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Sleep, Memory and Schizophrenia

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Neuropsychiatric disorders are primarily defined by waking phenomena, but sleep disturbances are a prominent feature and are often included in the DSM-IV 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 work documents 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 correlated⁵ 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 formation¹¹ 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, 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 (*i.e.*, 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, $p=.03$), and 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 EEG power in the sigma frequency

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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.¹⁴)

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 sleep¹⁵ and a rat model of schizophrenia suggests that there is a breakdown of this dialogue in schizophrenia.¹⁶ Future work will 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.^{17–19} This work is providing unprecedented opportunities for progress in understanding and treating schizophrenia. 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 schizophrenia²⁰ 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.

Cited Literature

1. Kraepelin, E. Dementia praecox and paraphrenia. Edinburgh, Scotland: E.S. Livingston; 1919.
2. Manoach DS, Cain MS, Vangel MG, Khurana A, Goff DC, Stickgold R. A failure of sleep-dependent procedural learning in chronic, medicated schizophrenia. *Biol Psychiatry*. 2004; 56(12): 951–956. [PubMed: 15601605]
3. Manoach DS, Thakkar KN, Stroynowski E, Ely A, McKinley SK, Wamsley E, Djonlagic I, Vangel MG, Goff DC, Stickgold R. Reduced overnight consolidation of procedural learning in chronic medicated schizophrenia is related to specific sleep stages. *J Psychiatr Res*. 2010; 44(2):112–120. [PubMed: 19665729]
4. Seeck-Hirschner M, Baier PC, Sever S, Buschbacher A, Aldenhoff JB, Goder R. Effects of daytime naps on procedural and declarative memory in patients with schizophrenia. *J Psychiatr Res*. 2011; 44(1):42–47.
5. Wamsley E, Tucker MA, Shinn AK, Ono KE, McKinley S, Ely AV, Goff DC, Stickgold R, Manoach DS. Reduced sleep spindles and spindle coherence in schizophrenia: Mechanisms of impaired memory consolidation? *Biol Psychiatry*. 2012; 71(2):154–161. [PubMed: 21967958]
6. Genzel L, Dresler M, Cornu M, Jager E, Konrad B, Adamczyk M, Friess E, Steiger A, Czisch M, Goya-Maldonado R. Medial Prefrontal-Hippocampal Connectivity and Motor Memory Consolidation in Depression and Schizophrenia. *Biol Psychiatry*. 2014
7. Manoach DS, Demanuele C, Wamsley EJ, Vangel M, Montrose DM, Miewald J, Kupfer D, Buysse D, Stickgold R, Keshavan MS. Sleep spindle deficits in antipsychotic-naïve early course schizophrenia and in non-psychotic first-degree relatives. *Frontiers in Human Neuroscience*. 2014; 8:762. [PubMed: 25339881]
8. Ferrarelli F, Huber R, Peterson MJ, Massimini M, Murphy M, Riedner BA, Watson A, Bria P, Tononi G. Reduced sleep spindle activity in schizophrenia patients. *Am J Psychiatry*. 2007; 164(3): 483–492. [PubMed: 17329474]
9. Ferrarelli F, Peterson MJ, Sarasso S, Riedner BA, Murphy MJ, Benca RM, Bria P, Kalin NH, Tononi G. Thalamic Dysfunction in Schizophrenia Suggested by Whole-Night Deficits in Slow and Fast Spindles. *Am J Psychiatry*. 2010; 167(11):1339–1348. [PubMed: 20843876]
10. Fogel SM, Smith CT. The function of the sleep spindle: A physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. *Neurosci Biobehav Rev*. 2011; 35(5): 1154–1165. [PubMed: 21167865]
11. Rosanova M, Ulrich D. Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. *Journal of Neuroscience*. 2005; 25(41):9398–9405. [PubMed: 16221848]
12. Kaestner EJ, Wixted JT, Mednick SC. Pharmacologically increasing sleep spindles enhances recognition for negative and high-arousal memories. *J Cogn Neurosci*. 2013; 25(10):1597–1610. [PubMed: 23767926]
13. Mednick SC, McDevitt EA, Walsh JK, Wamsley E, Paulus M, Kanady JC, Drummond SP. The critical role of sleep spindles in hippocampal-dependent memory: a pharmacology study. *J Neurosci*. 2013; 33(10):4494–4504. [PubMed: 23467365]
14. Goder R, Graf A, Ballhausen F, et al. Impairment of sleep-related memory consolidation in schizophrenia: relevance of sleep spindles? *Sleep Med*. 2015
15. Molle M, Born J. Slow oscillations orchestrating fast oscillations and memory consolidation. *Prog Brain Res*. 2011; 193:93–110. [PubMed: 21854958]
16. Phillips KG, Bartsch U, McCarthy AP, Edgar DM, Tricklebank MD, Wafford KA, Jones MW. Decoupling of sleep-dependent cortical and hippocampal interactions in a neurodevelopmental model of schizophrenia. *Neuron*. 2012; 76(3):526–533. [PubMed: 23141065]
17. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014; 511(7510):421–427. [PubMed: 25056061]
18. Purcell SM, Moran JL, Fromer M, Ruderfer D, Solovieff N, Roussos P, O'Dushlaine C, Chambert K, Bergen SE, Kahler A, Duncan L, Stahl E, Genovese G, Fernandez E, Collins MO, Komiyama NH, Choudhary JS, Magnusson PK, Banks E, Shakir K, Garimella K, Fennell T, DePristo M, Grant SG, Haggarty SJ, Gabriel S, Scolnick EM, Lander ES, Hultman CM, Sullivan PF, McCarroll

- SA, Sklar P. A polygenic burden of rare disruptive mutations in schizophrenia. *Nature*. 2014; 506(7487):185–190. [PubMed: 24463508]
19. Birnbaum R, Jaffe AE, Hyde TM, Kleinman JE, Weinberger DR. Prenatal expression patterns of genes associated with neuropsychiatric disorders. *Am J Psychiatry*. 2014; 171(7):758–767. [PubMed: 24874100]
20. Wamsley EJ, Shinn AK, Tucker MA, Ono KE, McKinley SK, Ely AV, Goff DC, Stickgold R, Manoach DS. The effects of eszopiclone on sleep spindles and memory consolidation in schizophrenia: a randomized placebo-controlled trial. *Sleep*. 2013; 36(9):1369–1376. [PubMed: 23997371]