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Original Article

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

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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 to determine whether pre-treatment sleep spindle density predicts treatment response to cognitive-behavioral therapy for insomnia.
Methods: Twenty-four participants with chronic primary insomnia participated in a 6-week cognitive-behavioral therapy for insomnia performed in groups of 4–6 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 7 days and overnight polysomnography, obtained at pre- and post-treatment. Spindle density during stage 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-month follow-up, as reflected by a 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.

1. 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

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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, and 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; however, 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 reported 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]. An 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 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 2 major domains. First, they correlate with overnight improvements of procedural and declarative memories and 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 toward 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]. An 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 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 and ISI and 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 than those with higher spindle density.

2. Materials and methods

2.1. Participants

Participants with chronic primary insomnia were recruited through online and print advertisements posted in the community and 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 in initiating sleep (defined as a sleep onset latency greater than 30 min), difficulties maintaining sleep (defined as wake after sleep onset (WASO) 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 3 months or more with sleep disturbances 3 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 use of recreational drugs or prescription drugs that might affect sleep. If currently taking sleep medication, participants were asked to stop that medication for 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). 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