nervous system active medications, reported caffeine intake >300mg/day, alcohol intake>3 drinks/day or 8 drinks/week, regular use of nicotine within 6 months of enrollment, use of illicit drugs, night/evening shift work, travel across ≥3 time zones in the month preceding enrollment, or excessive daytime sleepiness (defined as either baseline Epworth Sleepiness Scale ≥10 or mean sleep latency <8 minutes on multiple sleep latency testing) (Johns, 1991; Sullivan and Kushida, 2008). Participants also did not have clinically relevant sleep-related breathing or movement disorders, verified by clinical history and screening polysomnogram. Changes in sleep spindles induced by temazepam in this group of participants have been previously reported (Plante et al., 2015)

2.2. Sleep EEG

The EEG data utilized in this study occurred on two separate nights of sleep (within-subjects design) that each occurred prior to a supervised sleep restriction and recovery protocol. Participants took either placebo or oral temazepam 15mg prior to bedtime on study nights. The placebo night was drawn from the placebo-arm of a randomized study of an investigational drug; the temazepam night was drawn from an open-label extension arm of that parent study. All participants had spent at least two nights in the sleep laboratory during eligibility screening (including an hdEEG accommodation night) prior to recordings utilized in this study. Additionally, at least three weeks had elapsed since completing any prior sleep restriction protocols. Sleep-wake patterns were monitored between in-laboratory testing sessions via wrist-worn actigraphy (Actiwatch, Mini-Mitter, Bend, OR).

Sleep EEG was collected using an integrated recording for sleep staging (Alice® Sleepware; Philips Respironics, Murrysville, PA) with 256 channel hdEEG (Electrical Geodesics, Eugene, OR). Sleep staging was performed by a registered technologist according to standard criteria (Iber et al., 2007) based on 6 EEG channels at approximate 10–20 locations (F3, F4, C3, C4, O1, and O2) referenced to the mastoids, sub-mental electromyogram and electrooculogram. HdEEG signals were collected with a vertex reference and 500 Hz sampling rate.

2.3. EEG Spectral Analysis

HdEEG signals were first-order high-pass (0.1Hz) filtered and band-pass (0.3–50Hz) filtered in NetStation (Electrical Geodesics, Eugene, OR), then downsampled to 128 Hz, high-pass filtered (2-way least-squares FIR, 1Hz) and re-referenced to the average scalp voltage computed in all channels in MATLAB (MathWorks, Natick, MA). Semi-automatic artifact rejection was conducted to remove channels with interrupted contact with the scalp or high-frequency artifact. Spectral analysis of NREM sleep (all N2 and N3 epochs) was performed for each channel 6-second epochs (Welch's averaged modified periodogram with a Hamming window; frequency resolution 0.17Hz) to maintain congruence between spectral analysis and 30-second staging epochs (Goldstein et al., 2012; Plante et al., 2012). To verify that slow wave activity (power in the 1–4.5Hz band) declined across the night for both conditions, exponential decay functions were calculated using similar methods to prior investigations (Armitage et al., 2000; Dijk et al., 1990; Plante et al., 2012).

2.4. Analysis of Slow Wave Parameters

Slow wave detection was performed using similar methods previously described (Riedner et al., 2007). EEG signals were down-sampled to 128 Hz and band-passed (0.5–4Hz, stop-band 0.1 and 10 Hz) using a Chebyshev Type II filter in MATLAB. Slow waves were defined as negative deflections with 0.25–1.0 second consecutive zero crossings detected in artifact-free NREM epochs. Negative deflections were utilized because of their superior stability relative to more variable positive deflections. Slow wave incidence was defined as the number of detected slow waves relative to NREM sleep time. The peak amplitude of each wave between zero crossings was used to calculate average amplitude (peak amplitude divided by number of detected waves). A peak amplitude cut-off of 40μV was used to define high and low-amplitude waves (Duncan et al., 2012). Slow wave slopes were defined as the

amplitude of the most negative peak divided by the time from the previous zero crossing (first-segment slope) or the time until the next zero crossing (second-segment slope).

2.5. Statistics

Sleep staging variables, as well as spectral power and slow wave parameters were compared between conditions (placebo vs. temazepam) using paired t-tests. To increase signal-to-noise, hdEEG analyses were restricted to 173 channels overlying the scalp, defined by a plotting radius of 0.57 in the topoplot function of the EEGLAB plug-in for MATLAB (Delorme and Makeig, 2004). Global spectral power was derived using the average of these 173 channels. Topographic comparisons of spectral and slow wave data between conditions were performed using channel-by-channel paired t-tests. Statistical non-parametric mapping (SnPM) with suprathreshold cluster testing was utilized to correct for multiple comparisons of topographic data using a t-value threshold corresponding to alpha=0.05 for the uncorrected comparisons (Nichols and Holmes, 2002), with missing data for a given channel interpolated using the average of surrounding channels in order to maintain maximal degrees of freedom without altering the mean signal of the group. Since the principle aim of the study was to evaluate the effects of temazepam on slow waves, comparisons were limited to those between placebo and temazepam conditions for the entire night and within the first three sleep cycles. Sleep cycles were defined using previously described criteria (Kurth et al., 2010). All statistical analyses were performed using MATLAB (MathWorks, Natick, MA).

3. Results

3.1. Participant demographics, sleep staging, and spectral activity

Participants were young adults (23.5±3.6 years; range 18–29) and predominantly female (11 female; 7 male). Sixteen of the 18 participants had intact actigraphy for analysis (two had device failure). Using actigraphy, participants had similar average nocturnal sleep duration [placebo (PLC) 7.68±0.91 hours vs. temazepam (TMZ) 7.48±0.84 hours, (p=0.25) and bedtimes (PLC mean 00:03 hours and TMZ mean 00:08 hours) prior to hdEEG recordings for both conditions. There were no significant differences between PLC and TMZ during hdEEG recording nights using standard polysomnography scoring variables (Table 1).

Analyses of global (average of 173 channels) spectral power demonstrated TMZ was associated with significant reductions in slow wave activity (Table 1). This reduction in SWA occurred in the context of a broader reduction within a low frequency range from 1–8.67Hz (Figure 1). Both PLC and TMZ conditions demonstrated a similar pattern of exponential decline of SWA over the course of the night (Supplemental Figure 1), consistent with prior reports (Achermann and Borbély, 1987; Aeschbach et al., 1994b).

Topographic analysis demonstrated SWA was most prominent in frontal derivations for both PLC and TMZ conditions (Figure 2). Using data from the entire night, reduction in SWA in TMZ relative to PLC was greatest in frontal and centroparietal derivations (Figure 2). When differences in SWA between TMZ and PLC were compared within sleep cycles, there were no significant differences in SWA in NREM1 or NREM2, but widespread reductions with TMZ were observed in NREM3 (Figure 2). Exploratory topographic analyses of the broad

low-frequency range (1–8.67Hz) demonstrated nearly identical topographic and cycle-specific patterns as SWA (Supplemental Figure 2).

3.2. Slow Wave Incidence and Morphology

Incidence of all detected slow waves demonstrated a similar pattern to that observed for SWA, with broad decreases associated with TMZ using all-night data and within NREM3, but no significant topographic differences in NREM1 or NREM2 (Figure 3). There were no significant topographic differences in amplitude or slope of detected slow waves considered in aggregate using all-night or sleep cycle specific data.

The incidence of high amplitude (≥40μV) waves demonstrated a significant reduction in TMZ relative to PLC that was most prominent in frontal regions using all-night data (Figure 4). Similar to patterns observed for SWA, there were no significant reductions in incidence between conditions for NREM1 or NREM2, but broad frontal and centroparietal reductions were observed in NREM3. However, the amplitude of these waves in NREM1 was significantly lower for TMZ relative to PLC in frontal regions, without significant differences in later sleep cycles (Figure 4). Additionally, there was a corresponding decrease in first- and second-segment slopes of large amplitude waves in frontal regions associated with TMZ, which was most prominent in the first sleep cycle (Figure 4).

Unlike changes to high-amplitude waves that were observed during NREM1, changes in the incidence and morphology of low amplitude (<40μV) waves were restricted to NREM3 (Figure 5). Although reductions in incidence occurred across the scalp, the reductions in amplitude and second segment slope of these low-amplitude slow waves were most pronounced in frontal derivations (Figure 5).

4. Discussion

Consistent with prior investigations, our findings demonstrate that administration of the non-selective benzodiazepine temazepam significantly affects slow waves during non-rapid eye movement sleep. Our study which utilized high-density EEG recordings extends the previous literature by demonstrating that the effects of the drug varies by scalp topography, time of night, and the specific measure utilized to characterize slow waves.

In terms of spectral activity, our results are consistent with prior investigations that have demonstrated benzodiazepines are associated with reductions in spectral power within a broad low frequency range, inclusive of slow wave activity (Aeschbach et al., 1994a; Aeschbach et al., 1994b; Arbon et al., 2015; Borbély et al., 1985; Dijk et al., 1989). In addition, our results are similar to prior studies that have demonstrated that benzodiazepines reduce SWA primarily in the latter portion of the night (Aeschbach et al., 1994b). The reductions in SWA in this investigation paralleled reductions in the incidence of detected slow waves, suggesting that the decline in SWA induced by TMZ is due largely to a reduction in the incidence of these waveforms. This observation is consistent with prior research that has demonstrated that the normal homeostatic decline in SWA across the night is also related to decreased slow wave incidence, particularly of high amplitude waves (Vyazovskiy et al., 2011; Vyazovskiy et al., 2007).

It is noteworthy that our results suggest spectral analysis alone may be insufficient to fully characterize the effects of benzodiazepines on slow waves during sleep. In particular, we observed topographic changes to high-amplitude slow waves that occurred early in the night, and were more prominent in frontal EEG derivations. In this study, the magnitude of high-amplitude slow waves, as well as the slopes of these waves, were reduced by TMZ relative to PLC, but only in the first NREM cycle. These results would be consistent with prior research that has suggested morphological characteristics of slow waves, such as slow-wave slope, may be more sensitive to alterations in slow waves than SWA (Riedner et al., 2007). They also suggest that changes in spectral power caused by temazepam cannot universally be equated with changes in amplitude, despite prior reports of high concordance between these two factors (Geering et al., 1993).

Although this study was not designed to clarify the mechanism through which temazepam causes the observed alterations to the morphology of slow waves, reductions in the magnitude of high amplitude waves may result from enhanced GABA-A mediated inhibition within the cortex. The amplitude of EEG signals detected at the scalp generally reflects the extent of the excitability and synchrony of the underlying cortical populations (Buzsáki et al., 2012). Because benzodiazepines are allosteric modulators at the GABA-A receptor, increase the duration of inhibitory postsynaptic potentials, and prolong intracortical inhibition (Florian et al., 2008), these properties may have the net effect of reducing the magnitude of high amplitude slow waves during NREM sleep.

Interestingly, transcranial magnetic stimulation protocols have demonstrated a reduction in cortical effective connectivity during both NREM sleep and anesthesia induced by the benzodiazepine midazolam, suggesting a potentially shared underlying mechanism (Ferrarelli et al., 2010; Massimini et al., 2005). Modeling studies have additionally supported the notion that a shift in the balance between synaptic excitation and inhibition to favor inhibition, resulting from increased GABA release, most likely underlies the reduction in cortico-cortical signal transmission during NREM sleep (Esser et al., 2009). However, it is also conceivable that changes in effective connectivity and sleep slow waves are due to some other mechanism, such as alteration of bistability between the up and down-states of thalamocortical neurons, which may affect the generation of spontaneous slow waves (Tononi and Massimini, 2008). Thus, further research into the pathways through which benzodiazepines alter the incidence of electroencephalographic slow waves and their relationship to changes in cortical effective connectivity may prove a fruitful area of research.

The alterations in sleep slow waves induced by benzodiazepines observed in this study may also influence emerging research in novel pharmacologic approaches to the treatment of neuropsychiatric disorders. In particular, the N-methyl-d-aspartate (NMDA) antagonist ketamine, which has shown promise as a rapid antidepressant agent, has been shown to increase SWA and the magnitude of high amplitude slow waves (Duncan et al., 2012). Positive correlations have also been observed between slow wave parameters (SWA and the incidence of high-amplitude slow waves) and change in brain-derived neurotrophic factor (BDNF), which is hypothesized to play a role in the antidepressant mechanism of ketamine (Duncan and Zarate, 2013). Notably, cortical microinjections of BDNF in animal models

also result in increases in SWA, suggesting a causal link between BDNF expression and sleep regulation (Faraguna et al., 2008). As an antidepressant, ketamine also increases BDNF in responders compared to non-responders (Haile et al., 2014), and a positive relationship between slow wave parameters (SWA and amplitude) and change in BDNF among responders has also been demonstrated (Duncan et al., 2012). Because benzodiazepines have been shown to reduce BDNF in prior studies (Huang and Hung, 2009; Huopaniemi et al., 2004; Licata et al., 2013), although speculative, these agents may be antithetical to the antidepressant effects of ketamine, through reductions in slow wave activity, incidence, and morphology via reductions in this neurotrophic factor. Thus, further research that clarifies whether there is a causal link between reductions in slow waves and decline in BDNF induced by these drugs, and whether co-administration of benzodiazepines prior to sleep blunts the therapeutic response to ketamine, may help clarify the relationships between cortical plasticity, sleep slow waves, and the mechanisms underlying the thymoleptic properties of ketamine.

Beyond benzodiazepines, other pharmacologic agents may prove useful tools in evaluating the effects of GABAergic drugs on the functional effects of slow waves. Other agents that potentiate the GABA-A receptor, such gabadoxol and alcohol, have different effects on slow waves compared to non-selective benzodiazepines, with increased SWA in the first portion of the night (Dijk et al., 1992; Faulhaber et al., 1997). Thus, our results may not be extended to other agents that potentiate the GABA-A receptor, and extension to other non-selective benzodiazepines must be done with caution in light of a diversity of pharmacokinetic profiles among agents within this class (Müller and Stillbauer, 1983), which could theoretically result in variable effects on slow waves, particularly across the course of the night.

There are limitations of this study that merit discussion. First, this was a one-time fixed-dose study, and thus the observed differences between temazepam and placebo conditions may have differed if a higher dose were utilized or analysis was conducted after repeated nights of administration. The latter is particularly relevant since prior studies have demonstrated more pronounced reductions in slow wave counts and amplitude after several nights of benzodiazepine use (Johnson et al., 1979). Second, temazepam was administered in an un-blinded manner, which may have affected results. However, because double-blind protocols with temazepam administered at bedtime do not reliably mask active drug from placebo (Morin et al., 1995), it is unlikely our results would have differed using a blinded protocol. Third, as a consequence of the parent study from which the data used in this study were drawn, all placebo nights occurred prior to temazepam nights, and thus we cannot definitively rule out an effect of order influencing our results. However, the use of screening and accommodation studies prior to hdEEG nights utilized in these analyses limits the likelihood that order effects substantially altered findings. Fourth, our study design is not able to discern whether there is a causal relationship between observed changes in slow waves and alterations in sleep spindles induced by temazepam. However, given previously reported absence of correlation between these variables in this data set (Plante et al., 2015), it is less likely that alterations in sleep spindles cause changes in slow waves, or vice versa, and more likely that observed changes in these EEG waveforms reflect the impact of temazepam at the GABA-A receptor, which is widespread throughout the brain and

responsible for most of the physiologic activity of GABA in the CNS. Finally, specific pharmacokinetic data in our research participants were not available, which may have provided insight into the basis of the observed NREM period effects.

6. Conclusion

In conclusion, we have demonstrated temazepam results in global and topographic changes in slow wave activity, incidence, and morphology during NREM sleep. These findings suggest that benzodiazepines have myriad effects on spectral activity and slow wave morphology that vary depending on scalp topography, time of night, and method used to describe/quantify slow waves. Further research that explores the relationship between topographic changes in EEG waveforms induced by benzodiazepines and other related compounds, and their effects on cortical plasticity, sleep regulation, and neuropsychiatric disorders, is indicated to clarify the functional significance of these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Benzodiazepines alter slow waves during non-rapid eye movement (NREM) sleep, however, topographic effects on these waveforms are unclear
- In this study, temazepam reduced slow wave activity and incidence, most prominently in the latter portions of the sleep period
- Additionally demonstrated by high-density EEG, temazepam reduced the amplitude and slopes of frontal high-amplitude slow waves early during NREM sleep
- These results demonstrate benzodiazepines induce alterations in slow waves throughout the night that vary depending on cortical topography and measures used to characterize slow waves

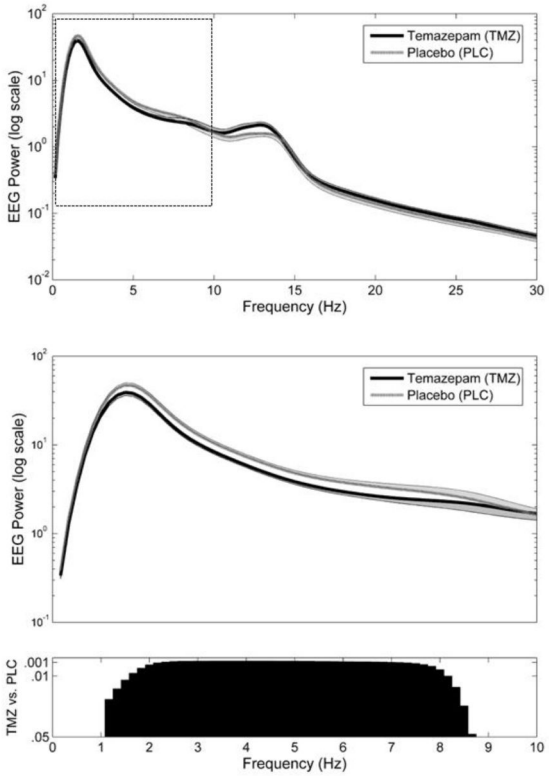

Fig 1.

Differences in global spectral power during NREM sleep in the low frequency range (inclusive of slow wave activity) between TMZ and PLC nights. Global (average 173 channels overlying the scalp) EEG spectral power ± SEM for TMZ and PLC plotted for each 0.17Hz frequency bin from 1–30Hz (top panel) and 1–10Hz (middle panel). Corresponding p-values for comparison between TMZ vs. PLC from 1–10Hz (lower panel). Significant differences in global power were observed between conditions for bins 1–8.67Hz.

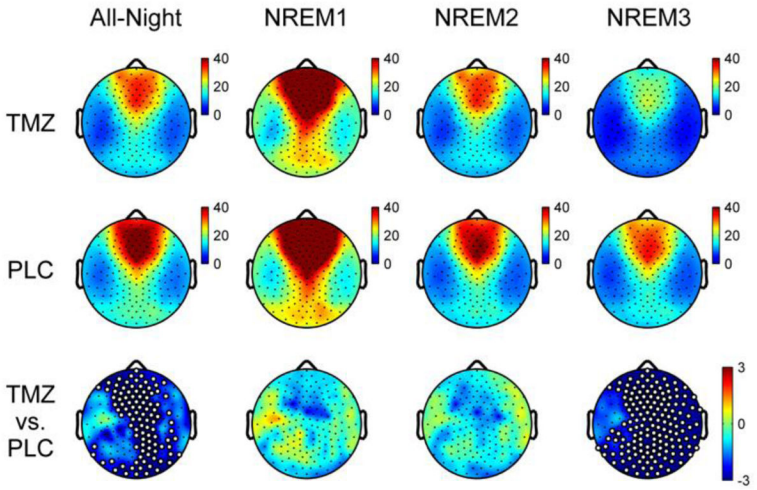

Fig 2.

Topographic SWA for TMZ and PLC nights for all-night NREM sleep and NREM episodes 1–3. Bottom row denotes t-values for channel-by-channel paired t-tests between TMZ and PLC. White dots denote significant channels after statistical non-parametric mapping with suprathreshold cluster test.

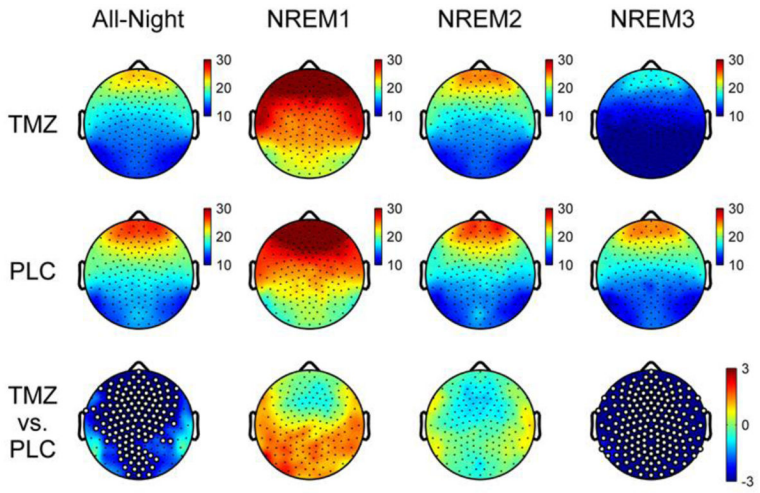

Fig 3.

Topographic slow wave incidence for TMZ and PLC nights for all-night NREM sleep and NREM episodes 1–3. Bottom row denotes t-values for channel-by-channel paired t-tests between TMZ and PLC. White dots denote significant channels after statistical non-parametric mapping with suprathreshold cluster test.

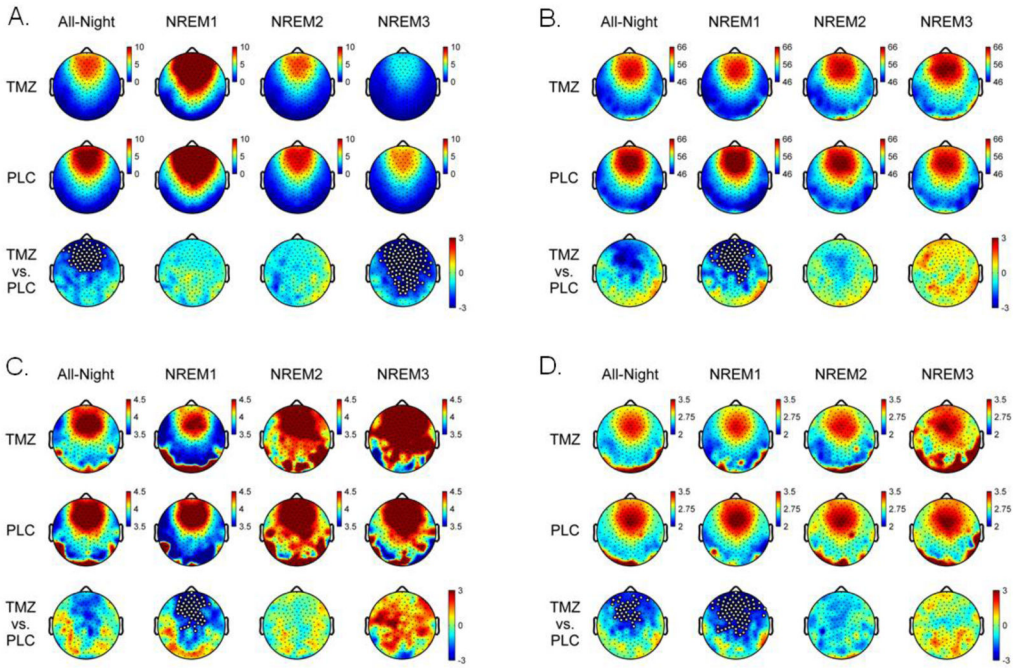

Fig 4.

Topographic slow wave incidence and morphology for high-amplitude (≥40 μV) slow waves. A) Incidence (waves/minute); B) amplitude (μV); C) 1st and D) 2nd segment slope (μV/sample). Bottom row denotes t-values for channel-by-channel paired t-tests between TMZ and PLC. White dots denote significant channels after statistical non-parametric mapping with suprathreshold cluster test.

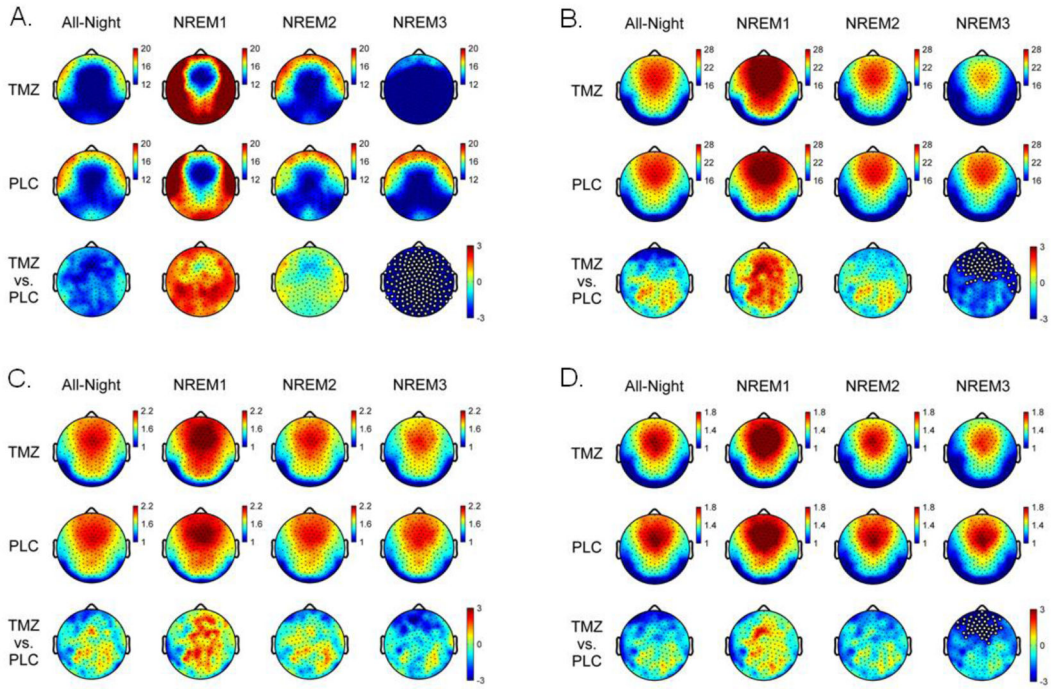

Fig 5.

Topographic slow wave incidence and morphology for low-amplitude (<40 μV) slow waves. A) Incidence (waves/minute); B) amplitude (μV); C) 1st and D) 2nd segment slope (μV/sample). Bottom row denotes t-values for channel-by-channel paired t-tests between TMZ and PLC. White dots denote significant channels after statistical non-parametric mapping with suprathreshold cluster test.

Table 1

Sleep staging and slow wave activity data.

	PLC	TMZ	p-value
TST (min)	424.7 (47.4)	436.6 (41.1)	0.32
WASO (min)	35.8 (32.1)	35.4 (43.7)	0.97
SE (%)	90.1 (8.5)	91.1 (9.1)	0.54
SOL (min)	12.2 (14.3)	7.4 (6.8)	0.16
N1 (min)	51.7 (34.6)	36.3 (25.0)	0.15
N2 (min)	260.7 (50.0)	280.5 (52.6)	0.19
N3 (min)	44.5 (30.5)	51.4 (25.5)	0.46
REM (min)	68.0 (32.2)	68.4 (33.8)	0.95
REM Latency (min)	144.5 (92.3)	141.8 (92.4)	0.93
SWA ($\mu V^2/Hz$)	21.2 (6.0)	17.2 (5.2)	0.002*

PLC, placebo; TMZ, temazepam; TST, total sleep time; WASO, wake after sleep onset; SE, sleep efficiency (TST/time in bed); SOL, sleep onset latency; N1/2/3, NREM stage 1/2/3; REM, stage rapid eye movement sleep; REML, REM latency (time from sleep onset to first REM sleep epoch); SWA, global slow wave activity (EEG power in 1–4.5Hz range average 173 channels overlying the scalp for all N2N3 sleep). Values are displayed as mean (standard deviation). P-value derived using 2-tailed, paired t-tests;

* indicates $p<0.05$.