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Sleep disturbances in schizophrenia: what we know, what still needs to be done

Rachel E. Kaskie[1], **Fabio Ferrarelli**[1,*]

[1]Department of Psychiatry, University of Pittsburgh, USA

Abstract

Sleep disturbances are commonly observed in schizophrenia (SCZ) and are associated with worse psychotic symptoms and poorer clinical outcomes. Early polysomnography studies have focused on characterizing differences in sleep architecture between patients with SCZ and healthy controls. More recently, research has focused on sleep-specific EEG oscillations, such as sleep spindles and slow waves, which reflect the integrity of underlying thalamo-cortical networks. Furthermore, high-density (hd)-EEG (>=64 channels), which affords enhanced spatial resolution, has been employed to better localize abnormalities in sleep characteristics and related thalamo-cortical circuits in patients with SCZ and related disorders. In this article, we will review the most relevant sleep abnormalities reported in SCZ, with an emphasis on recent findings, and propose directions for future research.

Keywords

schizophrenia; EEG; sleep; spindles; slow waves; cognition

Introduction

It has long been known that sleep disturbances occur frequently in patients with SCZ and are associated with more severe psychotic symptoms and worse clinical outcomes [1]*. Early polysomnography studies have focused on characterizing differences in sleep architecture between SCZ patients and healthy controls, and it has been shown that SCZ patients often experience delayed sleep onset, difficulty maintaining sleep, reduced total sleep time, and decreased sleep efficiency[2]. More recently, research has focused on sleep-specific EEG oscillations, such as sleep spindles and slow waves, which reflect the integrity of underlying thalamo-cortical networks [3]. Slow waves are 1 Hz, large amplitude oscillations that are primarily generated and coordinated within the cortex, whereas sleep spindles are 12–16 Hz,

*To whom correspondence should be addressed: Fabio Ferrarelli, MD, PhD, Assistant Professor of Psychiatry, Department of Psychiatry, University of Pittsburgh, 3501 Forbes Avenue, Suite 450, Pittsburgh, PA 15213, ferrarellif@upmc.edu.

Declaration of interests

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waxing and waning oscillations that are initiated by the thalamic reticular nucleus and regulated by thalamo-reticular and thalamo-cortical circuits. Abnormalities in sleep spindles, and to a lesser extent, slow waves have been reported by several recent studies [4]*. Furthermore, high-density (hd)-EEG (>=64 channels), which offers enhanced spatial resolution, has been employed to better localize abnormalities in sleep characteristics and related thalamo-cortical circuits in patients with SCZ and related disorders [5, 6]. Dysfunctions within the thalamo-cortical system are thought to play a critical role in the pathophysiology of SCZ[7], and sleep hd-EEG recordings can uniquely characterize the spatiotemporal dynamics of such dysfunctions. During sleep, possible confounds like presence of symptoms or cognitive effort are also minimized, thus better allowing for the assessment of intrinsic oscillatory properties and related molecular mechanisms of dysfunctional neural circuits in SCZ patients[8]*. Here, we will review the most relevant sleep abnormalities reported in SCZ, with an emphasis on recent findings, and propose directions for future research.

Sleep EEG abnormalities

Studies of SCZ have detected several abnormalities in sleep architecture, with earlier studies focusing on common features of sleep and how they relate to symptomatology. Initial studies found a reduction in slow wave sleep (SWS), which represents the deepest stage of non-rapid eye movement (NREM) sleep, in patients with SCZ relative to HC. Furthermore, SWS is the only significant predictor among other sleep variables (amount of stage 1 (N1), stage 2 (N2), and REM sleep) of future social functioning in SCZ, with number of hospitalizations also being a significant predictor [9]*. Percentage of REM sleep has also been correlated with symptom severity. SCZ patients showed a significant positive correlation of percentage of REM sleep with Brief Psychiatric Rating Scale (BPRS)[10] total score and Positive and Negative Syndrome Scale (PANSS)[11] positive score, and a negative correlation of REM latency with BPRS total score [12]. A recent meta-analysis has shown that patients with SCZ tend to have a decrease in total sleep time (TST), sleep onset latency (SOL), sleep efficiency (SE), decreased slow wave sleep (SWS), increased light sleep (N1), decreased REM duration and REM latency and increased REMs density (REMD) [13]. However, the authors also reported the inconsistency and heterogeneity of these findings, with SWS deficits present mostly in chronic patients with SCZ (>3 years) and no consistent abnormalities established in the sleep architecture of medication-naïve patients. We will further discuss the effects of medication on sleep EEG below.

Moving beyond sleep architecture, several recent studies have investigated EEG parameters, such as power in the delta (1–4 Hz) and sigma (12–16 Hz) frequency bands, that more closely reflect brain activity during sleep. Sleep EEG power in the delta and sigma range is largely contributed by slow waves and sleep spindles, the two main oscillatory activities occurring during NREM sleep. Slow waves are 1 Hz, high amplitude oscillations that characterize the deepest NREM sleep stage, also called slow wave sleep, whereas sleep spindles are 12–16 Hz, waxing and waning oscillations that represent the hallmark of stage 2 NREM sleep. It has been repeatedly found that patients with SCZ have a significant reduction in several spindle parameters, including amplitude, duration, and density across all NREM sleep periods [14], including a recent study wherein patients with SCZ were found to

have significantly more sleep stage transitions per hour of actual sleep time, more short awakenings, and reduced spindle density compared to healthy controls [15]. A reduction in spindle density is thought to support the hypothesis of dysfunctional thalamocortical activity in schizophrenia. More specifically, the thalamic reticular nucleus (TRN) has been implicated in the generation of sleep spindles, and dysfunction of the TRN is hypothesized to be behind the reduced spindle density observed in SCZ[16, 17]. A recent optogenetic study in PV-cre mice (animals that express Cre recombinase in parvalbumin expressing neurons) tested this hypothesis and found that a novel paradigm of optogenetic stimulation of TRN parvalbumin (PV) neurons elicited sleep spindles indistinguishable from naturally occurring spindles, but inhibition of these neurons failed to block sleep spindles. However, optogenetic stimulation of a major PV GABA-ergic inhibitory input arising from basal forebrain parvalbumin neurons did successfully inhibit spindle production [18]. A reduction in mediodorsal (MD) thalamus volume, but not of the lateral geniculate nucleus, has also been recently found in patients with SCZ relative to HC, and this reduction predicted a decrease in spindle density in the prefrontal (PFC) cortex of these patients [19]. These findings, which are consistent with evidence from post-mortem [20] and neuroimaging [7] studies, point to a TRN-MD-PFC circuit dysfunction in SCZ [8]. Findings on slow wave activity and related parameters in SCZ are more mixed, with a reduction in slow wave density as the most frequently, although inconsistently, reported deficit, as recently reviewed [4]. Of note, most of these sleep studies have been conducted in chronic patients with SCZ, with studies varying on whether their sample has taken antipsychotic medication.

Current research is investigating whether features of sleep change with illness progression by studying patients experiencing their first episode of psychosis (FEP). In FEP patients, spindle duration and spindle density have been found to be reduced in a front-central region compared to HC subjects, whereas spindle amplitude was no different. Furthermore, these reductions were found to be associated with worse negative symptoms [21]. Similar spindle deficits were reported by another research group in early course SCZ patients, as well as in first-degree relatives of SCZ probands relative to control groups [22]. In a FEP study of slow waves, patients were found to have significantly lower slow wave density compared to HC subjects in a larger frontal-central area, and this reduction was correlated with positive symptom severity [23]. Studies are also exploring the link between genetic risk for SCZ and spindle parameters. Interestingly, a study of healthy teenagers with a genetic risk for schizophrenia found that polygenic risk scores (PRS) were positively correlated with fast spindle (13–16Hz) amplitude, density, and intensity, and PRS in the CACNA1l region was positively correlated with slow spindle (10–13Hz) amplitude, duration, and intensity [24]**. Another sleep study found reduced spindle activity in unaffected first-degree relatives (FDR) of SCZ probands relative to healthy subjects (HS) with no family history of SCZ, thus suggesting that it may represent a candidate endophenotype (i.e., a biological marker that is heritable, quantitative trait associated with the illness, and observed in unaffected relatives of patients) for this disorders[25]. Altogether, these findings support a shared genetic pathway between SCZ and sleep spindles, though the nature and extent of this correlation needs to be further investigated.

Medication Effects on Sleep EEG

The effects of medication on sleep are also relevant, as many medications used to treat SCZ either directly affect sleep (by their sedating effect, like quetiapine and risperidone) or indirectly affect sleep (by leading to other changes, such as weight gain, like olanzapine and clozapine, that can contribute to the development of sleep disorders). For example, olanzapine has been found to significantly increase the amount of SWS and decrease sleep spindle density [26], and eszopiclone has been found to significantly increase the number of sleep spindles during sleep in SCZ [27]. However, one study reported no changes in the sleep EEG power of drug-free patients with SCZ after olanzapine was administered for 4 weeks [28]. We also found that patients with SCZ had marked spindle deficits compared to non-SCZ patients, despite both groups taking antipsychotic medications [29]. More recently, the effects of six weeks of olanzapine treatment on polysomnography and symptom severity, as measured by BPRS, PANSS, and Udvalg for Kliniske Undersogelser (UKU) side-effect rating scale[30], was investigated. Olanzapine significantly reduced symptom severity, as measured by the above scales, and also increased TST, SE, NREM stage 1 duration, stage 3 duration, stage 4 duration, and stage 4 percentage of TST, number of REM periods, REM duration, and REM percentage of TST [31]. Nonetheless, future studies are needed to explicitly investigate the effects of psychotropic medications on sleep spindle and slow wave parameters.

Sleep and Cognitive Function

Sleep and cognitive functioning are strongly linked, though how this link is affected in SCZ by disturbed sleep is not yet known. Diminished cognitive ability is a core feature of SCZ, as are circadian and sleep disturbances. Circadian disturbances include a delayed phase type, in which the timing of the desired sleep period is significantly delayed, an advanced phase type, in which one is unable to remain awake until the desired or socially accepted time, and an irregular sleep– wake type, in which one has no discernible 24-hour sleep–wake cycle. Several sleep studies have reported circadian rhythm disruption, including delayed phase shift and disturbed sleep-wake patterns in SCZ (for comprehensive reviews, see [32, 33]). To investigate the link between sleep and cognitive functioning, researches used wrist actigraphy and tests of cognitive performance and found that SCZ with a normal rest-activity cycle have better cognitive performance [34]. In a study of visual memory, patients with SCZ showed no significant improvement, while healthy controls had a significant improvement after sleep. Furthermore, sleep spindle activity in SCZ was correlated with sleep-associated facilitation of recognition accuracy for neutral, but not negative, pictures [35]. In a study by Baran and colleagues, SCZ patients were found to perform similarly to controls on a word pair memory task but they showed a deficit in sleep-dependent consolidation of word pair learning [36]. Additionally, SCZ showed intact consolidation of visuo-perceptual procedural memory, pointing to a specific deficit in verbal declarative memory [36]. Sleep-dependent improvement on motor learning tasks is also impaired in SCZ relative to healthy controls, and overnight improvement in SCZ only correlates with spindle number and density [37]. Similarly, for spindles in NREM stage 2 sleep, motor speed has been found to be positively correlated with frontal slow spindle density, though

cognitive impairment was not strongly associated with sleep spindle density or other characteristics [38].

In another elegant study investigating the link between sleep and memory performance, Manoach et al examined the significance of SW-spindle coupling and found that SCZ patients had greater improvement on a motor learning task when spindles reliably peaked later during the SW upstate [39]**. Altogether, these findings suggest that memory in SCZ may be dependent on the incidence of sleep spindles as well as on the timing and coordination between spindles and slow waves. An important implication of this work is that interventions aimed at ameliorating memory consolidation deficits in SCZ may need to both increase spindle occurrence and improve the coordination of slow wave/ spindle oscillations. Thus, future studies are needed to thoroughly test this hypothesis, which may lead to novel treatment options for cognitive deficits in SCZ.

Conclusions

A primary goal of future research will be to characterize in greater details slow wave and sleep spindle deficits in SCZ at illness onset. In recent studies, we found that both slow wave and sleep spindle deficits were present in FEP patients. However, it will be important to replicate these findings in larger group of patients, including SCZ and other psychotic disorders. This will help establish whether these sleep disturbances are consistently present in SCZ at the beginning of the illness. It will also contribute to the assessment of whether sleep spindles and slow wave deficits are specific for SCZ, or instead shared across psychotic disorders. Another critical goal will be to determine when in the disease course sleep disturbances become observable. This would change the putative implication of these disturbances in the pathophysiology of SCZ. Indeed, if sleep spindles and/or slow wave impairments precede the onset of SCZ, then it is plausible to conclude that these sleep impairments may play a causal role in the development and full manifestation of the illness and could be used to assess risk. Thus, future work should include longitudinal sleep EEG recordings in individuals at clinical high risk (CHR) for SCZ and related disorders to determine if these sleep parameters may, in fact, be a predictive biomarker for these illnesses.

It will also be important to establish how exposure to antipsychotic medication may affect these sleep abnormalities. Finally, future research will need to further examine the relationship between cognitive function and sleep disturbances. Cognitive dysfunctions are a core feature of SCZ, represent one of its most treatment refractory features, and are associated with worse quality of life in these patients [40]. Recent studies have demonstrated deficits in sleep-dependent memory consolidation in patients with SCZ, which were associated with reduced spindle activity [41]. By identifying the molecular and neural mechanisms underlying spindle deficits and related memory impairments, future studies may lead to novel treatment interventions to ameliorate cognitive functioning in patients with SCZ, thus significantly improving their quality of life.

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