Reduced Sleep Spindles in Schizophrenia: A Treatable Endophenotype That Links Risk Genes to Impaired Cognition?

Dara S. Manoach, Jen Q. Pan, Shaun M. Purcell, and Robert Stickgold

ABSTRACT

Although schizophrenia (SZ) is defined by waking phenomena, abnormal sleep is a common feature. In particular, there is accumulating evidence of a sleep spindle deficit. Sleep spindles, a defining thalamocortical oscillation of non–rapid eye movement stage 2 sleep, correlate with IQ and are thought to promote long-term potentiation and enhance memory consolidation. We review evidence that reduced spindle activity in SZ is an endophenotype that impairs sleep-dependent memory consolidation, contributes to symptoms, and is a novel treatment biomarker. Studies showing that spindles can be pharmacologically enhanced in SZ and that increasing spindles improves memory in healthy individuals suggest that treating spindle deficits in patients with SZ may improve cognition. Spindle activity is highly heritable, and recent large-scale genome-wide association studies have identified SZ risk genes that may contribute to spindle deficits and illuminate their mechanisms. For example, the SZ risk gene *CACNA1I* encodes a calcium channel that is abundantly expressed in the thalamic spindle generator and plays a critical role in spindle activity based on a mouse knockout. Future genetic studies of animals and humans can delineate the role of this and other genes in spindles. Such cross-disciplinary research, by forging empirical links in causal chains from risk genes to proteins and cellular functions to endophenotypes, cognitive impairments, symptoms, and diagnosis, has the potential to advance the mechanistic understanding, treatment, and prevention of SZ. This review highlights the importance of deficient sleep-dependent memory consolidation among the cognitive deficits of SZ and implicates reduced sleep spindles as a potentially treatable mechanism.

Keywords: Cognition, Endophenotype, Genetics, Memory, Schizophrenia, Sleep, Spindles

http://dx.doi.org/10.1016/j.biopsych.2015.10.003

Neuropsychiatric disorders are primarily defined by waking phenomena, but sleep disturbances are often a prominent feature. Although usually viewed as secondary, sleep deprivation can precipitate psychosis (1) and trigger or aggravate a range of neuropsychiatric conditions (2–6). Moreover, as has been shown in depression (7) and attention-deficit/hyperactivity disorder (4), treating sleep disturbances can improve symptoms and cognitive function. These findings suggest that abnormal sleep is not merely epiphenomenal but can directly contribute to the defining features of neuropsychiatric disorders. In schizophrenia (SZ), there is a specific deficit in sleep spindles, a defining thalamocortical oscillation of stage 2 non–rapid eye movement (NREM) sleep (N2). In this review, we describe the nature, correlates, and implications of this spindle deficit and place it in a hypothetical causal chain that links SZ risk genes to cognitive deficits and positive symptoms. Understanding the neural and genetic bases of spindle deficits can advance the mechanistic understanding and treatment of SZ.

ABNORMAL SLEEP IS A KEY FEATURE OF SZ AND POTENTIAL TARGET FOR TREATMENT

In SZ, sleep disturbances have been described since Kraepelin's work (8) and are associated with poorer coping skills and diminished quality of life (9,10). They are common in patients throughout the course of SZ (11), in individuals with prodromal symptoms (12,13), and in young relatives (14). Sleep disturbances are associated with the initial onset of psychosis and predict relapse in remitted patients (15,16). Findings of sleep disturbances in unmedicated and antipsychotic drug (APD)-naïve patients with SZ (17) indicate that disturbed sleep is not merely a medication side effect. In fact, APDs often normalize sleep (18), and withdrawal is associated with a progressive deterioration of sleep quality (19), which, in turn, is associated with relapse (16) and increased positive symptoms (20). Despite the clear association of disturbed sleep with SZ, the exact nature of the disturbance and its relation to pathophysiology, cognitive deficits, and symptoms are unclear. If specific

sleep abnormalities that contribute to the onset, relapse, and manifestations of SZ can be identified, they may serve as targets for intervention to prevent the emergence of SZ, remediate its course, and ameliorate core features.

We review evidence that a specific sleep abnormality—reduced sleep spindle activity—predates the onset of SZ, is present throughout its course, and contributes to cognitive deficits and symptoms. This evidence indicates that 1) individuals with SZ and their first-degree relatives have reduced sleep spindle activity, 2) spindle deficits are associated with impaired memory consolidation and positive symptoms, 3) SZ risk genes are associated with spindle deficits and implicate specific pathophysiologic mechanisms, 4) spindles can be enhanced, and 5) spindles may serve as a novel treatment biomarker associated with cognition.

SLEEP ABNORMALITIES IN SZ

The most common subjective sleep disturbances in SZ are difficulty initiating and maintaining sleep (i.e., insomnia) (15,17). Polysomnography studies variably show reduced sleep efficiency (the fraction of time in bed spent asleep), increased sleep onset latencies, and increased wake time after sleep onset in patients with SZ compared with healthy individuals (17,21). Studies also reported altered circadian rhythms (22) and increased rates of sleep disorders, including obstructive sleep apnea, movement disorders, parasomnias, and hypersomnolence (6,15).

Polysomnography studies document diverse abnormalities of sleep architecture (i.e., the distribution of time spent in different sleep stages) in patients with SZ. In humans, sleep is divided into rapid eye movement (REM) and NREM sleep, and NREM sleep is subdivided into three stages: N1–N3 (Figure 1) (23). N3, or slow-wave sleep, is characterized by large delta (.5–4 Hz) waves. Medicated and APD-naïve patients with SZ and first-degree relatives show N3 abnormalities including reduced duration and delta power (24–27). Abnormalities in REM sleep, usually decreased REM latency or increased REM density (REMs per minute), are also reported (25,26,28), but neither N3 nor REM abnormalities are consistently observed (28,29), and meta-analyses have not revealed systematic differences in patients with SZ compared with healthy or psychiatric control subjects (17,21).

Relatively few studies of SZ venture beyond architecture to examine the spectral characteristics of the sleep
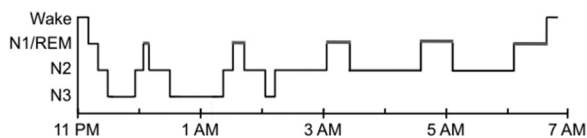

Figure 1. Normal sleep architecture. A normal night's sleep consists of five 90-min cycles that include rapid eye movement (REM) sleep (thicker black line). Most of the deep slow-wave sleep (N3) occurs early in the night, and most REM sleep occurs later in the night. N1 is a transitional state from wake to sleep, characterized by the disappearance of 8–12 Hz (alpha) waves from the electroencephalogram and appearance of slow (>.5 s) oscillating eye movements (23). N2 is defined by the presence of isolated sharp negative waves followed by a positive component, lasting >.5 s, and sleep spindles. N3 is defined by the presence of large (>75 μV peak-to-peak), slow (.5–2 Hz) waves occupying at least 20% of each 30-s epoch.

electroencephalogram (EEG). Recently, a fairly consistent literature has emerged showing a specific deficit in sleep spindle activity. Sleep spindles, a defining EEG oscillation of N2, are brief (~1 s) powerful bursts of 12–15 Hz activity organized in a waxing/waning envelope. Spindles also occur during N3 but are less dense (30). Most studies reviewed used N2 spindle density (number of spindles per minute) as the primary measurement, but the amplitude, duration, peak frequency, and sigma power (usually 12–15 Hz) of spindles are often reported, as are more general measures of NREM EEG sigma power, which correlate with spindle density (31). When summarizing the findings of multiple studies using different measures of spindles, we use the generic term "spindle activity."

SPINDLE MECHANISMS

There is considerable cross-species knowledge about sleep spindle mechanisms. Spindles are generated in the thalamic reticular nucleus (TRN) (32), a thin net-like structure around the thalamus comprised entirely of gamma-aminobutyric acid (GABA)-ergic neurons (33). TRN neurons project to glutamatergic thalamic neurons that project to the cortex. Cortical neurons send glutamatergic inputs back to N-methyl-D-aspartate (NMDA) receptors on TRN neurons (Figure 2). Thus, spindles are the product of a thalamocortical feedback loop that is regulated by GABAergic and NMDA receptor–mediated glutamatergic neurotransmission (34). Although the TRN can generate spindles in isolation (35,36), feedback from the cortex is necessary to synchronize spindles across cortical regions (30,37).

The voltage-dependent firing properties of TRN neurons are well described (38). Like most neurons, TRN cells fire in "tonic" mode at resting membrane potential, when most low-threshold Ca^{2+} channels are inactivated. However, when TRN neurons are relatively hyperpolarized to approximately −70 mV, these channels are de-inactivated, and the neurons fire in "burst" mode. During burst mode, a depolarizing input opens T-type Ca^{2+} channels, leading to low-threshold Ca^{2+} spikes and rhythmic bursts of action potentials. Rhythmic bursting in TRN neurons produces a powerful and prolonged inhibition followed by rebound spike-bursts in thalamocortical relay neurons that entrain cortical neurons to oscillate at spindle frequency (39). Dysfunction in spindle-generating circuitry is consistent with current models of SZ that implicate thalamocortical circuitry and GABAergic and NMDA receptor–mediated glutamatergic neurotransmission (40) and with evidence of TRN abnormalities in SZ (41).

SLEEP SPINDLES MEDIATE MEMORY CONSOLIDATION

After encoding, memories undergo "consolidation" processes that stabilize, enhance, integrate, and reorganize memory traces in the brain. These processes operate outside of conscious awareness while awake and during sleep. A wealth of molecular cellular, neural network, brain activation, and behavioral data from birds (42), rodents (43), cats (44), and humans (45) suggest an evolutionarily conserved function for sleep in the consolidation of multiple forms of memory.

Animal studies suggest that spindles are a key facilitator of the synaptic plasticity involved in memory. Experimental
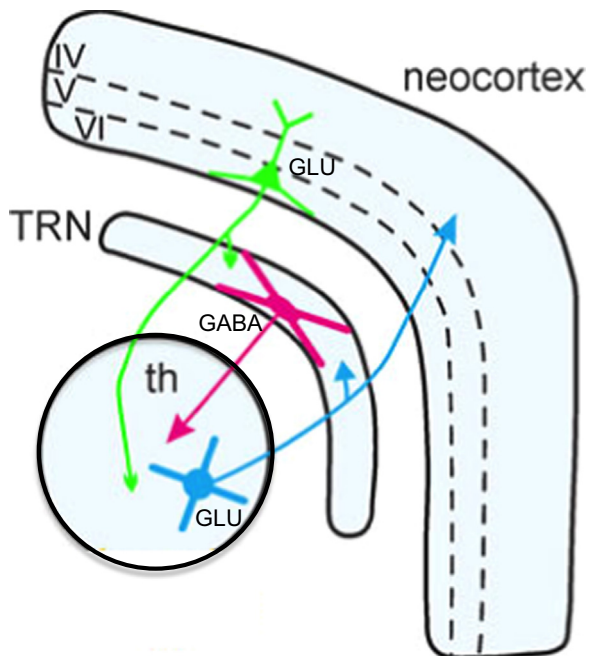
Figure 2. Thalamic reticular nucleus (TRN) circuitry for generating and synchronizing sleep spindles. The TRN, a net-like nucleus that sits between the rest of the thalamus and the neocortex, modulates thalamocortical activity. The TRN receives projections from thalamocortical and corticothalamic neurons. GABAergic TRN neurons project to thalamocortical relay neurons. Glutamatergic corticothalamic neurons send projections back to the TRN and other thalamic nuclei. GABA, gamma-aminobutyric acid; GLU, glutamate; th, thalamus. [Adapted with permission from Pinault (103).]

models suggest that spindles induce massive influxes of calcium ions into cortical pyramidal cells (46), where they would be expected to trigger known intracellular calcium-dependent mechanisms that produce synaptic plasticity (47). Trains of stimuli applied to rat cortical pyramidal cells that mimic the neuronal firing patterns that accompany spindles have been shown to induce an NMDA receptor–dependent short-term potentiation and L-type Ca^{2+} channel–dependent long-term potentiation (48).

In humans, spindles correlate with the sleep-dependent consolidation of procedural (49–54) and declarative (55–57) memory. In addition, EEG (50,55), magnetoencephalography (58), and subdural electrode grid (59) studies show increased spindle activity in specific circuits that were involved in presleep learning and that these learning-induced spindles predict sleep-dependent memory consolidation (50,55,58–60). Together, these findings suggest that spindles strengthen synapses to consolidate memory during sleep. There is also mounting evidence of a more general role for spindles in cognition based on their correlations with learning ability and IQ (61–63), relationships that may be mediated by memory enhancement.

Spindles act in concert with other NREM oscillations. They are temporally correlated with neocortical slow oscillations (.5–1 Hz) and hippocampal ripples (~200 Hz transient bursts of CA1 pyramidal cell activity), an orchestration that is thought to redistribute recently encoded memories from temporary dependence on the hippocampus to longer term representation in

the cortex (Figure 3) (43,64,65). In humans, hippocampal ripples are difficult to measure noninvasively, but simultaneous EEG and functional magnetic resonance imaging during sleep show that spindles are associated with increased functional connectivity between the hippocampus and neocortex (66). Evidence of a breakdown of this coordination is seen in a rat model of SZ (67). In SZ, there is reduced spindle coherence across the cortex (31). This reduced spindle coherence may reflect reduced modulation by slow oscillations, which are thought to synchronize spindles across the cortex in the service of memory consolidation (64,68).

SLEEP SPINDLE DEFICIT IN SZ

Three early studies of small samples ($n \leq 11$) of APD-naïve patients with a first episode of SZ (25,69) and unmedicated patients with SZ (70,71) did not find a spindle deficit (Table 1). However, a growing literature has reported marked reductions of spindle activity in medicated patients with chronic SZ (31,72–76) and medicated adolescents with early-onset SZ spectrum disorder (77). With the exception of increased sleep onset latency in two studies (74,75), the spindle deficit occurred in the context of normal sleep architecture and quality (e.g., efficiency, wake time after sleep onset), indicating that it is not secondary to sleep disruption. This contrast with reports of disrupted sleep in SZ (reviewed earlier) may reflect that sleep disruption primarily characterizes more acute phases of SZ and that APDs are sedating and tend to normalize sleep architecture (18). The effects of long-term APD treatment on spindles are unknown, but a single dose of olanzapine in SZ reduced spindle density (78), and acute administration of haloperidol to healthy participants did not affect spindle density (79).

A recent report extended the finding of reduced spindle density to APD-naïve patients with early-course SZ (but not to APD-naïve patients with a non-SZ psychotic disorder). A trend
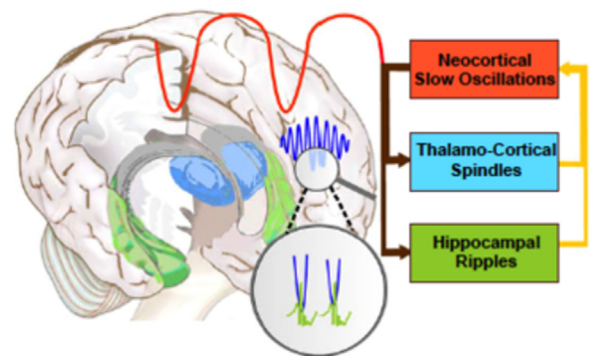

Figure 3. The coordination of sleep spindles with hippocampal ripples and neocortical slow oscillations in the service of consolidating new memories during sleep. During non–rapid eye movement sleep, neocortical slow oscillations drive the reactivation of hippocampal memory representations during sharp wave ripples (green) in the hippocampus together with spindles (blue) in the thalamic reticular nucleus (TRN). Hippocampal ripples nest in the troughs of spindles, which occur during the up states of slow oscillations. This dialogue between slow oscillations, spindles, and hippocampal ripples is thought to mediate the transfer of selected new memories from temporary dependence on the hippocampus to longer term representation in the neocortex (43). [Adapted with permission from Born and Wilhelm (150).]

Table 1. Studies of Spindle Density in Schizophrenia

Study	Medication Status	Patients (*n*)	Healthy Control Subjects (*n*)	Sleep Stage	Spindle Detection Method	Finding
Hiatt *et al.*, 1985 (71)	Unmedicated	5	5	Sampled from midpoints of NREM periods	Visual	Increased in NREM period 1
Van Cauter *et al.*,1991 (70)	Unmedicated	6	6	First NREM period	Visual	No difference
Poulin *et al.*, 2003 (25); Forest *et al.*, 2007 (69)[a]	APD-naïve	11	11	N2	Visual	No difference
Ferrarelli *et al.*, 2007 (74)[b]	Medicated	18	17	NREM during first sleep episode	Algorithm	Reduced
Ferrarelli *et al.*, 2010 (75)[b]	Medicated	49	44	NREM	Algorithm	Reduced
Manoach *et al.*, 2010 (73)	Medicated	14	15	N2	Algorithm	Reduced
Seeck-Hirschner *et al.*, 2011 (76)	Medicated	20	22	N2 during a nap	Visual	Reduced
Wamsley *et al.*, 2012 (31)	Medicated	21	17	N2	Algorithm	Reduced
Manoach *et al.*, 2014 (80)[c]	APD-naïve	15	25	N2	Algorithm	Reduced
Goder *et al.*, 2015 (72)	Medicated	16	16	N2	Algorithm and visual	Reduced
Tesler *et al.*, 2015 (77)[d]	Medicated	9	15	First hour of NREM	Algorithm	Reduced

APD, antipsychotic drug; NREM, non–rapid eye movement.

[a]The 8 patients reported in the study by Forest *et al.* are a subset of the 11 patients reported in the study by Poulin *et al.*

[b]Measures included spindle number and integrated spindle activity (calculated by integrating the absolute amplitude values of each spindle detected at every electrode, divided by the non-REM sleep duration) rather than density. Included psychiatric control groups whose integrated spindle activity was greater than patients with schizophrenia but did not differ from healthy control subjects.

[c]Included an APD-naïve nonschizophrenia psychotic control group (*n* = 11) whose spindle density was greater than patients with schizophrenia at a trend level and did not differ from healthy control subjects.

[d]Adolescents with early-onset schizophrenia spectrum disorder.

to reduced density and significantly reduced spindle amplitude was also seen in young (mean age, 14) nonpsychotic first-degree relatives of patients with SZ (80). These findings make it unlikely that the spindle deficit in SZ is due to APDs and suggest the possibility of diagnostic specificity, although replication in larger samples is necessary. Two other studies reported spindle deficits in SZ but not in a mixed psychiatric control group taking APDs (75) or in individuals with a history of depression (74), consistent with another report of normal spindles in depression (81). However, there are reports of various spindle abnormalities in other neurodevelopmental and neurodegenerative disorders characterized by cognitive impairment, including mental retardation (82), phenylketonuria (83), Williams' syndrome (84), autism (85,86), and Parkinson's disease with dementia (87). Whether the spindle deficits of SZ have unique characteristics and consequences remains to be determined.

Findings of spindle deficits throughout the course of SZ and in first-degree relatives implicate abnormal function of thalamocortical circuitry that may begin before the onset of SZ, consistent with the finding of reduced thalamic volume in adolescents at ultra-high risk for psychosis that correlates with sleep disturbance (12). This literature indicates that reduced spindle activity is unlikely to be secondary to APDs or chronicity and instead may be an endophenotype (a trait indicating genetic vulnerability) (88) of SZ.

REDUCED SPINDLES ARE ASSOCIATED WITH IMPAIRED COGNITION AND POSITIVE SYMPTOMS IN SZ

Although sleep is critical for memory, disrupted sleep impairs memory (89–91), and SZ is characterized by both abnormal

sleep and impaired memory, few studies have examined the connection. Emerging evidence suggests that reduced sleep spindles contribute to procedural and declarative memory impairments in SZ.

Using a well-validated probe of sleep-dependent motor procedural memory, the finger-tapping motor sequence task (Figure 4) (49,92), several studies demonstrated deficient sleep-dependent enhancement of motor learning in SZ. In healthy individuals, significant performance improvements occur after sleep but not while awake (49,93–95) and correlate with N2 duration (49) and spindle density (50,96,97). In contrast, medicated patients with chronic SZ fail to show significant sleep-dependent improvement despite normal learning during training (31,73,98–100), and this failure correlated with sleep spindle density in one study (31) but not in two others (73,100). Patients with SZ also show reduced sleep-dependent consolidation on a mirror tracing procedural motor task despite intact initial learning; this occurred in the context of reduced sleep spindles, but these deficits were not correlated (76). Sleep-dependent consolidation of declarative memory, tested with a picture recognition task, is also impaired and correlates with reduced sleep spindles (72). Spindle deficits also correlate with worse executive function and lower IQ in APD-naïve patients with early-course SZ and non-SZ psychotic disorders as well as in nonpsychotic first-degree relatives of patients with SZ (80).

A limitation of these studies is that the small sample sizes may leave them underpowered to detect meaningful effects and contribute to inconsistent findings. For example, in one motor sequence task study, the correlation between spindle density and overnight improvement in SZ was significant (r^{21} = .45, *p* = .04) (31), but in a smaller study with a similar effect size, it was not significant (r^{14} = .46, *p* = .10) (73).
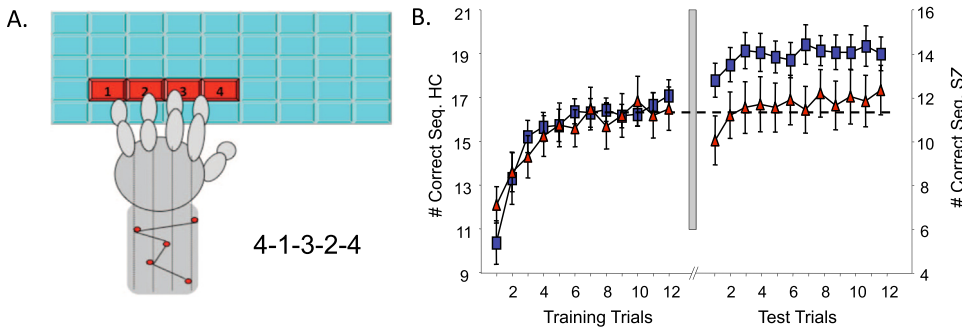
Figure 4. Finger-tapping motor sequence task. **(A)** The motor sequence task requires participants to type a 5-digit sequence (e.g., 4-1-3-2-4) repeatedly on a keyboard with the left hand "as quickly and accurately as possible" for 12 30-s trials separated by 30-s rest periods. Participants train before sleep and test on an additional 12 trials after sleep. The primary outcome measure is overnight improvement calculated as the percent increase in correctly typed sequences from the last three training trials to the first three test trials (49). **(B)** Sleep-dependent motor sequence task performance [data from Manoach *et al.* (98)]. (Left) At training, patients with schizophrenia (SZ; red triangles) and healthy control subjects (HC; blue squares) show a similar time course of improvement, although patients with SZ are slower overall (see y axis on right). (Right) Following a night of sleep, only the HC subjects show sleep-dependent improvement.

In summary, the evidence suggests that spindle deficits contribute to cognitive dysfunction in genetically high-risk individuals and in patients with early-course and chronic SZ, regardless of medications. These findings are congruent with the large basic literature showing robust correlations between spindle density and a range of cognitive measures including IQ (61).

If TRN dysfunction gives rise to spindle deficits in SZ, there may be other cognitive manifestations. The TRN is strategically positioned between other thalamic nuclei and the cortex to modulate thalamocortical interactions (Figure 2). Consequently, it plays an important role in waking cognition acting as an "attentional searchlight" (101). Different sectors of the TRN receive distinct inputs from the thalamus and neocortex and have distinct projections to thalamic nuclei (102,103). It is the TRN neurons that project to sensory rather than limbic thalamic nuclei that participate in spindle generation, in the inhibition of sensory processing during sleep, and in the augmentation of sensory processing during tasks requiring attention while awake (104). Schizophrenia is characterized by deficits in sensory gating (105), attentional modulation, and cortical gamma band oscillations, and all of these may depend on the modulation of the flow of information from the thalamus to the neocortex by the TRN (103,106,107). Abnormal cortical gamma oscillations in SZ are associated with cognitive deficits and are thought to reflect dysfunction of cortical parvalbumin-containing GABAergic interneurons (108), which are abnormal in SZ (109). Although there is a selective reduction of GABAergic parvalbumin interneurons in anteroventral thalamus (110), to our knowledge, TRN GABAergic parvalbumin neurons that generate spindles have not been studied. Dysfunction of the TRN in SZ may contribute to impairments in sensory gating, attention, and cortical gamma oscillations while awake and to spindle deficits during sleep.

Reduced spindle activity also correlates with increased positive symptom severity in medicated patients with early-onset SZ spectrum disorder (77) and in some (31,75), but not all (72), studies of medicated patients with chronic SZ. However, in APD-naïve patients with early-course SZ, reduced spindle density correlated with *decreased* positive symptoms (80). The opposite direction of these correlations may reflect differences in the pathophysiologic underpinnings of positive symptoms. In medicated patients with chronic SZ, residual positive symptoms have not responded to dopaminergic medications and may arise from GABA or NMDA hypofunction (111), whereas in patients with early untreated SZ, positive symptoms generally respond to APDs and may reflect dopamine hyperactivity (112). In healthy individuals, spindle density inversely correlates with magical ideation, an index of liability to delusional beliefs, and with glutamine and glutamate levels in the thalamus (113). Schizotypal traits, such as magical ideation, exist on a continuum in the general population and may share neural substrates with the psychotic symptoms of SZ. Although the mechanistic link of spindles to positive symptoms is less clear than the link for memory, both may reflect abnormal thalamocortical circuit function (114).

SLEEP SPINDLES AS A NOVEL TREATMENT BIOMARKER FOR IMPROVING COGNITION IN SZ

Cognitive deficits are the strongest predictor of functional outcome in SZ (115). Even after florid psychotic symptoms are controlled with APDs, debilitating cognitive deficits persist, and only ~20% of individuals with SZ are able to work (116). Although ameliorating cognitive deficits is a priority of the SZ research community, effective treatments are lacking (117). A better understanding of the pathophysiology of cognitive deficits is needed to guide the development of new treatments.

Although most data linking sleep spindles to cognitive impairments are correlational, more recent work supports a causal role for spindles in memory consolidation. In preliminary reports, optogenetic excitation of TRN neurons in mice increased sleep spindles and improved memory, whereas inhibiting TRN neurons decreased spindles and worsened memory (118,119). In healthy humans, increasing spindles with zolpidem (120,121), increasing sigma activity with transcranial stimulation (122,123), and enhancing the synchronization of sigma activity with slow oscillations using auditory closed-loop stimulation (68) all improve memory, whereas transcranial stimulation that decreases sigma activity impairs memory (124).

Only a few studies have attempted to improve cognition in SZ by manipulating spindles. In a small sample of patients, transcranial stimulation during N2 did not significantly alter sleep parameters, but it improved word list recall (125).

In a small preliminary study, eszopiclone, which acts on GABAergic neurons in the TRN (126), significantly increased spindles in SZ, but not sleep-dependent memory (127). In another study that did not include polysomnography, eszopiclone improved working memory in SZ, but not symptoms (128). This body of work provides an impetus to develop and test novel therapies for spindle deficits to improve cognition.

GENETIC MECHANISMS OF SLEEP SPINDLES

In twin studies, EEG sigma power is highly heritable (heritability estimate of 96%) (129) and shows high interindividual variability and within-individual stability, leading to its description as an "electrophysiological fingerprint" (129–131). Despite their high heritability, little is known about the genetic underpinnings of sleep spindles. Genome-wide association studies (GWAS) have been conducted for sleep disorders (132), sleep duration (133), and insomnia (134), but genetic studies of the sleep EEG used relatively small samples and only a few candidate genes (135). To understand genetic contributions to spindle deficits in SZ, it is important to conduct well-powered genetic studies of spindles in humans.

Like most human traits, sleep spindles likely have a complex genetic architecture, with allelic variants in many genes combining to influence spindle expression. GWAS with large sample sizes can capture the genetic variation resulting from common alleles. Alleles identified with statistical confidence can then help to establish the broader gene networks that underlie variation in spindles. GWAS data can also be used to estimate genetic correlations between pairs of traits or diseases: the extent to which genetic influences on one trait are shared by a second trait. If spindle deficits are an endophenotype of SZ, one would expect a significant degree of shared genetic influences (as genes that influence spindles will indirectly influence SZ risk). Contrasting the genetic association profiles across spindles, SZ, related disorders, and sleep phenotypes may illuminate causal relationships between these traits. It is now also feasible to sequence the entire exome or genome in large numbers of individuals—an approach that can identify rare variants that may have larger effects on spindles because rare variants are likely to have arisen recently (and might even be de novo in the proband) and are less subject than common variants to natural selection (136).

Recent genetic studies provide clues to potential mechanistic links between spindles and SZ. For example, the largest SZ GWAS to date (137) implicated common variants in *CACNA1I* in SZ risk. In addition, two missense de novo mutations of *CACNA1I* were identified in individuals with SZ in a trio study, although not at rates statistically above chance (138). *CACNA1I* encodes a T-type calcium channel (Cav3.3) expressed only in the brain and particularly in the TRN (139) (Allen Mouse Brain Atlas, available at mouse.brain-map.org;

GTEx, available at www.gtexportal.org), where it interacts with sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPases and small-conductance (SK)–type potassium channels to shape delta and sigma frequency oscillations (140). Analysis of the two de novo mutations found in SZ revealed that the R1346H variant produces a channel with defective protein maturation and channel trafficking, leading to reduced whole-cell currents in a heterologous expression system (manuscript in preparation). This reduction would be expected to reduce the overall expression of Cav3.3 and consequently the burst firing necessary for spindles. Consistent with this, knocking out *CACNA1I* in mice causes a spindle deficit (141). Studies now underway are examining the effects of *CACNA1I* on sleep spindles in humans and whether Cav3.3 channels are viable therapeutic targets. This evidence places reduced sleep spindle activity, a heritable component of the sleep EEG, and a putative endophenotype of SZ that may contribute to cognitive impairment and symptoms, in a hypothetical causal chain from risk gene to diagnosis (Figure 5).

CONCLUSIONS

This review expands current models of cognitive deficits in SZ by highlighting the importance of deficient sleep–dependent consolidation of procedural and declarative memory. It implicates reduced sleep spindles as a mechanism and suggests novel pathophysiologic targets for treatment. Going forward, we propose several potentially fruitful avenues of research.

First, it will be important to define the scope and consequences of the sleep-dependent memory deficit in SZ. Findings of dissociations (e.g., reduced motor procedural memory in the context of intact spatial memory) (76) suggest that only certain memory types are affected, perhaps those that rely on spindles. It will also be important to understand how memory deficits affect daily function. We have proposed that the sleep-dependent procedural memory deficit represents a breakdown of task automation (98,142), which normally renders performance faster, less variable, and less dependent on voluntary attention (143). A failure of automation requires the allocation of attentional resources to task demands that should have been automated by sleep, leaving fewer resources available for higher order task demands. The interaction between automatic and effortful processes is what allows a brain with limited capacity to carry out complex cognitive tasks. An impairment in sleep-dependent automation could contribute to the generalized cognitive deficits that are a hallmark of SZ (144), and treating it could improve function.

The work reviewed has implications for the development and testing of novel therapies to improve cognition, including pharmacologic and transcranial stimulation approaches. Because standard neuropsychological tests assess function
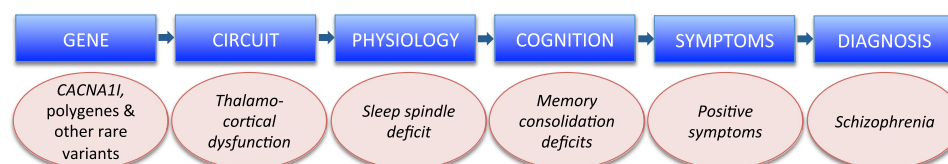

Figure 5. Hypothetical causal chain. The spindle deficit, a candidate endophenotype of schizophrenia, may link risk genes to fundamental cognitive deficits, symptoms, and diagnosis.

GENE → CIRCUIT → PHYSIOLOGY → COGNITION → SYMPTOMS → DIAGNOSIS

CACNA1I, polygenes & other rare variants | *Thalamo-cortical dysfunction* | *Sleep spindle deficit* | *Memory consolidation deficits* | *Positive symptoms* | *Schizophrenia*

in a single session, they miss critical aspects of learning and memory that depend on sleep. Accordingly, it will be important to include probes of sleep-dependent memory in clinical trials. In addition to increasing spindles in SZ, interventions may have to preserve or correct the temporal coordination of spindles with neocortical slow waves and hippocampal ripples to improve memory. It is unclear whether this orchestration of NREM sleep oscillations is preserved in SZ, and animal models are necessary to measure all three oscillations simultaneously. Understanding the pathophysiology and genetic mechanisms of spindle deficits in relation to memory in SZ can guide treatment development.

To evaluate the spindle deficit as an endophenotype it is important to determine its specificity to SZ and to establish its heritability and genetic architecture in larger studies. An impediment to large-scale genetic studies of spindles is the prohibitive cost and difficulty of conducting sleep studies. For this reason, it would be useful to develop waking assays of TRN function to serve as more accessible surrogate markers of spindle activity. Activity of the TRN has seldom been examined in vivo in humans because its size and location make it difficult to identify with neuroimaging (145). Animal models can illuminate the contribution of the TRN to waking cognition and its role in development. The TRN and spindles are thought to contribute to the development of thalamocortical connectivity and synaptic refinement (146,147), processes that may go awry in SZ (148,149).

In summary, cross-disciplinary research can foster a more complete understanding of the relationship of sleep spindles to cognition and SZ and can identify pathophysiologic targets for treatment. This line of work, by forging empirical links in causal chains from SZ risk genes to cellular and circuit dysfunction to spindle deficits, impaired memory, symptoms, and diagnosis, provides unprecedented opportunities to advance our understanding of the genetics and pathophysiology of SZ and could lead to improved treatment and possibly even prevention.

ARTICLE INFORMATION

From the Department of Psychiatry (DSM) and Psychiatric and Neuro-developmental Genetics Unit, Analytic and Translational Genetics Unit (SMP), Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; Athinoula A. Martinos Center for Biomedical Imaging (DSM), Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachusetts; Stanley Center for Psychiatric Research (DSM, JQP, SMP, RS), Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts; Division of Psychiatric Genomics (SMP), Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY; and Department of Psychiatry (RS), Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.

Address correspondence to Dara S. Manoach, Ph.D., Massachusetts General Hospital, 149 13th Street, Room 1.111, Charlestown, MA 02129; E-mail: dara@nmr.mgh.harvard.edu.

Received Jul 13, 2015; revised Sep 18, 2015; accepted Oct 5, 2015.

REFERENCES

1. Tyler DB (1955): Psychological changes during experimental sleep deprivation. Dis Nerv Syst 16:293–299.
2. Wehr TA, Sack DA, Rosenthal NE (1987): Sleep reduction as a final common pathway in the genesis of mania. Am J Psychiatry 144:201–204.
3. Breslau N, Roth T, Rosenthal L, Andreski P (1996): Sleep disturbance and psychiatric disorders: A longitudinal epidemiological study of young adults. Biol Psychiatry 39:411–418.
4. Huang YS, Guilleminault C, Li HY, Yang CM, Wu YY, Chen NH (2007): Attention-deficit/hyperactivity disorder with obstructive sleep apnea: A treatment outcome study. Sleep Med 8:18–30.
5. Germain A, Buysse DJ, Nofzinger E (2008): Sleep-specific mechanisms underlying posttraumatic stress disorder: Integrative review and neurobiological hypotheses. Sleep Med Rev 12:185–195.
6. Sateia MJ (2009): Update on sleep and psychiatric disorders. Chest 135:1370–1379.
7. Fava M, McCall WV, Krystal A, Wessel T, Rubens R, Caron J, et al. (2006): Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. Biol Psychiatry 59:1052–1060.
8. Kraepelin E (1919): Dementia Praecox and Paraphrenia. Edinburgh, Scotland: E.S. Livingston.
9. Hofstetter JR, Lysaker PH, Mayeda AR (2005): Quality of sleep in patients with schizophrenia is associated with quality of life and coping. BMC Psychiatry 5:13.
10. Goldman M, Tandon R, DeQuardo JR, Taylor SF, Goodson J, McGrath M (1996): Biological predictors of 1-year outcome in schizophrenia in males and females. Schizophr Res 21:65–73.
11. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. (2005): Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353:1209–1223.
12. Lunsford-Avery JR, Orr JM, Gupta T, Pelletier-Baldelli A, Dean DJ, Smith Watts AK, et al. (2013): Sleep dysfunction and thalamic abnormalities in adolescents at ultra high-risk for psychosis. Schizophr Res 151:148–153.
13. Miller TJ, Zipursky RB, Perkins D, Addington J, Woods SW, Hawkins KA, et al. (2003): The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. II. Baseline characteristics of the "prodromal" sample. Schizophr Res 61:19–30.
14. Keshavan MS, Diwadkar VA, Montrose DM, Stanley JA, Pettegrew JW (2004): Premorbid characterization in schizophrenia: the Pittsburgh High Risk Study. World Psychiatry 3:163–168.
15. Benson KL (2015): Sleep in schizophrenia: Pathology and treatment. Sleep Med Clin 10:49–55.
16. Dencker SJ, Malm U, Lepp M (1986): Schizophrenic relapse after drug withdrawal is predictable. Acta Psychiatr Scand 73:181–185.
17. Chouinard S, Poulin J, Stip E, Godbout R (2004): Sleep in untreated patients with schizophrenia: A meta-analysis. Schizophr Bull 30:957–967.
18. Krystal AD, Goforth HW, Roth T (2008): Effects of antipsychotic medications on sleep in schizophrenia. Int Clin Psychopharmacol 23:150–160.
19. Nofzinger EA, van Kammen DP, Gilbertson MW, Gurklis JA, Peters JL (1993): Electroencephalographic sleep in clinically stable schizophrenic patients: Two-weeks versus six-weeks neuroleptic-free. Biol Psychiatry 33:829–835.
20. Chemerinski E, Ho BC, Flaum M, Arndt S, Fleming F, Andreasen NC (2002): Insomnia as a predictor for symptom worsening following antipsychotic withdrawal in schizophrenia. Compr Psychiatry 43:393–396.
21. Benca RM, Obermeyer WH, Thisted RA, Gillin JC (1992): Sleep and psychiatric disorders. A meta-analysis. Arch Gen Psychiatry 49:651–668; discussion 669–670.
22. Rao ML, Gross G, Strebel B, Halaris A, Huber G, Braunig P, et al. (1994): Circadian rhythm of tryptophan, serotonin, melatonin, and pituitary hormones in schizophrenia. Biol Psychiatry 35:151–163.

23. Iber C, Ancoli-Israel S, Chesson AL, Quan SF (2007): The AASM Manual for the Scoring of Sleep and Associated Events: Rules. 2nd ed.In: Terminology, and Technical Specifications. Westchester, IL: American Academy of Sleep Medicine.

24. Feinberg I, Braun M, Koresko RL, Gottlieb F (1969): Stage 4 sleep in schizophrenia. Arch Gen Psychiatry 21:262–266.

25. Poulin J, Daoust AM, Forest G, Stip E, Godbout R (2003): Sleep architecture and its clinical correlates in first episode and neuroleptic-naive patients with schizophrenia. Schizophr Res 62:147–153.

26. Yang C, Winkelman JW (2006): Clinical significance of sleep EEG abnormalities in chronic schizophrenia. Schizophr Res 82:251–260.

27. Keshavan MS, Reynolds CF 3rd, Miewald MJ, Montrose DM, Sweeney JA, Vasko RC Jr, et al. (1998): Delta sleep deficits in schizophrenia: Evidence from automated analyses of sleep data. Arch Gen Psychiatry 55:443–448.

28. Tandon R, Shipley JE, Taylor S, Greden JF, Eiser A, DeQuardo J, et al. (1992): Electroencephalographic sleep abnormalities in schizophrenia. Relationship to positive/negative symptoms and prior neuroleptic treatment. Arch Gen Psychiatry 49:185–194.

29. Lauer CJ, Schreiber W, Pollmacher T, Holsboer F, Krieg JC (1997): Sleep in schizophrenia: A polysomnographic study on drug-naive patients. Neuropsychopharmacology 16:51–60.

30. De Gennaro L, Ferrara M (2003): Sleep spindles: An overview. Sleep Med Rev 7:423–440.

31. Wamsley E, Tucker MA, Shinn AK, Ono KE, McKinley S, Ely AV, et al. (2012): Reduced sleep spindles and spindle coherence in schizophrenia: Mechanisms of impaired memory consolidation? Biol Psychiatry 71:154–161.

32. Guillery RW, Harting JK (2003): Structure and connections of the thalamic reticular nucleus: Advancing views over half a century. J Comp Neurol 463:360–371.

33. Houser CR, Vaughn JE, Barber RP, Roberts E (1980): GABA neurons are the major cell type of the nucleus reticularis thalami. Brain Res 200:341–354.

34. Jacobsen RB, Ulrich D, Huguenard JR (2001): GABA(B) and NMDA receptors contribute to spindle-like oscillations in rat thalamus in vitro. J Neurophysiol 86:1365–1375.

35. Fuentealba P, Steriade M (2005): The reticular nucleus revisited: Intrinsic and network properties of a thalamic pacemaker. Prog Neurobiol 75:125–141.

36. Steriade M, Domich L, Oakson G, Deschenes M (1987): The deafferented reticular thalamic nucleus generates spindle rhythmicity. J Neurophysiol 57:260–273.

37. Contreras D, Destexhe A, Sejnowski TJ, Steriade M (1996): Control of spatiotemporal coherence of a thalamic oscillation by corticothalamic feedback. Science 274:771–774.

38. Sherman SM, Guillery RW (2006): Exploring the Thalamus and Its Role in Cortical Function, 2nd ed. Cambridge, MA: The MIT Press.

39. Contreras D, Steriade M (1996): Spindle oscillation in cats: The role of corticothalamic feedback in a thalamically generated rhythm. J Physiol 490(pt 1):159–179.

40. Zhang Y, Llinas RR, Lisman JE (2009): Inhibition of NMDARs in the nucleus reticularis of the thalamus produces delta frequency bursting. Front Neural Circuits 3:20.

41. Smith RE, Haroutunian V, Davis KL, Meador-Woodruff JH (2001): Expression of excitatory amino acid transporter transcripts in the thalamus of subjects with schizophrenia. Am J Psychiatry 158:1393–1399.

42. Dave AS, Yu AC, Margoliash D (1998): Behavioral state modulation of auditory activity in a vocal motor system. Science 282:2250–2254.

43. Siapas AG, Wilson MA (1998): Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. Neuron 21:1123–1128.

44. Frank MG, Issa NP, Stryker MP (2001): Sleep enhances plasticity in the developing visual cortex. Neuron 30:275–287.

45. Stickgold R, Walker MP (2013): Sleep-dependent memory triage: Evolving generalization through selective processing. Nat Neurosci 16:139–145.

46. Sejnowski TJ, Destexhe A (2000): Why do we sleep? Brain Res 886:208–223.

47. Ghosh A, Greenberg ME (1995): Calcium signaling in neurons: Molecular mechanisms and cellular consequences. Science 268:239–247.

48. Rosanova M, Ulrich D (2005): Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. J Neurosci 25:9398–9405.

49. Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R (2002): Practice with sleep makes perfect: Sleep-dependent motor skill learning. Neuron 35:205–211.

50. Nishida M, Walker MP (2007): Daytime naps, motor memory consolidation and regionally specific sleep spindles. PLoS One 2:e341.

51. Rasch B, Pommer J, Diekelmann S, Born J (2008): Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. Nat Neurosci 12:396–397.

52. Tamaki M, Matsuoka T, Nittono H, Hori T (2008): Fast sleep spindle (13-15 Hz) activity correlates with sleep-dependent improvement in visuomotor performance. Sleep 31:204–211.

53. Fogel SM, Smith CT (2006): Learning-dependent changes in sleep spindles and stage 2 sleep. J Sleep Res 15:250–255.

54. Peters KR, Ray L, Smith V, Smith C (2008): Changes in the density of stage 2 sleep spindles following motor learning in young and older adults. J Sleep Res 17:23–33.

55. Clemens Z, Fabo D, Halasz P (2006): Twenty-four hours retention of visuospatial memory correlates with the number of parietal sleep spindles. Neurosci Lett 403:52–56.

56. Clemens Z, Fabo D, Halasz P (2005): Overnight verbal memory retention correlates with the number of sleep spindles. Neuroscience 132:529–535.

57. Schabus M, Hoedlmoser K, Pecherstorfer T, Anderer P, Gruber G, Parapatics S, et al. (2008): Interindividual sleep spindle differences and their relation to learning-related enhancements. Brain Res 1191:127–135.

58. Tamaki M, Huang TR, Yotsumoto Y, Hamalainen M, Lin FH, Nanez JE Sr, et al. (2013): Enhanced spontaneous oscillations in the supplementary motor area are associated with sleep-dependent offline learning of finger-tapping motor-sequence task. J Neurosci 33:13894–13902.

59. Johnson LA, Blakely T, Hermes D, Hakimian S, Ramsey NF, Ojemann JG (2012): Sleep spindles are locally modulated by training on a brain-computer interface. Proc Natl Acad Sci U S A 109:18583–18588.

60. Bang JW, Khalilzadeh O, Hamalainen M, Watanabe T, Sasaki Y (2014): Location specific sleep spindle activity in the early visual areas and perceptual learning. Vision Res 99:162–171.

61. Fogel SM, Smith CT (2011): The function of the sleep spindle: A physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. Neurosci Biobehav Rev 35:1154–1165.

62. Schabus M, Hodlmoser K, Gruber G, Sauter C, Anderer P, Klosch G, et al. (2006): Sleep spindle-related activity in the human EEG and its relation to general cognitive and learning abilities. Eur J Neurosci 23:1738–1746.

63. Lustenberger C, Maric A, Durr R, Achermann P, Huber R (2012): Triangular relationship between sleep spindle activity, general cognitive ability and the efficiency of declarative learning. PLoS One 7:e49561.

64. Molle M, Born J (2011): Slow oscillations orchestrating fast oscillations and memory consolidation. Prog Brain Res 193:93–110.

65. Clemens Z, Molle M, Eross L, Barsi P, Halasz P, Born J (2007): Temporal coupling of parahippocampal ripples, sleep spindles and slow oscillations in humans. Brain 130:2868–2878.

66. Andrade KC, Spoormaker VI, Dresler M, Wehrle R, Holsboer F, Samann PG, et al. (2011): Sleep spindles and hippocampal functional connectivity in human NREM sleep. J Neurosci 31:10331–10339.

67. Phillips KG, Bartsch U, McCarthy AP, Edgar DM, Tricklebank MD, Wafford KA, et al. (2012): Decoupling of sleep-dependent cortical

and hippocampal interactions in a neurodevelopmental model of schizophrenia. Neuron 76:526–533.

68. Ngo HV, Martinetz T, Born J, Molle M (2013): Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. Neuron 78:545–553.

69. Forest G, Poulin J, Daoust AM, Lussier I, Stip E, Godbout R (2007): Attention and non-REM sleep in neuroleptic-naive persons with schizophrenia and control participants. Psychiatry Res 149:33–40.

70. Van Cauter E, Linkowski P, Kerkhofs M, Hubain P, L'Hermite-Baleriaux M, Leclercq R, et al. (1991): Circadian and sleep-related endocrine rhythms in schizophrenia. Arch Gen Psychiatry 48:348–356.

71. Hiatt JF, Floyd TC, Katz PH, Feinberg I (1985): Further evidence of abnormal non-rapid-eye-movement sleep in schizophrenia. Arch Gen Psychiatry 42:797–802.

72. Goder R, Graf A, Ballhausen F, Weinhold S, Baier PC, Junghanns K, et al. (2015): Impairment of sleep-related memory consolidation in schizophrenia: relevance of sleep spindles? Sleep Med 16:564–569.

73. Manoach DS, Thakkar KN, Stroynowski E, Ely A, McKinley SK, Wamsley E, et al. (2010): Reduced overnight consolidation of procedural learning in chronic medicated schizophrenia is related to specific sleep stages. J Psychiatr Res 44:112–120.

74. Ferrarelli F, Huber R, Peterson MJ, Massimini M, Murphy M, Riedner BA, et al. (2007): Reduced sleep spindle activity in schizophrenia patients. Am J Psychiatry 164:483–492.

75. Ferrarelli F, Peterson MJ, Sarasso S, Riedner BA, Murphy MJ, Benca RM, et al. (2010): Thalamic dysfunction in schizophrenia suggested by whole-night deficits in slow and fast spindles. Am J Psychiatry 167:1339–1348.

76. Seeck-Hirschner M, Baier PC, Sever S, Buschbacher A, Aldenhoff JB, Goder R (2011): Effects of daytime naps on procedural and declarative memory in patients with schizophrenia. J Psychiatr Res 44:42–47.

77. Tesler N, Gerstenberg M, Franscini M, Jenni OG, Walitza S, Huber R (2015): Reduced sleep spindle density in early onset schizophrenia: A preliminary finding. Schizophr Res 166:355–357.

78. Goder R, Fritzer G, Gottwald B, Lippmann B, Seeck-Hirschner M, Serafin I, et al. (2008): Effects of olanzapine on slow wave sleep, sleep spindles and sleep-related memory consolidation in schizophrenia. Pharmacopsychiatry 41:92–99.

79. Hirshkowitz M, Thornby JI, Karacan I (1982): Sleep spindles: Pharmacological effects in humans. Sleep 5:85–94.

80. Manoach DS, Demanuele C, Wamsley EJ, Vangel M, Montrose DM, Miewald J, et al. (2014): Sleep spindle deficits in antipsychotic-naïve early course schizophrenia and in non-psychotic first-degree relatives. Front Hum Neurosci 8:762.

81. Plante DT, Goldstein MR, Landsness EC, Peterson MJ, Riedner BA, Ferrarelli F, et al. (2013): Topographic and sex-related differences in sleep spindles in major depressive disorder: A high-density EEG investigation. J Affect Disord 146:120–125.

82. Shibagaki M, Kiyono S, Watanabe K (1982): Spindle evolution in normal and mentally retarded children: A review. Sleep 5:47–57.

83. De Giorgis GF, Nonnis E, Crocioni F, Gregori P, Rosini MP, Leuzzi V, et al. (1996): Evolution of daytime quiet sleep components in early treated phenylketonuric infants. Brain Dev 18:201–206.

84. Bodizs R, Gombos F, Kovacs I (2012): Sleep EEG fingerprints reveal accelerated thalamocortical oscillatory dynamics in Williams syndrome. Res Dev Disabil 33:153–164.

85. Limoges E, Mottron L, Bolduc C, Berthiaume C, Godbout R (2005): Atypical sleep architecture and the autism phenotype. Brain 128:1049–1061.

86. Tessier S, Lambert A, Chicoine M, Scherzer P, Soulieres I, Godbout R (2015): Intelligence measures and stage 2 sleep in typically-developing and autistic children. Int J Psychophysiol 97:58–65.

87. Latreille V, Carrier J, Lafortune M, Postuma RB, Bertrand JA, Panisset M, et al. (2015): Sleep spindles in Parkinson's disease may predict the development of dementia. Neurobiol Aging 36:1083–1090.

88. Gottesman II, Gould TD (2003): The endophenotype concept in psychiatry: Etymology and strategic intentions. Am J Psychiatry 160:636–645.

89. Chee MW, Chuah LY (2008): Functional neuroimaging insights into how sleep and sleep deprivation affect memory and cognition. Curr Opin Neurol 21:417–423.

90. Stickgold R, Walker MP (2007): Sleep-dependent memory consolidation and reconsolidation. Sleep Med 8:331–343.

91. Cipolli C, Mazzetti M, Plazzi G (2013): Sleep-dependent memory consolidation in patients with sleep disorders. Sleep Med Rev 17:91–103.

92. Karni A, Meyer G, Rey-Hipolito C, Jezzard P, Adams MM, Turner R, et al. (1998): The acquisition of skilled motor performance: Fast and slow experience-driven changes in primary motor cortex. Proc Natl Acad Sci U S A 95:861–868.

93. Gregory M, Agam Y, Selvadurai C, Nagy A, Vangel M, Tucker M, et al. (2014): Resting state connectivity immediately following learning correlates with subsequent sleep-dependent enhancement of motor task performance. Neuroimage 102(pt 2):666–673.

94. Walker MP, Brakefield T, Seidman J, Morgan A, Hobson JA, Stickgold R (2003): Sleep and the time course of motor skill learning. Learn Mem 10:275–284.

95. Fischer S, Nitschke MF, Melchert UH, Erdmann C, Born J (2005): Motor memory consolidation in sleep shapes more effective neuronal representations. J Neurosci 25:11248–11255.

96. Barakat M, Doyon J, Debas K, Vandewalle G, Morin A, Poirier G, et al. (2011): Fast and slow spindle involvement in the consolidation of a new motor sequence. Behav Brain Res 217:117–121.

97. Albouy G, Fogel S, Pottiez H, Nguyen VA, Ray L, Lungu O, et al. (2013): Daytime sleep enhances consolidation of the spatial but not motoric representation of motor sequence memory. PLoS One 8:e52805.

98. Manoach DS, Cain MS, Vangel MG, Khurana A, Goff DC, Stickgold R (2004): A failure of sleep-dependent procedural learning in chronic, medicated schizophrenia. Biol Psychiatry 56:951–956.

99. Genzel L, Ali E, Dresler M, Steiger A, Tesfaye M (2011): Sleep-dependent memory consolidation of a new task is inhibited in psychiatric patients. J Psychiatr Res 45:555–560.

100. Genzel L, Dresler M, Cornu M, Jager E, Konrad B, Adamczyk M, et al. (2015): Medial prefrontal-hippocampal connectivity and motor memory consolidation in depression and schizophrenia. Biol Psychiatry 77:177–186.

101. Crick F (1984): Function of the thalamic reticular complex: The searchlight hypothesis. Proc Natl Acad Sci U S A 81:4586–4590.

102. Zikopoulos B, Barbas H (2012): Pathways for emotions and attention converge on the thalamic reticular nucleus in primates. J Neurosci 32:5338–5350.

103. Pinault D (2004): The thalamic reticular nucleus: Structure, function and concept. Brain Res Rev 46:1–31.

104. Halassa MM, Chen Z, Wimmer RD, Brunetti PM, Zhao S, Zikopoulos B, et al. (2014): State-dependent architecture of thalamic reticular subnetworks. Cell 158:808–821.

105. Bramon E, Rabe-Hesketh S, Sham P, Murray RM, Frangou S (2004): Meta-analysis of the P300 and P50 waveforms in schizophrenia. Schizophr Res 70:315–329.

106. Ahrens S, Jaramillo S, Yu K, Ghosh S, Hwang GR, Paik R, et al. (2015): ErbB4 regulation of a thalamic reticular nucleus circuit for sensory selection. Nat Neurosci 18:104–111.

107. McAlonan K, Brown VJ, Bowman EM (2000): Thalamic reticular nucleus activation reflects attentional gating during classical conditioning. J Neurosci 20:8897–8901.

108. Uhlhaas PJ, Singer W (2010): Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci 11:100–113.

109. Hashimoto T, Volk DW, Eggan SM, Mirnics K, Pierri JN, Sun Z, et al. (2003): Gene expression deficits in a subclass of GABA neurons in the prefrontal cortex of subjects with schizophrenia. J Neurosci 23:6315–6326.

110. Danos P, Baumann B, Bernstein HG, Franz M, Stauch R, Northoff G, et al. (1998): Schizophrenia and anteroventral thalamic nucleus: selective

decrease of parvalbumin-immunoreactive thalamocortical projection neurons. Psychiatry Res 82:1–10.

111. Demjaha A, Egerton A, Murray RM, Kapur S, Howes OD, Stone JM, *et al*. (2014): Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. Biol Psychiatry 75:e11–e13.

112. Keshavan MS (1999): Development, disease and degeneration in schizophrenia: A unitary pathophysiological model. J Psychiatr Res 33:513–521.

113. Lustenberger C, O'Gorman RL, Pugin F, Tushaus L, Wehrle F, Achermann P, *et al*. (2015): Sleep spindles are related to schizotypal personality traits and thalamic glutamine/glutamate in healthy subjects. Schizophr Bull 41:522–531.

114. Vukadinovic Z (2011): Sleep abnormalities in schizophrenia may suggest impaired trans-thalamic cortico-cortical communication: Towards a dynamic model of the illness. Eur J Neurosci 34:1031–1039.

115. Green MF, Kern RS, Braff DL, Mintz J (2000): Neurocognitive deficits and functional outcome in schizophrenia: Are we measuring the "right stuff"? Schizophr Bull 26:119–136.

116. Insel TR (2009): Translating scientific opportunity into public health impact: A strategic plan for research on mental illness. Arch Gen Psychiatry 66:128–133.

117. Sergi MJ, Green MF, Widmark C, Reist C, Erhart S, Braff DL, *et al*. (2007): Social cognition [corrected] and neurocognition: Effects of risperidone, olanzapine, and haloperidol. Am J Psychiatry 164:1585–1592.

118. Shin H (2015): Optogenetic induced spindles alter sleep architecture in mice. Presented at the World Congress on Sleep Medicine, March 21–25, Seoul, Korea.

119. McCarley R, Thankachan S, McNally J, McKenna J, Strecker R, Brown R (2014): Optogenetic study of the role of parvalbumin-containing thalamic reticular nucleus neurons in spindle generation: Implications for schizophrenia. Presented at the American College of Neuropsychopharmacology Annual Meeting, December 7–11, Phoenix, Arizona.

120. Kaestner EJ, Wixted JT, Mednick SC (2013): Pharmacologically increasing sleep spindles enhances recognition for negative and high-arousal memories. J Cogn Neurosci 25:1597–1610.

121. Mednick SC, McDevitt EA, Walsh JK, Wamsley E, Paulus M, Kanady JC, *et al*. (2013): The critical role of sleep spindles in hippocampal-dependent memory: A pharmacology study. J Neurosci 33:4494–4504.

122. Marshall L, Helgadottir H, Molle M, Born J (2006): Boosting slow oscillations during sleep potentiates memory. Nature 444:610–613.

123. Del Felice A, Magalini A, Masiero S (2015): Slow-oscillatory transcranial direct current stimulation modulates memory in temporal lobe epilepsy by altering sleep spindle generators: A possible rehabilitation tool. Brain Stimul 8:567–573.

124. Marshall L, Kirov R, Brade J, Molle M, Born J (2011): Transcranial electrical currents to probe EEG brain rhythms and memory consolidation during sleep in humans. PLoS One 6:e16905.

125. Goder R, Baier PC, Beith B, Baecker C, Seeck-Hirschner M, Junghanns K, *et al*. (2013): Effects of transcranial direct current stimulation during sleep on memory performance in patients with schizophrenia. Schizophr Res 144:153–154.

126. Jia F, Goldstein PA, Harrison NL (2009): The modulation of synaptic GABA(A) receptors in the thalamus by eszopiclone and zolpidem. J Pharmacol Exp Ther 328:1000–1006.

127. Wamsley EJ, Shinn AK, Tucker MA, Ono KE, McKinley SK, Ely AV, *et al*. (2013): The effects of eszopiclone on sleep spindles and memory consolidation in schizophrenia: A randomized placebo-controlled trial. Sleep 36:1369–1376.

128. Tek C, Palmese LB, Krystal AD, Srihari VH, DeGeorge PC, Reutenauer EL, *et al*. (2014): The impact of eszopiclone on sleep and cognition in patients with schizophrenia and insomnia: A double-blind, randomized, placebo-controlled trial. Schizophr Res 160:180–185.

129. De Gennaro L, Marzano C, Fratello F, Moroni F, Pellicciari MC, Ferlazzo F, *et al*. (2008): The electroencephalographic fingerprint of sleep is genetically determined: a twin study. Ann Neurol 64:455–460.

130. Ambrosius U, Lietzenmaier S, Wehrle R, Wichniak A, Kalus S, Winkelmann J, *et al*. (2008): Heritability of sleep electroencephalogram. Biol Psychiatry 64:344–348.

131. Hori A (1986): Sleep characteristics in twins. Jpn J Psychiatry Neurol 40:35–46.

132. Raizen DM, Wu MN (2011): Genome-wide association studies of sleep disorders. Chest 139:446–452.

133. Parsons MJ, Lester KJ, Barclay NL, Nolan PM, Eley TC, Gregory AM (2013): Replication of genome-wide association studies (GWAS) loci for sleep in the British G1219 cohort. Am J Med Genet B Neuropsychiatr Genet 162:431–438.

134. Byrne EM, Gehrman PR, Medland SE, Nyholt DR, Heath AC, Madden PA, *et al*. (2013): A genome-wide association study of sleep habits and insomnia. Am J Med Genet B Neuropsychiatr Genet 162:439–451.

135. Landolt HP (2011): Genetic determination of sleep EEG profiles in healthy humans. Prog Brain Res 193:51–61.

136. Veltman JA, Brunner HG (2012): De novo mutations in human genetic disease. Nat Rev Genet 13:565–575.

137. Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014): Biological insights from 108 schizophrenia-associated genetic loci. Nature 511:421–427.

138. Gulsuner S, Walsh T, Watts AC, Lee MK, Thornton AM, Casadei S, *et al*. (2013): Spatial and temporal mapping of de novo mutations in schizophrenia to a fetal prefrontal cortical network. Cell 154:518–529.

139. Liu XB, Murray KD, Jones EG (2011): Low-threshold calcium channel subunit Ca(v) 3.3 is specifically localized in GABAergic neurons of rodent thalamus and cerebral cortex. J Comp Neurol 519:1181–1195.

140. Cueni L, Canepari M, Lujan R, Emmenegger Y, Watanabe M, Bond CT, *et al*. (2008): T-type Ca2+ channels, SK2 channels and SERCAs gate sleep-related oscillations in thalamic dendrites. Nat Neurosci 11:683–692.

141. Astori S, Wimmer RD, Prosser HM, Corti C, Corsi M, Liaudet N, *et al*. (2011): The Ca(V)3.3 calcium channel is the major sleep spindle pacemaker in thalamus. Proc Natl Acad Sci U S A 108:13823–13828.

142. Manoach DS, Stickgold R (2009): Does abnormal sleep impair memory consolidation in schizophrenia? Front Hum Neurosci 3:21.

143. Atienza M, Cantero JL, Stickgold R (2004): Posttraining sleep enhances automaticity in perceptual discrimination. J Cogn Neurosci 16:53–64.

144. Chapman LJ, Chapman JP (1978): The measurement of differential deficit. J Psychiatr Res 14:303–311.

145. Viviano JD, Schneider KA (2015): Interhemispheric interactions of the human thalamic reticular nucleus. J Neurosci 35:2026–2032.

146. Evrard A, Ropert N (2009): Early development of the thalamic inhibitory feedback loop in the primary somatosensory system of the newborn mice. J Neurosci 29:9930–9940.

147. Pinault D (2011): Dysfunctional thalamus-related networks in schizophrenia. Schizophr Bull 37:238–243.

148. Feinberg I (1982): Schizophrenia: Caused by a fault in programmed synaptic elimination during adolescence? J Psychiatr Res 17:319–334.

149. Vukadinovic Z (2012): Schizophrenia as a disturbance of cortical sensory maps. Transl Neurosci 3:388–398.

150. Born J, Wilhelm I (2012): System consolidation of memory during sleep. Psychol Res 76:192–203.