Sleep Medicine 16 (2015) 553–554

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Editorial

Sleep, memory and schizophrenia

Neuropsychiatric disorders are primarily defined by waking phenomena, but sleep disturbances are a prominent feature and often included in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition diagnostic criteria. In schizophrenia, sleep disturbances have been described since Kraepelin [1], but the nature of the disturbance and its relation to the pathophysiology, cognitive impairments, and symptoms of schizophrenia have been difficult to define. Recent studies have documented that patients with schizophrenia have marked impairments of sleep-dependent consolidation of motor procedural memory [2–6] and dramatically reduced sleep spindle activity [3–5,7–9]. These two deficits are correlated [5] and sleep spindles have long been associated with memory in healthy individuals (for review see [10]). Spindles are thought to promote the long-term potentiation necessary for memory formation [11] and pharmacologically increasing spindles can improve memory [12,13]. Together, these findings lead to the hypothesis that the reduction in sleep spindles in schizophrenia impairs memory consolidation [5]. The study by Göder and colleagues [14], reported in the current issue, extends this evidence by demonstrating that patients with schizophrenia also have a deficit in the sleep-dependent consolidation of declarative memory, tested with a picture recognition task, that correlates with their reduction in sleep spindles.

In this study, participants were shown emotional and neutral pictures. Recognition memory was tested both after a night of sleep and after an equivalent interval of daytime wake. Importantly, both groups performed above chance, and performance in the combined groups was better after the interval of sleep than wake (ie, there was a sleep benefit). But while both groups performed better after sleep than wake, the overall sleep benefit (measured as the difference between recognition after sleep and recognition after wake) was three times larger for the control participants (12%) than for the schizophrenia patients (4%; control *vs.* schizophrenia, $p = .03$). Additionally, while this benefit reached statistical significance for the controls ($p < .001$), it was only at a trend level for the patients ($p = .09$).

In agreement with earlier studies, schizophrenia patients also showed a marked reduction in sleep spindle density (spindles per minute) during N2 sleep, despite having comparable sleep architecture. In addition, they showed reduced electroencephalographic (EEG) power in the sigma frequency band (which corresponds to sleep spindles) during N2, but normal power in other frequency bands. Perhaps most interesting was the finding that sleep spindle density correlated with the sleep benefit in both groups, although only for the neutral pictures. (The lack of correlation for emotional pictures is not entirely surprising since sleep-dependent processing of emotional memories appears to rely on rapid eye movement (REM) sleep [15].

These findings extend the range of known impairments of sleep-dependent memory consolidation in schizophrenia beyond motor procedural memory to include declarative memory. In addition, together with a prior study [5], they demonstrate that both types of memory deficit correlate with reduced sleep spindles. The consolidation of declarative memory is thought to depend on a well-orchestrated dialogue between neocortical slow waves, thalamocortical spindles, and hippocampal sharp-wave ripples during sleep [16], and a rat model of schizophrenia suggests that there is a breakdown of this dialogue in schizophrenia [17]. Future work is needed to establish whether the coordination of these sleep oscillations is similarly impaired in humans with schizophrenia.

The current findings also reinforce the importance of deficient sleep-dependent memory processing among the cognitive deficits of schizophrenia, and provide further support for the contribution of sleep spindle deficits to cognitive dysfunction. Whether sleep spindle deficits also contribute directly to schizophrenia symptoms is less clear. While three studies have reported correlations between spindle deficits and positive symptoms in schizophrenia [5,7,9], the present study did not.

The present study and most prior studies linking sleep spindles and memory consolidation deficits in schizophrenia were conducted with chronic medicated patients, raising concerns that these deficits might be due to medications or to the complex sequelae of chronicity. But a recent study showed a spindle deficit that correlates with cognitive measures in both antipsychotic-naïve early course patients with schizophrenia and syndromally unaffected first-degree relatives of schizophrenia patients [7]. Thus, the spindle deficit is not simply a side-effect of medications or chronicity, and is even seen in relatives who have not developed, and for the most part will not develop, schizophrenia. This suggests that the spindle deficit is an endophenotype (a trait indicating genetic vulnerability) of schizophrenia.

Over the past few years, large-scale genetic studies have identified many risk genes for schizophrenia [18–20]. This work is providing unprecedented opportunities for progress in understanding and treating schizophrenia. Sigma power, which corresponds to the frequency of spindles, during non-rapid eye movement sleep is highly heritable and studies now underway will determine whether identified risk genes affect sleep spindles and the mechanisms of these effects. This work may open new avenues for the treatment of cognitive deficits. Unlike psychotic symptoms, which can usually be effectively controlled with medications, there is a dearth of effective treatments for cognitive deficits. Consequently, cognitive deficits often result in long-term disability and are the strongest predictor of functional outcome in schizophrenia. Studies showing that sleep spindles can be pharmacologically enhanced in

http://dx.doi.org/10.1016/j.sleep.2015.01.009

schizophrenia [21] and that increasing spindles improves memory in healthy individuals [12,13] suggest that sleep spindles are a novel target for ameliorating cognitive deficits in schizophrenia.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.01.009.

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