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# Reduced sleep spindles in schizophrenia: A treatable endophenotype that links risk genes to impaired cognition?

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## Abstract

Although schizophrenia 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. Here we review evidence that reduced spindle activity in schizophrenia 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 schizophrenia and that increasing spindles improves memory in healthy individuals suggest that treating spindle deficits in schizophrenia may improve cognition. Spindle activity is highly heritable and recent large-scale genome-wide association studies have identified schizophrenia risk genes that may contribute to spindle deficits and illuminate their mechanisms. For example, the schizophrenia risk gene *CACNA1I* encodes a calcium channel that is abundantly expressed in the thalamic spindle generator and plays a critical role in spindle activity in a mouse knockout. Future genetic studies of animals and humans can delineate the role of this and other genes in spindles. Such cross-

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disciplinary research, by forging empirical links in causal chains from risk genes to proteins and cellular functions, through to endophenotypes, cognitive impairments, symptoms and diagnosis, has the potential to advance the mechanistic understanding, treatment and prevention of schizophrenia. This review highlights the importance of deficient sleep-dependent memory consolidation among the cognitive deficits of schizophrenia and implicates reduced sleep spindles as a potentially treatable mechanism.

**Keywords**

schizophrenia; sleep; spindles; memory; cognition; genetics; endophenotype

## Introduction

Neuropsychiatric disorders are primarily defined by waking phenomena, but sleep disturbances are often a prominent feature. While 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 can improve both symptoms and cognitive function. This suggests 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 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. We conclude that 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 (8) and are associated with poorer coping skills and diminished quality of life (9, 10). They are common 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-naïve SZ patients (17) indicates that disturbed sleep is not merely a medication side-effect. In fact, antipsychotic drugs (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 relations to pathophysiology, cognitive deficits and symptoms is 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.

Here, 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 (*i*) individuals with SZ and their first-degree relatives have reduced sleep spindle activity, *(ii)* spindle deficits are associated with impaired memory consolidation and positive symptoms, (*iii*) SZ risk genes are associated with spindle deficits and implicate specific pathophysiologic mechanisms, *(iv)* spindles can be enhanced and *(iv)* 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 (PSG) 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 (WASO), in SZ patients compared with healthy individuals (see meta-analyses, 17, 21). Studies also report altered circadian rhythms (22) and increased rates of sleep disorders including obstructive sleep apnea, movement disorders, parasomnias and hypersomnolence (reviewed in, 6, 15).

PSG studies document diverse abnormalities of sleep architecture (*i.e.*, the distribution of time spent in different sleep stages) in SZ. In humans, sleep is divided into rapid eye movement (REM) and non-REM (NREM) sleep and NREM sleep is subdivided into three stages: N1-3 (Figure 1, 23). N3, or slow wave sleep (SWS), is characterized by large delta (. 5– 4Hz) waves. Medicated and APD-naïve SZ patients as well as first-degree relatives show N3 abnormalities including reduced duration and delta power (24-27). REM sleep abnormalities, usually decreased REM latency or increased REM density (rapid eye movements 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 SZ compared with healthy or psychiatric controls (17, 21).

Relatively few studies of SZ venture beyond architecture to examine the spectral characteristics of the sleep 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 (~1s) powerful bursts of 12-15Hz activity organized in a waxing/waning envelope. While spindles also occur during N3, they 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 (e.g., 31). When summarizing the findings of multiple papers 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 y-aminobutyric acid (GABA)-ergic neurons (33). TRN neurons project to glutamatergic thalamic neurons that project to the cortex. Cortical neurons, in turn, 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 GABA-ergic and NMDA-receptor mediated glutamatergic neurotransmission (34). While 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 −70mV, 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 both the 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 during wake and 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 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 Ca2+ channel-dependent long-term potentiation (48).

In humans, spindles correlate with the sleep-dependent consolidation of both 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 pre-sleep 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 (.5-1Hz) and hippocampal ripples (~200Hz 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 non-invasively, but simultaneous EEG and fMRI 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 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:511) of APD-naïve first-episode (25, 69) and unmedicated (70, 71) SZ patients did not find a spindle deficit (Table 1). A growing literature, however, reports marked reductions of spindle activity In chronic medicated SZ (31, 72-76) and medicated adolescents with early onset SZ spectrum disorder (77). Importantly, 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, WASO), indicating that it is not secondary to sleep disruption. This contrast with reports of disrupted sleep in SZ (reviewed above) 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 chronic 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 finding of reduced spindle density to early course APD-naïve SZ patients (but not to APD-naive non-SZ psychotic patients). A trend to reduced density and significantly reduced spindle amplitude was also seen in young (mean age=14) nonpsychotic first-degree relatives of SZ patients (80). These findings make it unlikely that the spindle deficit in SZ is due to APDs and suggest the possibility of diagnostic specificity, though 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). There are reports, however, of a variety of 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. This is consistent with the finding of reduced thalamic volume in ultra high-risk adolescents 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 both procedural and declarative memory impairments in SZ.

Using a well-validated probe of sleep-dependent motor procedural memory, the finger-tapping motor sequence task (MST, Figure 4, 49, 92), several studies have demonstrated deficient sleep-dependent enhancement of motor learning in SZ. In healthy individuals, significant performance improvements occur after sleep but not after wake (49, 93-95) and correlate with N2 duration (49) and spindle density (50, 96, 97). In contrast, chronic medicated SZ patients 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). SZ patients 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 early course patients with both SZ and non-SZ psychotic disorders as well as in in nonpsychotic first-degree relatives of SZ patients (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 MST study the correlation between spindle density and overnight improvement in SZ was significant ($r21=.45$, $p=.04$, 31) but in a smaller study with a similar effect size it was not ($r14=.46$, $p=.10$, 73). In summary, the evidence suggests that spindle deficits contribute to cognitive dysfunction in genetically high-risk individuals and in 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 during wake (104). SZ is characterized by deficits in sensory gating

(105), attentional modulation, and cortical gamma band oscillations, all of which 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 (PV)-containing GABAergic interneurons (108), which are abnormal in SZ (109). While there is a selective reduction of GABA PV interneurons in anteroventral thalamus (110), to our knowledge, the TRN GABA PV neurons that generate spindles have not been studied. In summary, TRN dysfunction in SZ may contribute to impairments in sensory gating, attention and cortical gamma oscillations during wake and to spindle deficits during sleep.

Reduced spindle activity also correlates with increased positive symptom severity in medicated early onset SZ spectrum disorder (77) and in some (31, 75) but not all (72) studies of chronic medicated SZ. In APD-naïve early course SZ, however, reduced spindle density correlated with *decreased* positive symptoms (80). The opposite direction of these correlations may reflect differences in the pathophysiological underpinnings of positive symptoms. In chronic medicated SZ, residual positive symptoms have not responded to dopaminergic medications and may arise from GABA or NMDA hypofunction (111), while in 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. While the mechanistic link of spindles to positive symptoms is less clear than that 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 the florid psychotic symptoms are controlled with APDs, debilitating cognitive deficits persist and only ~20% of individuals with SZ work (116). Although ameliorating cognitive deficits is a priority of the SZ research community, effective treatments are lacking (e.g., 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, 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, while 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, while 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 improved word list recall (125). In a small preliminary study, eszopiclone, which acts on GABA neurons in the TRN (126), significantly increased spindles in SZ but not sleep-dependent memory (127). In another study that did not include PSG measures, 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

EEG sigma power is highly heritable in twin studies (heritability estimate: 96%, 129) and shows both high inter-individual variability and within-individual stability, leading to its description as an “electrophysiological fingerprint” (129-131). Despite this, 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 due to 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 relations 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, since 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, though 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, GTex, mouse.brain-map.org, www.gtexportal.org) where it interacts with sarco/endoplasmic reticulum Ca2+-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 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 both procedural and declarative memory. It implicates reduced sleep spindles as a mechanism and suggests novel pathophysiological 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. This leaves fewer resources available for higher-order task demands. The interaction between automatic and effortful processes is what allows a limited capacity brain to carry out complex cognitive tasks. Thus, 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 pharmacological and transcranial stimulation approaches. As standard neuropsychological tests assess function in a single session, they miss the 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 sleep oscillations is preserved in schizophrenia, and animal models are necessary to simultaneously measure all three oscillations. 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. TRN activity

has seldom been examined *in vivo* in humans as 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 pathophysiological 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.

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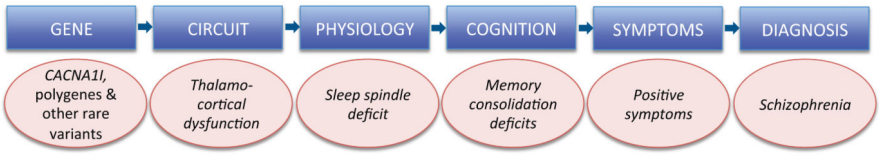


**Figure 1.**

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 of the REM sleep occurs later in the night. N1 is a transitional state from wake to sleep, characterized by the disappearance of 8-12HZ (alpha) waves from the EEG and appearance of slow (>0.5s) oscillating eye movements (23). N2 is defined by the presence of isolated sharp negative waves followed by a positive component, lasting >0.5s, and sleep spindles. N3 is defined by the presence of large (>75μV peak-to-peak, slow (0.5-2Hz) waves occupying at least 20% of each 30s epoch.

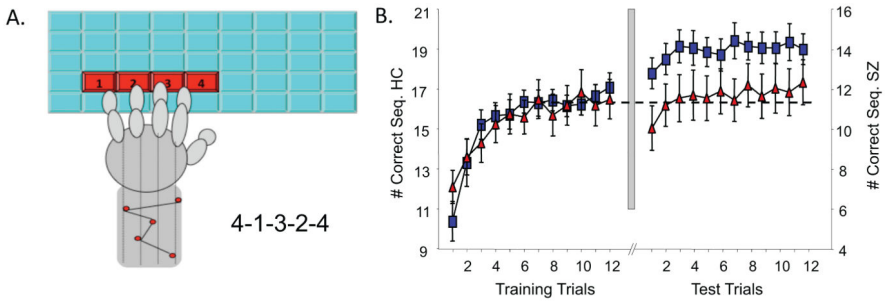


**Figure 2.**

Thalamic reticular nucleus (TRN) circuitry for generating and synchronizing sleep spindles (adapted from 103). The TRN, a netlike nucleus that sits between the rest of the thalamus and the neocortex, modulates thalmocortical activity. The TRN receives projections from both thalmocortical and corticothalamic neurons. GABAergic TRN neurons project to thalamocortical relay neurons. Glutamatergic corticothalamic neurons, in turn, send projections back to the TRN and other thalamic nuclei.

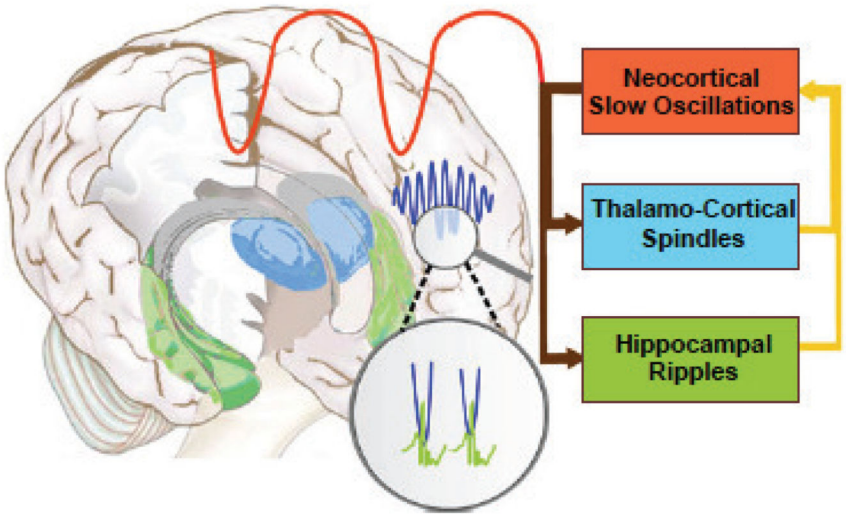


**Figure 3.**

The coordination of sleep spindles with hippocampal ripples and neocortical slow oscillations in the service of consolidating new memories during sleep (adapted from 150). During NREM 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 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).

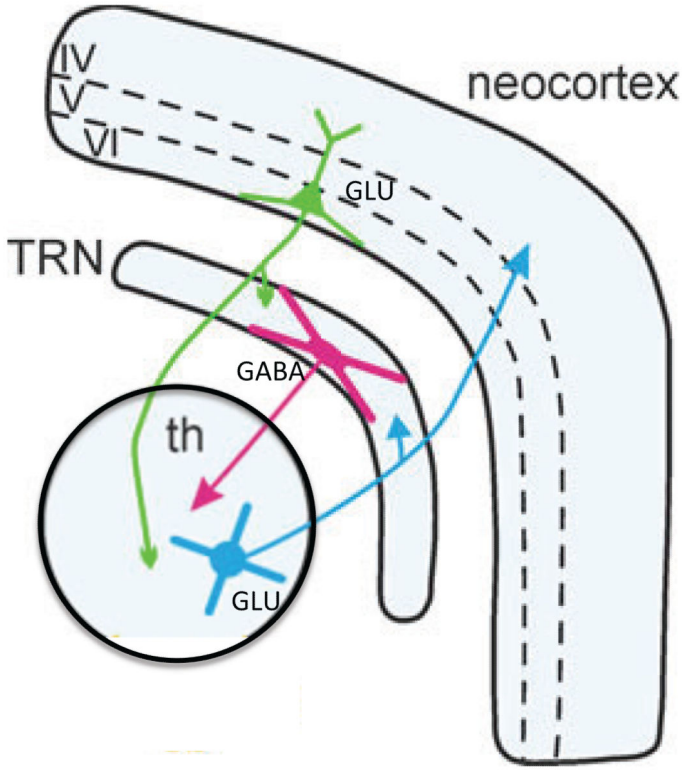


**Figure 4.**

Finger tapping Motor Sequence Task (MST). A. The MST requires participants to repeatedly type a 5-digit sequence (*e.g.*, 4-1-3-2-4) on a keyboard with the left hand, "as quickly and accurately as possible" for twelve 30 s trials separated by 30 s rest periods. Participants train before sleep and test on and 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 MST performance (data from 98). Left: At training, SZ patients (red triangles) and healthy controls (blue squares) show a similar time course of improvement, although SZ patients are slower overall (see y-axis on right). Right: Following a night of sleep, only the healthy controls show sleep-dependent improvement

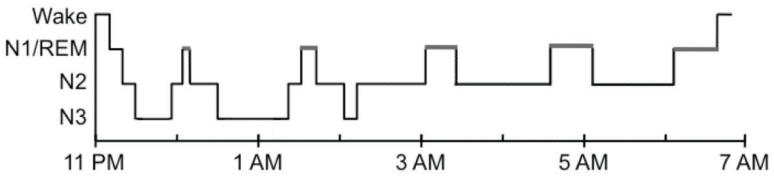


**Figure 5.**

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

## Table 1

Studies of spindle density in schizophrenia.

| Study | Medication status | Patient n | Healthy Control 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[1] (69) | APD-naïve | 11 | 11 | N2 | Visual | No difference |
| Ferrarelli et al., 2007[2] (74) | Medicated | 18 | 17 | NREM during first sleep episode | Algorithm | Reduced |
| Ferrarelli et al., 2010[2] (75) | 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[3] (80) | APD-naïve | 15 | 25 | N2 | Algorithm | Reduced |
| Goder et al., 2015 (72) | Medicated | 16 | 16 | N2 | Algorithm and visual | Reduced |
| Tesler et al., 2015[4] (77) | Medicated | 9 | 15 | First hour of NREM | Algorithm | Reduced |

[1] The eight patients reported in Forest et al., 2007 are a subset of the 11 reported in Poulin et al., 2003.

[2] 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 SZ patients but did not differ from healthy controls.

[3] Included an APD-naïve non-SZ psychotic control group (n=11) whose spindle density was greater than SZ patients at a trend level, and did not differ from healthy controls.

[4] Adolescents with early onset SZ spectrum disorder.