Sleep Spindles Predict Response to Cognitive Behavioral Therapy for Chronic Insomnia

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Abstract

Cognitive behavioral therapy (CBT-I) is a common and effective method for treating chronic insomnia, although patient responses to it are not uniform and research on predicting treatment response has mostly focused on psychological factors. Here, it is investigated whether brain oscillations during sleep at baseline, particularly sleep spindles, are predictive of treatment response. Twenty-four participants with chronic primary insomnia took part in a 6-week CBT-I performed in groups of 4 to 6 participants. Treatment response to CBT-I was assessed using the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI) measured at pre- and post-treatment. Secondary outcome measures included sleep diary (over seven days) and polysomnography (PSG) sleep efficiency (%) measured at pre- and post-treatment. Spindle density (as well as secondary measures of duration, amplitude, power, frequency, and spectral power in the sigma band) during stages N2-N3 sleep were extracted from the PSG recording at pre-treatment. Multiple regression assessed whether sleep spindle activity predicted treatment response to CBT-I. After controlling for baseline measures, age, sex, education level, treatment compliance, time in N2, and the location of the sleep recording, lower spindle density and sigma power at pre-treatment predicted poorer CBT-I response at post-treatment, as reflected by lower PSQI scores.

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INTRODUCTION

Insomnia is one of the most commonly reported sleep disturbances with an estimated 6-10% of adults meeting clinical criteria for an insomnia disorder, leading to health consequences and impairments in quality of life.[1, 2] Similar prevalence rates have also been noted in university students with around 9.5% meeting clinical criteria for chronic insomnia in one study.[3] Chronic insomnia is characterized by subjective reports of poor sleep quality related to one or more symptoms of: difficulty falling asleep, difficulty maintaining sleep and/or early morning awakenings with the inability to fall back asleep, despite adequate opportunity to sleep. These symptoms must persist for at least three months with sleep disturbances occurring three times a week or more, and must be related to impairments in daytime functioning.[4] Daytime impairments may include fatigue, sleepiness, problems with attention and memory, mood disturbances, reduced energy and motivation, and physiological effects such as headaches and gastrointestinal problems. Insomnia can broadly be conceptualized as either a primary condition, occurring in the absence of other medical or psychiatric problems, or a secondary condition occurring comorbid with another disorder or linked to an external cause (such as medication). Insomnia may be caused by other undiagnosed sleep disorders (such as sleep apnea), is often reported with psychiatric problems such as depression and anxiety, and is associated with medical conditions including heart disease and chronic pain.[2] As well, certain prescription, over-the-counter, and recreational drugs can cause sleep problems and either induce or exacerbate insomnia symptoms. It is therefore important when assessing insomnia complaints to identify whether any underlying factors or comorbidities may be relevant and design a treatment plan accordingly.

Insomnia symptoms often have a severe impact on quality of life and can lead to an increased risk of accidents, decreased work productivity and absenteeism.[5] Due to insomnia's

prevalence as well as the cost of treatments and impact on work productivity, it also leads to a severe economic burden both on the individual suffers and society. In Quebec, the total annual cost of insomnia was estimated to be $6.6 billion with $5 billion of that being productivity losses related to insomnia.[6] It is therefore imperative that insomnia is better understood, especially in regards to improving treatment efficacy.

Insomnia is primarily treated through two means: pharmacological interventions and cognitive behavioral therapy for insomnia (CBT-I).[2] Pharmacological treatment is commonly used due to its ease and availability and is most often hypnotic agents such as benzodiazepines or other benzodiazepine receptor agonists, although antidepressants, anticonvulsants, antipsychotics, and melatonin receptor agonists are also used. The drawbacks to this form of treatment are drug side effects most commonly including dizziness, drowsiness, lightheadedness, amnesia and gastrointestinal problems, as well as the development of tolerance and dependence which can lead to misuse.[2] This raises the question of the long-term efficacy of pharmacological interventions. Although some studies support the long-term benefits of hypnotic treatments,[7, 8] most indicate a short-term improvement with long-term improvements being associated with behavioral intervention such as CBT-I.[9-11] It is likely then that acute bouts of insomnia may be best addressed with pharmacological intervention while long lasting chronic insomnia may be better addressed by CBT-I.[12]

Cognitive behavioral therapy for insomnia (CBT-I) is a multimodal approach including an array of components aimed at addressing both poor sleep habits and behavior as well as dysfunctional beliefs about sleep. These components include stimulus control, sleep restriction, sleep hygiene, cognitive restructuring and relaxation techniques.[13] Stimulus control seeks to undo the association of the bed and bedroom with activities other than sleeping. Specifically, this

means avoiding all non-sleep activities while in bed, such as reading or watching TV (sex being the only exception), as well as leaving the bedroom if one is having difficulty falling asleep in order to avoid associating the bed with anxiety about sleep difficulties. Sleep restriction aims to consolidate sleep by limiting time in bed and creating a consistent sleep-wake schedule. Insomniacs often spend excessive amounts of time in bed trying to sleep which leads to inconsistent and fragmented sleep patterns. Sleep restriction attempts to undo this habit by at first inducing some partial sleep deprivation through restriction, which in turn leads to a greater homeostatic sleep drive in subsequent nights, and eventually more consolidated sleep as a whole. Sleep hygiene focuses on education about sleep and improvement in sleep-related behaviors. This consists of teaching basic knowledge about the process and functions of sleep itself as well as behavioral changes to improve sleep such as not having a visible clock near your bed. Cognitive restructuring attempts to address dysfunctional beliefs insomniacs may have about sleep. These beliefs may include unrealistic expectations about sleep, such as the idea that it is absolutely necessary to have 8 hours of sleep, or faulty beliefs about the causes or cures for insomnia, such as the idea that insomnia is caused purely by chemical imbalances that can only be treated with sleep medication. Relaxation techniques, such as meditation or progressive muscle relaxation, are also often taught to reduce arousal and anxiety related to sleep. CBT-I may be administered individually or in a group setting and can vary in terms of the length of the course of treatment and the components used. Overall, CBT-I has well documented efficacy[14, 15] with treatment response rates around 60-70% and remission rates around 40%.[16, 17] Its primary advantages over pharmacological interventions are the absence of drug-related side effects and dependency as well as the above mentioned long-term benefits, making it an ideal treatment for chronic insomnia.

Although the efficacy of CBT-I is robustly supported, not all patients respond to therapy. As with interventions for other psychiatric disorders, inter-individual differences can play a role in treatment response.[18] Already, inter-individual differences have shown to be important risk factors for developing insomnia with individuals of poor general health, poor mental health, and prone to increased stress reactivity and hyperarousal being at higher risk.[19-21] It is possible that inter-individual differences within the population of insomniacs may as well be predictive of response to CBT-I and account for differences in treatment outcomes.

Previous research on predicting treatment outcomes for CBT-I has produced mixed results implicating a number of different possible individual factors. Personality traits have shown to be predictive with a study of elderly insomniacs finding those who were more traditional, conventional and rigid showing better improvements in sleep duration after therapy.[22] Greater baseline insomnia severity has also been demonstrated to predict better treatment response, although this is not consistent across all studies.[23-28] Similarly, those with greater dysfunctional beliefs about sleep at baseline showed more improvement post therapy than those with less pronounced belifs[29], although not in all studies.[24] Higher levels of depression and anxiety were also found to be predictive of better CBT-I response[23], although again this effect was inconsistent and not found in several studies.[30, 31] Another factor common to all psychological interventions that have shown to be predictive for CBT-I is the quality of the therapeutic alliance, particularly based on the initial expectations insomniacs had of the therapy outcome.[32] Those with low pre-treatment expectations but perceiving the therapist to have a higher affiliation showed the most improvement while those who perceived the therapist as critically confrontational reported less treatment satisfaction and were more likely to drop out of the therapy.[32] Lastly, adherence to the CBT-I treatment itself such as attending sessions,

implementing behavioral changes, and actively engaging in the therapeutic process has been shown to be related to treatment success.[33]

One area that has not received much attention is examining sleep micro-architecture at baseline as a predictor. Briefly, the architecture of sleep in humans has been classified by electroencephalographic (EEG) recordings of sleeping subjects with stages of sleep being categorized by various aspects of the recorded waveforms as well as recordings of eye movements and muscle tone. Broadly, sleep is divided into two main types: non-rapid-eye-movement (NREM) sleep and rapid-eye-movement (REM) or paradoxical sleep. NREM sleep is divided into three stages, which are characterized by increasing synchrony of neural oscillations, observed as high amplitude, low-frequency waveforms. Stage one NREM represents an intermediary stage between wakefulness and sleep characterized by the transition of the alpha rhythm (8-13 Hz) to the theta rhythm (4-7 Hz) as the individual proceeds into stage two NREM. Stage two is the most prominent stage of sleep in adult humans constituting around half of total sleep and is identified primarily by the appearance of transient EEG events: sleep spindles and K-complexes. As sleep deepens and stage three NREM is entered, the EEG is characterized by high amplitude, low-frequency delta waves (0.5-4 Hz), lending the name slow wave sleep. Conversely, REM sleep is identified by its high frequency, low amplitude EEG activity, often resembling that of waking, along with rapid eye movements and a reduced muscle tone. The only previous study to examine EEG measures as a predictor of treatment response showed that lower EEG delta power in the first NREM sleep cycle at baseline predicts better response to CBT-I.[34] Another component of sleep architecture that may be of interest in this area are sleep spindles.

Sleep spindles are transient oscillations of around 12-14 Hz (sigma band) seen in EEG recordings that occur predominantly in stage N2 of NREM sleep and are produced by the

interplay of thalamic and cortical neurons.[35] Functionally, spindles have been associated with the retention of memory traces overnight as well as cognitive abilities.[36-40] For example, after a declarative learning task spindle density during sleep was found to be increased compared to a control task and was highly correlated with recall performance.[36] Of more specific interest to insomnia, spindles have also been shown to be related to the gating of external stimuli, particularly acoustic, during sleep, and may more broadly be related to sleep stability. One of the earliest studies to demonstrate a causal relationship between spindles and sleep quality was a study in cats, which used an instrumental conditioning task to increase the sensorimotor rhythm (SMR), an EEG oscillation recorded predominately over the sensorimotor cortex in waking with a range of around 12-15 Hz (similar to that of spindles). It was found that reinforcing the SMR during wake led to an increase in spindle activity during sleep as well as longer epochs of undisturbed sleep.[41] More recent animal studies have further supported this relationship. Transgenic mice over expressing an ion channel related to spindle generation displayed less fragmented NREM sleep and a higher auditory arousal threshold than wild types when sleeping.[42] Similarly, using optogenetic stimulation of the thalamic reticular nucleus to induce spindles in mice lead to an increase in both spindle density and NREM sleep duration. Studies in humans have found similar results but are limited by the difficulty in experimentally manipulating spindles in humans. Combined EEG-fMRI studies have shown that sounds played during sleep will consistently activate the auditory cortex except when the sound occurs during spindles.[43, 44] Further, individuals with lower spindle densities were shown to be more likely aroused from sleep when sounds (such as traffic noise or a telephone ringing) were played during sleep than those with higher spindle densities.[45] Taken together, these studies suggests that

spindles serve as a sleep protective mechanism that may help maintain sleep in the face of noise, and may be related to the overall stability of NREM sleep.

It is therefore plausible that differences in spindles may be related to the lower quality and often fragmented sleep seen in chronic insomnia. There is a great deal of inter-individual differences in sleep spindle measures. The earliest studies on this indicated that spindle density could vary greatly from one individual to another, but importantly remained stable and consistent across multiple nights in each individual.[46, 47] Later research also found stable individual differences in spindle EEG frequencies, even going so far as to refer to this as an "EEG fingerprint".[48, 49] These findings point to spindles being a stable, individual trait. Individual differences in spindle activity are most often quantified by differences in spindle density. This measure is particularly useful and common in spindle research as it is a measure of the average number of spindles per given time period (usually per 30 sec or 1 min) of NREM sleep (or another sleep stage of interest) and therefore is less dependent on NREM sleep duration (or another sleep stage of interest) than the absolute number of spindles. Spindles can be measured through other standard metrics used in other studies such as their duration,[50, 51] amplitude,[50, 51] power,[48] frequency[49-51], or spectral power in the sigma band[49-51] (the EEG band of spindles) but density is the most robustly studied and consistently used in previous literature, particularly in identifying differences in spindle activity between individuals.

It may be the case that spindle differences at the individual level represent a predisposing factor to insomnia. This was demonstrated in a longitudinal academic stress study in which university students completed an insomnia questionnaire and had a night of sleep recorded at the beginning of the academic semester and later filled out the same questionnaire at the end of the semester during exam time. It was observed that students with lower spindle density in the first

sleep cycle and lower spindle amplitude in the first and third sleep cycles as well as lower spectral sigma power at the beginning of the semester prospectively reported a greater increase in insomnia symptoms in response to the stress of exams at the end of the semester.[50] This suggests an association between lower spindle characteristics and the development of insomnia symptoms in response to stress. This finding contrasts with the absence of reported difference in number and density of spindles between insomniacs and good sleepers at the group level.[52] Such absence of group differences does not exclude the possibility of a subgroup of insomniacs in which spindle characteristics may perpetuate sleep problems. This is supported by the observation that chronic insomnia is not a homogenous disorder in how it develops and presents among sufferers, but rather that there are multiple sub-types[53] likely with distinct etiologies, and differences in spindles may represent one of many possible factors related to the development of insomnia. Spindles as an innate neurophysiological risk factor also fit with one of the main overarching theories of insomnia that suggest insomniacs are in a state of hyperarousal.[54] Spindles are related to the gating of external stimuli so it is possible that a vulnerability to sleep disruption caused by lower spindles may contribute to this hyperarousal in some insomniacs, but not all. Since spindle measures constitute a trait, they will be unlikely to be modified with CBT-I, and thus lower spindle characteristics in a subgroup of insomniacs might hinder the effects of CBT-I leading to differences in treatment response. Particularly, this hindrance could be related to the stimulus control and sleep hygiene components of CBT-I that seek to make the bedroom a quiet, relaxing environment associated with restful sleep. If spindles are related to overall sleep stability and the gating of external stimuli during sleep, then lower spindle activity may contribute to a state of physiological hyperarousal that will make it difficult to achieve stable

sleep, even with the best efforts of the insomnia sufferer to make the bedroom environment less stimulating and associate it with restful sleep.

The purpose of this study was to assess whether inter-individual differences in spindle measures prospectively predict response to CBT-I among chronic primary insomniacs. Spindle density was the main predictor of interest, although secondary analyses using spindle duration, amplitude, power, frequency, and sigma power as predictors were also carried out. As well, delta power was also tested to try to replicate previous results, that found that lower delta power in the first sleep cycle at baseline predicted better response to CBT-I.[34] Primary outcomes of interest were changes in sleep and insomnia questionnaires (Pittsburgh Sleep Quality Index, PSQI; Insomnia Severity Index, ISI) from pre-treatment to post-treatment, and secondary outcomes were changes in sleep efficiency from sleep diaries and polysomnography (PSG; from baseline to post-treatment). Changes in these variables were examined in relation to spindle measures at pre-treatment. We hypothesized that insomniacs with lower spindle activity would show poorer improvement in CBT-I outcomes, compared to those with higher spindle activity.

METHOD

Participants

Participants with chronic primary insomnia were recruited via online and print advertisements posted in the community as well as from physician referral. Prospective participants were initially screened over the phone for inclusion and exclusion criteria, followed by a semi-structured in-person medical interview to determine eligibility. Participants had to meet the ICSD-3 diagnostic criteria for chronic insomnia disorder, i.e. difficulty initiating sleep, difficulty maintaining sleep, and/or early morning awakenings, combined with daytime impairment for a duration of three months or more with sleep disturbances three times a week or

more.[55] Exclusion criteria were being less than 18 years of age, having major psychiatric or medical conditions including sleep disorders other than insomnia, recent shift work or changes in time zones over the past 2 months, and using recreational drugs or prescription drugs that might affect sleep. If currently taking sleep medication, participants were asked to stop that medication at least 1 week before the first PSG assessment and until the end of the post-treatment assessment. Participants subsequently underwent a PSG to rule out the presence of other sleep disorders contributing to insomnia symptoms, particularly sleep apnea (an apnea-hypopnea index > 5/h was an exclusion criterion). Out of 86 potential participants screened over the phone, a total of 49 completed the in-person semi-structured interview; 38 were deemed eligible and 29 agreed to enter the study protocol. Of those, 2 dropped out midway through the CBT-I sessions for personal reasons, 2 completed the CBT-I sessions but dropped out before the post-treatment assessments, and 1 was excluded due to presenting persistent flu-like symptoms during the course of the CBT-I sessions (after completion of the study this participant was diagnosed with irritable bowel syndrome and attributed these symptoms to this). Unfortunately, data was only available for 2 of the 4 drop-outs. In total, 24 (19 females, 5 males; M_{age} = 42.84, SD = 15.7) participants completed the treatment and were included in the final analysis (See Table 1 for demographic and baseline sleep parameters). All participants signed an informed consent form before entering the study, which was approved by the Concordia University Human Research Ethics Committee.

Procedure

After enough participants were deemed eligible following a PSG screening to form a treatment cohort (4-6 people), participants were scheduled for a second sleep recording night within a month before the beginning of the CBT-I sessions, as well as given a sleep diary to

complete for one week and two questionnaires, the Pittsburgh Sleep Quality Index (PSQI)[56] and the Insomnia Severity Index (ISI).[57] Participants then completed six, weekly group sessions of CBT-I. Within a month of completion, participants were scheduled for a third sleep recording night and again given a sleep diary to complete for a week along with the two aforementioned questionnaires. Follow-ups were later conducted by phone 3 months and 1 year following CBT-I completion and consisted again of the same two questionnaires (see Fig. 1 for a schematic of the study procedure), although the focus of the analyses presented here is limited to the pre- to post-treatment effects only.

Self-reported sleep measures

Sleep quality and insomnia symptoms were assessed through standardized questionnaires and sleep diaries completed both before and after CBT-I. The first questionnaire used was the Pittsburgh Sleep Quality Index (PSQI), a self-report measure of general sleep quality over the past month. The PSQI consists of 7 sub-components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of medication, and daytime dysfunction) calculated through 4 free response questions related to the timing of sleep habits and 6 Likert-style questions. PSQI scores fall on a scale from 0-21 (with higher scores indicating worse sleep quality) and have been shown to have an average of 10.38 (SD = 4.57) in insomniacs with an overall Cronbach α of 0.83.[56] The second questionnaire used was the Insomnia Severity Index (ISI), a self-report measure of the nature, severity and impact of current insomnia symptoms. The ISI consists of 7 Likert-style questions with a total score ranging from 0-28 (with higher scores indicating more severe insomnia) and average reported in insomniacs of 19.7 (SD = 4.1) with an overall Cronbach α of 0.74.[57] While all 24 participants completed these questionnaires at baseline and immediately after CBT-I, 17 completed the PSQI and 18 the ISI at

3 months. At 1 year, 19 participants completed both PSQI and ISI. PSQI and ISI scores were the primary outcome variables used to assess CBT-I responses. In addition to these questionnaires, sleep diaries based on the consensus sleep diary were given to the participants.[58] They were administered only at pre- and post-treatment, for seven days at each assessment. Sleep efficiency (as defined by the ratio total sleep time/time in bed, in %) was extracted from sleep diaries by averaging daily values over seven days, including both weekends and weekdays. Sleep efficiency derived from sleep diaries was used as a secondary variable to assess response to CBT-I. Sleep diaries were fully completed by 22 out of the 24 participants. Also of interest as a possible predictor of treatment response was adherence to treatment measured from the Spousal Rated Adherence Questionnaire (SRAQ)[59]. This questionnaire was created specifically to measure adherence to the different components of CBT-I, originally to be done by a therapist or spouse but adapted in the present study as a self report questionnaire administered midway through the therapy sessions.

Sleep recordings

Sleep recordings (PSG) were obtained at pre- and post-treatment. Participants completed three nights of PSG at the PERFORM Centre Sleep Laboratory at Concordia University. The first night served as an initial screening (for sleep apnea) and habituation night, while the second served as the baseline experimental night to provide sleep measures before CBT-I; they were conducted at least 3 days apart. The third PSG was performed within a month following the last CBT-I session. For a subset of participants (25%), PSG recordings were conducted at home (ambulatory mode) due to ongoing renovations of the sleep laboratory. Since these recordings were not conducted in a laboratory environment, there was no habituation night and those 6 participants therefore had two ambulatory PSG recordings (the first at baseline and the second

after CBT-I). Comparisons were made to ensure there were no relevant differences from these home recordings (see Results section). All PSG recordings (both in-lab and ambulatory) were performed using the same equipment and recording parameters: 34-channel Embla Titanium system (Natus Medical, San Carlos, CA, USA) with EEG referenced to linked mastoids (bandpass filter 0.3-100 Hz, sampling rate 512 Hz), electrooculography (EOG) and electromyography (EMG). Additionally, the first in-lab (habituation) and ambulatory PSG recordings included thoracic and abdominal respiration belts, nasal-oral thermocouple airflow, and transcutaneous finger pulse oximetry to allow for sleep apnea screening. All participants were asked to abstain from caffeine and alcohol on each day of PSG recording. Bedtime and awakening times were determined by the participant in accordance with their habitual sleep schedule.

Sleep stages were scored according to standard criteria,[60] and changes in sleep efficiency from baseline to post-CBT-I were calculated as a secondary outcome measure of treatment response. Sleep spindles were detected automatically during N2 and N3 stages of sleep from the C4-O2 derivation. This was chosen due to the prominent detection of spindles over central leads.[61] The spindle detection method (Aseega software, Physip, Paris, France) was based on data-driven criteria using multiple iterations in order to cope with inter-subject and inter-recording variability.[62] It was based on an iterative approach. The first iteration aimed at determining recording-specific thresholds, based on EEG power ratios in delta, alpha and sigma bands. The second iteration provided precise temporal localization of the events. The final iteration enabled the validation of detected events based on frequency and duration criteria (> 0.5s). Iteration 1 and 3 dealt with raw EEG data, while iteration 2 was applied on the EEG filtered in the spindle (sigma) frequency range using frequency bands adapted to each individual

based on his/her global spectral profile (median values for low and high bands were 11.9 and 15.9 Hz respectively; means values for low and high bands were 11.8 and 15.8 respectively). Spindles were quantified according to average density (number per 30 sec. epoch), duration (in seconds), power (in squared microvolts), amplitude (maximum, in microvolts), and frequency (in hertz). These spindle characteristics were computed for N2-N3 NREM sleep for the whole night. (See figures 2 and 3 for examples EEG traces of spindles taken from two participants) After automatic EEG artifact rejection, EEG power in the adapted sigma frequency range during total N2-N3 NREM sleep was calculated using Hanning window and normalized to the global spectral power for each 30-sec. epoch. Average EEG sigma power was used as an additional measure of spindle activity. Likewise, EEG power in the delta frequency range (0.7-4Hz) was also calculated, both during total N2-N3 NREM sleep and during the first sleep cycle of N2-N3, because EEG delta power during the first NREM sleep cycle was previously shown to be a predictor of CBT-I treatment response.[34]

Cognitive-behavioral therapy for insomnia (CBT-I)

All participants underwent CBT-I following their baseline assessment. This treatment consisted of an empirically-supported 6-week group CBT-I, adapted from Morin (1993),[63] comprising 6 modules: psychoeducation about sleep and circadian rhythms; relaxation; sleep hygiene; stimulus control; sleep restriction; and cognitive therapy.[63] Each group included 4 to 6 participants, for a total of 5 CBT-I groups in the present study. A licensed clinical psychologist with training and experience in CBT-I conducted the treatment. Each weekly session lasted 90 minutes.

Statistical Analysis

Independent samples t-tests were first used to compare PSG and spindle variables in home recorded versus lab recorded subjects to confirm no major differences. As well,

independent samples t-tests were used to compare drop-outs with those who completed the study in order to assess possible differences. Paired t-tests were performed on all outcome measures to confirm treatment response as well as on all spindle and EEG measures to confirm group stability from pre to post treatment. Additionally, intraclass correlations (ICC) for each spindle measure were calculated to assess stability at the individual level a using a single measure, absolute agreement, two-way mixed effects model. Finally, to more broadly assess the relationship between spindle measures between each other and at both time points, an inter-correlation matrix of all spindle measures at both time points was created. Additionally, an inter-correlation matrix of all insomnia outcome measures at both time points was created and ICCs were calculated for corresponding measures at each time point, using the same method as above.

Multiple regression was used to assess whether baseline spindle density (as well as spindle amplitude, power, duration, frequency, and sigma power) predicted the outcome measures (PSQI, ISI, sleep efficiency derived from sleep diaries and PSG) at post-treatment, when controlling for the same outcome measure at baseline, demographic characteristics (age, sex, and education years), treatment compliance, sleep time in N2, and the location of the recording (home versus laboratory). A secondary analysis was performed using delta power as a predictor, in order to replicate previous results.[64] For each outcome measure, a series of multiple regressions were performed with the outcome measure at post-treatment as the dependent variable and the predictors being added in blocks to the regression model. The first block added the same outcome measure at pre-treatment to account for baseline differences, the second block added demographic predictors (age, sex, and years of education), the third block added treatment compliance as measured by SRAQ scores, the fourth block added N2 duration (to account for the possibility that any significant spindle effects are actually just related to differences in N2), the

fifth block added the location of the recording (to account for possible differences in the recordings as a result of some being done at home) and the final block added spindle density (or one of the secondary spindle/EGG predictors: duration, amplitude, power, frequency, sigma power, delta power, or delta power in first sleep cycle). For each outcome measure, a number of regression models were created following this same design with the only difference being what spindle/EEG predictor is added in the last block. This allowed each separate spindle measure to be tested after controlling for the predictors added in previous blocks, as well as to assess the R^2 change from each block of predictors. Coefficients and effect sizes for each predictor are reported from the block in which that predictor was added. For instance, values for SRAQ are taken from the third block which contains SRAQ, demographics, and baseline. Values for N2 duration are taken from the fourth block which contains N2 duration, SRAQ, demographics, and baseline. Values for spindle density (or other spindle/EEG predictors) were taken from the fifth block which contains spindle density, N2 duration, SRAQ, demographics, and baseline. To illustrate the relationships between spindles measures and treatment responses, correlations between spindle parameters at pre-treatment and outcome measures following CBT-I were calculated using Pearson's product-moment correlation. All results were considered significant at $p \leq .05$ level. Analyses were conducted with SPSS (IBM, New York, NY, USA) software.

RESULTS

Differences between home and lab recordings

Only the first cohort (six participants) were recorded at home for both for pre- and post-CBT-I recordings. All other cohorts (18 participants in total), had all their recordings done at the sleep lab. Independent sample t-tests revealed no significant differences on any spindle measures between home and lab recordings, and no significant differences on almost all PSG variables as

well. In home recordings there was longer sleep latency at post-treatment than in lab recordings ($t = 2.27$, $df = 21$, $p = .034$) and in home recordings there was a greater percentage of N2 at both pre- ($t = 2.13$, $df = 21$, $p = .045$) and post-treatment ($t = 2.11$, $df = 21$, $p = .047$) than in lab recordings (for complete list of means, standard deviations, and mean differences for all parameters, see Table 1). These differences are unlikely to have an influence on the overall results as differences in N2 are taken into account in the multiple regressions.

Differences between drop-outs and completers

Limited data was available for the few drop-outs in the study with pre-treatment data only available for two of the four drop-outs. Independent samples t-tests revealed no significant group differences on any spindle, sleep diary or questionnaire measure. There were however some differences in PSG measures. The two drop-outs had significantly longer overall sleep duration ($t = 2.27$, $df = 24$, $p = .033$), as well as longer N2 duration ($t = 2.21$, $df = 24$, $p = .037$), and shorter REM duration ($t = 3.27$, $df = 24$. $p = .003$) and smaller REM percentage ($t = 2.56$, $df = 24$, $p = .017$). With limited data it is hard to draw conclusions about the drop-outs, however the PSG differences are unlikely to be biasing as N2 duration is accounted for in the regression models and differences in REM and total sleep duration are unlikely to be related to spindles. For complete list of means, standard deviations, and mean differences for all parameters, see Table 2.

Changes in sleep quality after treatment

Paired sample t-tests indicated a significant decrease for both PSQI ($t = 6.60$, $df = 23$, $p = .000$) and ISI ($t = 9.74$. $df = 23$, $p = .000$) from pre-treatment to post treatment indicating a significant improvement in sleep. ISI was reduced on average by 8 points from pre- to post-treatment (Table 3) which corresponds to an effect size comparable to previous effects reported in randomized controlled trials.[65] At post-treatment, 50% of participants were considered on

remission (as defined by an ISI score below 8)[65]. For sleep efficiency measures, there was a significant increase in sleep efficiency from pre- to post-treatment as measured by sleep diaries ($t = -3.93$, $df = 21$, $p = .001$), and trend towards significant increase in sleep efficiency as measured by PSG recordings ($t = -1.99$, $df = 22$, $p = .059$). For means, standard deviations, mean changes and complete list of parameters see Table 3.

Stability of spindle activity following treatment

Paired sample t-tests revealed no significant changes at the group level on spindle measure from pre- to post-treatment and ICCs confirmed stability at the individual level as well: density ($t = 0.83$, $df = 22$, $p = .418$; ICC = 0.81, $p = .000$), duration ($t = 0.51$, $df = 22$, $p = .615$; ICC = 0.91, $p = .000$), amplitude ($t = 0.13$, $df = 22$, $p = .895$; ICC = 0.59, $p = .002$), power ($t = -0.50$, $df = 22$, $p = .960$; ICC = 0.71, $p = .000$), frequency ($t = -0.09$, $df = 22$, $p = .929$; ICC = 0.80, $p = .000$), and sigma power ($t = -0.03$, $df = 22$, $p = .980$; ICC = 0.70, $p = .000$). This indicates that spindle activity is a stable trait not impacted by CBT-I. For means, standard deviations and mean changes of all spindle measures, see Table 4. In general, different spindle measures tended to highly correlated with one another (except for spindle frequency) and this pattern was observed at both time points. In line with the above reported ICCs, each different spindle measure at pre-treatment was highly correlated with its corresponding measure at post-treatment (see Table 5 for complete intercorrelation matrix of all spindle measures at both time points).

Inter-correlations of outcome variables

An inter-correlation matrix of outcome variables (PSQI, ISI, sleep diary sleep efficiency and PSG sleep efficiency) at both pre- and post-treatment revealed some associations amongst the variables. At pre-treatment PSQI was negatively correlated with sleep diary sleep efficiency

(r = -0.51, p = .015), and there was a trend towards a significant positive correlation between PSQI and ISI (r = 0.38, p = .067). Interestingly, at post-treatment the outcome measures tend to be more correlated with one another, with sleep diary sleep efficiency being negatively correlated with both PSQI (r = -0.50, p = .017) and ISI (r = -0.47, p = .029) and a significant positive correlation between PSQI and ISI (r = 0.53, p = .008). The negative correlations with sleep diary sleep efficiency make sense as higher sleep efficiency implies higher sleep quality whereas higher PSQI or ISI implies poorer sleep quality. ICCs revealed a positive association between ISI from pre- to post-treatment. See Table 6 for complete inter-correlation matrix of all outcome measures at both time points.

Sleep spindle activity as predictor of treatment response

Multiple regression assumptions were first checked using normal probability plots to confirm normal distribution, standardized residual/predictive value plots to confirm homoscedasticity, and variance inflation factors (VIFs) were checked to assess possible multicolinearity, with no VIFs exceeding 3.5 and most in the range of 1-2 for variables in all models. After using multiple regression controlling for baseline measures, age, sex, education years, treatment compliance, N2 duration, and recording location spindle density and sigma power were found to be predictive of treatment outcome. For PSQI, spindle density (B = -2.29, SE = 1.07, β = -0.61, t = -2.14, p = .049, adjusted R^2 = 0.21, R^2 change = 0.16; see Figure 4 for scatter plot) and sigma power (B = -86.17, SE = 37.86, β = -0.67, t = -2.28, p = .038, adjusted R^2 = 0.24, R^2 change = 0.17; see Figure 5 for scatter plot) were inversely related to PSQI at post-treatment, indicating greater spindle density and sigma power at baseline is predictive of lower PSQI scores at post-treatment, indicating better sleep quality (see Table 7 for complete list of coefficients and effect sizes for all PSQI predictors). For ISI, no predictive effect of any spindle

parameter was found (see Figure 6 for scatter plot of spindle density with ISI), and baseline ISI score was found to be predictive of ISI score post treatment (B = 0.70, SE = 0.26, β = 0.50, t = 2.68, p = .014, adjusted R^2 = 0.21, R^2 change = 0.25; see Figure 7 for scatter plot; see Table 8 for complete list of coefficients and effect sizes for all ISI predictors). No predictors were related to either sleep diary sleep efficiency (see Table 9 for complete list of coefficients and effect sizes for all sleep diary sleep efficiency predictors; see Figure 8 for scatter plot of spindle density with sleep diary sleep efficiency) or PSG sleep efficiency (see Table 10 for complete list of coefficients and effect sizes for all PSG sleep efficiency predictors; see Figure 9 for scatter plot of spindle density with PSG sleep efficinecy). Secondary analysis also found no relation between delta power at pre-treatment or delta power in the first NREM sleep cycle at pre-treatment and any of the outcome measures.

DISCUSSION

These results indicate that subjective sleep quality (as measured by PSQI) after CBT-I treatment in chronic insomnia is associated with differences in sleep spindle density and sigma power at baseline, above the effects of baseline measures, age, sex, education level, treatment adherence, N2 duration, and recording location, although given the large number of regression models ran it is possible this result may simply be due to multiple comparisons. This study is unique in that it is one of the few to examine the relationship between sleep EEG micro-architecture and response to treatment in insomnia, and the first to specifically examine spindles in this regard. Another distinct advantage to this study is the spindle detection method using adapted frequency bands, a method that allows a more accurate measure of spindle parameters as it takes into account the individual differences in global spectral profiles, whereas using fixed bands might under-detect spindles in individuals whose bands are slightly shifted. Unfortunately,

a main weakness of the current study stems from a small sample size, limiting the power of statistical tests. However, given the specific exclusion criteria, large time commitment, and the necessity of much personal effort needed to complete the study and all its measures in full, it is not surprising that the sample was limited and there was some attrition, with four drop-outs over the course of the study. The only area where the attrition was an issue was in follow-ups done after the therapy which 9 out of the 24 participants did not complete. All 24 participants completed the primary portion of the study, focusing on pre- to post-CBT-I effects, although some did not complete the 3 month or 1 year follow-ups. The participants who did not complete these follow-ups were not considered drop-outs as the primary focus was simply on the pre- to post-CBT-I effects. For these reasons, this follow up data was not analyzed here. This is unfortunate as with the current analysis conclusions can't be made about the relationship between spindles and long term treatment outcomes, although this may be possible with more complex statistical methods such as hierarchical linear modeling, which is better suited to deal with missing data points. There is also the possibility that the significant results reported here may simply be the result of multiple comparisons as a number of regressions were carried out. If a Bonferroni adjustment were used, the critical p value would be .002, making the findings no longer significant. However the primary spindle variable of interest was density which only makes up 4 of the 32 regressions and provides the results of most interest, whereas the other regressions focused on secondary spindle predictors that were not the main focus of the study. Another weakness of the study is the fact that one of the treatment cohorts had their sleep recordings done at home, as opposed to the rest which were done in the sleep lab. This could potentially bias the spindle and PSG variables related to the home recordings as sleeping in one's home, in a familiar bed is quite different than sleeping in the laboratory, in which the setting is

less familiar. However, there didn't appear to be any relevant differences in the spindle and PSG variables from these recordings, except a higher percentage of N2 in the home recordings at both time points. This difference may be related to the fact that in home recordings there tended to be less N1 than in lab recordings (although this difference was not statistically significant), suggesting that at home it may have been easier for subjects to transition from wake to N2, perhaps due to the comfort and familiarity of sleeping at home. However, these differences in N2 are unlikely to have influenced the results as differences in N2 are accounted for as a predictor in the multiple regressions. Despite these weaknesses, this study provides interesting preliminary results about the relationship between sleep spindles and treatment outcome in insomnia.

Overall, the CBT-I treatment was successful as on average participants improved on self-reported sleep measures including PSQI, ISI and sleep diary measures of WASO and sleep efficiency. Spindle density and sigma power at baseline were predictive only of PSQI with the greater magnitude of these spindle characteristics being related to lower PSQI at post-treatment. The lack of a spindle effect for ISI is surprising given the findings for the PSQI, and especially given the trend for correlation between the two but this may be explained by a lack of statistical power. Likewise, the lack of a predictive effect of spindles on sleep diary may also be due to weak statistical power. The absence of any effect for PSG sleep efficiency is not surprising given the fairly small change from pre- to post-treatment and a high pre-treatment average (82%). As well, PSG measures are effective at characterizing only the objective aspects of insomnia, such as longer sleep latency or night time awakenings, however many sufferers report poor sleep quality but may have relatively normal sleep parameters as measured by PSG. Surprisingly, only spindle density and sigma power were found to be predictive, despite the fact that both these measures tend to be highly correlated with spindle duration, power, and amplitude (see Table 5),

which were not predictive. It may be the case that the most important aspect of spindles for sleep stability is their greater occurrence rather than their individual "strengths" so to speak, as indicated by longer durations or greater power and amplitude. Given that most previous research on spindles and sleep stability have focused on density, this result would seem to make sense. Overall, spindles appear to be predictive but it is unclear how universal this may be across different kinds of outcome measurements or whether aspects of spindles besides density are important.

Interestingly, no association was found with delta power at baseline and treatment outcomes, contrary to a previous study by Krystal and Edinger.[34] In the current study, delta power was analyzed for all-night NREM sleep (N2-N3) as well as the first sleep cycle (as was examined in the previous study), however neither was found to be predictive. This may be due to differences in the age range of participants between studies. In the previous study, subjects ranged between 40 and 80 years old with an average of 54.9 years, whereas in the present study subjects ranged from around 19 to 72 years with an average age of 42.84 years and half of the subjects below the age of 40. This is relevant as delta rich slow wave sleep has been noted to decrease with age, particularly around 30-40 years.[66] It may be the case that lower first cycle delta power is only predictive in older individuals who as a group already have lower baseline delta power than younger individuals. Methodological differences in the spectral analyses may as well have contributed to this difference, as the present study used frequency bands adapted for each subject based on their global spectral profile whereas the previous study used fixed frequency bands for all subjects.

Overall, previous work has already shown that lower spindle density may be a predisposing factor in developing sleep problems in response to stress[50] and this current study

indicates that weaker spindle parameters may as well hinder response to CBT-I treatment. Lower spindle parameters may be indicative of an innate biological vulnerability to developing and perpetuating insomnia. However, it has been noted that spindle measures are not significantly different between chronic insomniacs and good sleepers at the group level.[52] Therefore, it is likely that within the population of insomniacs there may be a sub-type of sufferers who represent a specific phenotype resistant to CBT-I treatment due to these lower spindle parameters.

Given previous research on sleep spindles, the most likely interpretation for why weaker spindles might hinder CBT-I treatment is the relationship between spindles and sleep stabiliy. Sleep spindles have been associated with the gating of external auditory stimuli during sleep.[43, 44] This helps to isolate the cortex from noise that could disrupt sleep and greater spindle density has been associated with the ability to maintain stable sleep in the face of noise.[45] It is possible that those participants with weaker spindle traits may simply have more difficulty maintaining stable sleep despite their best efforts to incorporate the components of CBT-I and improve their sleep. This explanation fits with one of the overarching theories of insomnia, which posits that insomniacs are in a psycho-physiological state of hyperarousal.[54] Weaker spindles may lead to a lower arousal threshold during sleep which when combined with other predisposing factors leads to the development of an insomnia phenotype resistant to CBT-I. If this is the case, then weaker spindles may particularly hinder certain CBT-I components. The most likely candidates are the stimulus control and sleep restriction components. Stimulus control seeks to condition the bed and bedroom to be less arousing by associating it with only sleep related activity, and importantly reducing noise to create a quiet environment conducive to sleep. If spindle differences are an element of hyperarousal, particularly by reducing sleep stability to noise, then

they may make this conditioning harder to accomplish. As well, sleep restriction seeks to consolidate sleep through by setting particular sleep and wake times, leading to partial deprivation at first, to drive consolidated sleep on subsequent nights. If spindles are related to the general ability to maintain long, stable, consolidated periods of sleep then this too may be difficult to accomplish in those with weaker spindles.

If weaker spindles do represent a new insomnia subtype this could have important clinical implications. These individuals may simply not benefit as much from typical CBT-I as other insomnia sufferers and may need more specialized CBT-I that is focused more on stimulus control and noise reduction or they be more suited for other forms of intervention such as pharmacological intervention. This is of particular note as CBT-I can often be expensive and time-consuming and these individuals may become frustrated with a lack of improvement leading to a worsening of symptoms. This suggests that insomnia treatment should be more individualized and spindle parameters at baseline may be an important factor in recommending particular lines of treatment. However, in the current study insomniacs were not able to be divided into meaningful groups based on spindle characteristics so the idea of a new subtype is tentative.

Spindles being of clinical relevance also may point to more novel forms of treatment that seek to modify brain oscillations. As noted here spindle parameters did not change in response to therapy and previous research has indicated that spindles represent an individual trait that does not change significantly from night to night.[48, 49] This supports our overall hypothesis that lower spindle parameters may be a biomarker of poorer response to CBT-I as spindles do not improve or change in response to CBT-I. However, it may be possible to alter spindle parameters with other kinds of external intervention. Although spindles are stable from night to night of normal

sleep, there is some evidence that they can be manipulated. Two such approaches that have already been used to varying degrees of success in the treatment of insomnia are directly altering brain activity with artificial stimulation, such as transcranial magnetic stimulation (TMS), and using biofeedback and conditioning to alter brain activity, most often in the frequency range of spindles.

TMS uses a magnetic coil placed on the scalp to induce a small electrical current in the underlying brain tissue, which can have either an excitatory or inhibitory effect depending on the stimulation protocol. Much research has been devoted to the use of TMS in treating neuropsychiatric disorders, particularly depression and motor disorders with mixed results.[67] TMS to treat insomnia is mostly unexplored but it is possible TMS could be used to induce spindle activity as a form of therapy. Studies have used TMS[68] and transcranial direct electrical stimulation[69] (a similar procedure that uses low current delivered via scalp electrodes) to induce slow waves in healthy sleeping subjects, which concurrently increased spindle activity. The latter study particularly noted an increase in activity in the slow spindle range (8-12 Hz) and an increased performance on a verbal memory task after brain stimulation during sleep compared to a sham. However, only a single study using repetitive TMS (rTMS) to treat primary insomnia has been done.[70] In this study, 120 patients were recruited who met DSM-IV criteria for chronic insomnia as well as PSG criteria related to sleep latency, duration, and efficiency. Patients were randomly assigned to undergo treatment for two weeks in one of three groups: rTMS (applied for 30 min once a day over the dorsolateral prefrontal cortex), psychotherapy (with typical CBT-I components), or medication (2 mg estazolam nightly). All participants underwent PSG recordings and completed the PSQI before and after treatment. Phone call follow-ups using the PSQI were used to assess recurrence of symptoms after 3 months. Results of this study were

promising in that participants undergoing rTMS showed improvements on all PSG sleep parameters and PSQI, as well as low recurrence rates at follow-up (36%) especially compared with the medication group (96%), and therapy group (56%). However, a major weakness of the study is a lack of any kind of control group, particularly a sham TMS condition. As well, the inclusion criteria did not seem to exclude participants with other psychiatric problems, medical conditions or screen for additional sleep disorders. Unfortunately, this indicates the results are tentative at best. As well, there is no indication of a connection between the rTMS procedure used and spindles and the stimulation procedure was quite different than the one previously used to induce slow waves and spindles.[68] It is possible that TMS may be a future form of treatment for insomnia, but much more research is required to determine its efficacy and whether its therapeutic effect (if any) is related to spindles.

Another approach to insomnia treatment instead uses biofeedback and conditioning to increase activity in the frequency band of spindles. This is done by conditioning the sensorimotor rhythm (SMR), an EEG oscillation recorded predominately over the sensorimotor cortex in waking with a range of around 12-15 Hz (similar to that of spindles). One of the earliest studies on the SMR in cats demonstrated that instrumental conditioning reinforcing the SMR during wake led to an increase in spindle activity during sleep as well as longer epochs of undisturbed sleep.[41] SMR conditioning was later applied to insomniacs along with another biofeedback protocol focusing on relaxation therapy achieved through EMG-theta feedback, and it was found that both these methods improvement sleep quality to some extent, although this improvement was only observed in home sleep diaries, not in laboratory PSG recordings, and these studies were conducted before development of standardized questionnaires like the PSQI and ISI.[71, 72] Interestingly, it was noted in these studies that pre-treatment characteristics were related to which

type of biofeedback training was most effective. Insomniacs with high psychological or muscular tension before treatment responded best to EMG-theta feedback while those who were relaxed but still reported sleep problems pre-treatment responded better to SMR conditioning. However, these early studies lacked control conditions and didn't report whether actual changes in sleep EEG were observed after training. Later more comprehensive studies in both healthy sleepers[73], as well as insomniacs[74], showed that SMR conditioning improved sleep quality measures, enhanced sleep spindles, and improved overnight memory consolidation, although these latter two effects were much less pronounced and robust in insomniacs. Although the ability to alter spindles may be at odds with previous observations of individual spindle stability, biofeedback conditioning may prove to be a useful, cost-effective treatment for insomnia in the future, but further work is necessary to validate its effects.

A final possibility for enhancing sleep spindles with outside intervention is through pharmacological means. Little research has been done in this area outside of investigations of prescription hypnotic agents already used to treat insomnia. Increase of spindle activity has been noted in response to barbiturates[75], benzodiazepines[76, 77], and non-benzodiazepine hypnotics[78, 79]. Melatonin supplements have as well been noted to increase spindle activity,[80] but their use in treating chronic insomnia lacks conclusive evidence.[81] Unfortunately, it is impossible to untangle the spindle promoting effect of these drugs from the other sleep-promoting effects and remains to be seen if more spindle specific compounds are ever discovered.

In summary, sleep spindle density and sigma power at baseline before beginning CBT-I may be predictive of whom will respond to this form of treatment, as measured by PSQI. These spindle differences within the population of chronic insomniacs may be an endogenous biomarker that identifies a particular phenotype of insomnia. This new finding may guide future

algorithms for insomnia treatment, which should be tailored based on individual differences. Future research should seek to elucidate the mechanistic interaction between spindles and poor CBT-I response, as well as evaluate which therapeutic interventions would be most effective for this population, including the investigation of newer techniques aimed at altering brain oscillations during sleep.

FIGURES AND TABLES

Figure 1: A schematic representation of the course of the study indicating at what time points measurements were taken.

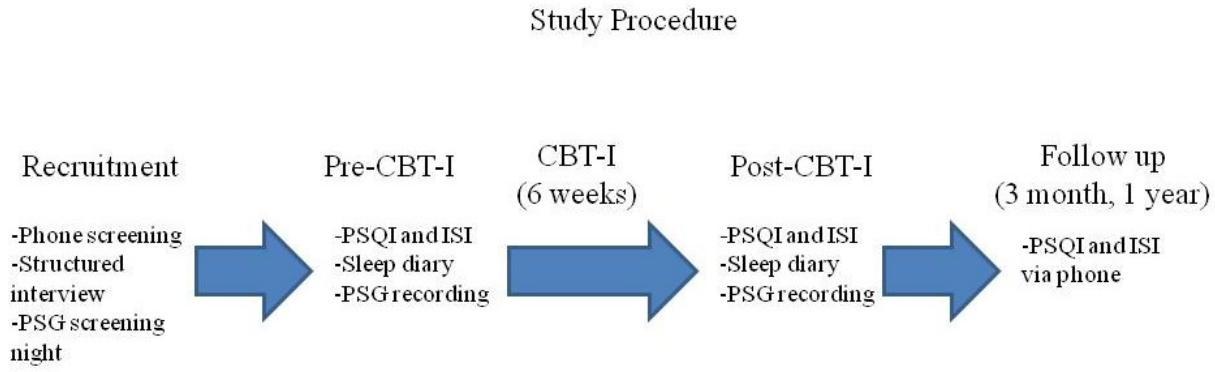

Figure 2: Pairs of sleep spindles in 31 year old female participant with high average spindle measures. Density = 2.76 per 30 sec epoch; Duration = 1.02 sec; Amplitude = 19.70 μV; Power = 107.90 μV^2; Sigma power = 0.10 μV^2 per 30 sec epoch.

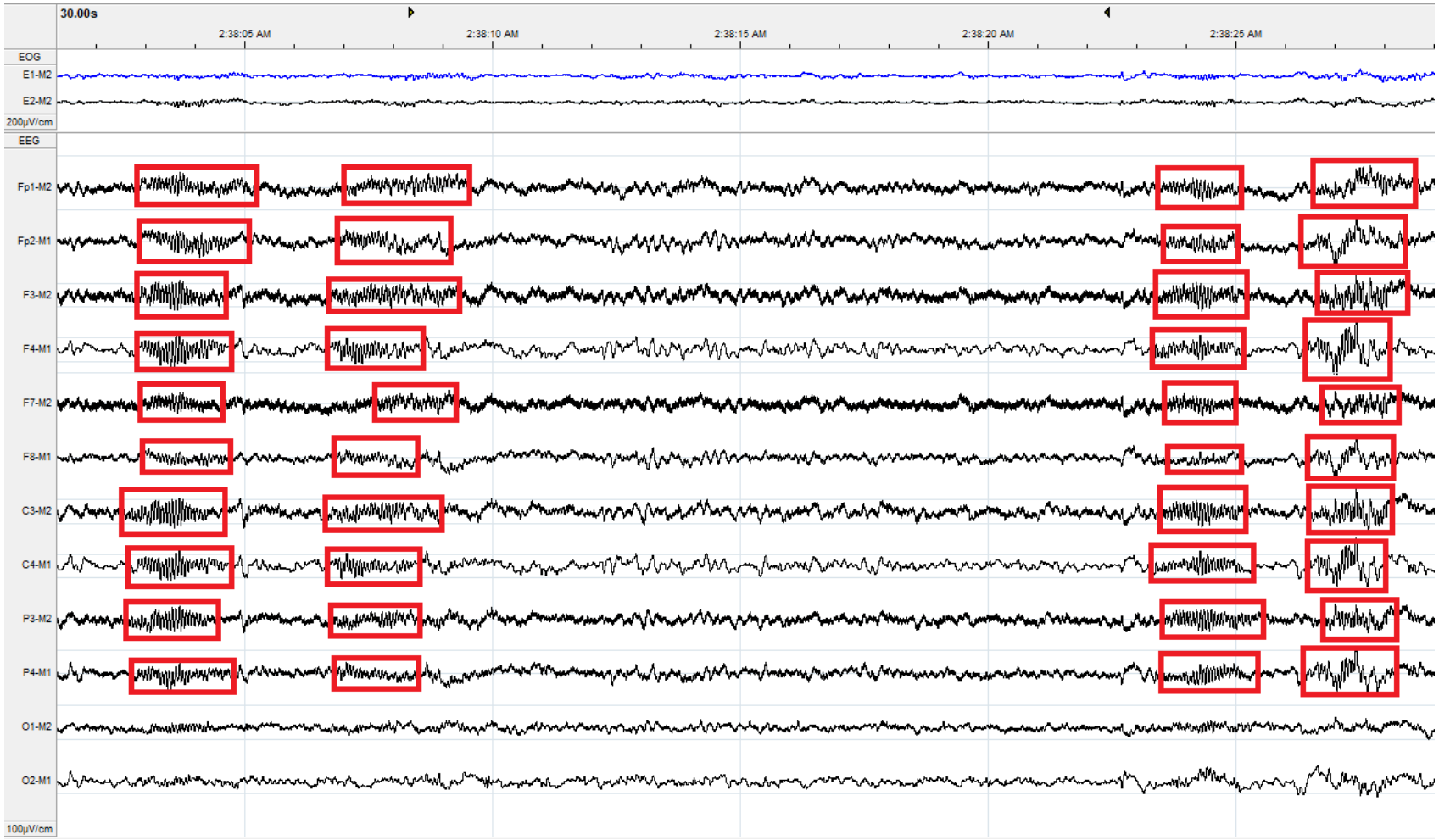

Figure 3: Sleep spindle in 72 year old female participant with low average spindle measures. Density = 0.16 per 30 sec epoch; Duration = 0.69 sec; Amplitude = 6.70 μV; Power = 12.10 μV^2; Sigma power = 0.02 μV^2 per 30 sec epoch.

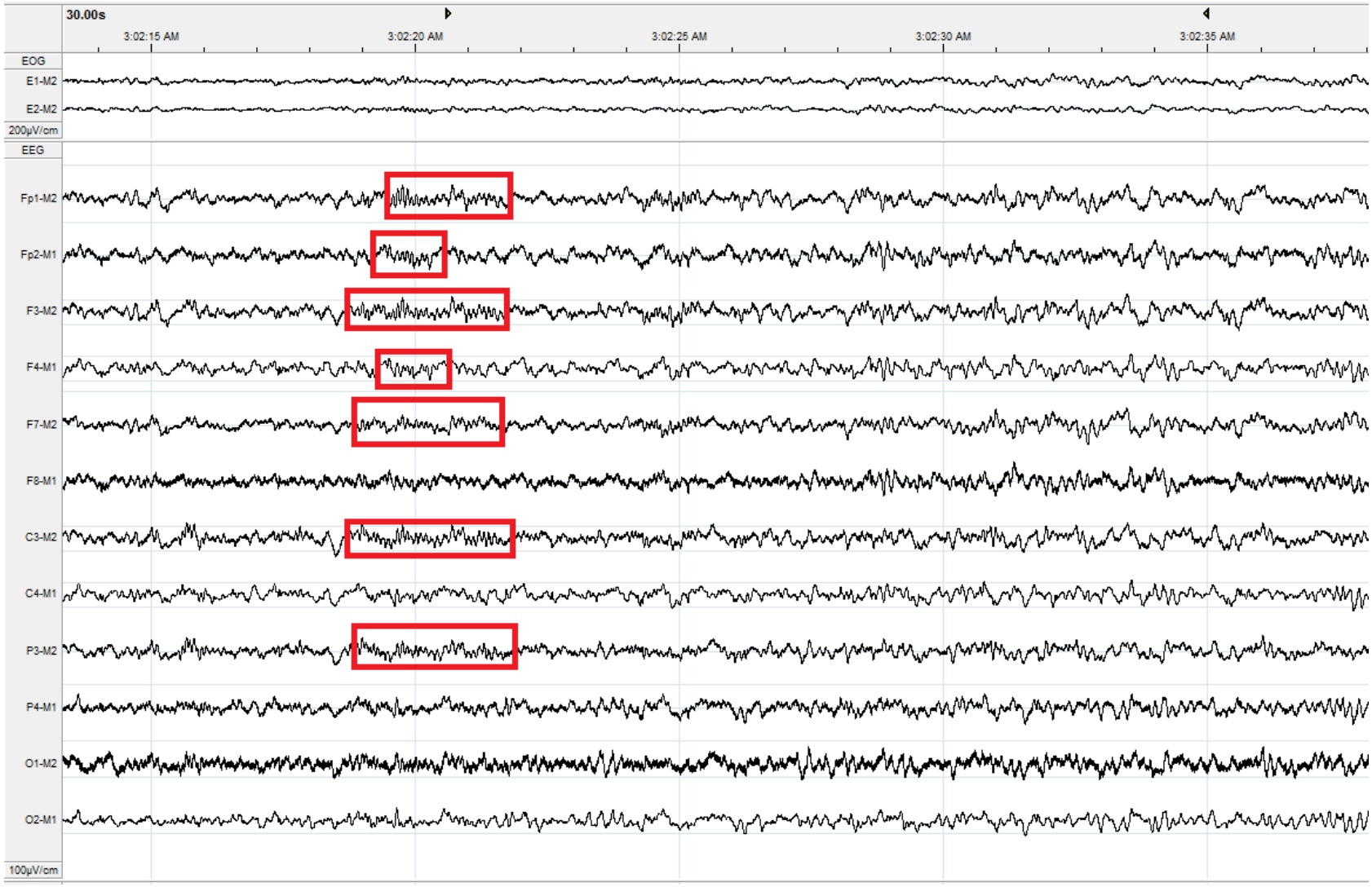

Figure 4: Correlation plot between spindle density at baseline and post-treatment PSQI scores.

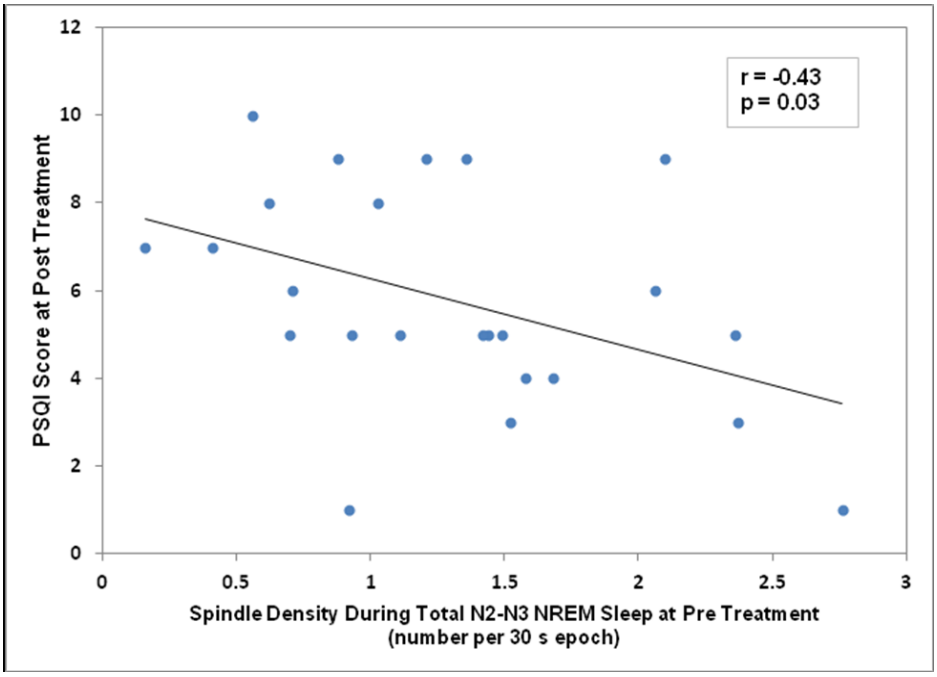

Figure 5: Correlation plot between sigma power at baseline and post-treatment PSQI scores.

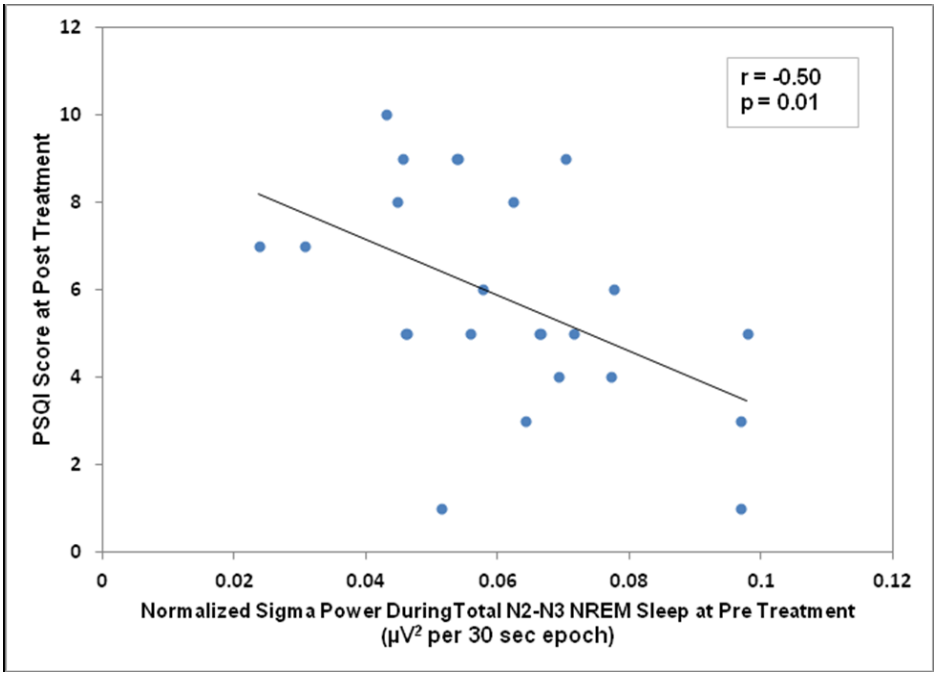

Figure 6: Correlation plot between spindle density at baseline and post-treatment ISI scores.

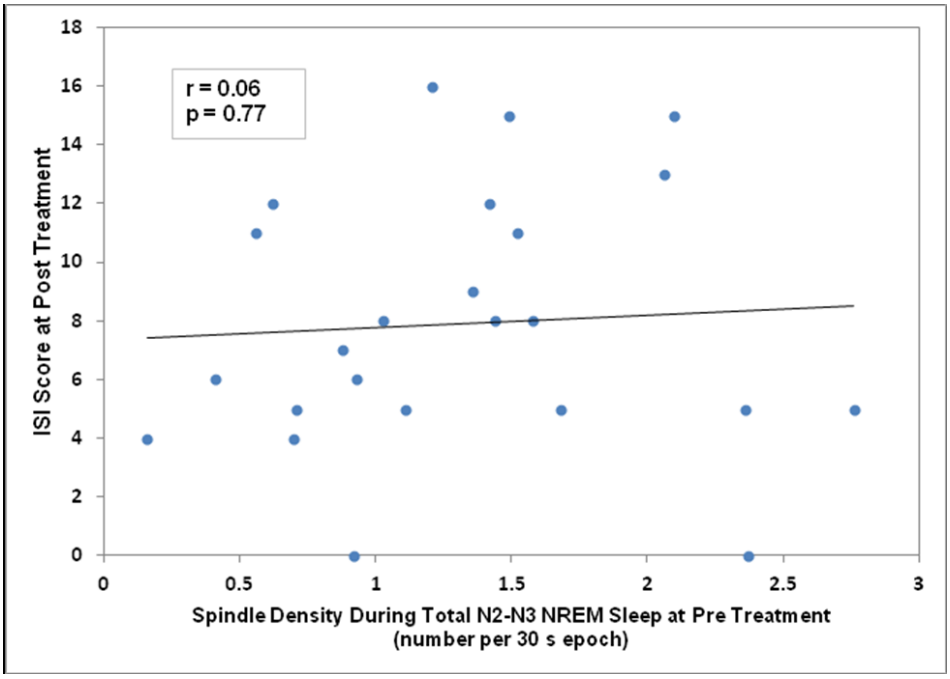

Figure 7: Correlation plot between ISI scores at baseline and post-treatment ISI scores.

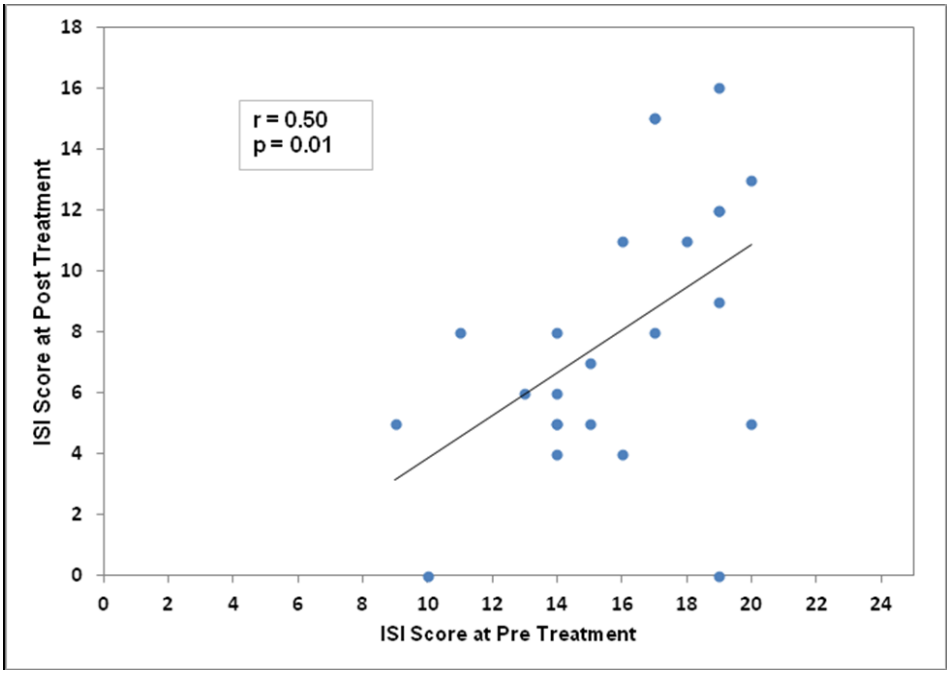

Figure 8: Correlation plot between spindle density at baseline and post-treatment sleep diary sleep efficiency.

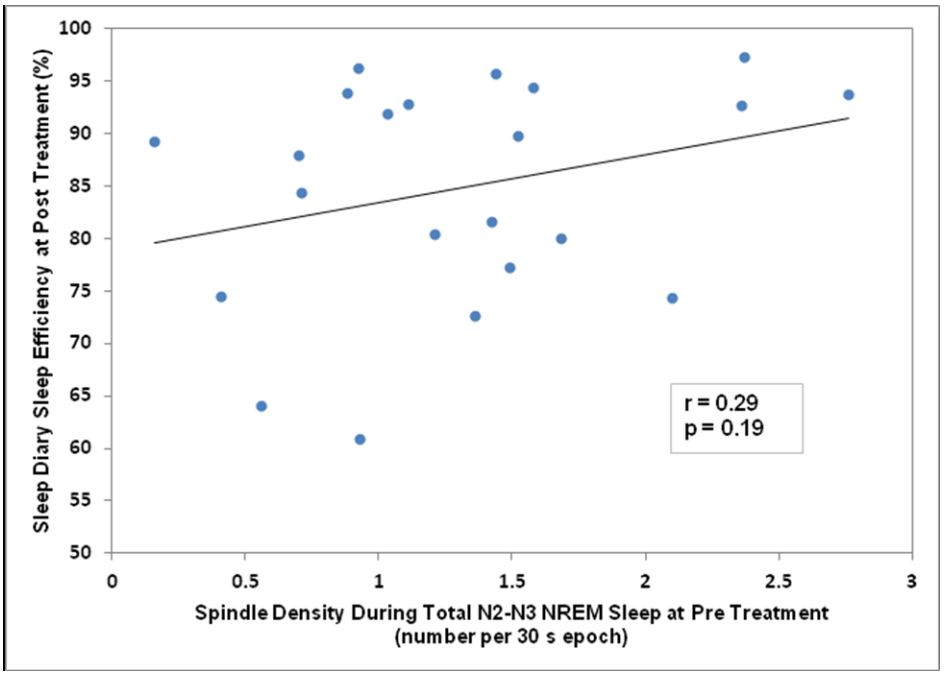

Figure 9: Correlation plot between spindle density at baseline and post-treatment PSG sleep efficiency.

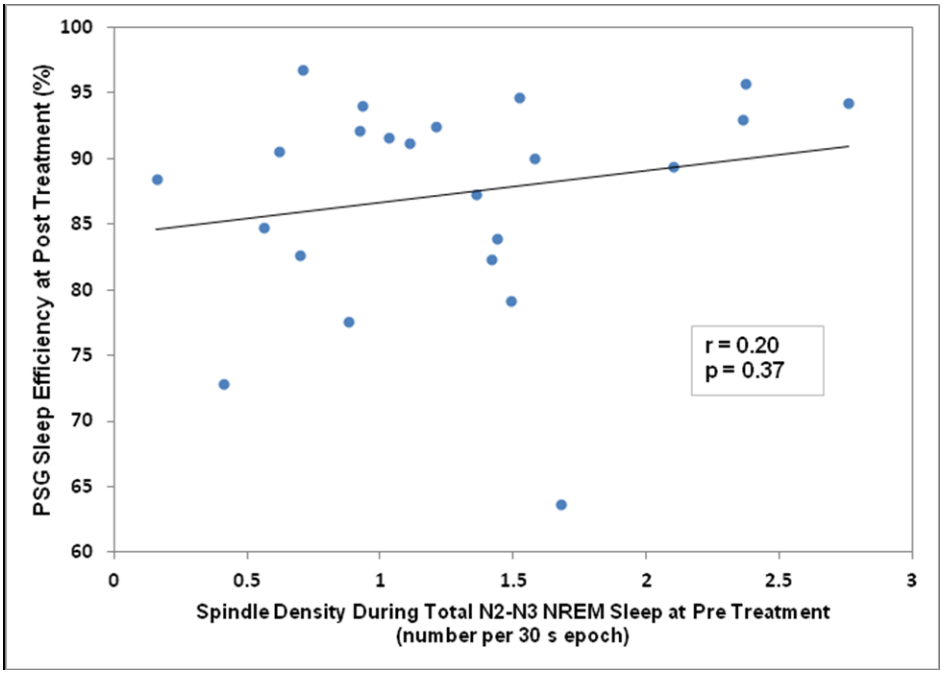

Table 1: Spindle and PSG measures of participants in cohort 1(ambulatory home recordings; N = 6, 4 females) and cohorts 2-5 (sleep lab recordings, N = 18; 15 females) compared by independent samples t-test for both pre- and post-treatment. Sigma and delta power values are normalized to global spectral power.

Parameters	*Cohort 1 Mean (SD)*	*Cohort 2-5 Mean (SD)*	*Mean difference*	*t value*	*p value*
Pre Spindle Density (num per 30 sec epoch)	1.12 (0.33)	1.37 (0.75)	0.25	-0.77	.450
Pre Spindle Duration (sec)	0.85 (0.03)	0.89 (0.13)	0.04	-1.29	.212
Pre Spindle Amplitude (μV)	7.2 (1.69)	10.51 (4.11)	3.31	-1.90	.071
Pre Spindle Power (μV^2)	14.15 (6.08)	33.68 (25.28)	19.53	-1.85	.078
Pre Spindle Frequency (Hz)	13.88 (0.28)	13.85 (0.39)	-0.03	0.19	.850
Pre Sigma Power (μV^2 per 30 sec epoch)	0.06 (0.01)	0.06 (0.02)	0	-0.57	.576
Pre Delta Power (μV^2 per 30 sec epoch)	0.53 (0.05)	0.50 (0.05)	-0.03	1.44	.164
Pre Delta power in first sleep cycle (μV^2)	0.54 (0.07)	0.54 (0.10)	0	-0.12	.907
Pre PSG sleep efficiency (%)	89.02 (4.32)	78.39 (13.20)	-10.63	1.91	.069
Pre PSG WASO (min)	32.70 (20.83)	86.28 (69.18)	53.58	-1.85	.079
Pre PSG sleep latency (min)	21.60 (21.57)	20.09 (16.31)	-1.51	0.18	.858
Pre PSG TST (min)	381.50 (25.56)	377.08 (65.42)	-4.42	0.16	.875
Pre PSG N1 % of TST	4.47 (2.15)	12.24 (10.53)	7.77	-1.77	.091
Pre PSG N1 Duration (min)	16.67 (7.33)	45.53 (40.84)	28.86	-1.70	.104
Pre PSG N2 % of TST	67.62 (7.95)	59.33 (8.36)	-8.29	2.13	.045*
Pre PSG N2 Duration (min)	256.50 (25.58)	222.81 (40.77)	-33.69	1.89	.072
Pre PSG N3 % of TST	7.60 (9.56)	10.12 (6.35)	2.52	-0.74	.467
Pre PSG N3 Duration (min)	30.33 (40.72)	40.08 (26.76)	9.75	-0.68	.505
Pre PSG REM % of TST	20.45 (2.41)	17.87 (4.90)	-2.58	1.23	.232
Pre PSG REM Duration (min)	78.08 (11.02)	70.17 (23.85)	-7.91	0.78	.446
Post Spindle Density (num per 30 sec	1.33 (0.53)	1.16 (0.74)	-0.17	0.53	.599

epoch)					
Post Spindle Duration (sec)	0.89 (0.03)	0.87 (0.11)	-0.02	0.53	.605
Post Spindle Amplitude (μV)	8.32 (2.26)	10.54 (4.29)	2.22	-1.20	.244
Post Spindle Power (μV^2)	19.75 (9.71)	33.93 (28.13)	14.18	-1.19	.246
Post Spindle Frequency (Hz)	13.88 (0.21)	13.86 (0.39)	-0.02	0.15	.886
Post Sigma Power (μV^2 per 30 sec epoch)	0.07 (0.02)	0.06 (0.02)	-0.01	1.42	.170
Post PSG sleep efficiency (%)	88.52 (8.12)	86.92 (8.29)	-1.6	0.41	.687
Post PSG WASO (min)	29.58 (25.25)	45.58 (33.05)	16	-1.07	.295
Post PSG sleep latency (min)	19.30 (8.61)	10.24 (8.37)	-9.06	2.27	.034*
Post PSG TST (min)	405.67 (90.31)	371.87 (66.72)	-33.8	0.96	.341
Post PSG N1 % of TST	5.00 (4.09)	8.01 (5.60)	3.01	-1.20	.244
Post PSG N1 Duration (min)	18.25 (10.80)	29.68 (21.78)	11.43	-1.22	.236
Post PSG N2 % of TST	68.25 (6.32)	60.04 (8.68)	-8.21	2.11	.047*
Post PSG N2 Duration (min)	270.17 (45.20)	225.32 (51.68)	-44.85	1.88	.074
Post PSG N3 % of TST	7.52 (4.45)	11.70 (7.45)	4.18	-1.29	.213
Post PSG N3 Duration (min)	30.33 (18.90)	42.47 (26.06)	12.14	-1.04	.310
Post PSG REM % of TST	20.23 (6.99)	19.14 (5.78)	-1.09	0.38	.708
Post PSG REM Duration (min)	87.00 (47.41)	72.94 (28.36)	-14.06	0.87	.392

PSG, polysomnography; WASO, wake after sleep onset; TST, total sleep time
**Significant at p≤0.05*

Table 2: Insomnia outcome, PSG, and spindle measures of participants who dropped out for which data was available (N = 2; 2 females) compared to participants who completed the study (N = 24; 19 females). Sigma and delta power values are normalized to global spectral power.

Parameters	*Drop-Out Mean (SD)*	*Completer Mean (SD)*	*Mean difference*	*t value*	*p value*
PSQI	10.00 (7.07)	10.91 (3.52)	0.91	-0.39	.698
ISI	21.50 (7.78)	15.91 (3.13)	-5.59	1.03	.487
SLD sleep efficiency (%)	56.62 (39.94)	72.21 (12.45)	15.59	-0.55	.679
SLD WASO (min)	133.21 (151.02)	55.59 (40.08)	-77.62	0.73	.600
SLD sleep latency (min)	41.86 (29.90)	48.42 (40.95)	6.56	-0.29	.812
SLD sleep duration (min)	325.00 (247.49)	348.20 (81.69)	23.2	-0.13	.916
PSG sleep efficiency (%)	91.85 (4.31)	82.43 (10.69)	-9.42	1.20	.241
PSG WASO (min)	35.90 (19.66)	67.49 (60.44)	31.59	-0.79	.437
PSG sleep latency (min)	7.45 (1.77)	20.82 (17.57)	13.37	-1.05	.306
PSG TST (min)	472.25 (12.37)	385.76 (44.95)	-86.49	2.27	.033*
PSG N1 % of TST	4.05 (1.20)	9.77 (9.59)	5.72	-0.89	.382
PSG N1 Duration (min)	19.00 (4.95)	37.98 (38.32)	18.98	-0.72	.482
PSG N2 % of TST	62.50 (3.96)	61.38 (9.08)	-1.12	0.13	.899
PSG N2 Duration (min)	294.75 (10.96)	235.78 (33.84)	-58.97	2.21	.037*
PSG N3 % of TST	7.50 (4.67)	9.80 (7.12)	2.30	-0.34	.741
PSG N3 Duration (min)	35.75 (22.98)	38.89 (30.18)	3.14	-0.05	.961
PSG REM % of TST	26.00 (0.42)	19.07 (3.65)	-6.93	2.56	.017*
PSG REM Duration (min)	122.75 (5.30)	74.30 (19.06)	-48.45	3.27	.003**
Pre Spindle Density (num per 30 sec epoch)	1.00 (0.13)	1.27 (0.67)	0.27	-0.64	.531
Pre Spindle Duration (sec)	0.90 (0.13)	0.88 (0.11)	-0.02	0.20	.844
Pre Spindle Amplitude (μV)	11.90 (0.28)	10.05 (3.54)	-1.85	0.79	.439

Pre Spindle Power (μV^2)	38.60 (1.13)	30.03 (23.28)	-8.57	0.58	.569
Pre Spindle Frequency (Hz)	13.70 (0.14)	13.86 (0.37)	0.16	-0.61	.551
Pre Sigma Power (μV^2 per 30 sec epoch)	0.05 (0.01)	0.06 (0.02)	0.01	-0.61	.545

PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; WASO, wake after sleep onset; SLD, sleep diary; PSG, polysomnography; TST, total sleep time
**Significant at p≤0.05, **Significant at p≤0.01*

Table 3: Demographic characteristics and sleep measures of participants at baseline (pre-treatment) and immediately after CBT-I (post-treatment) (N = 24, 19 females; N = 22 for sleep diary measures)

Parameters	*Pre-treatment Mean (SD)*	*Post-treatment Mean (SD)*	*Mean difference*	*t value*	*p value*
Age	42.84 (15.7)	-	-	-	-
Education years	16 (3.09)	-	-	-	-
Insomnia duration years	14.76 (15.70)	-	-	-	-
PSQI	10.91 (3.52)	5.83 (2.55)	-5.08	6.60	.000**
ISI	15.91 (3.13)	8.17 (4.51)	-7.74	9.74	.000**
SLD sleep efficiency (%)	72.21 (12.45)	84.8 (10.61)	12.59**	-3.93	.001**
SLD WASO (min)	55.59 (40.08)	25 (22.93)	-30.59**	3.28	.004**
SLD sleep latency (min)	48.42 (40.95)	19.59 (15.27)	-28.83**	3.12	.005**
SLD sleep duration (min)	348.2 (81.69)	382.52 (60.18)	34.32	-1.82	.083
PSG sleep efficiency (%)	82.43 (10.69)	87.34 (8.09)	4.91	-1.99	.059
PSG WASO (min)	67.49 (60.44)	41.4 (31.49)	-26.09	2.29	.032*
PSG sleep latency (min)	20.82 (17.57)	12.6 (9.19)	-8.22	2.11	.046*
PSG TST (min)	385.76 (44.95)	380.68 (72.95)	-5.08	0.30	.770
PSG N1 % of TST	9.77 (9.59)	7.22 (5.33)	-2.55	1.71	.102
PSG N1 Duration (min)	37.98 (38.32)	26.70 (19.95)	-11.28	1.87	.075
PSG N2 % of TST	61.38 (9.08)	62.18 (8.8)	0.8	-0.56	.580
PSG N2 Duration (min)	235.78 (33.84)	237.02 (53.03)	1.24	-0.12	.916
PSG N3 % of TST	9.8 (7.12)	10.61 (6.96)	0.81	-0.47	.646
PSG N3 Duration (min)	38.89 (30.18)	39.30 (24.59)	0.41	-0.07	.946
PSG REM % of TST	19.07 (3.65)	19.42 (5.97)	0.35	2.02	.763
PSG REM Duration (min)	74.30 (19.06)	76.61 (33.70)	2.31	-0.31	.758

PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; WASO, wake after sleep onset; SLD, sleep diary; PSG, polysomnography; TST, total sleep time
**Significant at p≤0.05, **Significant at p≤0.01*

Table 4: Spindle measures of participants at pre- and post-treatment. Sigma power value is normalized to global spectral power (N = 24, 19 females)

Parameters	*Pre-treatment Mean (SD)*	*Post-treatment Mean (SD)*	*Mean difference*	*t value*	*p value*
Spindle Density (num per 30 sec epoch)	1.27 (0.67)	1.20 (0.68)	-0.07	0.83	.418
Spindle Duration (sec)	0.88 (0.11)	0.88 (0.10)	0	0.51	.615
Spindle Amplitude (μV)	10.05 (3.54)	9.96 (3.94)	-0.09	0.13	.895
Spindle Power (μV^2)	30.03 (23.28)	30.23 (25.25)	0.20	-0.05	.960
Spindle Frequency (Hz)	13.86 (0.37)	13.87 (0.34)	0.01	-0.09	.929
Sigma Power (μV^2 per 30 sec epoch)	0.06 (0.02)	0.06 (0.02)	0	-0.03	.980

***Significant at p≤0.01*

Table 5: Inter-correlation matrix for all spindle measures pre- and post-treatment, intra-class correlations are presented for corresponding measures at pre/post (bolded cells)

		Density (Pre)	Duration (Pre)	Amplitude (Pre)	Power (Pre)	Frequency (Pre)	Sigma Power (Pre)	Density (Post)	Duration (Post)	Amplitude (Post)	Power (Post)	Frequency (Post)	Sigma Power (Post)
Density (Pre)	Pearson's r												
	p value												
Duration (Pre)	Pearson's r	.803**											
	p value	.000											
Amplitude (Pre)	Pearson's r	.448*	.595**										
	p value	.028	.002										
Power (Pre)	Pearson's r	.575**	.614**	.953**									
	p value	.003	.001	.000									
Frequency (Pre)	Pearson's r	-.067	-.210	-.130	-.147								
	p value	.755	.324	.545	.493								
Sigma Power (Pre)	Pearson's r	.949**	.790**	.381	.481*	-.160							
	p value	.000	.000	.066	.017	.455							
Density (Post)	Pearson's r	.811**	.613**	.347	.442*	.106	.773**						
	p value	.000	.002	.105	.035	.630	.000						
Duration (Post)	Pearson's r	.786**	.911**	.362	.397	-.159	.761**	.705**					
	p value	.000	.000	.090	.061	.469	.000	.000					
Amplitude (Post)	Pearson's r	.495*	.426*	.586**	.580**	.115	.374	.384	.346				
	p value	.016	.043	.002	.004	.601	.079	.070	.106				
Power (Post)	Pearson's r	.546**	.421*	.672**	.714**	.060	.443*	.421*	.314	.955**			
	p value	.007	.046	.000	.000	.785	.034	.046	.145	.000			
Frequency (Post)	Pearson's r	-.042	-.112	-.035	-.029	.797**	-.117	.123	-.038	.031	.022		
	p value	.850	.612	.875	.895	.000	.596	.577	.862	.889	.921		
Sigma Power (Post)	Pearson's r	.659**	.473*	.156	.222	.039	.699**	.831**	.572**	.423*	.445*	.049	
	p value	.001	.023	.478	.309	.859	.000	.000	.004	.045	.034	.825	

**Significant at p≤0.05, **Significant at p≤0.01*

Table 6: Inter-correlation matrix of all outcome measures at pre- and post-treatment, intra-class correlations are presented for corresponding measures at pre/post (bolded cells)

		PSQI (Pre)	ISI (Pre)	Sleep Diary Sleep Efficiency (Pre)	PSG Sleep Efficiency (Pre)	PSQI (Post)	ISI (Post)	Sleep Diary Sleep Efficiency (Post)	PSG Sleep Efficiency (Post)
PSQI (Pre)	Pearson's r								
	p value								
ISI (Pre)	Pearson's r	.380							
	p value	.067							
Sleep Diary Sleep Efficiency (Pre)	Pearson's r	-.512*	-.264						
	p value	.015	.236						
PSG Sleep Efficiency (Pre)	Pearson's r	-.329	-.358	.085					
	p value	.117	.086	.708					
PSQI (Post)	Pearson's r	.072	.094	-.020	-.304				
	p value	.197	.661	.930	.148				
ISI (Post)	Pearson's r	.122	.151**	-.040	-.194	.532**			
	p value	.569	.009	.861	.363	.008			
Sleep Diary Sleep Efficiency (Post)	Pearson's r	-.299	-.145	.100	.275	-.503*	-.465*		
	p value	.176	.519	.240	.216	.017	.029		
PSG Sleep Efficiency (Post)	Pearson's r	.015	-.024	.031	.201	-.165	-.085	.240	
	p value	.948	.913	.891	.150	.453	.700	.282	

***Significant at p≤0.01*

**Significant at p≤0.05*

Table 7: Coefficients and effect sizes for predictors in the multiple regressions with PSQI as outcome measure. Coefficients and effect sizes for each predictor are taken from the block of the regression in which that predictor is entered. Each spindle/EEG predictor represents a separate regression. (N = 24, 19 females) **Significant at p≤0.05*

	Predictors	***Post CBT-I PSQI***									
Model		*B*	*SE*	*β*	*t value*	*p value*	*Adjusted R^2*	*R^2 change*	*F change*	*p value*	*Partial eta^2*
1	**Pre CBT-I PSQI**	0.13	0.15	0.19	0.90	.377	-0.01	0.04	0.81	.377	0.04
2	**Sex**	-0.73	1.35	-0.12	-0.54	.597	-0.04	0.12	0.79	.514	0.01
	Age	0.01	0.04	0.08	0.34	.740					0.01
	Education years	-0.22	0.19	-0.28	-1.19	.249					0.07
3	**SRAQ**	-0.24	0.16	-0.32	-1.51	.148	0.03	0.10	2.29	.148	0.10
4	**PSG N2 Duration**	0.00	0.02	0.00	0.01	.990	-0.03	0.00	0.00	.990	0.00
5	**Home vs. lab**	-2.33	1.59	-0.41	-1.46	.162	0.04	0.09	2.14	.162	0.09
6	**Spindle density**	-2.29	1.07	-0.61	-2.14	.049*	0.21	0.16	4.59	.049*	0.16
6	**Spindle duration**	-7.87	9.59	-0.35	-0.82	.424	0.02	0.03	0.67	.424	0.03
6	**Spindle amplitude**	-0.23	0.21	-0.36	-1.08	.297	0.05	0.05	1.17	.297	0.05
6	**Spindle power**	-0.04	0.03	-0.41	-1.39	.185	0.09	0.08	1.93	.185	0.08
6	**Spindle frequency**	1.18	1.69	0.17	0.70	.496	0.00	0.02	0.49	.496	0.02
6	**Sigma power**	-86.17	37.86	-0.67	-2.28	.038*	0.24	0.17	5.18	.038*	0.17
6	**Delta Power**	2.45	14.48	0.05	0.17	.868	-0.03	0.00	0.03	.868	0.00
6	**Delta Power in first sleep cycle**	-6.63	6.71	-0.23	-0.99	.339	0.03	0.04	0.98	.339	0.04

Table 8: Coefficients and effect sizes for predictors in the multiple regressions with ISI as outcome measure. Coefficients and effect sizes for each predictor are taken from the block of the regression in which that predictor is entered. Each spindle/EEG predictor represents a separate regression. (N = 24, 19 females) **Significant at p≤0.05*

	Predictors	***Post CBT-I ISI***									
Model		*B*	*SE*	*β*	*t value*	*p value*	*Adjusted R^2*	*R^2 change*	*F change*	*p value*	*Partial eta^2*
1	**Pre CBT-I ISI**	0.70	0.26	0.50	2.68	.014*	0.21	0.25	7.15	.014*	0.25
2	**Sex**	-1.28	2.31	-0.12	-0.56	.585	0.13	0.04	0.31	.821	0.01
	Age	-0.01	0.06	-0.05	-0.24	.813					0.00
	Education years	-0.18	0.30	-0.13	-0.59	.563					0.01
3	**SRAQ**	-0.46	0.25	-0.35	-1.84	.083	0.23	0.11	3.37	.083	0.11
4	**PSG N2 Duration**	0.04	0.03	0.33	1.15	.265	0.24	0.04	1.33	.265	0.04
5	**Home vs. lab**	-1.85	2.56	-0.19	-0.72	.479	0.22	0.02	0.53	.479	0.02
6	**Spindle density**	0.97	1.91	0.15	0.51	.618	0.18	0.01	0.26	.618	0.01
6	**Spindle duration**	19.76	13.27	0.49	1.49	.157	0.27	0.07	2.22	.157	0.07
6	**Spindle amplitude**	-0.10	0.36	-0.09	-0.29	.777	0.17	0.00	0.08	.777	0.00
6	**Spindle power**	-0.01	0.06	-0.07	-0.26	.802	0.17	0.00	0.07	.802	0.00
6	**Spindle frequency**	-1.42	2.76	-0.12	-0.51	.615	0.18	0.01	0.26	.615	0.01
6	**Sigma power**	25.34	65.29	0.11	0.39	.703	0.17	0.01	0.15	.703	0.01
6	**Delta Power**	22.40	22.99	0.26	0.97	.345	0.22	0.03	0.95	.345	0.03
6	**Delta Power in first sleep cycle**	9.28	10.80	0.19	0.86	.404	0.20	0.03	0.74	.404	0.03

Table 9: Coefficients and effect sizes for predictors in the multiple regressions with sleep diary sleep efficiency as outcome measure. Coefficients and effect sizes for each predictor are taken from the block of the regression in which that predictor is entered. Each spindle/EEG predictor represents a separate regression. (N = 22, 19 females)

	Predictors	***Post CBT-I SD Sleep Efficiency***									
Model		*B*	*SE*	*β*	*t value*	*p value*	*Adjusted R^2*	*R^2 change*	*F change*	*p value*	*Partial eta^2*
1	**Pre CBT-I SD Sleep Efficiency**	0.13	0.19	0.16	0.71	.486	-0.02	0.03	0.50	.486	0.03
2	**Sex**	-4.24	7.09	-0.16	-0.60	.558	-0.12	0.07	0.44	.731	0.02
	Age	-0.17	0.17	-0.26	-1.03	.319					0.06
	Education years	0.33	0.81	0.10	0.40	.692					0.01
3	**SRAQ**	1.31	0.74	0.42	1.79	.093	0.01	0.15	3.19	.093	0.15
4	**PSG N2 Duration**	0.01	0.09	0.02	0.07	.945	-0.06	0.00	0.01	.945	0.00
5	**Home vs. lab**	-2.76	7.61	-0.12	-0.36	.722	-0.12	0.01	0.13	.722	0.01
6	**Spindle density**	7.66	5.88	0.48	1.30	.215	-0.07	0.09	1.70	.215	0.09
6	**Spindle duration**	38.68	40.70	0.41	0.95	.359	-0.13	0.05	0.90	.359	0.05
6	**Spindle amplitude**	0.10	1.29	0.03	0.07	.943	-0.21	0.00	0.01	.943	0.00
6	**Spindle power**	0.03	0.17	0.07	0.19	.853	-0.21	0.00	0.04	.853	0.00
6	**Spindle frequency**	-11.38	8.06	-0.40	-1.41	.181	-0.05	0.10	1.99	.181	0.10
6	**Sigma power**	331.18	190.77	0.61	1.74	.106	0.02	0.14	3.01	.106	0.14
6	**Delta Power**	-75.25	75.88	-0.37	-0.99	.339	-0.12	0.05	0.98	.339	0.05
6	**Delta Power in first sleep cycle**	8.97	32.28	0.08	0.28	.786	-0.20	0.00	0.08	.786	0.00

Table 10: Coefficients and effect sizes for predictors in the multiple regressions with PSG sleep efficiency as outcome measure. Coefficients and effect sizes for each predictor are taken from the block of the regression in which that predictor is entered. Each spindle/EEG predictor represents a separate regression. (N = 24, 19 females)

	Predictors	***Post CBT-I PSG Sleep Efficiency***									
Model		*B*	*SE*	*β*	*t value*	*p value*	*Adjusted R^2*	*R^2 change*	*F change*	*p value*	*Partial eta^2*
1	**Pre CBT-I PSG Sleep Efficiency**	0.17	0.16	0.23	1.08	.292	0.01	0.05	1.17	.292	0.05
2	**Sex**	-5.70	5.15	-0.27	-1.12	.283	-0.07	0.07	0.50	.668	0.06
	Age	-0.08	0.14	-0.16	-0.60	.557					0.02
	Education years	-0.04	0.63	-0.02	-0.07	.945					.0.00
3	**SRAQ**	-0.30	0.59	-0.13	-0.51	.615	-0.12	0.01	0.26	.615	0.01
4	**PSG N2 Duration**	0.05	0.08	0.20	0.58	.573	-0.16	0.02	0.33	.573	0.02
5	**Home vs. lab**	1.03	5.74	0.06	0.18	.860	-0.24	0.00	-0.03	.860	0.00
6	**Spindle density**	4.20	4.24	0.35	0.99	.339	-0.24	0.06	0.98	.339	0.06
6	**Spindle duration**	33.16	31.32	0.46	1.06	.308	-0.23	0.06	1.12	.308	0.06
6	**Spindle amplitude**	0.64	1.02	0.28	0.62	.543	-0.29	0.02	0.39	.543	0.02
6	**Spindle power**	0.14	0.14	0.41	1.03	.319	-0.23	0.06	1.07	.319	0.06
6	**Spindle frequency**	-8.66	6.44	-0.40	-1.34	.200	-0.17	0.10	1.81	.200	0.10
6	**Sigma power**	177.39	147.84	0.43	1.20	.250	-0.20	0.08	1.44	.250	0.08
6	**Delta Power**	-5.80	52.21	-0.04	-0.11	.913	-0.32	0.00	0.01	.913	0.00
6	**Delta Power in first sleep cycle**	13.89	26.96	0.15	0.52	.614	-0.30	0.02	0.27	.614	0.02

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