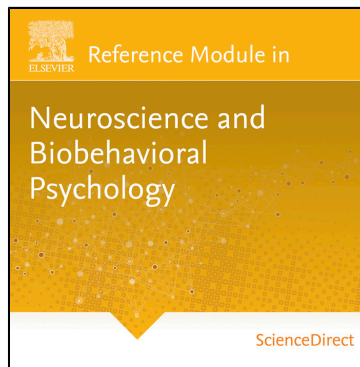


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## Schizophrenia, Other Neuropsychiatric Disorders and Sleep<sup>☆</sup>

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### Glossary

**Amygdala** The amygdalae (singular: amygdala) are almond-shaped groups of neurons located in the medial temporal lobes of the brain, adjacent to the hippocampi. They are part of the limbic system and play a critical role in emotional processing and emotional learning and memory.

**Declarative memory** Memory for facts and events, which can be recalled to conscious awareness and reported verbally, hence the term “declarative.” It is often divided into semantic and episodic memory, the former referring to knowledge and the latter referring memories of specific events.

**Functional connectivity MRI** An analysis method to characterize the coordination of activity across the brain by measuring correlations in functional MRI activation. These methods can be used to identify functionally affiliated brain regions that comprise a network.

**Limbic system** A connected network of brain structures that form the inner border of the cortex and play a critical role in emotion and memory.

**Memory consolidation** Processes that stabilize, enhance, integrate and reorganize memory traces in the brain. These processes operate outside of conscious awareness during periods of wake and sleep.

**Obstructive Sleep Apnea** A sleep disorder caused by obstruction of the upper airways during sleep, and resulting in snoring, hypoxia, and gasping, which results in brief awakenings at rates of up to 100 per hour. The most common cause in adults is excessive soft tissue surrounding the airways in the neck. In children, OSA is typically due to obstruction of the airways by enlarged adenoids and tonsils and can be effectively treated with adenotonsillectomy (i.e., surgical removal of the adenoids and tonsils).

**Prefrontal cortex** A region of heteromodal association cortex in the frontal lobe that is thought to be involved in a diverse set of cognitive control functions that serve to coordinate goal-oriented mental activity across the brain.

**Procedural memory** Memory for learning and knowing “how” as opposed to “what,” specifically the memory for skills and habits.

Abnormal sleep is a prominent feature of the major neuropsychiatric disorders and is often included in the DSM-IV diagnostic criteria. While often viewed as secondary, as these disorders may themselves diminish sleep quality, sleep deprivation can precipitate psychosis, and there is growing evidence that sleep disorders can aggravate, trigger, and even *cause* a range of psychiatric conditions. Moreover, as has been shown in major depressive disorder (MDD), treating sleep can improve psychiatric symptoms, suggesting that disrupted sleep contributes to the clinical syndrome. In addition to its effects on symptoms, sleep disturbance, which is well known to impair emotional regulation and cognition in otherwise healthy individuals, may contribute to or cause the disabling and often treatment-refractory cognitive deficits seen in neuropsychiatric disorders. While the articles in this section

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address the alterations in sleep seen in various psychiatric disorders, we focus here on evidence that these alterations can precede, contribute to the development of, and exacerbate these disorders. We first provide a brief overview of the evidence that disrupted sleep can contribute to mood disorders and post-traumatic stress disorder in adults as well as to attention deficit hyperactivity disorder and autism spectrum disorder in children. We then provide a more detailed description of abnormal sleep in schizophrenia and its possible contribution to cognitive deficits and symptoms. We conclude that abnormal sleep contributes substantially to disability in the major neuropsychiatric disorders and that understanding this contribution may open new avenues to treatment.

### **Emotional Memory, Mood Disorders, and Sleep**

One's mood and emotional state are strongly modulated by the recall of emotional memories. In depression there is a strong bias toward remembering negative emotional events. For example, depressed individuals remember negative words, but not positive or neutral words, better than non-depressed individuals, and when learning negative words, show increased activation of the amygdala, which correlates with depression severity. In fact, amygdala hyperactivity to negative stimuli and reduced communication between prefrontal and limbic regions (as measured by functional connectivity MRI), including the amygdala, are reliable findings in MDD. This suggests that a failure of top-down control of the emotional limbic system by the prefrontal cortex contributes to depression. Recent work has shown that sleep deprivation in healthy individuals has strikingly similar effects both on the encoding and processing of negative emotional experiences and on amygdala reactivity and connectivity. Like depressed individuals, sleep-deprived participants show a bias toward remembering negative over positive and neutral words. Seung-Schik Yoo and colleagues have reported that sleep-deprived participants show dramatically increased amygdala responses while viewing negative, but not neutral stimuli, and decreased communication between the amygdala and medial prefrontal cortex. In a study by Lisa Chuah and colleagues, reduced communication between prefrontal regions and amygdala in sleep-deprived individuals was associated with greater vulnerability to distraction by negative emotional stimuli during a cognitive task. This provides a potential mechanism for the common observation that emotions are more likely to interfere with problem-solving after a night of poor sleep. Thus, sleep deprivation fundamentally alters the way the brain processes emotion. Such experimental evidence of causal links between sleep deprivation, negative memory bias, poor concentration and aberrant neural processing of negative emotional stimuli raises the question of whether insomnia, a key symptom of MDD, may be a predisposing, precipitating and perpetuating factor in depression. Insomnia and nightmares have also been shown to increase the risk of suicide, a leading cause of death, even after controlling for the presence and severity of depression, hopelessness, anxiety, PTSD diagnosis and substance abuse.

While establishing the direction of causality and understanding the mechanisms underlying the well-established association of insomnia and depression are daunting tasks, when depression occurs in the context of other sleep disorders, particularly obstructive sleep apnea (OSA), the direction of causality is clearer. OSA can lead to severe sleep fragmentation with as many as a 100 brief arousals per hour. It is primarily an anatomical disorder, caused either by structural anomalies that restrict the airway or, more commonly, by excess soft tissue in the neck secondary to obesity. There is a 2.5- to 4-fold increased risk of MDD in individuals with even moderate OSA (less than 15 arousals per hour). A 1989 study by Richard Millman and colleagues demonstrated that the use of continuous positive airways pressure (CPAP) to treat OSA in patients with co-morbid MDD was associated with a reduction of depressive symptoms to sub-clinical levels. While not placebo controlled, this study suggests that disrupted sleep contributes to depressive symptoms in individuals with OSA and that treatment of OSA can alleviate depression. A 2003 population study by Maurice Ohayon showed that individuals with MDD showed a fivefold increased risk of OSA or other DSM-IV breathing-related sleep disorders, and that these sleep disorders were present in nearly a fifth of all individuals with MDD. Thus, even this one form of disordered sleep may contribute to depression in a substantial proportion of individuals with MDD.

It is common knowledge that a poor night's sleep can make you more emotional the next day. Thus, it is not surprising to find evidence that sleep disruption contributes to affective dysregulation in healthy individuals and in neuropsychiatric disorders. Multiple lines of evidence suggest that circadian and sleep-wake processes play a causal role in precipitating episodes in bipolar disorder. Sleep disturbances are among the most prominent correlates of both manic and depressive episodes, and sleep deprivation can predict and trigger mania. In a compelling demonstration of this, Tom Wehr and colleagues in 1982 studied rapidly cycling bipolar patients who underwent 40 h of experimental sleep deprivation during a depressive episode. Of the nine patients who participated, eight switched out of depression and seven were rated as manic or hypomanic at the end of the 40 h. This suggests that sleep loss has a significant role in the genesis of mania.

Despite the seemingly prominent role of sleep in affective disorders, the mechanisms of these relations have been minimally studied and are likely to be complex. For example, the findings described above suggest that sleep loss in MDD can either cause or exacerbate depression, but acute sleep deprivation can also lead to symptomatic relief, even in treatment-resistant MDD, and in bipolar patients, it can trigger mania. In some studies, rapid eye movement (REM) sleep deprivation alone led to improvement of depression in MDD. Unfortunately, this is not very useful from a clinical perspective, as symptoms return as soon as the patient sleeps. But it raises important mechanistic questions about the relationship between sleep and mood disorders. Understanding these mechanisms, and the contribution of sleep to pathogenesis, has the potential to substantially advance treatment.

## Sleep and Post-traumatic Stress Disorder

Insomnia is one of the most commonly reported symptoms of PTSD. The DSM-IV criteria for PTSD include, "difficulty falling or staying asleep that may be due to recurrent nightmares during which the traumatic event is relived." Here the associated sleep disorder is not only a generalized disruption of sleep but also a specific disorder of dreaming. It is important to note that the nightmares of PTSD are distinctly different from the nightmares experienced more generally in the population, in that they appear to be near veridical replays of traumatic events. Such replay of episodic memories is highly uncommon in normal dreams, occurring in less than 1%–2% of dream reports according to a 2003 study by Magdalena Fosse and colleagues.

While PTSD is listed as an Anxiety Disorder in DSM-IV and as a Trauma- and Stress-Related Disorder in DSM-V, it could arguably also be classified as a memory disorder in that it arises from a failure to adequately process the memory of traumatic events. We have argued elsewhere that such processing normally "acts over days to months to reduce both the intrusiveness of the memory and the affect associated with such recall and to integrate the memory into the individual's larger network of related memories. In doing so, it provides a meaningful and accurate understanding of both the event and its implications for the individual's future. When this processing fails, PTSD develops." Such an analysis of PTSD is relevant here because these forms of off-line memory processing appear to occur preferentially, and in some cases exclusively, during sleep. Consistent with this, Edward Pace-Schott and colleagues have proposed that sleep disturbance results in failure of extinction memory (learning that something that was once dangerous is no longer so) to persist and generalize, and that this is an important mechanism by which sleep disruption contributes to the development and perpetuation of PTSD. The incorporation of traumatic memories into dream content in unaltered form suggests that the normal brain mechanisms that integrate these episodic memories into general semantic memory networks during sleep have failed. Thus, in the case of PTSD, a disruption of sleep-dependent memory processing may be the actual cause of the disorder, preventing the normal processing of the traumatic memory and alleviation of its associated distress. This is still an active field of research, and others have proposed that the therapeutic use of sleep-deprivation or psychopharmacological agents immediately following the traumatic event can disrupt the consolidation of emotional memories and thereby prevent PTSD.

## Sleep and Attention-Deficit Hyperactivity Disorder

Most parents know that tired children often become hyperactive. Then perhaps it is not so surprising that between a quarter and half of children with ADHD reportedly have sleep disturbances, compared to 7% of other children. Often the sleep disturbance is OSA, which, in children, is more likely to be associated with ADHD than depression. In a 2007 study by Yu-Shu Huang and colleagues, children comorbid for OSA and ADHD were treated either with methylphenidate (Ritalin) or adenotonsillectomy. A comparison of treatment outcomes revealed that ratings of overall ADHD severity, inattention, and hyperactivity all improved more in the surgical group than the methylphenidate group, suggesting that, as with adult depression, ADHD in children can be exacerbated, and possibly even caused, by disrupted sleep. Treating such sleep disorders can alleviate ADHD symptoms and may thereby avoid both the need for long-term medication and its side-effects.

## Sleep and Autism Spectrum Disorders

Sleep disturbances are also prominent in ASD, a group of neurodevelopmental disorders characterized by marked impairments in socialization and communication as well as restricted, repetitive and stereotyped patterns of behavior. ASD is associated with difficulty initiating and maintaining sleep (i.e., insomnia), the severity of which correlates with emotional disturbances, attention deficits, and aggressive behavior. This suggests that disrupted sleep exacerbates some of the most disabling symptoms of ASD. Abnormal sleep may also play a role in a core cognitive characteristic of ASD—the tendency to focus on details, sometimes at the expense of perceiving larger patterns (i.e., not seeing the forest for the trees)—that is sometimes referred to as "weak central coherence." Studies demonstrate that individuals with ASD have difficulty seeing gestalts, getting the gist of an event, and extracting "rules" from experience, processes that, in typically developing individuals, all show evidence of sleep dependent improvement. Sleep plays a key role in condensing and extracting meaning from the overwhelming amount of information encountered during the day. These sleep-dependent processes are particularly important for understanding social situations, in which one must integrate and interpret information to accurately perceive abstract attributes such as attitudes, goals, and intentions, and to truly "get" the gist. Jessica Payne and colleagues have shown that sleep facilitates getting the gist in neurotypical individuals. In one study of memory for word lists, sleep selectively enhanced the false recall of semantically related "gist" words that weren't on the lists, resulting in a less accurate, but arguably more useful, abstract memory. On this same task, Beversdorf and colleagues showed that individuals with autism were better able to discriminate the actual words from the semantically related lures suggesting a more accurate, but less abstract memory. As Beversdorf studied only the immediate recognition of list items, it is unclear whether sleep would facilitate gist recall in ASD, as it does in typical individuals. More generally, this raises the question of whether abnormal sleep in ASD, in addition to contributing to behavioral dysregulation, may also play a role in the development and maintenance of its characteristic cognitive style and social processing deficits.

## Bidirectional Relations Between Sleep and Neuropsychiatric Disorders

In the sections above we have focused on the ability of disrupted sleep to exacerbate, trigger and even cause specific psychiatric disorders. But these disorders also disrupt sleep. Thus, a vicious cycle may develop, where sleep disruption worsens the psychiatric condition and the psychiatric condition worsens the sleep. For example, in PTSD, one could imagine a traumatic event leading to acute anxiety that then disrupts sleep. If this sleep disruption impairs sleep-dependent memory processing and causes or is accompanied by recurrent nightmares replaying the traumatic experience, this could further increase anxiety and arousal, initiating a positive feedback cycle that reinforces the symptoms of PTSD. Studies of both depression and ADHD suggest that breaking the vicious cycle by treating the sleep disruption can cause clinically meaningful reductions in psychiatric symptoms. In the section below, we provide a selective review of the literature on abnormal sleep in schizophrenia with a focus on the role of sleep spindles in the cognitive deficits that are integral to the disorder. We propose that sleep may be a viable target for treatment-refractory cognitive deficits.

## Sleep and Schizophrenia

Schizophrenia is a neurodevelopmental disorder in which genetic and environmental risk factors interact, leading to the emergence of symptoms usually in late adolescence or early adulthood. These symptoms include “positive” psychotic symptoms such as hallucinations and delusions and “negative” symptoms such as amotivation, social withdrawal, and apathy. Schizophrenia is also characterized by cognitive deficits that often predate the onset of symptoms, persist throughout the course of illness and are also seen in otherwise unaffected first degree family members, suggesting that they reflect genetic vulnerability to schizophrenia. Sleep disturbances have been noted since the initial descriptions of schizophrenia by Emil Kraepelin and are associated with poorer coping skills and diminished quality of life. Sleep disturbances are a common complaint throughout the course of schizophrenia, including during the prodrome. They are anecdotally associated with the initial onset of psychosis, and often herald psychotic decompensation in remitted patients. The presence of sleep disturbance in antipsychotic-naïve and unmedicated patients indicates that abnormal sleep is not merely a side-effect of medications, but instead may be a core feature of schizophrenia. In fact, antipsychotic medications often normalize sleep in schizophrenia, and medication withdrawal has been associated with a progressive deterioration of sleep quality, which, in turn, is associated with psychotic relapse and increased severity of positive symptoms.

Although disturbed sleep is a prominent feature of schizophrenia, it has been difficult to specify the exact nature of the abnormalities. The most common subjective sleep complaints in schizophrenia are difficulty initiating and maintaining sleep (i.e., insomnia), which have been verified by polysomnographic (PSG) studies. PSG studies have also reported diverse abnormalities of sleep architecture (i.e., the amount and distribution of time spent in different sleep stages). The most consistently reported electrophysiological sleep abnormality is a decrease in the amount of deep slow wave sleep (SWS). Decreases in REM latency and increases in REM density have also been reported, but neither the SWS nor REM sleep abnormalities are consistently observed and meta-analytic studies have not revealed systematic differences in either SWS or REM sleep in schizophrenia patients compared to either healthy or psychiatric controls. This lack of consistency may reflect the underlying pathophysiological and phenotypic heterogeneity of schizophrenia. In addition, by affecting neurotransmitter systems that play important roles in sleep regulation, treatments for schizophrenia, including antipsychotic, anticholinergic, and anti-adrenergic medications, may contribute to variability in sleep measurements.

Relatively few studies have gone beyond sleep architecture to examine changes in the characteristics of the EEG power spectrum during sleep in schizophrenia. There have been reports of reduced delta activity and power during SWS. Recently, a fairly consistent literature has emerged showing a specific deficit in sleep spindle activity in schizophrenia. Sleep spindles, a defining thalamocortical oscillation of Stage 2 non-REM sleep, are seen on the EEG as brief (~1 s), powerful bursts of 12–15 Hz synchronous activity. Recent findings from Dara Manoach and colleagues of reduced sleep spindle activity in both early course schizophrenia patients who have never taken antipsychotic medications and nonpsychotic first-degree relatives of schizophrenia patients suggest that reduced spindle activity is unlikely to be secondary to medications or chronicity and instead may be an endophenotype of schizophrenia (a trait indicating genetic vulnerability).

## Sleep Spindles, Memory Consolidation and Positive Symptoms in Schizophrenia

A wealth of data suggests an evolutionarily conserved function for sleep in the consolidation of multiple forms of memory. Animal studies indicate that sleep spindles, by inducing massive influxes of calcium ions into cortical pyramidal cells, can trigger the intracellular mechanisms that are required for synaptic plasticity and long-term potentiation, a key cellular mechanism of memory. In humans, spindles have been shown to correlate with overnight consolidation of both procedural and declarative memory. In addition, in the sleep that follows learning, there is increased spindle activity in the specific circuits that were involved in encoding the new information. These learning-induced spindles predict overnight improvement in memory. There is also mounting evidence of a more general role for spindles in cognition based on their correlations with learning ability and IQ, relationships that may be mediated by memory enhancement. This raises the intriguing question of whether the marked reduction in sleep spindles in schizophrenia contributes to its core cognitive deficits.

In healthy young adults, overnight improvement on simple procedural motor skill tasks correlates with the number and density of sleep spindles. Despite normal learning during training, schizophrenia patients do not show significant sleep-dependent

improvement, an impairment that correlates with the number and density of sleep spindles. Sleep-dependent consolidation of declarative memory, tested with a picture recognition task, is also impaired in schizophrenia and correlates with reduced sleep spindles. The spindle deficit also correlates with IQ and executive function in antipsychotic naïve patients with schizophrenia and first-degree relatives. This body of literature suggests that spindle deficits contribute to deficient sleep-dependent memory consolidation and more general cognitive dysfunction in schizophrenia. Interestingly, sleep spindle abnormalities have also been reported in other neurodevelopmental and neurodegenerative disorders characterized by cognitive impairment including mental retardation, phenylketonuria, autism and Parkinson's disease with dementia. Whether the spindle deficits of schizophrenia have unique characteristics and consequences remains to be determined.

Reduced spindle activity also correlates with increased positive symptom severity in studies of chronic medicated schizophrenia, but with *decreased* positive symptoms in antipsychotic naïve early course schizophrenia. The opposite direction of these correlations may reflect differences in the pathophysiological underpinnings of positive symptoms that are present before treatment versus residual positive symptoms that have not responded to antipsychotic medications. While the mechanistic link of spindles to positive symptoms is less clear than that for memory, both may reflect abnormal thalamocortical circuit function.

### **Mechanisms of Abnormal Spindles in Schizophrenia**

Schizophrenia is a disorder that affects distributed neural circuitry and involves dysfunction in multiple neurotransmitter systems. Dysregulation of thalamocortical circuitry and of the gamma-aminobutyric acid (GABA) and the N-methyl-D-aspartate acid (NMDA) glutamatergic neurotransmitter systems are central to current models of schizophrenia. They are particularly relevant here because both GABA and NMDA receptors are critical for the generation of sleep spindles, which originate in the thalamic reticular nucleus (TRN) and are coordinated by thalamocortical circuitry. While the TRN can generate spindles in the absence of projections from the cortex, cortical inputs appear to be critical for modulating the synchronization of spindle oscillations across the cortex. Findings from Erin Wamsley and colleagues that in addition to the reductions in spindle activity, schizophrenia patients show reduced spindle coherence across the cortex, suggests dysfunction in the cortical as well as thalamic components of the spindle generating network. Reduced and less synchronous spindle activity due to thalamocortical dysfunction could interfere with sleep-dependent memory processing by preventing the simultaneous reactivation of memory components stored across visual, spatial, emotional and goal representation networks, leading to a fragmentation of memory and cognition. Findings of reduced spindle coherence during sleep parallel reports of reduced coherence of neural activity during both wakeful resting states and cognitive performance in schizophrenia.

### **Possible Functional Consequences of Impaired Sleep-Dependent Procedural Memory Consolidation**

Sleep-dependent memory processes can lead to the automation of procedural tasks, resulting in performance that is faster, more accurate, less variable, and less dependent on voluntary attention. This is paralleled by more efficient patterns of brain activation, particularly in the prefrontal cortex. A fundamental breakdown in sleep-dependent automation in schizophrenia would make it necessary to reallocate limited-capacity attentional resources to procedural task elements that, in healthy individuals, become automated as a function of sleep. This would leave fewer attentional resources available for higher-order task demands (i.e., those that require cognitive control). It is this interaction between automatic and controlled processes that normally allows our limited capacity brain to carry out complex cognitive tasks. Since almost all tasks have procedural components that could be automated by sleep, an impairment in sleep-dependent automation in schizophrenia, possibly mediated by the loss of sleep spindles, could contribute substantially to the generalized cognitive deficits that are a hallmark of schizophrenia and compromise quality of life.

### **Future Research Directions**

The relations of abnormal sleep to the pathophysiology and manifestations of schizophrenia remain understudied and poorly understood. This review highlights the importance of deficient sleep-dependent memory consolidation among the cognitive deficits of schizophrenia and identifies reduced sleep spindles as a potential underlying mechanism. Studies showing that spindles can be pharmacologically enhanced in schizophrenia and that increasing spindles improves memory in healthy individuals suggest that treating spindle deficits in schizophrenia may improve cognition. Since cognitive deficits are the strongest predictor of functional outcome in schizophrenia and effective treatments are lacking, this is an important new avenue of investigation. Spindle activity is highly heritable and recent large-scale genome-wide association studies have identified schizophrenia risk genes that may contribute to spindle deficits. Future genetic studies of spindles in animals and humans may illuminate the mechanisms of the spindle deficit in schizophrenia and provide molecular targets for treatment.

### **General Summary**

Sleep facilitates a wide range of processes that mediate the evolution of memories, including emotional memories, over time. These sleep-dependent processes aid in the stabilization, strengthening, integration, and reorganization of memories to increase their durability and flexibility, and to automate functions that depend on them. Given the ubiquity of abnormal sleep in the

neuropsychiatric disorders, it is worth considering why its potential contribution to symptoms and cognitive deficits has been relatively neglected by the research and clinical communities. For clinicians, it comes as no surprise to learn that patients with ASD or ADHD have disturbed sleep. But upon reflection, they would be hard pressed to come up with a convincing scientific explanation of why a sleep disruption should be present. One might suggest that the hyperactivity often seen in these patients would lead to sleep disruption but one could equally well argue that hyperactivity should lead to deeper, sounder sleep, as a day of unusually intense activity would typically produce. The neglect may reflect the prevailing tendency to regard disturbed sleep as secondary to neuropsychiatric disorders combined with a lack of awareness of the critical role of sleep in affective regulation and cognition. It may also reflect the fact that although the sleep disturbances of patients are often sufficiently severe as to warrant independent clinical attention, they are seldom the primary complaint. It is almost as if the association between psychiatric disorders and sleep disruption is so pervasive that it can be taken for granted and no explanation seems necessary. Here, we make the case that studying sleep abnormalities in relation to cognitive deficits and symptoms can provide insight into the pathophysiology of specific neuropsychiatric disorders and provide novel treatment approaches.

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