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Sleep spindles may predict response to cognitive behavioral therapy for chronic insomnia

Running head: Spindles and CBT-I response

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Abstract

Background: While cognitive-behavioral therapy for insomnia constitutes the first-line treatment for chronic insomnia, only few reports have investigated how sleep architecture relates to response to this treatment. In this pilot study, we aimed at determining whether sleep spindle density at pre-treatment predicts treatment response to cognitive behavioral therapy for insomnia.

Methods: Twenty-four participants with chronic primary insomnia took part in a 6-week cognitive behavioral therapy for insomnia performed in groups of 4 to 6 participants. Treatment response was assessed using the Pittsburgh Sleep Quality Index and the Insomnia Severity Index measured at pre- and post-treatment and at 3- and 12-months follow-up assessments. Secondary outcome measures were extracted from sleep diaries over seven days and one overnight polysomnography, obtained at pre- and post-treatment. Spindle density during stages N2-N3 sleep was extracted from polysomnography at pre-treatment. Hierarchical linear modeling analysis assessed whether sleep spindle density predicted response to cognitive behavioral therapy.

Results: After adjusting for age, sex and education level, lower spindle density at pre-treatment predicted poorer response over the 12-months follow-up, as reflected by smaller reduction in Pittsburgh Sleep Quality Index over time. Reduced spindle density also predicted lower improvements in sleep diary sleep efficiency and wake after sleep onset immediately after treatment. There were no significant associations between spindle density and changes in the Insomnia Severity Index or polysomnography variables over time.

Conclusion: These preliminary results suggest that inter-individual differences in sleep spindle density in insomnia may represent an endogenous biomarker predicting responsiveness to cognitive behavioral therapy. Insomnia with altered spindle activity might constitute an insomnia

subtype characterized by a neurophysiological vulnerability to sleep disruption associated with impaired responsiveness to cognitive behavioral therapy.

INTRODUCTION

Insomnia is one of the most commonly reported sleep complaints with an estimated 6-10% of adults meeting clinical criteria for chronic insomnia disorder, leading to detrimental health consequences and impairment in quality of life [1]. The first-line treatment for chronic insomnia is cognitive behavioral therapy for insomnia (CBT-I), a multimodal approach including elements such as stimulus control, sleep restriction, sleep hygiene, cognitive restructuring and relaxation techniques [2]. CBT-I has well documented efficacy with treatment response rates around 60-70% and remission rates around 40% [3, 4]. However, approximately half of those treated will maintain persistent insomnia symptoms after CBT-I. In this context the search for predictors of CBT-I treatment response is of prime importance to identify individuals who should be prioritized for CBT-I.

Previous research on predicting treatment outcomes for CBT-I has produced mixed results. While demographic variables (e.g., age, sex, education level) were not found to be associated with treatment outcome [5-7], some studies reported that greater severity of insomnia at baseline predicted better treatment outcomes, but these results were inconsistent across studies [5, 7, 8]. Results were also inconsistent for psychological factors: elevated anxiety and depression were associated with better CBT-I outcomes in some studies [5] but not others [9]; greater dysfunctional beliefs about sleep predicted better CBT-I treatment outcomes [10], but not in all studies [7]. Objective sleep duration was also investigated, some studies reporting that insomniacs with short sleep showed poorer CBT-I response [11], while others found no difference in CBT-I treatment outcome between insomniacs with short sleep and those with normal sleep duration [12]. One area that has not received much attention is sleep micro-architecture. The only previous study to investigate this domain showed that lower

electroencephalography (EEG) delta power in the first non-rapid-eye-movement (NREM) sleep cycle at pre-treatment predicted better response to CBT-I [13]. To our knowledge, no study has specifically assessed sleep spindle activity in relation to CBT-I outcomes.

Sleep spindles are transient oscillations of around 11-15 Hz (sigma band) seen in EEG recordings that occur predominantly in stage N2, but also persist in stage N3 of NREM sleep. They are produced by the interplay of specific thalamic nuclei (reticular thalamic and thalamo-cortical neurons) and cortical neurons [14]. Spindle activity – as measured by averaged spindle density – is considered as an individual trait; while spindle density shows variability between individuals, it remains stable across multiple nights within individuals [15, 16]. Interindividual differences in spindle activity have been proposed to reflect a genetically determined trait [17]. Spindles have been shown to display functional properties that can be grouped in two major domains. First, they correlate with overnight improvements of procedural and declarative memories as well as with general intellectual abilities, which suggests that spindle density is a biomarker of neural development and offline memory consolidation [18, 19]. Second, spindles have also been related to the gating of external stimuli, particularly acoustic stimuli, during sleep. Neuroimaging studies have shown that sounds played during NREM sleep consistently activated the auditory cortex except when the sound occurred during spindles [20]. Furthermore, individuals with lower spindle density were shown to be more vulnerable to sleep disruption from external sounds than those with higher spindle activity [21]. This suggests that spindles serve as a sleep protective mechanism that may help maintain sleep when exposed to noise.

Lower spindle density might thus affect sleep quality and represent a predisposing factor to the development of insomnia. This was demonstrated in a longitudinal study that assessed sleep changes in response to a relatively well-standardized naturalistic stressor, final

examinations among university students. Individuals with lower spindle density at the start of the semester prospectively reported a greater increase in insomnia symptoms towards the end of the semester, a period of higher academic stress [22]. However, this finding contrasts with the absence of group differences between chronic insomniacs and good sleepers in the number and density of sleep spindles [23]. One explanation for these seemingly discrepant findings is that chronic insomnia is a broad phenotype that likely encompasses different subtypes with distinct aetiologies [24]. Given its relationships with sleep stability and with the development of insomnia, spindle activity might constitute a factor distinguishing specific subtypes of insomniacs, i.e. a low-spindle insomnia subtype characterized by a neurophysiological trait vulnerability to sleep disruption, and a subtype with preserved spindle activity in which other factors (e.g. psychological) would play a more predominant role in the persistence of insomnia. Such spindle-based phenotyping of chronic insomnia would be likely to impact responsiveness to CBT-I, and therefore have clinical relevance. Indeed, CBT-I has been developed to target the psychological factors contributing to the perpetuation of insomnia rather than the physiological processes associated with insomnia [25], and might thus be less effective for individuals in which a neurophysiological vulnerability to insomnia is elicited by a reduced spindle density .

The purpose of this pilot study was to assess whether inter-individual differences in spindle density prospectively predict response to CBT-I among chronic primary insomniacs. Primary outcomes of interest were changes in sleep quality and insomnia severity questionnaires (Pittsburgh Sleep Quality Index, PSQI; Insomnia Severity Index, ISI) from pre-treatment to 12 months post-treatment. Secondary outcomes were pre- to immediate post-treatment changes in PSQI, ISI, as well as sleep variables derived from sleep diaries and polysomnography (PSG). Changes in these variables were examined in relation to spindle density at pre-treatment. We

hypothesized that insomniacs with lower spindle density would show poorer improvement in CBT-I outcomes, compared to those with higher spindle density.

MATERIALS AND METHODS

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. During that interview, eligibility was reviewed and confirmed by a licensed neurologist with expertise in sleep medicine (TD). Participants had to meet the ICSD-3 diagnostic criteria for chronic insomnia disorder, which were operationalized as difficulties initiating sleep (defined as a sleep onset latency greater than 30 min.) and/or difficulties maintaining sleep (defined as wake after sleep onset greater than 30 min.) and/or early morning awakenings (defined as final awakening time earlier than desired by at least 30 min.), combined with significant impairment of daytime functioning, for a duration of three months or more with sleep disturbances three times a week or more [26]. Exclusion criteria were being less than 18 years of age, having major psychiatric or medical conditions including sleep disorders other than insomnia (e.g., sleep apnea, restless legs syndrome and periodic limb movement disorder), 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 screening PSG to rule out the presence of other sleep disorders contributing to insomnia symptoms, particularly sleep apnea and periodic limb movement disorder (an apnea-hypopnea index > 5/h and an index of periodic limb movements during sleep > 15/h were exclusion criteria). 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. 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 a written informed consent form before entering the study, which was approved by the Concordia University Human Research Ethics Committee.

Procedure

After participants were deemed eligible following the screening PSG, they underwent a second sleep recording night within a month before the beginning of the CBT-I sessions, and completed a sleep diary for one week and two standardized sleep questionnaires: the Pittsburgh Sleep Quality Index (PSQI) [27] and the Insomnia Severity Index (ISI) [28]. Participants then completed six, weekly group sessions of CBT-I. Within a month of completion, participants completed a third overnight sleep recording, sleep diaries for one week along with the two aforementioned questionnaires. Follow ups were later conducted by phone 3 months and 12

months following CBT-I completion and consisted again of the same two questionnaires (ISI, PSQI).

Self-reported sleep measures

Sleep quality and insomnia severity 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 [27]. 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 timing of sleep habits and 6 Likert style questions. Total PSQI score falls on a scale from 0-21 (with higher scores indicating worse sleep quality) and has been shown to display an average of 10.38 (SD = 4.57) in insomniacs with an overall Cronbach α of 0.83 [27]. The second questionnaire used was the Insomnia Severity Index (ISI), a self-report measure of the nature, severity and impact of current insomnia symptoms [28]. The ISI consists of 7 Likert style questions with a total score ranging from 0-28 (with higher scores indicating more severe insomnia) and an average score reported in insomniacs of 19.7 (SD = 4.1) with an overall Cronbach α of 0.74 [28]. Total PSQI and ISI scores were used for statistical analyses. 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 the PSQI and the same 19 also completed the 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 [29]. 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 %), wake after sleep onset (WASO, as defined by the duration of awakenings after sleep onset), sleep latency (i.e., latency to sleep onset) and sleep duration (i.e., total sleep time) were extracted from sleep diaries by averaging daily values over seven days, including both weekends and weekdays. Sleep efficiency, WASO, sleep latency and sleep duration derived from sleep diaries were used as secondary variables to assess response to CBT-I. Sleep diaries were completed by 22 out of the 24 participants at both pre- and post-treatment.

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 adaptation night, while the second served as the baseline experimental night to provide sleep measures before CBT-I (including sleep spindles); 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 adaptation night for these 6 participants who thus had two ambulatory PSG recordings (the first at baseline and the second after CBT-I). However, 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 (adaptation) and ambulatory PSG

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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 visually scored according to standard criteria [30] and changes in PSG sleep efficiency, WASO, sleep latency and sleep duration from baseline to post-CBT-I were calculated as secondary outcome measures of treatment response. Sleep spindles were automatically detected 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 [31]. 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 [32]. 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). 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. In addition, after automatic EEG artifact rejection, EEG power in the adapted sigma frequency range during

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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 [13]. Finally, EEG power in other frequency bands relevant to sleep, using bands adapted to each individual, were also calculated for total N2-N3 NREM sleep: theta (median values for frequency range: 4 and 7.9 Hz), alpha (median range: 7.9-11.9 Hz), and beta (median range: 15.9-50 Hz). These calculations were made to allow comparisons with previous reports describing changes in sleep EEG power spectra following CBT-I [33].

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 [25], comprising 6 modules: psychoeducation about sleep and circadian rhythms (week 1); stimulus control (week 1); sleep restriction (week 2); sleep hygiene (week 2); cognitive therapy (week 4); and relaxation (week 5) [25]. Stimulus control and sleep restriction were also discussed at each session following the introduction of these therapeutic strategies. Each group included 4 to 6 participants, for a total of 5 CBT-I groups in the present study. The treatment was conducted by a licensed clinical psychologist with training and experience in CBT-I (JPG). Each weekly session lasted 90 minutes.

Statistical Analysis

Hierarchical linear modeling (HLM) evaluated changes in insomnia symptoms assessed via questionnaires, sleep diaries and PSG from pre- to post-treatment and follow-ups. More specifically, HLM assessed the trajectories of changes in total PSQI and ISI scores from pre-treatment to the 12-months assessment (four time points: pre-treatment, post-treatment, 3 and 12 months after treatment), and changes in PSQI, ISI, as well as sleep efficiency, WASO, sleep latency and sleep duration derived from sleep diaries and PSG from pre- to post-treatment (two time points: pre- and post-treatment). The main analysis included time, spindle density and their interaction in the model, and evaluated whether pre-treatment spindle density predicted the trajectory of changes in PSQI and ISI across the four assessment points. Secondary analyses, also including time, spindle density and their interaction in the model, then assessed whether spindle density predicted changes in PSQI, ISI, as well as sleep efficiency, WASO, sleep latency and sleep duration derived from sleep diaries and PSG from pre- to post-treatment. Our hypothesis was focused on spindle density as our main variable of interest, as this measure is commonly reported as the primary spindle variable given its stability across nights [23, 34]. Each of the other standard spindle measures (spindle amplitude, power, duration, frequency, sigma power) [35] and delta power was used as an exploratory variable, replacing spindle density in the model for exploratory analyses evaluating if these measures predicted treatment response. Additional analyses tested whether sleep spindle density, other spindle measures, as well as EEG spectral power in other major frequency ranges relevant to sleep (delta, theta, alpha, beta), changed from pre- to post-treatment. All analyses were conducted while adjusting for age, sex, and years of education. HLM was used given the nested nature of the data with individual subjects being treated in 5 treatment groups. HLM allowed to robustly estimate the trajectories of change in

PSQI and ISI for all participants despite some missing data [36]. To illustrate the relationships between spindle density and treatment responses, correlations between spindle density at pre-treatment and sleep changes following CBT-I were also 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) and SAS (SAS, Cary, NC, USA) softwares.

RESULTS

Changes in sleep quality after treatment

HLM analyses showed significant decreases for both PSQI (beta = -1.92, SE = 0.32, t = -5.98, p < 0.001) and ISI (beta = -3.18, SE = 0.39, t = -8.23, p < 0.001) from pre-treatment to 12 months post-treatment, indicating significant insomnia reduction over time. ISI was reduced on average by 8 points from pre- to post-treatment (table 1) and by 10 points from pre-treatment to 12 months follow-up, which corresponds to an effect size comparable to previous effects reported in randomized controlled trials [37]. At post-treatment, 50% of participants were considered on remission (as defined by an ISI score below 8) [37] and this percentage was further increased to 68% at 12 months. On the sleep diary measure, there was a significant increase in sleep efficiency from pre- to post-treatment (beta = 12.59, SE = 3.2, t = 3.93, p < 0.001). On objective PSG measures, there was a significant increase in sleep efficiency from pre- to post-treatment (beta = 6.05, SE = 2.67, t = 2.27, p = 0.03). For means and complete list of parameters see Table 1.

Parameters	Pre-treatment Mean (SD)	Post-treatment Mean (SD)	Mean difference
Age	42.84 (15.7)	-	-
Education years	16 (3.09)	-	-

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PSQI	10.91 (3.52)	5.83 (2.55)	-5.08**
ISI	15.91 (3.13)	8.17 (4.51)	-7.74**
SLD sleep efficiency (%)	72.21 (12.45)	84.8 (10.61)	12.59**
SLD WASO (min)	55.59 (40.08)	25 (22.93)	-30.59**
SLD sleep latency (min)	48.42 (40.95)	19.59 (15.27)	-28.83**
SLD sleep duration (min)	348.2 (81.69)	382.52 (60.18)	34.32
PSG sleep efficiency (%)	82.43 (10.69)	87.34 (8.09)	4.91*
PSG WASO (min)	67.49 (60.44)	41.4 (31.49)	-26.09*
PSG sleep latency (min)	20.82 (17.57)	12.6 (9.19)	-8.22*
PSG sleep duration (min)	385.76 (44.95)	380.68 (72.95)	-5.08
PSG N1 % of TST	9.77 (9.59)	7.22 (5.33)	-2.55
PSG N2 % of TST	61.38 (9.08)	62.18 (8.8)	0.8
PSG N3 % of TST	9.8 (7.12)	10.61 (6.96)	0.81
PSG REM % of TST	19.07 (3.65)	19.42 (5.97)	0.35
Spindle density (nb/30sec N2-N3)	1.27 (0.67)	1.2 (0.68)	-0.07
Spindle duration (sec)	0.88 (0.11)	0.88 (0.1)	-0.005
Spindle amplitude (microV)	10.05 (3.54)	9.96 (3.94)	-0.1
Spindle power (microV^2)	30.03 (23.28)	30.23 (25.25)	0.2
Spindle frequency (Hz)	13.86 (0.37)	13.87 (0.35)	0.004
Sigma power (normalized)	0.06 (0.02)	0.06 (0.02)	0.0001

Table 1: 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). *PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; WASO, wake after sleep onset; SLD, sleep diary; PSG, polysomnography; TST, total sleep time*
$* p≤0.05; ** p≤0.01$

Sleep spindle density as predictor of treatment response

Bivariate Pearson correlations between spindle density at pre-treatment and changes in self-reported sleep measures over time were significant for PSQI (r = -0.5, p = 0.01), sleep diary

sleep efficiency (r = 0.47, p = 0.03) (Fig. 1) and WASO (r = -0.46, p = 0.03), but not for ISI (r = -0.16, p = 0.44). Main analyses using HLM revealed that PSQI changes across the 12-month follow-up period were significantly predicted by spindle density, even after adjusting for age, sex and years of education (Table 2). Exploratory analyses revealed that spindle amplitude, power, duration, as well as sigma power (but not spindle frequency) at baseline also predicted PSQI changes over time (Table 2). Lower spindle activity at baseline was associated with smaller decreases in PSQI over time, reflecting poorer responses to CBT-I across the follow-up. These relationships were also significant when evaluating the effects of spindle activity (density, amplitude, power, duration and sigma power) on PSQI changes from pre- to immediate post-treatment (e.g., for spindle density, beta = -4.66, SE = 1.11, t = -4.18, p < 0.001). ISI changes across the follow-up period were not significantly predicted by spindle density or any other spindle measures at baseline. However, when restricting the analysis to ISI changes from pre- to post-treatment, there was a marginally significant effect of spindle amplitude (beta = -0.42, SE = 0.24, t = -1.78, p = 0.09) and spindle power (beta = -0.07, SE = 0.04, t = -1.83, p = 0.08), reflecting a trend for an association between lower spindle activity and poorer CBT-I response as indexed by lower decreases in ISI.

HLM analyses also indicated that pre-treatment spindle density, as well as spindle amplitude, power, duration, and sigma power predicted changes in sleep diary sleep efficiency and WASO, but not in sleep latency or duration, as secondary outcome variables from pre- to post-treatment (Table 2). Lower spindle activity at pre-treatment was associated with smaller increases in sleep efficiency and smaller decreases in WASO from sleep diaries, reflecting poorer responses to CBT-I. Changes in PSG-derived sleep efficiency, WASO, sleep latency and

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sleep duration from pre- to post-treatment were not significantly predicted by any of the spindle measures.

Parameters	Δ PSQI				Δ ISI			
	beta	SE	t value	p value	beta	SE	t value	p value
Spindle density	**-1.41**	**0.63**	**-2.24**	**0.03***	**-0.60**	**0.75**	**-0.80**	**0.42**
Spindle duration	-10.14	4.22	-2.40	0.02*	-3.98	5.04	-0.79	0.43
Spindle amplitude	-0.20	0.10	-2.00	0.05*	-0.07	0.12	-0.61	0.55
Spindle power	-0.03	0.01	-2.00	0.05*	-0.02	0.02	-1.09	0.28
Spindle frequency	0.14	1.05	0.14	0.89	-0.21	1.27	-0.16	0.87
Sigma power	-55.98	20.77	-2.70	0.01**	-27.22	26.24	-1.04	0.30
	Δ SLD Sleep Efficiency				Δ SLD WASO			
	beta	SE	t value	p value	beta	SE	t value	p value
Spindle density	**16.26**	**4.79**	**3.39**	**0.00****	**-47.69**	**14.22**	**-3.35**	**0.00****
Spindle duration	90.48	36.77	2.46	0.02*	-278.03	107.01	-2.6	0.02*
Spindle amplitude	2.30	0.92	2.49	0.02*	-8.24	2.67	-3.08	0.00**
Spindle power	0.31	0.13	2.35	0.03*	-1.16	0.4	-2.92	0.00**
Spindle frequency	-10.99	10.41	-1.06	0.31	5.07	31.72	0.16	0.87
Sigma power	603.43	157.09	3.84	0.00**	-1581.39	505.14	-3.13	0.00**
	Δ SLD Sleep Latency				Δ SLD Sleep Duration			
	beta	SE	t value	p value	beta	SE	t value	p value
Spindle density	**-11.29**	**17.3**	**-0.65**	**0.52**	**44.17**	**35.68**	**1.24**	**0.23**
Spindle duration	-38.36	120.54	-0.32	0.75	116.53	255.53	0.46	0.65
Spindle amplitude	-1.21	3.18	-0.38	0.71	7.69	6.53	1.18	0.25
Spindle power	-0.09	0.46	-0.19	0.85	1.04	0.95	1.09	0.29
Spindle frequency	41.34	28.63	1.44	0.17	-28.76	64.14	-0.45	0.66

Sigma power	-654.18	585.12	-1.12	0.28	1922.22	1201.91	1.6	0.13

Table 2: Interactions between *spindle density* during stages N2-N3 of NREM sleep at pre-treatment and treatment responses as reflected by change in *PSQI* and *ISI* from baseline to the 12- month post-treatment assessment (primary outcomes) and change in sleep diary *sleep efficiency, WASO, sleep latency and sleep duration* from pre-treatment to immediate post-treatment (secondary outcomes). Exploratory analyses on interactions between other pre-treatment spindle parameters (duration, amplitude, power, frequency, sigma) and treatment responses are also shown.* *p≤0.05, ** p≤0.01. These analyses are adjusted for differences in age, sex, and years of education.*
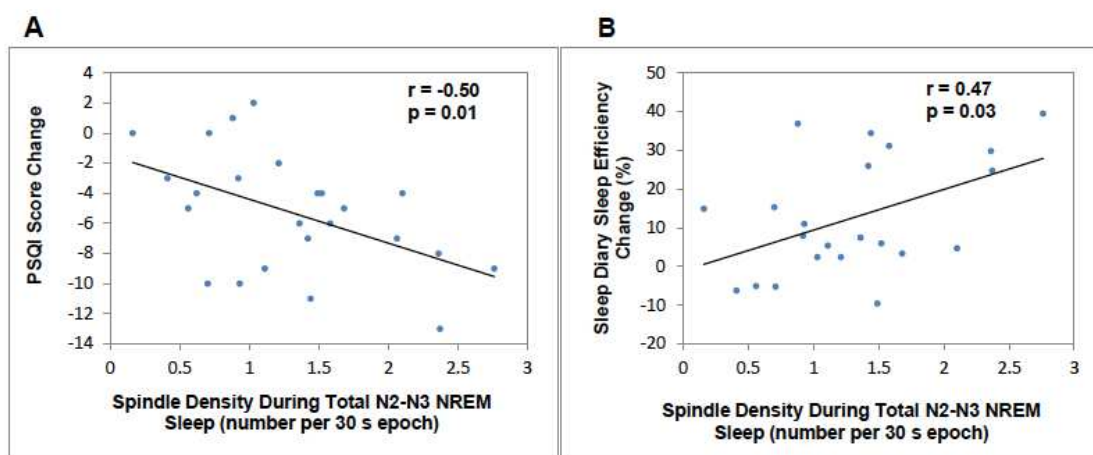

Figure 1. Correlations between spindle density and sleep changes following CBT-I.
Scatter plots showing the correlations between average spindle density in total N2-N3 NREM sleep at pre-treatment and change in PSQI (A) or change in sleep diary sleep efficiency (B) from pre- to post-treatment.

Exploratory analyses showed that EEG delta power at pre-treatment during total NREM sleep was not predictive of changes in PSQI (beta = -0.18, SE = 7.51, t = -0.02, p = 0.98) or ISI (beta = 4.82, SE = 8.98, t = 0.54, p = 0.59) across the follow-up period. Likewise, EEG delta power during the first NREM sleep cycle was not predictive of changes in PSQI (beta = -4.68, SE = 4.06, t = -1.15, p = 0.25) or ISI (beta = 5.52, SE = 11.20, t = .49, p = 0.63) across the follow-up period. Finally neither total EEG delta power nor delta power during the first sleep

cycle were predictive of changes in PSQI, ISI, as well PSG and sleep diary variables (sleep efficiency, WASO, sleep latency and sleep duration) from pre- to post-treatment.

Changes in spindle activity following treatment

HLM revealed no significant change in any of the spindle parameters from pre- to post-treatment: spindle density (beta = -0.08, SE = 0.09, t = -0.89, p = 0.38), duration (beta = -0.005, SE = 0.009, t = -0.48, p = 0.63), amplitude (beta = 0.04, SE = 0.73, t = 0.05, p = 0.96), power (beta = 0.48, SE = 3.89, t = 0.12, p = 0.9) and frequency (beta = 0.005, SE = 0.05, t = 0.10, p = 0.92). Further, no significant treatment-related changes were observed for EEG sigma power (beta = -0.00008, SE = 0.003, t = -0.02, p = 0.98), delta power (beta = -0.002, SE = 0.009, t = -0.18, p = 0.86), theta power (beta = 0.006, SE = 0.006, t = 0.97, p = 0.34), alpha power (beta = -0.002, SE = 0.004, t = -0.45, p = 0.66) or beta power (beta = -0.005, SE = 0.005, t = -1.03, p = 0.31).

DISCUSSION

These preliminary results provide support to our hypothesis that spindle density at pre-treatment predicts individual's response to CBT-I, both in the short- (immediate post-treatment) and long-term (12-month follow-up). In this pilot study, CBT-I was associated with sustained improvements in insomnia symptoms with effect sizes comparable to published randomized controlled trials [37]. Sleep spindle density at pre-treatment was predictive of these improvements, particularly in PSQI and sleep diary sleep efficiency and WASO, with lower spindle density being related to smaller improvements in these sleep quality measures. Marginally significant effects were also observed between spindle activity and pre- to post-

treatment change in ISI score. These results suggest that sleep spindle activity might thus identify a specific insomnia phenotype with a physiological vulnerability to sleep disruption that is less responsive to CBT-I.

Previous work suggests that lower spindle density may be a predisposing factor in the development of exacerbation of sleep problems in response to stress [22] and this current study suggests that weaker spindle density might also hinder response to CBT-I treatment. Current knowledge on sleep spindles suggests two non-mutually exclusive interpretations for why weaker spindles might hinder CBT-I treatment. Sleep spindles have been associated with the gating of external auditory stimuli during sleep [20], and thus contribute to isolate the cortex from noise that could disrupt sleep. Accordingly, greater spindle density has been associated with the ability to maintain stable sleep in the face of noise [21]. Individuals with weaker spindle traits may thus have more difficulty maintaining stable sleep despite their efforts to incorporate the CBT-I components due to a persistence of lower arousal threshold to external stimulation during sleep. This is in line with our findings that lower spindle activity predicts worse improvements in sleep diary variables related sleep stability, i.e. sleep efficiency and WASO, but not in sleep duration or latency to sleep onset, which suggests that spindle activity may be more predictive of changes in sleep maintenance difficulties rather than sleep initiation problems. In addition, since spindle activity is associated with memory consolidation and general intellectual abilities [18, 19], insomniacs with weaker spindles may also have more difficulties incorporating CBT-I components into their daily lives because of their lower ability to learn new information and strategies efficiently. However, education level – as a proxy for overall cognitive abilities - was not found to be predictive of CBT-I response for any of our sleep outcomes in the present study, which makes this second interpretation less likely than the former. Our findings also fit

with an overarching theory of insomnia, which posits that insomniacs are in a psycho-physiological state of hyperarousal [38]. Reduced spindle activity may contribute to a state of physiological hyperarousal through a lower arousal threshold to external stimulation during sleep, while a state of psychological hyperarousal may be more prominent in insomniacs with preserved spindle activity. As CBT-I has been developed to target the psychological components of hyperarousal rather than its physiological components [25], it would be expected as less effective for individuals in which reduced spindle density would exacerbate physiological hyperarousal.

In line with the concept of spindle density as a trait-like biomarker, spindle measures did not change after CBT-I, which suggests that spindle activity is a stable trait not impacted by CBT-I. This is important given that psychological factors previously studied as predictors of treatment response (e.g., depression, anxiety, dysfunctional beliefs about sleep) showed significant changes following CBT-I [5, 7, 9], which suggests that their relationships with CBT-I response might represent an epiphenomenon of their propensity to change with CBT-I rather than true vulnerability factors that predict treatment response. Besides spindle activity, there was no significant change of EEG spectral power in any of the frequency bands relevant to sleep (delta, theta, alpha, sigma, beta) following CBT-I. These findings contrast with those previously reported on a sample of 9 individuals with chronic insomnia, showing an increase in slow wave activity (0.5-4.75Hz) and decreases in the other frequency bands, including sigma, after 8 weeks of CBT-I [33]. Several methodological differences might explain this discrepancy. For example, we did not use fixed frequency bands (as in [33]) but resorted to adapted frequency bands reflecting the individual spectral profile. In addition, our findings were based on a larger sample of 24 individuals providing a better estimate of EEG changes in response to treatment. Other

sample characteristics might also have contributed to these differences. For instance, average PSG sleep efficiency and total sleep time were lower in that previous study (67.41% and 323.67 min.) than in our sample (82.43% and 348.2 min.), which might suggest that changes in EEG spectral power following CBT-I are predominantly found in chronic insomniacs with more objective sleep disturbances.

In contrast to a previous study by Krystal and Edinger, no association was found between delta power at baseline and treatment outcomes [13]. The previous study found an effect only for delta in the first cycle. Here, there was no effect of delta power either during the whole night or in the first sleep cycle only. 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 [39]. 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 (e.g., frequency bands) may also have contributed to this difference.

There are some limitations to our study. Firstly, it was designed as a pilot study to provide preliminary findings that would guide future larger confirmatory studies. Indeed, the absence of significant effects on ISI was likely due to a lack of statistical power, as suggested by the marginal effects observed between spindle amplitude or power and ISI. This lack of power might also explain the absence of significant effects on PSG-derived sleep outcomes (e.g., PSG sleep efficiency and WASO), particularly given that the magnitude of changes in these PSG

variables following CBT-I was more limited compared to the corresponding sleep diary variables (e.g., mean sleep efficiency increase was of 4.9% for PSG and 12.6% for sleep diaries). In addition, the recording of multiple PSG nights at each assessment time and/or the use of other objective assessments such as actigraphy over several days might also be useful in future replication studies to assess relationships with objective sleep outcomes, given the night-to-night variability in insomnia symptoms. Secondly, in the absence of a control group or a control intervention, we cannot evaluate whether these predictive relationships were specific to CBT-I. Future studies should investigate if spindle activity also predicts sleep changes following other interventions or the natural course of insomnia over time. Thirdly, a minority (6) of our participants underwent home-based ambulatory PSG while the majority (18) had their PSG performed in the laboratory. To minimize the impact of this difference in recording environment, we used similar PSG systems and recording parameters for both ambulatory and lab-based PSG. In addition, we also ran additional analyses excluding the 6 participants recorded from home, and found that the effects of spindle density on sleep changes following CBT-I remained significant (e.g., effects of spindle density on PSQI changes: beta = -4.1, SE = 1.34, t = -3.05, p = 0.009). This suggests that the presence of ambulatory recordings did not confound our results.

If our results are replicated, the present findings may have clinical implications. In a personalized medicine approach, spindle activity as a neurophysiological predictor of treatment response could serve as a prognostic tool to guide the selection of the most appropriate treatment regimen. The identification of reliable predictors of treatment response is critical in a context of limited CBT-I accessibility, in order to prioritize CBT-I resources to those patients who are the most likely to respond. Spindle activity is an objective trait biomarker that can be measured in various clinical settings, including ambulatory sleep recordings with a limited number of

channels, and could thus be implemented as a prognostic biomarker in clinical practice for the design of the individualized therapeutic approach. Furthermore, these findings may point to other forms of treatment modifying brain oscillations that may be effective for the insomnia phenotype characterized by low spindle activity. By targeting sleep spindles, these alternative treatments would aim at reversing the specific neural abnormalities characterizing subgroups of insomniacs. Previous studies have shown that it is possible to alter spindle parameters with pharmacological treatments (e.g., benzodiazepine and non-benzodiazepine hypnotic drugs) [40], as well as non-pharmacological interventions such as transcranial direct electrical stimulation [41] and neurofeedback [42]. Further investigation is needed to assess whether these treatments could be of interest for insomniacs for whom lower responsiveness to CBT-I would be expected. Larger clinical trials will be needed to test these potential clinical implications.

In summary, our results provide preliminary evidence that sleep spindle density at pre-treatment might predict who will show better response to CBT-I. Spindle density within the population of chronic insomniacs may be an endogenous biomarker that contributes to identify different phenotypes of insomnia with different treatment responsiveness. This new finding may guide future algorithms for insomnia treatment, which could be tailored based on these individual differences. Future studies are needed to confirm and extend these findings in larger samples, including insomniacs with comorbid medical or psychiatric conditions. Further research should also seek to evaluate which therapeutic interventions would be most effective in insomniacs with lower spindle activity, including the investigation of pharmacological and non-pharmacological treatments altering brain oscillations during sleep.

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Highlights

- Spindles may predict responsiveness to cognitive-behavioral therapy for insomnia (CBT-I).

- Lower spindle density was prospectively associated with smaller responses to CBT-I.

- Spindles might thus constitute a biomarker identifying patients less responsive to CBT-I.