Schizophrenia Bulletin vol. 44 no. 1 pp. 7–14, 2018
doi:10.1093/schbul/sbx151
Advance Access publication November 9, 2017

Basic Neuroscience Illuminates Causal Relationship Between Sleep and Memory: Translating to Schizophrenia

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Patients with schizophrenia are often plagued by sleep disturbances that can exacerbate the illness, including potentiating psychosis and cognitive impairments. Cognitive dysfunction is a core feature of schizophrenia with learning and memory being particularly impaired. Sleep disruptions often accompanying the illness and may be key mechanism that contribute to these core dysfunctions. In this special translational neuroscience feature, we highlight the role of sleep in mediating cognitive function, with a special focus on learning and memory. By defining dysfunctional sleep architecture and rhythms in schizophrenia, we focus on the disarray of mechanisms critical to learning and memory and postulate an association between sleep disturbances and cognitive impairments in the disorder. Lastly, we review preclinical models of schizophrenia and highlight exciting translational research that may lead to new therapeutic approaches to alleviating sleep disturbances and effectively improving cognitive function in schizophrenia.

Key words: sleep/schizophrenia/cognition/memory/spindles/animal models

Disturbances in sleep are more common in individuals with schizophrenia than in the general population,[1] presenting a clinical need to diagnose, understand the impact, and effectively treat these problems. Sleep disturbances often present before the hallmark clinical diagnosable symptoms and may serve as strong predictors for manifestation of psychosis, as well as cognitive and mood disturbances. This special feature focuses on the relationship between sleep problems and impairments in learning and memory, a core cognitive symptom of schizophrenia. Further elucidating these relationships through translational neuroscience research may facilitate efforts to treat sleep problems and potentially improve cognitive dysfunction in schizophrenia.

To introduce the notion that sleep disruptions in patients with schizophrenia likely contribute to learning and memory dysfunction, background on sleep, sleep deprivation, and sleep disturbances in schizophrenia will be presented first. We will then discuss basic neuroscience research that supports the causal role of sleep in memory processes and highlight research that supports the hypothesis that poor sleep outcomes contribute to cognitive dysfunction in schizophrenia. Lastly, we discuss research that has investigated sleep in animal models that serve as useful tools to translationally study schizophrenia. Taken together, the goal of this special translational neuroscience feature is to highlight current research and encourage further research that unravels the neurobiological mechanisms between sleep disturbances and learning and memory impairments in schizophrenia.

Introduction to Sleep

There remains no consensus theory on the purpose of sleep, but it is vital to all living beings. Past and current hypotheses of the function of sleep include energy conservation, restoration, plasticity, memory consolidation, and housekeeping to maintain brain homeostasis. Therefore, it is highly likely that sleep serves multiple functions. Sleep is a daily, cyclic process that is divided into phases of rapid eye movement (REM) and non-rapid eye movement (NREM) sleep.[2] Sleep stages are specifically characterized by electroencephalogram (EEG) oscillations. NREM sleep is divided into 3 stages, denoted 1–3, which progress to increasingly deeper sleep and are characterized by distinct sleep spindles and slow waves. Stage 3 is often referred to as slow wave sleep (SWS) because of the large delta (0.5–2 Hz) waves. SWS is also considered the deepest sleep. During REM sleep, also referred to as paradoxical sleep, the EEG looks very similar to being awake, however muscle tone is completely suppressed during this

stage. Dreaming often occurs during REM sleep. A typical night of normal sleep for a human consists of 4–5 sleep cycles, each initiated with NREM sleep and concluding with REM sleep, and lasting about 90 min.[3,4]

The sleep/wake cycle is coordinated by interplay between circadian and homeostatic mechanisms. The circadian rhythm arises from the hypothalamic suprachiasmatic nuclei, which coordinate information from photoreceptor cells in the retina that respond to light and an array of entrained cues. The entrained cues include information about levels of arousal, locomotor activity, feeding, social interactions, sleep deprivation, and body temperature.[5] The homeostatic mechanisms at play regulate the duration and type of sleep based on the body's need for sleep, determined by sleep pressure which increases during wakefulness and declines during sleep. Under normal, healthy conditions, the circadian and homeostatic mechanisms operate in synchrony and influence the quality and length of an individual's sleep.[6]

Sleep deprivation in healthy individuals negatively impacts brain function and can result in psychotic-like features, impaired cognition,[7] and mood alterations[8] that are remarkably similar to core features of schizophrenia. Inadequate sleep can be due to either a decrease in the amount of sleep or poor quality of sleep. The latter depends on the number of awakenings during the night. As the first study of sleep deprivation was conducted over 100 years ago,[9] significant progress in understanding the role of sleep and the consequences of being sleep deprived have been made over the last century. The deleterious effects of sleep deprivation are not limited to, but include (1) cognitive impairments, (2) mental health disturbances, including hallucinations, delusions, and depressed mood, (3) impairments in immune function, and (4) increased risk of chronic life-threatening disorders such as cardiovascular disease and diabetes.[10,11] In the laboratory setting, sleep deprivation in healthy individuals has been investigated as a model of psychosis.[7,12] A side-by-side comparison of sleep deprivation and symptoms of schizophrenia illustrates a conspicuous similarity between the two, as shown in figure 1. Of note, cognition is impaired across multiple domains, especially learning and memory, under both sleep deprivation conditions and in the illness.

Sleep in Schizophrenia

While in the general population approximately 30% of people complain of intermittent problems with sleep, approximately 50–80% of patients with schizophrenia report sleep problems.[1] Sleep disturbances in patients with schizophrenia have been described since the first clinical reports of the disorder. German psychiatrist Emil Kraepelin first wrote about abnormal sleep in schizophrenia in the late 19th century and recommended "rest in bed" and "care for sleep" as important requisites for treatment.[13] The eloquently evocative First Person Account pieces in *Schizophrenia Bulletin* regularly reflect on disturbances in sleep that are habitually plaguing

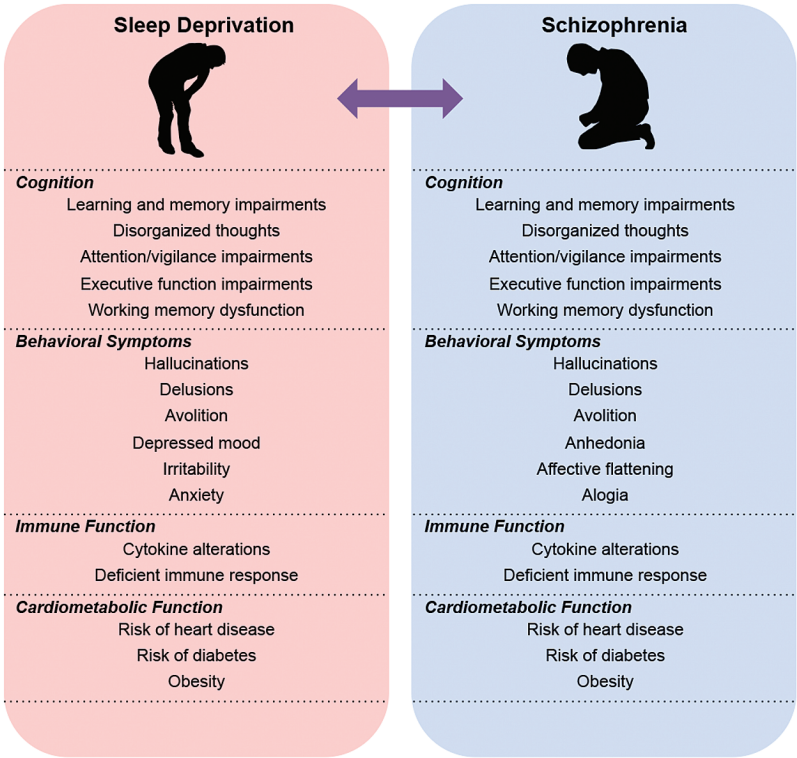

Fig. 1. Illustration of the striking similarities between symptoms of sleep deprivation and schizophrenia.

individuals living with the disorder. Personal accounts by those suffering from schizophrenia have described trouble falling asleep,[14–16] prolonged periods of not sleeping,[17] paranoia when considering sleep,[18] and perpetual feelings of stress because of the inability to sleep.[17,19] These accounts have been quantified objectively in the laboratory setting and support the notion that patients suffer from sleep disturbances.[20–23] In many cases, sleep dysfunction is correlated to the severity of psychotic[24–26] and cognitive[27] symptoms in an individual with schizophrenia, and episodes of insomnia often precede exacerbation of psychotic symptoms.[28]

Traditionally, sleep problems have been regarded as secondary to the primary diagnostic criteria for schizophrenia. However in other mental disorders, such as depression, mania and hypomania, anxiety, and post-traumatic stress disorder (PTSD), problems with sleep are core to the symptomology.[29] In line with compelling observational research showing that sleep problems worsen many hallmark features of the illness and that sleep disturbances often present before the full-blown onset of schizophrenia,[30] sleep problems may actually be a core pathophysiological component of schizophrenia. In spite of the converging evidence for disordered sleep in schizophrenia, no rigorously controlled laboratory studies have investigated the impact of sleep loss on core features of schizophrenia. Therefore, it remains unclear if the sleep disruptions are actually primary to psychosis in schizophrenia. Sleep loss studies in stabilized patients are needed to address this question and the contribution of transdiagnostic associations, ie, core antecedents of the disorder that may be impacting sleep, should be carefully considered.[31,32]

Complaints of insomnia, the inability to sleep, in patients with schizophrenia have been verified by polysomnography (PSG) recordings—multi-parametric tests to study sleep—that document decreased sleep efficiency (total sleep time divided by the time spent in bed), increased latency of sleep onset, and increased time awake after sleep onset not due to apnea or other sleep disorders.[33,34] As these PSG findings have also been confirmed in antipsychotic-naïve and unmedicated patients, it suggests that sleep disturbances are not simply a side-effect of medications, but may rather be classified as features of the disorder.[35,36] Changes in circadian rhythmicity, including phase advances and alterations in hormone secretion, have also been reported.[37,38] Moreover, patients with schizophrenia are increasingly diagnosed with comorbid sleep disorders including breathing disorders (eg, obstructive sleep apnea), hypersomnolence, movement disorders during sleep (eg, restless leg syndrome or periodic limb movement disorder), and parasomnias.[39,40] A thorough discussion of comorbidity of these sleep disorders in patients with schizophrenia is beyond the scope of the present special feature and the reader is referred to Klingaman et al[41] for further review.

Striking and diverse abnormalities in sleep architecture, defined as the amount and pattern spent in different stages, have been reported in PSG studies with schizophrenia patients (see Chan et al[42] for comprehensive review). The heterogeneity of the disorder mirrors the array of abnormalities in PSG measurements reported in patients with schizophrenia. Most frequently, studies have reported a reduction in the total time sleeping and a greater latency to fall asleep. Decreases in REM latency and duration, as well as reductions in total NREM for a night of sleep have been commonly reported in patients with schizophrenia.[43–47]

Given that antipsychotic medications may impact sleep architecture in patients, studies have also been conducted in antipsychotic-naïve patients and antipsychotic-withdrawal patients. Two meta-analyses report that antipsychotic-free patients display disrupted sleep compared to healthy controls.[35,42] Withdrawal from antipsychotic medications has been reported to impact sleep architecture, warranting caution when interpreting results from these studies.[42] Traditionally antipsychotic treatment, including first- and second-generation medications, has improved patients' sleep by increasing the total time sleeping and the efficiency of sleep.[1,48]

In summary, sleep problems are significantly higher in schizophrenia when compared to the general population, and detrimentally impact clinical outcome that includes cognitive function. Data from a recent randomized control trial (OASIS) provide strong evidence that sleep loss causally contributes to psychotic experiences[49] and places new attention on sleep alterations in schizophrenia as primary outcomes of the illness.

Role of Sleep in Memory Processes: Implications for Schizophrenia

Sleep is vital for brain plasticity and memory consolidation.[11,50–52] It is, thus, paramount to consider the physiological role of sleep when discussing how malfunctions in sleep may contribute to psychotic features and compromise cognitive function in schizophrenia. While the intricacies of sleep contributing to memory processes remain unclear and disputed, there is substantial evidence supporting a role of slow wave oscillations, thalamocortical sleep spindles, and hippocampal sharp wave-ripples that occur during NREM sleep and theta oscillations and ponto-geniculo-occipital (PGO) waves that occur during REM sleep.[53] The "active systems consolidation" hypothesis suggests that representations of memory are reprocessed during NREM sleep that occurs subsequent to learning. This model proposes that new information is initially encoded into the hippocampus and when NREM sleep occurs, the memory representations become reactivated and unified with pre-existing information in the neocortex.[53] Of note, recent reports have challenged a solo role of the hippocampus to encode new information,

placing attention on the neocortex to encode and consolidate newly acquired information.[54] Alternatively, the "synaptic homeostasis" hypothesis suggests that SWS indirectly influences memory. Accordingly, synapses that are potentiated during an encoding event are subsequently downscaled during SWS, such that weak connections are selectively eliminated.[55–57]

These two hypotheses are certainly not mutually exclusive,[58] signifying the importance of neocortical regions as well as the hippocampus to encode new information. During NREM sleep that occurs post-learning, slow waves that originate in neocortical networks entrain hippocampal sharp wave-ripples that propagate the replay and an active reorganization of the memory in the hippocampus and the neocortex. Subsequently, sleep spindles, which are short, distinct waves of 12–16 Hz oscillations that occur during stage 2 of NREM sleep, are relayed between the thalamic nuclei and cortex for synchronization and sustainment across sleep periods,[59] and assist in modulating memory consolidation and plasticity.[60] Finally, memory consolidation has been shown to rely on the temporal coordination between hippocampal sharp wave-ripples, SWS, and spindles[61] and disruption in this temporal coordination has been reported in a rodent model relevant to the study of schizophrenia, further discussed below.[62]

Hippocampus-generated theta oscillations (4–8 Hz), PGO waves, and high cholinergic tone during REM sleep are also hypothesized to contribute to memory consolidation.[53] While REM sleep has been implicated in specifically consolidating perceptual memory[63–65] and emotional memory,[66] the exact contribution of REM to memory consolidation processes remains to be fully understood.[67] Causal evidence for hippocampal theta rhythmicity in memory consolidation was recently demonstrated in a mouse model wherein optogenetic silencing of inhibitory neurons in the medial septum ablated REM. Notably, suppression of REM sleep theta oscillations in these animals significantly impaired their ability to learn a hippocampal-dependent memory task.[68]

Sleep-dependent memory consolidation is compromised in patients with schizophrenia. Recent research in patients has focused on identifying abnormalities in specific rhythms during NREM such as slow oscillations and sleep spindles. Preclinical studies in animals and human studies have demonstrated an increase in density of spindles after learning.[69–71] Sleep spindles are implicated in promoting both procedural[72,73] and declarative[74,75] memory consolidation. Investigators have used a motor sequence task (MST) to assess sleep-dependent motor procedural memory and found that an improvement in performance after sleep was correlated with sleep spindle density.[73,76,77] Of note, patients with schizophrenia perform worse than controls on the MST, lack a significant performance improvement on the MST after sleep,[78–80] and have reduced spindle density that is correlated with the poorer MST performance.[80] Deficits in sleep spindles have also been correlated with poor outcomes in sleep-dependent consolidation of a declarative memory task in patients with schizophrenia.[81] Recent efforts have extended this work to focus on the role of temporal coordination of spindles and SWS in memory consolidation in schizophrenia.[82] Results showed that spindle number and density were decreased but spindle-SWS coordination was normal in medicated patients with schizophrenia. The spindle-SWS coordination was related to improvement in procedural memory performance following a night's sleep in patients. Therefore, enhancing spindles and spindle-SWS coordination may enhance memory function in schizophrenia. It is important to note that hippocampal sharp wave-ripples, a key component in the temporally coordinated network involved in memory consolidation,[61] are challenging to measure with noninvasive methods in humans. Taken together, deficits in sleep spindles in patients with schizophrenia may serve as one marker of impaired thalamocortical circuit function, sleep-dependent memory processing, and possibly a mechanism for memory impairments in the disorder. However, despite a rich body of evidence, the exact relationship of spindle deficits in schizophrenia, including unmedicated and first-episode psychosis patients, to cognitive dysfunctions in the disorder remains to be fully characterized.

Sleep in Animal Models Relevant for Schizophrenia Etiology

Animal models have proven instrumental to understanding pathophysiological mechanisms of schizophrenia, and particular emphasis has been placed on modeling dysfunctions in cognition. Sleep abnormalities have been only marginally investigated in preclinical models, but the work thus far provides resounding support for dysfunctional sleep as a neurobiological characteristic of schizophrenia. Preclinical genetic, prenatal, and neurotransmitter models pertaining to schizophrenia and sleep dysfunction are reviewed below.

Genetic

Disrupted-in-schizophrenia-1 (DISC1) has been identified as a leading genetic factor for various mental illnesses, including schizophrenia,[83] and a role for DISC1 in regulating sleep has been described in both the *Drosophila melanogaster* fruit fly[84] and mice.[85] Another genetic mouse model with a deficit in stable tubule only polypeptide (STOP) also displays neurophysiological and neuroanatomical abnormalities that resemble deficits seen in schizophrenia. The STOP null mice present cognitive and behavioral impairments, including deficits in hippocampal-dependent learning and abnormal social behaviors,[86–88] and assessments of sleep-wake patterns in this mouse model indicate less total sleep and fragmentation

in sleep-wake periods, further validating this model for the study of schizophrenia.[89,90]

Prenatal

The neurodevelopmental hypothesis of schizophrenia suggests that insults during early brain development increase the risk of subsequent manifestation of the disorder in adulthood.[91] The prenatal insult MAM-17 neurodevelopmental model induces a disruption in hippocampal and prefrontal embryogenesis with the administration of an antimitotic agent, methylazoxymethanol-acetate (MAM), on embryonic day 17 to pregnant rat dams.[92] Disrupted coordination between neocortical slow-waves, hippocampal ripples, and subsequent prefrontal cortical spindles during NREM sleep have been characterized in adult offspring. The fragmentation in NREM and impairments in slow-wave propagation highlight circuitry-based deficits that are postulated to be disrupted in schizophrenia, and the model provides translational value to investigating these deficits.[62]

Persistent sleep alterations, including increased sleep fragmentation and decreased duration of SWS relative to total sleep time, have been reported in a rat model of prenatal stress exposure. In addition, the adult offspring in this model have a dysfunctional hypothalamo-pituitary-adrenal axis, display cognitive impairments, and present abnormal circadian timing.[93,94]

Prenatal exposure to an inflammatory mimetic, lipopolysaccharide (LPS), a component of the outer-membrane of Gram-negative bacteria that mimics an inflammatory stimulus, has also been shown to significantly alter sleep-wake architecture and induce significantly longer average NREM bout durations during the dark phase in mice. Additionally, exposure to inflammation in utero was shown to adversely impact delta power during NREM such that the ratios of delta power were no longer diurnally altered over the 24 h cycle.[95]

Neurotransmitter

Lastly, both glutamatergic and cholinergic transmission are critically involved in cognition,[96,97] schizophrenia pathophysiology,[98] sleep-dependent plasticity,[99] and modulation of sleep and arousal.[100–102] As such, the role of the kynurenine pathway, and kynurenic acid (KYNA), an endogenous antagonist of α7 nicotinic acetylcholine (α7nACh) and glutamate NMDA receptors, in particular, in mediating a relationship between sleep and cognitive function is currently under investigation.[103,104] Distinct abnormalities in tryptophan metabolism via the kynurenine pathway have been reported in schizophrenia. Specifically, KYNA is increased in the postmortem brain tissue and cerebrospinal fluid samples of patients with schizophrenia.[105,106] In line with the neurodevelopmental hypothesis of schizophrenia etiology, models to study the KYNA hypothesis of schizophrenia have been developed,[107] and studies linking sleep and cognitive dysfunctions in adulthood are ongoing.[108]

In summary, emerging evidence indicates that sleep alterations occur in a variety of rodent models of schizophrenia that translate to findings in humans. Although these combined results are intriguing, greater progress is needed to determine if these sleep alterations are causally linked to cognitive impairments or other behavioral phenotypes that represent features of schizophrenia.

Closing Remarks

This feature focused on sleep disruptions in patients with schizophrenia as contributing factors to cognitive impairments in the disorder. As discussed, it has been consistently shown that nightly disruptions in sleep serve as a strong predictor of poor functioning the next day and greater severity of symptoms in individuals with schizophrenia. Treating sleep disturbances in schizophrenia, through the use of cognitive behavioral therapy, medications,[31,32] or other treatments specific to the sleep disorder diagnosis, should be further explored to understand how such interventions directly or indirectly improve cognitive symptoms.

Psychiatrists, sleep medicine practitioners, and researchers alike are encouraged to increasingly work together and bring further attention to sleep problems in patients with schizophrenia. The ultimate goal should be to further our understanding of the abnormalities and to improve cognition, physical and mental health for patients. As discussed, several caveats should be also be considered as progress is made in this field, including transdiagnostic associations that may contribute to sleep disturbances and the use of medications among the mentally ill population.[26,31,32]

In this translational piece, we highlighted key advancements in understanding the sleep disturbances in schizophrenia and the contribution of these disruptions to cognitive dysfunction, specifically memory, in schizophrenia. Preclinical research that investigates the basic neurobiological mechanisms between sleep and memory may better inform our understanding of the interplay between sleep disturbances and cognitive impairments in schizophrenia. Therapeutic approaches that improve sleep have the potential to improve cognitive function, the quality of life for patients, and may serve as preemptive interventions for exacerbation of schizophrenia symptomology.

Funding

The study was supported by the National Institutes of Health (K12 HD43489-14, P50 MH103222, R01 MH094520, and R01 NS102209-01).

References

1. Cohrs S. Sleep disturbances in patients with schizophrenia: impact and effect of antipsychotics. *CNS Drugs*. 2008;22:939–962.
2. Avidan AY, Zee PC. *Handbook of Sleep Medicine*. 2nd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011.
3. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. The new sleep scoring manual—the evidence behind the rules. *J Clin Sleep Med.* 2007;3:107.
4. Rechtschaffen A, Kales A. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. Washington: US Government Printing Office; 1968.
5. Reppert SM, Weaver DR. Coordination of circadian timing in mammals. *Nature*. 2002;418:935–941.
6. Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annu Rev Physiol*. 2010;72:517–549.
7. Killgore WD. Effects of sleep deprivation on cognition. *Prog Brain Res*. 2010;185:105–129.
8. Pires GN, Bezerra AG, Tufik S, Andersen ML. Effects of acute sleep deprivation on state anxiety levels: a systematic review and meta-analysis. *Sleep Med*. 2016;24:109–118.
9. Patrick G, Gilbert J. On the effects of loss of sleep. *Psychol Rev.* 1896;3:469.
10. Colten HR, Altevogt BM; Institute of Medicine (U.S.) Committee on Sleep Medicine and Research. *Sleep Disorders and Sleep Deprivation an Unmet Public Health Problem*. Washington, DC: Institute of Medicine, National Academies Press; 2006:1 online resource (xviii, 404 p.).
11. Krause AJ, Simon EB, Mander BA, et al. The sleep-deprived human brain. *Nat Rev Neurosci*. 2017;18:404–418.
12. Kahn-Greene ET, Killgore DB, Kamimori GH, Balkin TJ, Killgore WD. The effects of sleep deprivation on symptoms of psychopathology in healthy adults. *Sleep Med*. 2007;8:215–221.
13. Kraepelin E, Barclay RM, Robertson GM. *Dementia Præcox and Paraphrenia*. Edinburgh: E. & S. Livingstone; 1919.
14. Beattie L. Experiences of a first-episode psychosis by a psychology graduate student. *Schizophr Bull*. 2016. doi: 10.1093/schbul/sbw071. [Epub ahead of print]
15. Bruni C. Immediate intervention: life-long success. *Schizophr Bull*. 2014;40:3–4.
16. Jepson J. Bad day. *Schizophr Bull*. 2013;39:1173.
17. Anonymous. Intrusive thoughts, impulses, and schizoaffective disorder. *Schizophr Bull.* 2016. doi:10.1093/schbul/sbw107. [Epub ahead of print]
18. Gray B. Hidden demons: a personal account of hearing voices and the alternative of the hearing voices movement. *Schizophr Bull*. 2008;34:1006–1007.
19. Anonymous. Thought-action-fusion. *Schizophr Bull.* 2015. [Epub ahead of print]
20. Xiang YT, Weng YZ, Leung CM, Tang WK, Lai KY, Ungvari GS. Prevalence and correlates of insomnia and its impact on quality of life in Chinese schizophrenia patients. *Sleep*. 2009;32:105–109.
21. Afonso P, Figueira ML, Paiva T. Sleep-wake patterns in schizophrenia patients compared to healthy controls. *World J Biol Psychiatry*. 2014;15:517–524.
22. Palmese LB, DeGeorge PC, Ratliff JC, et al. Insomnia is frequent in schizophrenia and associated with night eating and obesity. *Schizophr Res*. 2011;133:238–243.
23. Ma XR, Song GR, Xu XB, Tian T, Chang SH. The prevalence of sleep disturbance and its socio-demographic and clinical correlates in first-episode individuals with schizophrenia in rural China. *Perspect Psychiatr Care*. 2016. [Epub ahead of print]
24. Afonso P, Brissos S, Figueira ML, Paiva T. Schizophrenia patients with predominantly positive symptoms have more disturbed sleep-wake cycles measured by actigraphy. *Psychiatry Res*. 2011;189:62–66.
25. Freeman D, Pugh K, Vorontsova N, Southgate L. Insomnia and paranoia. *Schizophr Res*. 2009;108:280–284.
26. Reeve S, Sheaves B, Freeman D. The role of sleep dysfunction in the occurrence of delusions and hallucinations: a systematic review. *Clin Psychol Rev*. 2015;42:96–115.
27. Bromundt V, Köster M, Georgiev-Kill A, et al. Sleep-wake cycles and cognitive functioning in schizophrenia. *Br J Psychiatry*. 2011;198:269–276.
28. Monti JM, Monti D. Sleep in schizophrenia patients and the effects of antipsychotic drugs. *Sleep Med Rev*. 2004;8:133–148.
29. Kocsis RN. Diagnostic and statistical manual of mental disorders: fifth edition (DSM-5). *Int J Offender Ther.* 2013;57:1546–1548.
30. Keshavan MS, Montrose DM, Miewald JM, Jindal RD. Sleep correlates of cognition in early course psychotic disorders. *Schizophr Res*. 2011;131:231–234.
31. Mulligan LD, Haddock G, Emsley R, Neil ST, Kyle SD. High resolution examination of the role of sleep disturbance in predicting functioning and psychotic symptoms in schizophrenia: a novel experience sampling study. *J Abnorm Psychol*. 2016;125:788–797.
32. Waite F, Myers E, Harvey AG, et al. Treating sleep problems in patients with schizophrenia. *Behav Cogn Psychother*. 2016;44:273–287.
33. Anderson KN, Kelly TP, Griffiths TD. Primary sleep disorders can cause long-term sleep disturbance in patients with autoimmune mediated limbic encephalitis. *Clin Neurol Neurosurg*. 2013;115:1079–1082.
34. Monti JM, BaHammam AS, Pandi-Perumal SR, et al. Sleep and circadian rhythm dysregulation in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;43:209–216.
35. Chouinard S, Poulin J, Stip E, Godbout R. Sleep in untreated patients with schizophrenia: a meta-analysis. *Schizophr Bull*. 2004;30:957–967.
36. Poulin J, Chouinard S, Pampoulova T, Lecomte Y, Stip E, Godbout R. Sleep habits in middle-aged, non-hospitalized men and women with schizophrenia: a comparison with healthy controls. *Psychiatry Res*. 2010;179:274–278.
37. Martin JL, Jeste DV, Ancoli-Israel S. Older schizophrenia patients have more disrupted sleep and circadian rhythms than age-matched comparison subjects. *J Psychiatr Res*. 2005;39:251–259.
38. Rao ML, Gross G, Strebel B, et al. Circadian rhythm of tryptophan, serotonin, melatonin, and pituitary hormones in schizophrenia. *Biol Psychiatry*. 1994;35:151–163.
39. Benson KL. Sleep in schizophrenia: impairments, correlates, and treatment. *Psychiatr Clin North Am*. 2006;29:1033–1045; abstract ix.
40. Sateia MJ. Update on sleep and psychiatric disorders. *Chest*. 2009;135:1370–1379.

41. Klingaman EA, Palmer-Bacon J, Bennett ME, Rowland LM. Sleep disorders among people with schizophrenia: emerging research. *Curr Psychiatry Rep*. 2015;17:79.
42. Chan MS, Chung KF, Yung KP, Yeung WF. Sleep in schizophrenia: a systematic review and meta-analysis of polysomnographic findings in case–control studies. *Sleep Med Rev*. 2017;32:69–84.
43. Benson KL, Faull KF, Zarcone VP Jr. Evidence for the role of serotonin in the regulation of slow wave sleep in schizophrenia. *Sleep*. 1991;14:133–139.
44. Hudson JI, Lipinski JF, Keck PE Jr, et al. Polysomnographic characteristics of schizophrenia in comparison with mania and depression. *Biol Psychiatry*. 1993;34:191–193.
45. Tandon R, Shipley JE, Taylor S, et al. Electroencephalographic sleep abnormalities in schizophrenia. Relationship to positive/negative symptoms and prior neuroleptic treatment. *Arch Gen Psychiatry*. 1992;49:185–194.
46. Hoffmann R, Hendrickse W, Rush AJ, Armitage R. Slow-wave activity during non-REM sleep in men with schizophrenia and major depressive disorders. *Psychiatry Res*. 2000;95:215–225.
47. Hiatt JF, Floyd TC, Katz PH, Feinberg I. Further evidence of abnormal non-rapid-eye-movement sleep in schizophrenia. *Arch Gen Psychiatry*. 1985;42:797–802.
48. Krystal AD, Goforth HW, Roth T. Effects of antipsychotic medications on sleep in schizophrenia. *Int Clin Psychopharmacol*. 2008;23:150–160.
49. Freeman D, Sheaves B, Goodwin GM, et al. The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis. *The Lancet Psychiatry*. 2017;4:749–758.
50. Diekelmann S, Born J. The memory function of sleep. *Nat Rev Neurosci*. 2010;11:114–126.
51. Graves L, Pack A, Abel T. Sleep and memory: A molecular perspective. *Trends Neurosci*. 2001;24:237–243.
52. Stickgold R, Walker MP. Sleep-dependent memory triage: evolving generalization through selective processing. *Nat Neurosci*. 2013;16:139–145.
53. Rasch B, Born J. About sleep's role in memory. *Physiol Rev*. 2013;93:681–766.
54. Preston AR, Eichenbaum H. Interplay of hippocampus and prefrontal cortex in memory. *Curr Biol*. 2013;23:R764–R773.
55. Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull*. 2003;62:143–150.
56. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. *Sleep Med Rev*. 2006;10:49–62.
57. Tononi G, Cirelli C. Sleep and synaptic down-selection. In: Buzsaki G, Christen Y, eds. *Micro-, Meso- and Macro-Dynamics of the Brain*. Cham (CH): Springer; 2016:99–106.
58. Genzel L, Kroes MC, Dresler M, Battaglia FP. Light sleep versus slow wave sleep in memory consolidation: a question of global versus local processes? *Trends Neurosci*. 2014;37:10–19.
59. Huguenard JR, McCormick DA. Thalamic synchrony and dynamic regulation of global forebrain oscillations. *Trends Neurosci*. 2007;30:350–356.
60. Mölle M, Born J. Slow oscillations orchestrating fast oscillations and memory consolidation. *Prog Brain Res*. 2011;193:93–110.
61. Maingret N, Girardeau G, Todorova R, Goutierre M, Zugaro M. Hippocampo-cortical coupling mediates memory consolidation during sleep. *Nat Neurosci*. 2016;19:959–964.
62. Phillips KG, Bartsch U, McCarthy AP, et al. Decoupling of sleep-dependent cortical and hippocampal interactions in a neurodevelopmental model of schizophrenia. *Neuron*. 2012;76:526–533.
63. Karni A, Tanne D, Rubenstein BS, Askenasy JJ, Sagi D. Dependence on REM sleep of overnight improvement of a perceptual skill. *Science*. 1994;265:679–682.
64. Mednick S, Nakayama K, Stickgold R. Sleep-dependent learning: a nap is as good as a night. *Nat Neurosci*. 2003;6:697–698.
65. Stickgold R, Whidbee D, Schirmer B, Patel V, Hobson JA. Visual discrimination task improvement: a multi-step process occurring during sleep. *J Cogn Neurosci*. 2000;12:246–254.
66. Deliens G, Gilson M, Peigneux P. Sleep and the processing of emotions. *Exp Brain Res*. 2014;232:1403–1414.
67. Genzel L, Spoormaker VI, Konrad BN, Dresler M. The role of rapid eye movement sleep for amygdala-related memory processing. *Neurobiol Learn Mem*. 2015;122:110–121.
68. Boyce R, Glasgow SD, Williams S, Adamantidis A. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. *Science*. 2016;352:812–816.
69. Eschenko O, Mölle M, Born J, Sara SJ. Elevated sleep spindle density after learning or after retrieval in rats. *J Neurosci*. 2006;26:12914–12920.
70. Gais S, Mölle M, Helms K, Born J. Learning-dependent increases in sleep spindle density. *J Neurosci*. 2002;22:6830–6834.
71. Schabus M, Gruber G, Parapatics S, et al. Sleep spindles and their significance for declarative memory consolidation. *Sleep*. 2004;27:1479–1485.
72. Fogel SM, Smith CT. Learning-dependent changes in sleep spindles and Stage 2 sleep. *J Sleep Res*. 2006;15:250–255.
73. Nishida M, Walker MP. Daytime naps, motor memory consolidation and regionally specific sleep spindles. *PLoS One*. 2007;2:e341.
74. Clemens Z, Fabó D, Halász P. Twenty-four hours retention of visuospatial memory correlates with the number of parietal sleep spindles. *Neurosci Lett*. 2006;403:52–56.
75. Schabus M, Hoedlmoser K, Pecherstorfer T, et al. Interindividual sleep spindle differences and their relation to learning-related enhancements. *Brain Res*. 2008;1191:127–135.
76. Fischer S, Nitschke MF, Melchert UH, Erdmann C, Born J. Motor memory consolidation in sleep shapes more effective neuronal representations. *J Neurosci*. 2005;25:11248–11255.
77. Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R. Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron*. 2002;35:205–211.
78. 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;56:951–956.
79. Manoach DS, Thakkar KN, Stroynowski E, et al. Reduced overnight consolidation of procedural learning in chronic medicated schizophrenia is related to specific sleep stages. *J Psychiatr Res*. 2010;44:112–120.
80. Wamsley EJ, Tucker MA, Shinn AK, et al. Reduced sleep spindles and spindle coherence in schizophrenia: mechanisms of impaired memory consolidation? *Biol Psychiatry*. 2012;71:154–161.
81. Göder R, Graf A, Ballhausen F, et al. Impairment of sleep-related memory consolidation in schizophrenia: relevance of sleep spindles? *Sleep Med*. 2015;16:564–569.
82. Demanuele C, Bartsch U, Baran B, et al. Coordination of slow waves with sleep spindles predicts sleep-dependent memory consolidation in schizophrenia. *Sleep*. 2017;40. doi:10.1093/sleep/zsw013. [Epub ahead of print]

83. Chubb JE, Bradshaw NJ, Soares DC, Porteous DJ, Millar JK. The DISC locus in psychiatric illness. *Mol Psychiatry*. 2008;13:36–64.
84. Sawamura N, Ando T, Maruyama Y, et al. Nuclear DISC1 regulates CRE-mediated gene transcription and sleep homeostasis in the fruit fly. *Mol Psychiatry*. 2008;13:1138–1148, 1069.
85. Jaaro-Peled H, Altimus C, LeGates T, et al. Abnormal wake/sleep pattern in a novel gain-of-function model of DISC1. *Neurosci Res*. 2016;112:63–69.
86. Powell KJ, Hori SE, Leslie R, et al. Cognitive impairments in the STOP null mouse model of schizophrenia. *Behav Neurosci*. 2007;121:826–835.
87. Fournet V, Schweitzer A, Chevarin C, et al. The deletion of STOP/MAP6 protein in mice triggers highly altered mood and impaired cognitive performances. *J Neurochem*. 2012;121:99–114.
88. Volle J, Brocard J, Saoud M, et al. Reduced expression of STOP/MAP6 in mice leads to cognitive deficits. *Schizophr Bull*. 2013;39:969–978.
89. Profitt MF, Deurveilher S, Robertson GS, Rusak B, Semba K. Disruptions of sleep/wake patterns in the stable tubule only polypeptide (STOP) null mouse model of schizophrenia. *Schizophr Bull*. 2016;42:1207–1215.
90. Andrieux A, Salin PA, Vernet M, et al. The suppression of brain cold-stable microtubules in mice induces synaptic defects associated with neuroleptic-sensitive behavioral disorders. *Genes Dev*. 2002;16:2350–2364.
91. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry*. 1987;44:660–669.
92. Lodge DJ, Grace AA. Gestational methylazoxymethanol acetate administration: a developmental disruption model of schizophrenia. *Behav Brain Res*. 2009;204:306–312.
93. Dugovic C, Maccari S, Weibel L, Turek FW, Van Reeth O. High corticosterone levels in prenatally stressed rats predict persistent paradoxical sleep alterations. *J Neurosci*. 1999;19:8656–8664.
94. Mairesse J, Silletti V, Laloux C, et al. Chronic agomelatine treatment corrects the abnormalities in the circadian rhythm of motor activity and sleep/wake cycle induced by prenatal restraint stress in adult rats. *Int J Neuropsychopharmacol*. 2013;16:323–338.
95. Adler DA, Ammanuel S, Lei J, et al. Circadian cycle-dependent EEG biomarkers of pathogenicity in adult mice following prenatal exposure to in utero inflammation. *Neuroscience*. 2014;275:305–313.
96. Levin ED, McClernon FJ, Rezvani AH. Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. *Psychopharmacology (Berl)*. 2006;184:523–539.
97. Robbins TW, Murphy ER. Behavioural pharmacology: 40+ years of progress, with a focus on glutamate receptors and cognition. *Trends Pharmacol Sci*. 2006;27:141–148.
98. Timofeeva OA, Levin ED. Glutamate and nicotinic receptor interactions in working memory: importance for the cognitive impairment of schizophrenia. *Neuroscience*. 2011;195:21–36.
99. Aton SJ, Seibt J, Dumoulin M, et al. Mechanisms of sleep-dependent consolidation of cortical plasticity. *Neuron*. 2009;61:454–466.
100. Dash MB, Douglas CL, Vyazovskiy VV, Cirelli C, Tononi G. Long-term homeostasis of extracellular glutamate in the rat cerebral cortex across sleep and waking states. *J Neurosci*. 2009;29:620–629.
101. Datta S. Cellular and chemical neuroscience of mammalian sleep. *Sleep Med*. 2010;11:431–440.
102. Papouin T, Dunphy JM, Tolman M, Dineley KT, Haydon PG. Septal Cholinergic neuromodulation tunes the astrocyte-dependent gating of hippocampal NMDA receptors to wakefulness. *Neuron*. 2017;94:840–854.e7.
103. Baratta AM, Buchla AD, Fabian CB, Pocivavsek A. 0257 Effects of acute sleep deprivation in rats: sexually dimorphic increase in hippocampal kynurenic acid and impaired contextual memory. *Sleep* 2017;40(suppl 1):A94–A95.
104. Pocivavsek A, Baratta AM, Mong JA, Viechweg SS. Effects of actue kynurenine challenge on sleep-wake architecture in male rats. *Sleep* 2017. doi.org/10.1093/sleep/zsx141. [Epub ahead of print]
105. Schwarcz R, Rassoulpour A, Wu HQ, Medoff D, Tamminga CA, Roberts RC. Increased cortical kynurenate content in schizophrenia. *Biol Psychiatry*. 2001;50:521–530.
106. Erhardt S, Blennow K, Nordin C, Skogh E, Lindström LH, Engberg G. Kynurenic acid levels are elevated in the cerebrospinal fluid of patients with schizophrenia. *Neurosci Lett*. 2001;313:96–98.
107. Notarangelo FM, Pocivavsek A. Elevated kynurenine pathway metabolism during neurodevelopment: implications for brain and behavior. *Neuropharmacology*. 2017;112:275–285.
108. Baratta AM, Buck SA, Mong JA, Pocivavsek A. Acute kynurenine challenge disrupts sleep-wake architecture and impairs contextual memory in adult rats. *Society for Neuroscience Annual Meeting* 2017.