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OPTIMIZING COMPUTATION OF OVERNIGHT DECLINE IN DELTA POWER: EVIDENCE FOR SLOWER RATE OF DECLINE IN DELTA POWER IN INSOMNIA PATIENTS

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Abstract

Objective: To determine the best of commonly used methods for computing the rate of decline in non-rapid eye movement (NREM) sleep EEG delta power overnight (Delta Decline) in terms of vulnerability to missing data and to evaluate whether this rate is slower in insomnia patients than healthy controls (HC).

Methods: Fifty-one insomnia patients and 53 HC underwent 6 nights of polysomnography. Four methods for estimating Delta Decline were compared (exponential and linear best-fit functions using NREM 1) episode mean, 2) peak, and 3) total delta power and 4) delta power for all available NREM epochs). The best method was applied to compare groups on linear and exponential rates of Delta Decline.

Results: Best-fit models using all available NREM epochs were significantly less vulnerable to deviation due to missing data than other methods. Insomnia patients displayed significantly slower linear and exponential Delta Decline than HC.

Conclusions: Computing Delta Decline using all available NREM epochs was the best of the methods studied for minimizing the effects of missing data. Insomnia patients display slower Delta Decline, which is not explained by differences in total sleep time or wake after sleep onset.

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Conflict of Interest Statement

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Significance: This study supports using all available NREM epochs in Delta Decline computation and suggests a slower rate in insomnia.

Keywords

insomnia disorder; EEG; spectral analysis; homeostatic sleep drive; delta power

1. INTRODUCTION

Insomnia disorder is associated with distress and daytime impairment as well as substantial societal costs in terms of greater health care utilization and reduced work productivity (Leger and Bayon, 2010). Although both pharmacological and behavioral interventions target this disorder, they are limited in their efficacy (Edinger et al., 2001b, Krystal et al., 2002, Morin et al., 1994, Murtagh and Greenwood, 1995), in part due to incomplete understanding of insomnia pathophysiology (Nowell et al., 1997). Several leading models have been proposed, including: dysfunction of sleep homeostatic mechanisms; abnormality of circadian clock function; and hyperarousal defined as hyperactivity of systems that override normal sleep/wake function (Pigeon and Perlis, 2006, Richardson, 2007).

In this study, we further evaluate the model positing that insomnia is associated with sleep homeostasis dysfunction, which could be due to factors diminishing homeostatic drive or arousal interfering with the homeostatic process or its dissipation over the night. The impetus for this focus is our prior work indicating that decreased homeostatic sleep drive, as indicated by a slower decline in non-rapid eye movement (NREM) EEG delta power over the night, predicts a better response to cognitive behavioral therapy for insomnia, and improvement resulting from cognitive behavioral therapy for insomnia is associated with an increase in homeostatic sleep drive (i.e., an increase in the rate of decline in NREM sleep EEG delta power over the night) among insomnia patients. Further, these changes in NREM delta power and cognitive behavioral therapy for insomnia improvement were both correlated with an increased period of waking during the day, reinforcing that the rate of decline in NREM delta power is reflecting homeostatic sleep drive and also supporting an association between the cognitive behavioral therapy for insomnia therapeutic effect and increased sleep drive (Krystal and Edinger, 2010).

There are several observations that support the hypothesis that insomnia disorder is associated with a decrease in homeostatic sleep drive. One key observation is based on the assumption that insomnia patients experience either sleep loss or insufficiently restorative sleep and, as a result, would be expected to be sleepier than healthy controls without sleep complaints if their sleep homeostatic mechanisms were functioning properly (Pigeon and Perlis, 2006). In contrast, evidence provided by 5 studies using the multiple sleep latency test (i.e., an objective test of sleepiness) have indicated that patients with insomnia disorder are either less sleepy during the day than healthy controls, or manifest the same propensity to fall asleep during the day (Bonnet and Arand, 2000, Dorsey and Bootzin, 1997, Edinger et al., 2008, Mendelson et al., 1984, Seidel et al., 1984). Two additional studies have employed sleep deprivation to assess the degree to which insomnia patients exhibit a post-deprivation recovery response indicative of sleep homeostatic mechanisms. These studies indicated that

a sleep homeostatic response exists in insomnia patients. However, a greater degree of sleep deprivation is required to elicit a comparable degree of recovery response in insomnia patients compared with healthy controls, suggesting an abnormality in the sleep homeostatic system (Edinger et al., 2004, Stepanski et al., 2000).

Lastly, several studies have assessed stage 3 sleep or NREM sleep EEG delta power in insomnia patients based on the assumptions that 1) recovery sleep following sleep deprivation is generally associated with an enhancement of both stage 3 sleep and all-night averaged NREM EEG delta power and 2) that insomnia patients should have increases in these parameters as they experience at least intermittent sleep loss (Dijk et al., 1990a). Evidence for dysfunction in sleep homeostasis has been found in terms of a decrease in stage 3 and/or all-night averaged EEG delta power in insomnia patients compared with healthy controls (Gaillard, 1976, 1978, Gillin et al., 1979, Reynolds et al., 1984, Sewitch, 1987) though two studies failed to find reductions in one or both of these parameters (Krystal et al., 2002, Perlis et al., 2001).

Notably, no studies have assessed sleep homeostasis in insomnia employing the best established measure of sleep homeostasis, the rate of decline in EEG delta power over the course of the night. Initial delta power peak and the rate of decline of delta power over the night have been convincingly demonstrated to reflect homeostatic sleep drive accumulated prior to sleep based on studies using naturalistic conditions, sleep deprivation, sleep extension, and napping methodologies using both human and animal samples (Achermann et al., 1993, Borbely et al., 1981, Brunner et al., 1993, Brunner et al., 1990, Dijk, 1995, Dijk et al., 1990a, Dijk et al., 1990b, 1991a, Dijk et al., 1991b, Dijk et al., 1993, Endo et al., 1997, Franken et al., 1991, Tobler and Borbely, 1986, Werth et al., 1996).

In the current study, we compared initial NREM EEG delta power and the rate of decline in NREM EEG delta power over the night in adults with insomnia disorder and healthy controls (HC) without sleep complaints. Importantly, our samples did not differ in group-average total sleep time, which is consistent with prior studies showing that 40 – 50% of insomnia patients do not have short total sleep time as measured by PSG compared to healthy controls (Carskadon et al., 1976, Dorsey and Bootzin, 1997, Edinger and Fins, 1995, Edinger et al., 2000, Frankel et al., 1976, Salinpascual et al., 1992, Sugerman et al., 1985, Vanable et al., 2000, Zucconi et al., 1996). Thus, the measure of homeostatic sleep drive used in this study (i.e., the rate of decline of delta power over the night) may assess differences in sleep need occurring in insomnia patients versus control groups or may possibly reflect the impact of elevated arousal on this measure. Specifically, if insomnia patients evidence slower rate of delta decline overnight, this may suggest an actual or apparent (due to hyperarousal) lower sleep need in this population.

Based on prior literature, we hypothesized that patients with insomnia disorder would display a lower initial delta power peak and more gradual rate of decline in delta power over the sleep period compared to HC even after controlling for sleep disruptions (i.e., wake time after sleep onset) and total sleep time. We controlled for wake time after sleep onset as it could undermine the process of dissipation of homeostatic sleep drive (i.e., a less rapid rate of decline of delta power over the night) and could reflect, at least in part, the degree of

hyperarousal (Krystal and Edinger, 2010). Further, we examined group differences in both the linear and exponential decline in delta declines overnight. While studies of overnight delta dynamics in *groups* of individuals have suggested that delta power declines exponentially during sleep (Borbely and Achermann, 1999), there is no evidence to support whether delta power declines fit an exponential pattern within a particular individual. Thus, we computed the data to fit both a linear and exponential function to assess the best method to evaluate overnight delta dynamics.

Before we could carry out these comparisons, we first had to determine which method to use for computing the best-fit exponential and linear functions of NREM EEG delta power over the night. Although delta decline is considered by the field to be the best established measure of sleep homeostasis, there are several options that have been utilized in the published literature and there is no current consensus on the best method for computing delta decline. These include computing best-fit functions using: 1) the peaks of EEG delta power in each NREM episode (Krystal and Edinger, 2010, Walacik-Ufnal et al., 2017); 2) the average EEG delta power in each NREM episode (Armitage et al., 2007, Brower et al., 2011, Maric et al., 2017, Robillard et al., 2010, Rusterholz et al., 2010, Rusterholz et al., 2017); and 3) the total power in each NREM episode (Campbell et al., 2016, Feinberg and Campbell, 2003). In addition, we considered a fourth method in which we utilized EEG delta power for all available NREM epochs based on the principles that: 1) it was preferable to have the method not be dependent on defining NREM episodes as the definitions of NREM episodes vary and are of necessity somewhat arbitrary; and 2) it was desirable to use as many points as possible in order to estimate best-fit functions because there is inevitably missing data due to artifacts which diminish epochs available for use in computation.

To date, there have not been any studies determining which among these methods is preferable. As a result, we first sought to determine which of these methods is optimal in terms of one of the critical challenges facing computation of the rate of decline in NREM EEG delta power: there are nearly always artifacts or stage/state transitions in NREM epochs leading to data exclusion in these estimates. Not removing such epochs leads to significant deviation in estimated values (Sutherland et al., 2009), and it is evident that with enough missing data, significant deviation of the estimated exponential and linear functions from the "true value" (i.e., the value determined if no epochs are missing) will occur. To this end, we compared these methods in terms of the degree to which the estimated values deviated from the "true value" with systematically varying numbers of randomly selected missing epochs.

We then applied that method to test our primary hypotheses that a lower initial delta power peak and a slower rate of decline in delta power will be observed in individuals with insomnia disorder compared to healthy controls (HC). If a decrease in the rate of decline in NREM EEG delta power over the night in insomnia patients is found it would further support the presence of dysfunctional homeostatic sleep drive in insomnia patients as well as the use of insomnia treatments improving homeostatic sleep drive such as sleep restriction therapy. Importantly, these indices may improve our capacity to personalize treatment for insomnia by identifying individuals for whom such interventions are particularly likely to be effective.

2. METHODS

2.1 Design

The current retrospective study used a cross-sectional design to investigate group differences in the rate of decline of delta power overnight and initial delta power peak among individuals with insomnia disorder and HC without sleep complaints. Study procedures were approved by the Institutional Review Boards of Duke University and VA Medical Center in Durham, NC, and participants provided written informed consent prior to enrollment. Participants were compensated for their time and reimbursed for parking expenses at the conclusion of study involvement.

2.2 Participants

Participants ranged in age from 20 – 80 years and were a subset of those involved in a prior study examining the home and laboratory sleep patterns of adults with insomnia disorder and HC (Edinger et al., 1997, Edinger et al., 2001a, Edinger et al., 2008, Edinger et al., 2013). The 104 participants included in the current study were those for whom PSG data were suitable for spectral analysis, and adults with insomnia disorder and HC were matched for age and sex. Participants were recruited via posted announcements at a VA and Duke University Medical Center, flyers posted in public libraries, letters mailed to individuals in Duke's Center for the Study of Aging and Human Development Subject Pool, and face-to-face solicitations of patients presenting to the Duke Sleep Disorders Center.

Potential participants completed a screening procedure consisting of structured psychiatric (First et al., 1995) and sleep (Schramm et al., 1993) interviews, a medical examination, a thyroid-stimulating hormone level screening, and 1 to 2 nights of PSG to rule out occult primary sleep disorders. Inclusion criteria for the insomnia disorder group included sleep complaints consistent with DSM criteria (i.e., ≥ 6 months of difficulty initiating or maintaining sleep or nonrestorative sleep with accompanying daytime deficits) (American Psychiatric Association. and American Psychiatric Association. Task Force on DSM-IV., 1994, American Psychiatric Association. and American Psychiatric Association. Work Group to Revise DSM-III., 1987). Inclusion criteria for the HC group included absence of sleep complaints and major medical or psychiatric conditions. Exclusion criteria for the full sample included presence of a sleep-disruptive medical condition (e.g., rheumatoid arthritis), a current Axis I psychiatric condition (other than insomnia disorder), sedative hypnotic dependence and unwillingness/inability to suspend these medications for the study duration, use of psychotropic medication, an apnea-hypopnea index (AHI) ≥ 15, a periodic limb movement-related arousal index ≥ 15, comorbid sleep disorders in addition to insomnia, and failure to complete a sleep diary (used to ensure accurate Time in Bed (TIB) for data collected at home).

In addition, we included in the analysis only sleep studies having NREM data that was artifact-free for more than 10% of the total sleep time. Although this number is somewhat arbitrary, it was selected to minimize spurious findings due to inadequate sampling of data over the night while maximizing power to detect effects. To ensure the validity of selecting this cutoff, the primary analyses were repeated using cutoffs for artifact-free total sleep time

ranging from 5 – 20%. Details from these additional analyses are included in the results section below.

2.3 Polysomnography

Participants underwent 6 nights of PSG total with 3 consecutive nights conducted in a university medical center sleep laboratory and 3 consecutive nights conducted at home. The order of PSG locations (lab or home) was randomly determined so that approximately one-half of participants in each group underwent lab-based PSG first and the other half completed home-based PSG first. The range of time between lab and home PSGs ranged from 4 to 30 days apart. PSG recordings were obtained using 8-channel Oxford Medilog 9000 or 9200 series ambulatory cassette recorders (Edinger et al., 1989, Edinger et al., 1991). The monitoring montage included two electroencephalogram (EEG) channels (C_3 – A_2, O_Z – C_Z), bilateral electrooculogram (EOG), submental electromyogram (EMG), two channels of anterior tibialis EMG (left and right leg), and a nasal-oral thermistor. PSG was accompanied by a paper and pencil sleep diary, which was used to verify accuracy of home-based PSG sleep data (e.g., TIB).

An Oxford Vision System (Oxford Instruments Inc., Oxford, UK) was used to digitize EEG data at 128 Hz with 8-bit accuracy with filter settings of 0.5 and 64 Hz (with −3 dB roll off at both ends and a 3rd order Butterworth anti-aliasing filter at 64 Hz). The digitized data were scored by co-author ADK, who is board-certified in sleep medicine, highly experienced in scoring sleep studies for both clinical and research purposes, and was blind to participant group. Standard scoring criteria (Iber et al., 2007, Krystal et al., 2002, Rechtshaffen and Kales, 1968) were used to assign sleep stages and identify respiratory events (e.g., apneas, hypopneas), periodic limb movements, and periodic limb movement arousals. PSG data from the first night (age 60+) or first two nights (age 20–59) were used to rule out obstructive sleep apnea and periodic limb movement disorder.

2.4 EEG Analysis

Spectral analysis was carried out using a single C3-A2 (left central to right mastoid) channel and only included 30 second epochs that were free of movements, artifacts, arousals, or transitions between sleep stages as verified by co-author ADK. The EEG data underwent autoregressive high-pass filtering (i.e., ½ Hz) and Hanning windowing followed by fast Fourier transformation in 2-second epochs averaging over time and frequency. Consistent with prior spectral analysis literature, power spectral estimates (μV^2) were derived for 6 bands, including delta (0.5–3.5 Hz), theta (4.0–8.0 Hz), alpha (8.5–12 Hz), sigma (12.5–16 Hz), beta (16.5–30 Hz), and gamma (30.5–60 Hz) and the two-second epoch estimates averaged within each 30 second epoch of data to generate power spectral estimates for these 6 frequency bands for each 30 second epoch (Buysse et al., 2008, Krystal et al., 2002, Merica et al., 1998, Perlis et al., 2001). As previously reported, this analysis was conducted using custom software written in Visual C++ by coauthor ADK, which employed MATLAB (the MathWorks, Inc., Natick, MA) for computing fast Fourier transforms (Krystal et al., 2002).

The rate of decline of delta power over the night was calculated by fitting both linear and exponential best-fit lines using the least squares method. The least squares method was applied only to the epochs of NREM sleep which were without movements, artifacts, or state transitions retaining the original times that these epochs occurred in the computation (i.e., computation of best-fit functions was carried out with these epochs retaining their temporal positions and with absent data for epochs with movement, artifacts, state transitions or where there was REM or waking). NREM sleep included stages N2 and N3 sleep as stage N1 sleep typically includes movement artifacts that greatly limit the amount of usable data. Supplementary Table 1 provides information about the number of NREM epochs per night included in the primary analyses for the sample. The mean number of artifact-free, movement-free, transition-free NREM sleep epochs for studies for individuals with insomnia was 192 (SD = 98) and for HC was 198 (SD = 97), and the number of NREM sleep epochs did not differ between groups ($p = .65$). The initial delta power was the delta power at the time of sleep onset derived from the best-fit linear and exponential functions of delta power over the night.

2.5 Comparison of Methods for Computing Rate of Delta Power Decline Over the Night

We utilized a Monte-Carlo simulation approach to estimate and compare the vulnerability to missing data of the four methods for computing best-fit linear and exponential functions. This method was carried out with data from one PSG recording each from 20 unique subjects (i.e., 20 total recordings) with insomnia disorder from a prior study (Krystal and Edinger, 2010) where at least 120 epochs of artifact-free, movement-free, transition-free NREM sleep data were available. The mean number of artifact-free, movement-free, transition-free NREM sleep epochs for these studies was 219. For each study we generated indices of how eliminating an increasing number of epochs affects the estimates of slope (linear function) and time-constant (exponential function) of delta power over the night. We did this by computing estimates for 100 randomly selected combinations of missing epochs for each number of missing epochs, from 1 missing epoch to all but 3 missing epochs (3 epochs is the minimum needed to fit the functions). Specifically, we carried out estimates for the best fit functions for 100 different single missing epochs, followed by 100 different combinations of two missing epochs, followed by 100 different combinations of three missing epochs, etc., up to 100 different combinations where all but 3 epochs were missing.

As the primary index of vulnerability to missing epochs we computed the rate of change of the linear slope in delta power and the time constant of the exponential rate of decline in delta power estimates (both based on linear regressions) as a function of missing epochs. The slower the rate of change resulting from the linear regressions the less the values deviate from the “true value” (i.e., the rate of decline with all available NREM epochs without movement, artifact, or state transitions utilized) as greater numbers of epochs are missing. A value of 0 indicates that the values stay the same as the “true value” for all numbers of epochs missing. As a result, the slower the rate of decline with missing epochs, the better the method in terms of vulnerability to missing data such as artifacts. It is important to note that review of the raw plots of deviation from the true value versus missing epochs does not indicate the presence of a linear relationship. In fact, there was not a simple or consistent relationship between deviation and number of missing epochs. In order to deal with this

complexity and our inability to employ a function that would consistently accurately fit the data, we chose to use the linear rate of change with missing epochs as an indicator of the general trend of how the deviation increases with the number of missing epochs as a metric for comparison of methods. We did so with the understanding that it was, in general, not the case that this was based on there being a linear relationship between deviation and number of missing epochs.

We then carried out a repeated measures analysis of variance comparing the rates of change as a function of missing epochs for the regression lines for the 4 different methods (i.e., NREM episode mean, NREM peak, total delta power, delta power for all available NREM epochs). As a secondary measure we computed the standard deviation of the rate of decline estimates (linear slope and exponent) over the 100 iterations for all numbers of epochs removed. We selected the standard deviation as a second, variability measure based on the assumption that some participants' data will be inherently less deviant and the standard deviation may differentiate methods in terms of vulnerability to missing epochs. Although there are limitations to the utility of the standard deviation measure in terms of its sensitivity to variation in studies with many epochs, given that there are a range of epochs across the included studies and because we used multiple measures, this should not interfere with the goal of comparing the vulnerability of the methods. Lower values of the standard deviation indicate less variation as a function of the particular epochs selected for removal and, as a result, less deviation from the "true value" due to missing epochs as a result of artifacts, state transitions, etc.

2.6 Statistical Analysis of Rate of Decline in Insomnia vs HC Subjects

Analyses were conducted using SAS statistical software (SAS Institute, Inc., Cary, NC) using two-tailed tests of significance. Linear mixed effects models (PROC MIXED) employing maximum likelihood estimation and an unstructured covariance structure analyzed group differences in initial delta power peak and delta power decline overnight. Each model estimated a random intercept for the variable of interest (linear delta power decline, exponential delta power decline, or initial delta power) over time (i.e., night) for each subject and fixed effects included sex, place (home versus lab), group (insomnia versus HC), night (1 – 6), and their interactions (including 2-, 3-, and 4-way interactions) as well as age. Age and sex were selected as covariates because of prior literature indicating the impact of these characteristics on EEG spectral indices (Armitage et al., 2001, Armitage et al., 2000, Rediehs et al., 1990, Reynolds et al., 1985, Smith et al., 1977). In addition, as described above, wake time after sleep onset was included as an additional covariate in regressions examining group differences in linear and exponential declines in delta slope due to the likelihood that delta power declines are impacted by sleep disturbances. Mixed effects procedures were employed to prevent listwise deletion due to missing data.

3. RESULTS:

3.1 Comparison of Methods of Computing the Rate of Decline in Delta Power

Table 1 includes a comparison of the indices of vulnerability to missing data for all 4 methods for both linear and exponential models of the rate of decline in delta power over the

night. The rate of change in the rate of decline in delta power estimates as a function of number of epochs missing indicated that using all available NREM epochs had a slower rate of decline with increasing numbers of missing epochs for both linear ($p<0.0002$) and exponential ($p<0.0009$) models of delta power over the night. This method was also associated with lower standard deviations than the other 3 methods for both linear and exponential models (see Table 1). The second best method for determining linear and exponential decline in NREM EEG delta power over the night by these methods was the mean of NREM EEG Delta Power in each episode of NREM sleep. Thus, based on vulnerability to missing data due to artifacts, etc., fitting the best-fit function of all available NREM sleep epochs was the preferred method and was used to compare insomnia patients and HC.

3.2 Demographics

Of the 104 individuals enrolled in the current study, 51 (28 females) met criteria for insomnia disorder whereas the remaining 53 (29 females) met inclusion criteria for HC. The insomnia disorder and HC groups did not significantly differ in age (F [1, 102] = .40, P = 0.53), sex (X^2 [1] = 0.0, P = 0.99), ethnicity (X^2 [4] = 1.89, P = 0.76), years of education (F [1, 102] = 0.69, P = 0.41), or average total sleep time over the six nights studied (F [1, 102] = 0.60, P = .55). Table 2 provides demographic and PSG sleep information about the sample. The frequency of short sleepers (TST < 6 hours) did not differ by group (see Supplementary Table 2). Additional information about spectral analysis variables among individuals in the insomnia and HC groups is provided in Supplementary Table 3.

3.3. Characteristics of Delta Decline and Initial Delta Peak Variables

The mean linear delta decline for the insomnia group was −2.02 (SD = 1.96) and −2.92 for HC (SD = 1.84), and the mean initial delta peak for the insomnia group was 1763.67 (SD = 978.89) and 2154.50 for HC (SD = 1317.43). Levene's test for equality of variances suggested equality of variances across groups for both linear delta decline (F = .75, p = .39) and initial delta peak (F = 2.33, p = .13). However, Shapiro-Wilks tests of normality suggested the distributions of both variables were non-normal and leptokurtic (p's < .05). We tested a family of transformations to normalize the distribution, and applied the technique that best led to distributions that approximated the normal distribution - a BoxCox transformation with lambda values chosen to maximize the loglikelihood for a normal distribution (Osborne, 2010). Prior to applying BoxCox, the data were shifted so that all values were positive. The selected lambda values were 1.45 and .40 for linear delta decline and initial delta peak, respectively. We similarly applied the BoxCox transformation to the exponential delta decline and initial delta peak. The analyses reported below use the transformed variables.

3.4 Group Differences in Initial Delta Power and Slope of Delta Power Overnight

A linear mixed effects regression model covarying for sex, place of recording (home vs. lab), time, and their interactions as well as age revealed that adults with insomnia disorder displayed a significantly slower linear decline in delta power overnight compared to HC (F [1, 59] = 8.36, P < 0.01). In addition to the group difference, increasing age was significantly associated with slower declines in linear delta power overnight (F [1, 59] = 21.45, P

< .0001). All other main and interaction effects were non-significant. When controlling for the wake time after sleep onset effect, the group effect on linear delta decline overnight remained significant (F [1, 58] = 7.75, $P < 0.01$). In addition, increased age (F [1, 58] = 9.87, $P = .003$) and wake time after sleep onset (F [1, 58] = 12.52, $P < 0.001$) were also significantly related to slower linear declines in delta power overnight. See figures 1 and 2.

Similarly, adults with insomnia disorder exhibited a significantly slower exponential decline in delta power overnight compared to HC, over and above the effects of sex, place of recording, time, and their interactions as well as age (F [1, 7] = 9.77, $P = .02$). In this model, greater age was also related to slower exponential decline in delta power overnight (F [1, 7] = 9.26, $P = 0.02$). The group (F [1, 6] = 9.16, $P = 0.02$) and age (F [1, 6] = 7.23, $P = 0.04$) effects on the exponential decline in overnight delta power remained significant after controlling for wake time after sleep onset. See figure 3.

As noted above, this analysis sampled sleep studies wherein NREM data for more than 10% of the total sleep time was able to be included in analysis because it was free of artifacts, stage-transitions, and events such as leg movement or apneas. As this was an arbitrary cutoff we carried out exploratory analyses with a range of required artifact-free data from 5 – 20%. The group difference in delta decline remained significant for models including sleep studies in which artifact-free NREM data for 7 – 19% of total sleep time was included, and became a trend in models including sleep studies in which NREM data for 6% or 20% of total sleep time was included.

Controlling for sex, place, time, and their interactions as well as age, adults with insomnia disorder exhibited lower initial delta power peak compared to HC in the linear model (F [1, 59] = 4.56, $P = .04$). Additionally, increasing age was significantly associated with reduced initial delta power peak (F [1, 59] = 10.61, $P = .002$) in the linear model. The group effect was similar in the exponential model, with adults with insomnia disorder displaying a non-significant trend toward a lower initial delta power compared to HC (F [1, 7] = 3.73, $P = .09$). No additional main or interaction effects were significant in the linear or exponential models. See figure 4.

We again carried out exploratory analyses with a range of required artifact-free NREM data from 5 – 20%. The group effect in initial delta power remained significant for models including sleep studies in which NREM data for 8 – 12% of total sleep time was included. Overall, these results suggest that insomnia patients display lower initial delta power peak compared to their healthy peers.

4. DISCUSSION

The current study compared initial NREM EEG delta power and the rate of decline of delta power overnight in individuals with insomnia versus healthy controls without sleep complaints. In order to execute these comparisons we first compared 4 methods for computing the rate of decline in NREM EEG delta power over the night based on one key attribute: the degree to which they are affected by epochs that are missing because of movement, artifact, or stage-transitions using a single night of data. The examined methods

included fitting best-fit linear and exponential models of: the peak values of NREM EEG delta power in each NREM episode, the total NREM EEG delta power in each NREM episode, the mean NREM EEG delta power in each NREM episode, and all available NREM EEG epochs over the night. We found that using all available NREM epochs was superior to the other approaches for both linear and exponential models in terms of reduced vulnerability to missing data and the particular distribution of the missing data. As a result, this method is recommended for use in future studies.

Using this method, results indicated that individuals with insomnia displayed a slower rate of linear and exponential decline in delta power overnight than did healthy adults. This finding was robust when controlling for a range of additional factors, including age, sex, and location of recording (home or laboratory) and was detected with the inclusion criterion of having NREM data that was artifact-free for more than 10% of the total sleep time (remaining significant between 7 – 19%). In addition, adults with insomnia displayed a lower initial delta power compared to HC, and this finding remained significant with greater power to detect effects through the inclusion of more people (8% of total sleep time was artifact-free NREM) or improving data quality (12%).

There may be several reasons for a slower decline in delta power overnight among patients with insomnia. Adults with insomnia may suffer from a relative deficit in homeostatic sleep drive compared to their healthy counterparts, which would be consistent with the prior evidence of diminished homeostatic sleep drive in insomnia patients reviewed in the introduction (e.g., Edinger et al., 2008). Alternatively, patients may experience hyperarousal or alterations in sleep inducing/maintaining mechanisms that undermine the homeostatic sleep drive process.

Importantly, this abnormality in the rate of decline of delta power overnight was found in a sample of adults with insomnia who did not differ on average from healthy controls in PSG-measured total sleep time displayed over the 6 night study. As a result, we can conclude that, given a similar amount of sleep, insomnia patients may build up less homeostatic sleep drive which would be expected to manifest in difficulties falling and staying asleep compared with healthy individuals without sleep complaints. In addition, the current findings are robust after controlling for wake time after sleep onset, suggesting that the slower rate of delta power decline in individuals with insomnia reported in this study is not explained by the impact of nocturnal awakenings on overnight delta power dynamics. Whether dysfunction of homeostatic sleep drive is a fundamental mechanism underlying the sleep problems observed in insomnia patients or whether this dysfunction is driven by another pathophysiologic process remains unknown.

These findings complement our prior study indicating that a slower rate of decline in NREM sleep EEG delta power over the night predicts greater improvement with cognitive behavioral therapy for insomnia and that the degree of improvement in insomnia symptoms with cognitive behavioral therapy for insomnia is correlated with the degree of increase in the rate of decline in delta power over the night (Krystal and Edinger, 2010). The fact that the current findings indicate that, in general, those with insomnia disorder have a diminished rate of decline in delta power over the night suggests that cognitive behavioral therapy for

insomnia is likely to be helpful for the majority of insomnia patients by targeting and normalizing decreased homeostatic sleep drive. Additionally, these findings speak to the importance of cognitive behavioral therapy for insomnia components that target increasing homeostatic sleep drive such as sleep restriction therapy. Finally, these results suggest that the rate of decline in delta power has potential as a means of personalizing treatment for insomnia by helping to identify individuals for whom such interventions are particularly likely to be effective.

This study should be considered in the context of several limitations. First, the sample used in this investigation included research volunteers who were largely Caucasian. Thus, results may not generalize to more diverse or clinically severe populations. Secondly, although slower rates of decline in delta power overnight in groups with the same mean total sleep time may suggest lower sleep need among individuals with insomnia, we cannot rule out the possibility that our groups differed in sleep need not because one group consisted of insomnia patients and the other of healthy controls, but because the individuals in the two groups happened to include individuals who differed in sleep need by chance due to factors other than insomnia status. Thirdly, although the filtering and windowing processes used in the current study are consistent with prior literature for measuring slow wave activity, the methods used are not conducive to examination of lower frequencies (e.g., ¼ hz).

Despite these limitations, the current study provides strong support for divergent rates of decline in delta power overnight among individuals with insomnia disorder versus healthy controls, suggesting deficient homeostatic sleep drive or possibly elevated arousal interfering with homeostatic sleep drive, among individuals with insomnia disorder. Future studies should examine the relationship of overnight delta power to daytime sleepiness (e.g., Multiple Sleep Latency Test) (Richardson et al., 1978) and neurocognitive and functional impairment in individuals with insomnia disorder. Additionally, future studies should expand on prior work investigating the effects of both behavioral (e.g., cognitive behavioral therapy for insomnia) and pharmacological interventions on the rate of decline of overnight delta power among individuals with insomnia as well as the physiologic mechanisms underlying these effects (Krystal and Edinger, 2010). Finally, given that our results suggest a lower initial delta power peak among insomnia patients compared to healthy controls, comparisons between the measures reported in this paper versus measures such as the delta sleep ratio (i.e., ratio of slow wave activity between the first two NREM episodes (Kupfer et al., 1990)) in predicting clinical outcomes and treatment response may be of particular interest and should be the focus of future work.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The views expressed herein are exclusively those of the authors and do not necessarily reflect the views of the Department of Veterans Affairs.

Abbreviations:

NREM	Non-Rapid Eye Movement
HC	Healthy Controls

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HIGHLIGHTS

- Overnight delta decline is an important measure yet there is no standard method for computation.
- Computing overnight delta decline using all NREM epochs minimizes vulnerability to missing data.
- Insomnia patients display a slower rate in overnight delta decline compared to healthy controls.

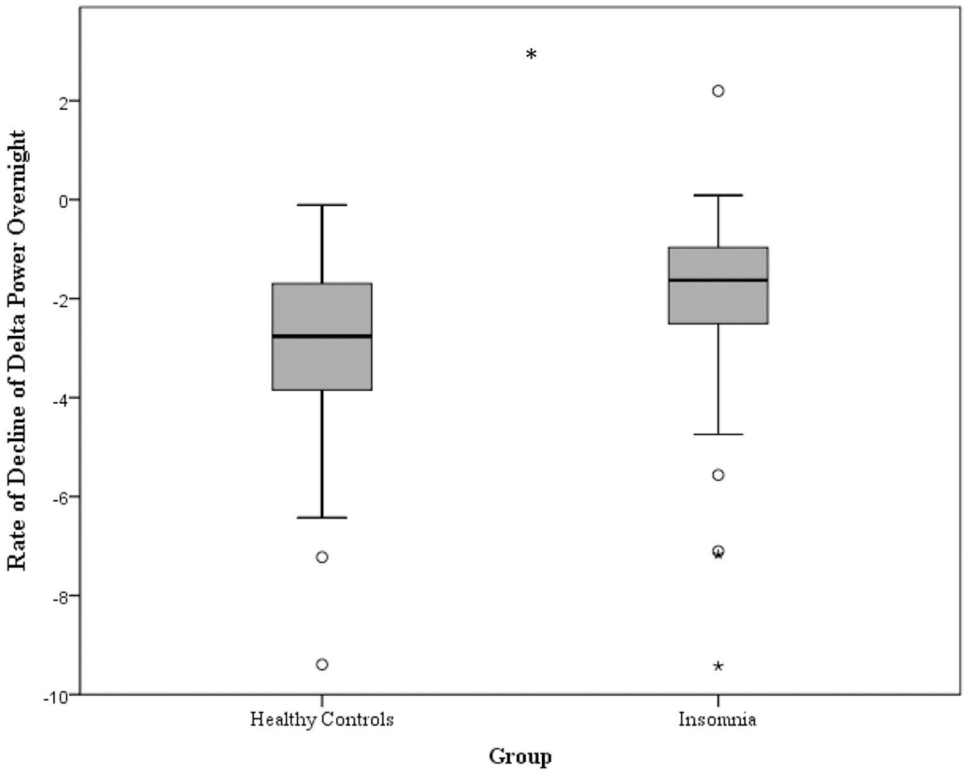

Figure 1.

Group differences in slope of delta power overnight. Asterisk (*) denotes $p < .05$. Note: for ease of interpretation, original values are shown prior to BoxCox transformation.

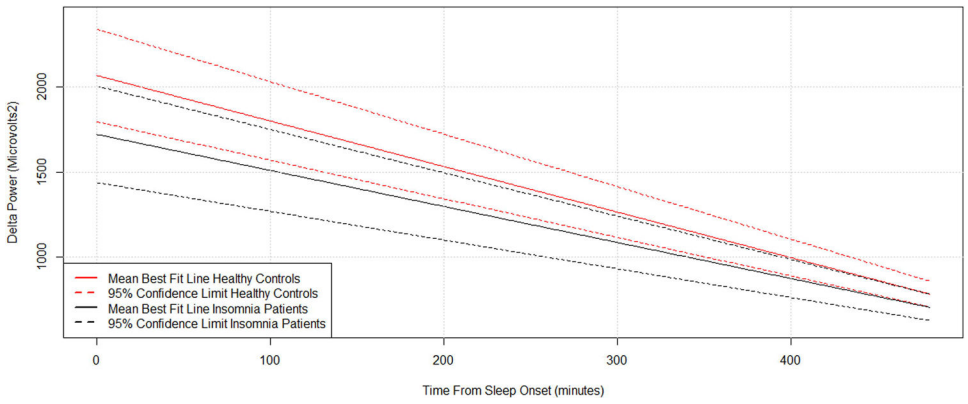

Figure 2.

Best fit line of delta power over the night with 95% confidence limits in insomnia patients versus healthy controls.

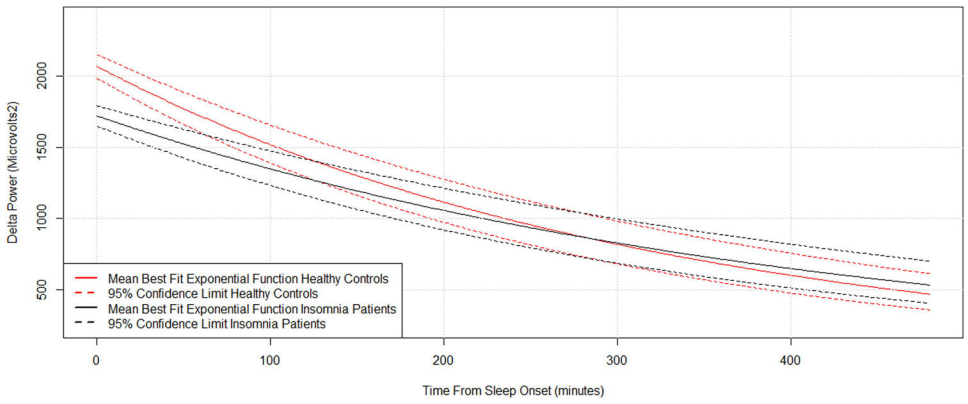

Figure 3.

Best fit exponential function of delta power over the night with 95% confidence limits in insomnia patients versus healthy controls.

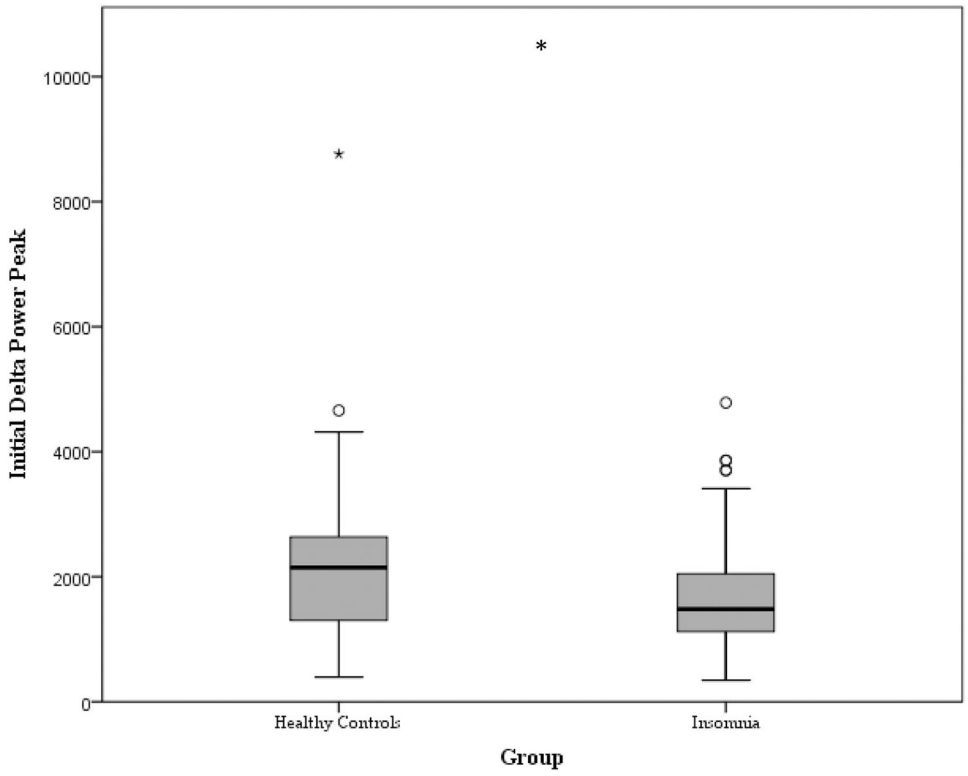

Figure 4.

Group differences in initial delta power peak. Asterisk (*) denotes $p < .05$. Note: for ease of interpretation, original values are shown prior to BoxCox transformation.

Table 1

Comparison of methods for comparing rate of decline in delta power.

Method	Linear Models of Delta Decline Over the Night*		Exponential Models of Delta Decline Over the Night+	
	ROC of Linear Delta Decline as a Function of Missing Epochs (SD in ROC Across Subjects)[1*]	Mean SD of Linear Delta Decline[2]	ROC of Exponential Delta Decline as a Function of Missing Epochs (SD in ROC of Exponent Across Subjects)[3+]	Mean SD of Exponential Delta Decline[4]
Peak Power in NREM Episodes	0.012 (0.013)	0.94	$2.4x10^{-5}$ ($4.0x10^{-5}$)	0.0033
Total Power in NREM Episodes	0.86 (1.4)	44.4	0.0057 (0.011)	0.28
Mean Power in NREM Episodes	0.0028 (0.0064)	0.18	$6.5x10^{-6}$ ($1.8x10^{-5}$)	0.00038
Best Fit Function Using All Available NREM Epochs	0.00036 (0.00059)	0.083	$6.9x10^{-7}$ ($1.0x10^{-6}$)	0.00015

Note:

Abbreviations: ROC, rate of change; SD, Standard Deviation.

*Best-Fit Line Using All Available Epochs Significantly Smaller than Other Best-Fit Line Methods ($p<0.0002$) in Terms of Slope of Values as a Function of Missing Epochs.

+Best-Fit Exponential Using All Available Epochs Significantly Smaller than Other Best-Fit Exponential Methods ($p<0.0009$) in Terms of Slope of Values as a Function of Missing Epochs.

1.Generated by computing an average of slope estimates for 100 Simulations for Each Number of Missing Epochs and then computing the rate of decline in that average over number of missing epochs. The units are μV2/min/epochs missing.

2.Represents the Average Across Subjects of the Standard Deviation of the Slope of Best Fit Line of Delta Power Averaged Over Estimates Obtained for Each Number of Missing Epochs (For Each Number of Missing Epochs a Standard Deviation of the Slope is Obtained Based on Generating a Slope Estimate for 100 Simulations)

3.Generated by computing an average of estimates of the Exponent of the Best Fit Exponential Function for Delta Power for 100 Simulations for Each Number of Missing Epochs and then computing the rate of decline in that average over number of missing epochs. The units are μV2/min/epochs missing.

4.Represents the Average Across Subjects of the Standard Deviation of the exponent of the Best Fit Exponential Function of Delta Power Averaged Over Estimates Obtained for Each Number of Missing Epochs (For Each Number of Missing Epochs a Standard Deviation of the Estimate is Obtained Based on Generating an Exponent Estimate for 100 Simulations)

Table 2

Demographics of the sample. Note: there are no significant differences in demographic variables between groups. “Presenting Problem” variables only apply to insomnia group.

Demographic characteristic	**Insomnia (n = 51)**	**HC (n = 53)**	
Age, years, mean (SD)	42.67 (16.51)	40.70 (15.55)	
Years of education, mean (SD)	15.86 (2.68)	16.28 (2.50)	
Sex, female, *n*	28	29	
Ethnicity, *n*			
Caucasian	38	44	
African American	8	6	
Other	5	3	
Duration of insomnia, years, mean (SD)	10.52 (8.97)	–	
Presenting problem, *n*			
Onset difficulty	9	–	
Maintenance difficulty	12	–	
Both onset and maintenance difficulty	27	–	
Non-restorative sleep	3	–	
PSG sleep variables, mean (SD)	**Insomnia (n = 51)**	**HC (n = 53)**	***t* statistic (*p* value)**
Total Sleep Time, minutes	379.2 (69.50)	386.7 (58.91)	0.60 (055)
Sleep Efficiency, percentage	82.42 (10.97)	88.41 (11.30)	2.75 (0.007)
Wake After Sleep Onset, minutes	3.47 (0.74)	3.03 (0.62)	−3.37 (0.001)
Sleep Onset Latency, minutes	2.94 (0.90)	2.55 (0.82)	−2.34 (0.02)
Stage 1 Sleep, percentage	10.80 (0.04)	9.18 (0.04)	−1.94 (0.06)
Stage 2 Sleep, percentage	49.32 (8.28)	49.15 (7.68)	−0.10 (0.92)
Slow Wave Sleep, percentage	18.68 (8.61)	20.75 (9.14)	1.19 (0.24)
Rapid Eye Movement Sleep, percentage	20.75 (4.07)	20.48 (5.31)	−0.29 (0.77)

Abbreviation: PSG, polysomnography; HC, healthy controls.