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Sleep and Plasticity in Schizophrenia

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Abstract

Schizophrenia is a devastating mental illness with a worldwide prevalence of approximately 1 %. Although the clinical features of the disorder were described over one hundred years ago, its neurobiology is still largely elusive despite several decades of research. Schizophrenia is associated with marked sleep disturbances and memory impairment. Above and beyond altered sleep architecture, sleep rhythms including slow waves and spindles are disrupted in schizophrenia. In the healthy brain, these rhythms reflect and participate in plastic processes during sleep. This chapter discusses evidence that schizophrenia patients exhibit dysfunction of sleep-mediated plasticity on a behavioral, cellular, and molecular level and offers suggestions on how the study of sleeping brain activity can shed light on the pathophysiological mechanisms of the disorder.

Keywords

Sleep; Schizophrenia; Plasticity; EEG; Thalamocortical circuits

1 Introduction

Schizophrenia is a chronic mental illness, characterized by psychosis and other symptoms that result in significant cognitive, social, and occupational dysfunction. The lifetime

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prevalence of schizophrenia has been estimated at about 1 % of the population worldwide, with males and females equally affected. In addition to its positive (e.g., hallucinations, delusions) and negative (e.g., apathy, anhedonia) symptoms, schizophrenia is associated with marked sleep disturbances and cognitive deficits. Because diagnosis is based solely on clinical criteria, it is likely that schizophrenia is not a single disease entity but rather may include a group of disorders resulting in similar clinical symptomatology. Sleep may be of particular relevance to schizophrenia, since abnormal brain connectivity and plasticity are thought to be core pathological features of the disorder and both are reflected in the sleep electroencephalogram (EEG) (Stephan et al. 2006). Furthermore, electro-physiological measurements during sleep eliminate many factors that confound waking assessments of brain activity and cognition, including movement, attention, motivation, and comprehension of instructions. Consequently, sleep provides a unique modality for investigating neuropathological mechanisms, biological markers, and therapeutic targets for schizophrenia. This chapter discusses the evidence that schizophrenia patients exhibit dysfunction of sleep-mediated plasticity on a behavioral, cellular, and molecular level and offers suggestions on how further study of sleeping brain activity can shed light on the pathophysiological mechanisms of the disorder.

2 Description of the Disorder

Schizophrenia tends to appear in late adolescence or early adulthood, with earlier onset in men than in women. Diagnosis of schizophrenia is based on the presence of two or more characteristic positive and negative symptoms that persist for at least 1 month, in conjunction with significant dysfunction in work, interpersonal relations and/or self-care, and continuous signs of illness that are present for at least 6 months (DSM V, (American Psychiatric Association 2013). Diagnostic criteria are summarized in Table 1. The vast majority of individuals afflicted with the disorder remain at least partially ill, with either a stable course or progressive deterioration; full remission is uncommon. Schizophrenia is associated with a 10- to 25-year reduction in life expectancy; this is related both to elevated rates of suicides and accidents, which are closely associated with the illness itself, and higher rates of medical disorders (e.g., cardiovascular disease and cancer), which are related to comorbid factors such as increased substance use, poor diet, side effects of anti-psychotic medications, and suboptimal medical care (Laursen et al. 2012).

Whereas the clinical features of schizophrenia have been described for over one hundred years (Bleuler 1911), the neurobiology of the disorder is still largely elusive despite decades of research. A large body of evidence now exists identifying biological abnormalities that characterize schizophrenia and many competing theories have been put forward to explain the pathophysiological mechanisms that might explain these observations (MacDonald and Schulz 2009). Some key theories are summarized in Table 2. A number of studies indicate that abnormalities in neurotransmitter pathways, gray and white matter structures, and cortical circuits that are involved in both sleep and brain plasticity may underlie specific symptoms and neurocognitive deficits in schizophrenia. Dysfunction of thalamocortical circuits is of particular interest, as these connections are thought to play a central role in coordinating sleep-mediated plasticity.

2.1 Sleep Patterns in Schizophrenia

After the neurophysiological identification of rapid eye movement (REM) sleep in the early 1950s, schizophrenia was one of the first disorders to be studied using polysomnography, motivated by the apparent similarities between dreaming and the positive symptoms of schizophrenia (hallucinations, delusions). Although schizophrenia did not turn out to be a disorder of REM sleep intrusion into wakefulness (Dement 1955; Rechtschaffen et al. 1964), sleep disturbance can be a significant clinical symptom and objective sleep EEG abnormalities have been identified across numerous studies. During periods of acute psychosis, sleep is often severely affected, with profound insomnia, reduced total sleep time, and fragmented sleep. In terms of sleep architecture, sleep recordings in schizophrenic patients have fairly consistently documented objective evidence of insomnia, including prolonged latency to sleep, reduced sleep efficiency, and reduced total sleep amount (Benca et al. 1992; Chouinard et al. 2004). Decrements in the amounts of visually scored deep stage 3 sleep (N3), also called slow wave sleep (SWS), have also been reported in some (Hiatt et al. 1985; Keshavan et al. 1998; Sekimoto et al. 2007; Zarcone et al. 1987), but not in all studies (Kempenaers et al. 1988; Lauer et al. 1997; Tandon et al. 1992). REM sleep abnormalities in schizophrenia have not been demonstrated consistently, although a number of early studies suggested that schizophrenics, like patients with mood disorders, had reduced latency to REM sleep (Kupfer et al. 1970). However, several meta-analyses have failed to support any consistent changes in latency to REM sleep or REM sleep amounts (Benca et al. 1992; Chouinard et al. 2004).

2.2 Memory Deficits in Schizophrenia

One of the most debilitating manifestations of disrupted brain plasticity in schizophrenia is impaired memory in several domains. Verbal declarative memory deficits are the most consistently found impairments in schizophrenia, confirmed by several meta-analyses (Cirillo and Seidman 2003; Sitskoorn et al. 2004; Snitz et al. 2006). Verbal declarative memory is memory for facts, ideas, stories, or events that can be consciously recalled. Impairments are present throughout the course of the illness, and in high-risk subjects and non-psychotic relatives of individuals with schizophrenia, suggesting that these deficits are partly associated with a genetic vulnerability to the disorder (Gur et al. 2007; Sitskoorn et al. 2004). Working memory is the ‘scratch pad of the mind,’ used for holding and manipulating information online during a cognitive task (Baddeley 1992). Schizophrenia patients have impaired working memory (Horan et al. 2008) and in unaffected offspring reduced performance predicted the later development of psychosis (Erlenmeyer-Kimling et al. 2000). Procedural learning is non-declarative memory for the performance of perceptual or motor tasks. Most studies report normal procedural learning in schizophrenia patients (Clare et al. 1993; Weickert 2002). However, these reports were derived from testing within a single session. Since healthy individuals show improvement in procedural memory after a night of sleep, Manoach et al. (2004) investigated the influence of sleep on learning in patients with schizophrenia. Despite normal learning within a training session, schizophrenics failed to show an improvement after a night of sleep, in contrast to healthy individuals, indicating a failure of sleep-mediated procedural memory consolidation in schizophrenia.

3 Neurochemical Abnormalities and Sleep-Dependent Plasticity

Neurotransmitter systems implicated in the pathogenesis of schizophrenia include dopamine, gamma-aminobutyric acid (GABA), acetylcholine, glutamate, and neuromodulators such as melatonin and orexin. These systems play important roles in neuroplasticity. Furthermore, sleep–wake regulation is achieved through a complex interaction of neurotransmitters in distributed brain regions; thus, abnormalities in these systems in schizophrenia are likely to impinge upon sleep and sleep-related plasticity.

3.1 Dopamine

Numerous studies show that dopamine (DA) neurotransmission is reduced in the cortex and elevated in the striatum in schizophrenia (Abi-Dargham et al. 2012; Fusar-Poli and Meyer-Lindenberg 2013; Howes et al. 2012). Dopaminergic circuits regulate both neuroplasticity and sleep–wake cycles. DA is a powerful modulator of synaptic plasticity via complex signaling that varies by receptor type and neural circuit. DA exerts its effects via G-protein-coupled receptors that may be excitatory (D1) or inhibitory (D2), with downstream effects on membrane excitability, synaptic transmission, protein trafficking, and gene transcription (Tritsch and Sabatini 2012). DA promotes wake and suppresses REM and non-REM (NREM) sleep, acting through projections from the ventral tegmental area, substantia nigra pars compacta, and ventral periaqueductal gray matter to inhibit sleep-promoting neurons in the basal forebrain, midbrain, brainstem, and hypothalamus (Monti and Jantos 2008). Although the impact of DA dysfunction on sleep-dependent plasticity has not yet been examined in schizophrenia, several lines of evidence suggest that it deserves further attention.

Firstly, the efficacy of the psychostimulant modafinil and its effects on sleep EEG are modulated by the presence of a polymorphism in the catechol-o-methyl transferase (COMT) gene, which is more common in schizophrenia patients than in the general population (Bodenmann et al. 2009; Bodenmann and Landolt 2010). COMT is an enzyme that degrades dopamine, and the polymorphism predicts reduced cognitive performance (Weinberger et al. 2001). The genotype's interaction with modafinil suggests that COMT may play a role in altered sleep–wake regulation in schizophrenia. Secondly, elevated levels of D4 receptors (members of the D2-like receptor family) have been reported in schizophrenia (Seeman et al. 1993). D4 receptors are present in the pineal gland, where they decrease melatonin release through binding of adrenergic receptors. The pineal gland regulates sleep–wake rhythms through the circadian release of melatonin; therefore, the increase of D4 receptors in schizophrenia could contribute to the irregular sleep–wake patterns observed in the disorder (González et al. 2012). Moreover, the thalamic reticular nucleus (TRN), the structure responsible for generating sleep spindles, is rich in D4 receptors. D4 receptors are present presynaptically on GABA-containing projections from the globus pallidus to the TRN (Gandia et al. 1993; García-Cabezas et al. 2007), and activation of the D4 receptors reduces GABA release onto the TRN (Govindaiah et al. 2010). Thus, an excess of D4 receptors in schizophrenia could disrupt TRN control of thalamocortical oscillations, which coordinate sleep-related plasticity. However, the origins of these projections and the effects of dopamine on TRN neurons are still controversial (Florán et al. 2004; Mrzljak et al. 1996). Finally, in

schizophrenia patients, working memory impairment correlates with increased D1-receptor binding potential in prefrontal cortex, suggesting a compensatory upregulation of the receptor in response to cortical DA deficiencies (Abi-Dargham et al. 2002). Animal studies suggest that prefrontal D1 receptors sustain the activity of prefrontal neurons while a stimulus is held in memory, and this persistent activity is considered the neural correlate of working memory (Gao et al. 2001). At first glance, working memory might be considered a purely waking function; however, working memory performance is improved by prior sleep (Kuriyama et al. 2008) and impaired by sleep deprivation (Drummond et al. 2012; Hagewoud et al. 2010). Sleep may therefore be a useful tool for probing abnormal DA function and working memory in schizophrenia.

3.2 Acetylcholine

Reduced cholinergic activity and abnormal cholinergic transmission have been found consistently in schizophrenia (Crook et al. 2000; 2001; Raedler et al. 2003) and are related to cognitive symptoms in animal models (Sarter et al. 2012). Although acetylcholine (ACh) is excitatory, AChRs are located both pre- and post-synaptically, allowing for a complex role in fine-tuning neuronal excitability (Drever et al. 2011). ACh can both facilitate and inhibit long-term potentiation (LTP) through graded effects on the responsiveness of glutamatergic and GABAergic cells in the hippocampus that mediate memory formation (Drever et al. 2011) and DA neurons in the ventral tegmental area that mediate reward and addiction (Gao et al. 2001). ACh also supports longer-term changes in cortical circuits by promoting synchronous cortical and subcortical firing; this may facilitate long-term plasticity by increasing the baseline excitability of neurons, which are then more responsive to modulation by other transmitters (Picciotto et al. 2012). Cholinergic transmission in the brainstem is important for the initiation and coordination of REM sleep (Jones 2005; Marks and Birabil 1998). Administration of muscarinic agonists induces shorter REM latencies in healthy individuals. In schizophrenia patients, the effect is much more pronounced than in healthy controls, suggesting a muscarinic cholinergic supersensitivity in the disease (Riemann et al. 1994). Cholinergic tone is normally high during REM sleep and low during NREM sleep, and in healthy young men, pharmacologically lowering REM cholinergic tone impairs consolidation of motor memory (Rasch et al. 2009), while pharmacologically elevating NREM ACh tone impairs consolidation of verbal declarative memory (Gais and Born 2004). Therefore, the contribution of ACh dysfunction to impaired sleep-dependent memory in schizophrenia warrants further investigation.

3.3 Glutamate

Glutamate is the most prevalent excitatory neurotransmitter in the central nervous system, and dysfunctions of glutamatergic neurotransmission are hypothesized to be an important mechanism of schizophrenia pathophysiology (Table 2). In particular, abnormalities in the N-methyl-D-aspartate receptor (NMDAR), a glutamate-gated ion channel, are thought to contribute to disrupted synaptic plasticity in the disorder (Marsman et al. 2013). Multiple signaling pathways modulating sleep and synaptic plasticity converge on the NMDA receptor, for example, D1 agonists and D2 antagonists increase NMDAR-dependent LTP, whereas D2 agonists decrease LTP (Centonze et al. 2004; Tseng and O'Donnell 2004) and acetylcholine modulates NMDA-dependent LTP and long-term depression (LTD) in visual

cortex (Kirkwood et al. 1999) and hippocampus (Yun et al. 2000). In mice, sleep deprivation altered the ratio between LTP and LTD, a key cellular mechanism of neural plasticity, and changed the subunit composition of NMDARs (Kopp et al. 2006). Low doses of NMDAR antagonists produce arousal, while high doses produce sedation (Siegel 2011). Ketamine, a NMDAR antagonist that induces schizophrenia-like symptoms, disrupts thalamocortical rhythmicity (Buzsáki 1991), which is important for sleep-dependent memory processes. The role of the thalamocortical system in sleep-dependent plasticity is discussed in further detail below.

4 Structural and Functional Abnormalities

Gray matter atrophy and disrupted white matter connectivity have been reported consistently in schizophrenia, especially in frontal and temporal areas and in thalamocortical networks, including the thalamic radiation which carries fibers from the thalamus to prefrontal areas (Borgwardt et al. 2008; Gaser et al. 2004; Heinrichs and Zakzanis 1998; Kawada et al. 2009; Kyriakopoulos and Frangou 2009; McIntosh et al. 2008; Nuechterlein 1983; Ren et al. 2013; Snitz et al. 2006). Functional magnetic resonance imaging (fMRI) has revealed abnormal patterns of activity in the default mode network, a highly interconnected brain system that subserves self-referential thought and interpretation of the external environment (Hasenkamp et al. 2011; Ren et al. 2013; Skudlarski et al. 2010). These findings are in keeping with the view that disordered brain connectivity is central to schizophrenia (Stephan et al. 2006) (Table 2). Interestingly, the functional findings did not co-localize with anatomical abnormalities in gray or white matter in the same subjects. Abnormal functional connectivity may reflect reorganization of functional networks in response to declining structural connections. Sleep EEG patterns reflect propagation of neural activity through structural and functional networks; therefore, the use of EEG systems with high spatial resolution could further characterize the relationship between altered anatomical and functional connectivity in schizophrenia. An advantage of EEG recordings is the ability to monitor activity on a timescale closer to neuronal signaling (milliseconds) than fMRI (seconds). For example, by performing source modeling analysis of scalp-recorded EEG slow waves, it is possible to track the origin and propagation of slow waves along a mesial cortical highway, and the propagation of this wave is thought to play a role in coordinating neuronal plastic activity (Massimini et al. 2004). This technique has yet to be applied to schizophrenia.

In task-related studies of schizophrenia, abnormal prefrontal cortical activation is the most established finding, often associated with impaired performance in cognitive paradigms involving working memory (Barch et al. 2012), reinforcement learning (Ragland et al. 2012), and executive functions (Carter et al. 2012). Increased prefrontal activity in schizophrenia patients has been interpreted as a failure of automation, the shift from controlled effortful cognitive performance to less attention-demanding strategies. Automation has been proposed to be accomplished by a system-level reorganization of memory traces during sleep, a process reflected in EEG waveforms including spindles and slow waves (Manoach and Stickgold 2009). Therefore, investigating sleep EEG in conjunction with learning tasks could shed light on the biological basis of dysfunctional memory processes in schizophrenia.

5 Genetic Factors

A strong familial risk for schizophrenia has long been recognized, and a meta-analysis of twin studies calculated that 80 % of the probability of developing schizophrenia could be attributed to genetic factors (Sullivan et al. 2003). Over 50 candidate genes have been identified, yet no gene or genetic factor is shared by all schizophrenia patients. Recent genome-wide association studies have found an increased frequency of single nucleotide polymorphisms (SNPs) in schizophrenia (Lee et al. 2012). SNPs are the most common form of genetic variation within the general population and are therefore not unique to schizophrenia. However, SNPs may confer additional risk on individuals already predisposed to the illness. Their increased incidence in schizophrenia may explain the complex and heterogeneous phenotypes encountered in the disorder, and support a polygenic inheritance pattern. One SNP associated with schizophrenia is a functional polymorphism in the COMT gene (Cross-Disorder Group of the Psychiatric Genomics Consortium et al. 2013). As described earlier, COMT is an enzyme that regulates extracellular dopamine concentration in prefrontal cortex and the polymorphism leads to dopamine deficiency, which could impair sleep-dependent plasticity via altered oscillatory activity in the prefrontal cortex and thalamic reticular nucleus. Indeed, lower performance on working memory and prefrontal executive tasks is predicted by the presence of the COMT val allele in healthy controls, schizophrenia patients, and relatives of patients (Weinberger et al. 2001). The COMT SNP also influences sleep–wake regulation. Specifically, carriers of the val allele required a much lower dose of the stimulant modafinil to maintain attention during sleep deprivation (Bodenmann et al. 2009). Non-schizophrenia subjects with the val/val variant showed increased EEG activity in the high slow wave range (3.0–6.75 Hz) and the beta range (>16.75 Hz) during recovery sleep following modafinil treatment (Bodenmann and Landolt 2010). The ability of the COMT SNP to explain phenotypic variation in sleep architecture and EEG has not yet been explored in schizophrenia.

A well-researched gene consistently associated with schizophrenia is disrupted-in-schizophrenia 1 (DISC1), which encodes a multifunctional scaffold protein. It is implicated in neuronal migration and maturation during development, as well as in synaptic plasticity in the adult brain (Chubb et al. 2008). DISC1 also impacts sleep; transgenic flies expressing human DISC1 displayed increased duration of sleep bouts but normal circadian rhythms, suggesting a role for DISC1 in regulating sleep homeostasis (Sawamura et al. 2008). In the mouse brain, DISC1 is expressed only in some brain structures, including regions important for sleep and plasticity such as the hippocampus, parts of the neocortex, hyphothalamus, stria terminalis, and TRN. Furthermore, DISC1 is highly expressed in the TRN during development, in a period when thalamocortical connections take shape (Austin et al. 2004). Given their crucial role in sleep-dependent plasticity, abnormal development of thalamocortical circuits would have far-reaching effects on sleep and cognition, in keeping with the view of schizophrenia as a neurodevelopmental disorder.

6 Sleep-Specific EEG Rhythms in Schizophrenia

Whereas early studies of sleep in schizophrenia focused on visually scored sleep architecture in 30-s epochs, modern automated analyses allow a more detailed assessment of sleep-

specific rhythms by measuring power density and waveform counts. High-density EEG recordings from 256 channels, as opposed to 6 or less in conventional polysomnography, afford sufficient spatial resolution to examine regional variation. Slow waves and spindles, the characteristic waveforms of NREM sleep, play important roles in neuroplasticity and have been studied extensively in schizophrenia. Interestingly, intracortical recordings in humans have shown that rather than being global brain phenomena, both slow waves and spindles can occur in local circuits as temporally and spatially independent phenomena (Nir et al. 2011). Furthermore, localized, use-dependent changes suggest that spindles and slow waves reflect the ability of local circuits to be plastic (Fisher and Vyazovskiy 2014; Goel et al. 2014; Huber et al. 2004). Therefore, sleep EEG could provide a powerful tool for testing the functionality of distinct circuits in schizophrenia.

6.1 Slow Wave Abnormalities in Schizophrenia

During the deepest stage of NREM sleep, the EEG is dominated by large slow waves in the delta frequency range (0.5–4 Hz) as detailed in Chap. 1 of this volume. At the cellular level, slow waves reflect synchronized transitions in large populations of cortical pyramidal neurons between a depolarized upstate (a state of increased firing) and a hyperpolarized downstate (a state of decreased firing) (Steriade et al. 1993). This slow oscillation is cortically generated and maintained (Amzica and Steriade 1995; Timofeev et al. 2000), but is shaped by the thalamus (Steriade et al. 1993). High-density EEG recordings show that cortical slow waves typically originate in frontal regions (the insula and cingulate gyrus) and travel in an anterior–posterior direction along the cingulate gyrus and neighboring regions (Murphy et al. 2009). This coincides with a major white fiber pathway identified by diffusion spectrum imaging (DSI) (Hagmann et al. 2008). Studies of sleep and learning demonstrate that slow waves reflect plastic changes. For example, when sleep was recorded following training on a visuomotor task, the cortex showed an increase in slow wave activity in task-relevant areas, which correlated with improved task performance the following morning (Huber et al. 2004). SWS also positively correlated with overnight improvement on tests of visual (Stickgold et al. 2000) and verbal declarative memory (Plihal and Born 1997). Moreover, selectively suppressing slow waves without shortening sleep time was detrimental to motor sequence learning (Landsness et al. 2011).

Slow wave deficits in schizophrenia have been frequently but inconsistently reported. Several studies have found that patients spend less time in visually scored stage N3. Automated analyses showed reduced power in the slow wave frequency range (0.5–4 Hz) and a lower count of slow waves across the total sleep period (Keshavan et al. 1998; Sekimoto et al. 2007). Differences in slow wave topography have also been reported. Whereas healthy controls showed significantly higher slow wave counts in right frontal and central regions, this asymmetry was lacking in patients with schizophrenia (Sekimoto et al. 2011). Slow wave deficits have been reported in medicated (Göder et al. 2004; Sekimoto et al. 2007), unmedicated (Feinberg et al. 1969), first-episode neuroleptic naïve (Poulin et al. 2003), and remitted (Kupfer et al. 1970; Traub 1972) patients. Furthermore, a reduced slow wave count has been identified in non-psychotic first-degree relatives of schizophrenia patients, suggesting it may be a trait linked to predisposition to the disease (Keshavan et al. 2004). However, a number of studies have found no deficits in visually scored N3 or in

automated measures of slow wave incidence, amplitude, or slope in medicated patients (Ferrarelli et al. 2010a; Manoach et al. 2010), or neuroleptic naïve patients (Forest et al. 2007). A meta-analysis of unmedicated patients also failed to confirm abnormalities in SWS as a percentage of total sleep time in schizophrenics (Chouinard et al. 2004). Inconsistencies between reports could be due to factors including sample size, medication status, and methodological differences such as slow wave detection algorithms. Alternatively, given the heterogeneous nature of the disorder, it may be that slow wave deficits are present only in a subset of schizophrenic patients.

Göder et al. (2004) examined the relationship between SWS and plasticity in chronically medicated schizophrenia patients and healthy controls matched for age, sex, and education level. Compared to controls, patients exhibited significantly shorter SWS duration and poorer visuospatial memory performance. SWS duration was positively correlated with memory performance in patients but not in controls (the lack of correlation in controls may have been due to a ceiling effect on performance). A subsequent study found that greater SWS duration was associated with better verbal declarative memory the following morning in chronically medicated schizophrenia patients (Göder et al. 2008). Furthermore, enhancing slow waves using transcranial direct current stimulation during NREM sleep improved verbal memory retention in medicated schizophrenia patients (Göder et al. 2013). These studies establish that the correlation of SWS with memory performance that was previously demonstrated in healthy individuals is also present in schizophrenia patients. Furthermore, reduced SWS in the disorder correlates with reduced cognitive performance, suggesting that in schizophrenia, learning deficits may be related to dysfunction in SWS-mediated plasticity. The studies described above relied on visually scored measures of SWS. Automated analyses that may be useful in future are the slope and amplitude of slow waves, which reflect synaptic strength (Esser et al. 2007; Vyazovskiy et al. 2009). Such measures could provide more detailed insight into the mechanism by which slow wave deficits contribute to impaired learning in schizophrenia.

Slow wave power is high at birth, increases steeply in the first few years of life, and then decreases dramatically during adolescence (Buchmann et al. 2011; Feinberg and Campbell 2010; Tarokh and Carskadon 2010). This inverted u-shaped pattern parallels other markers of neural development throughout childhood and adolescence, including synaptic density (Huttenlocher and Dabholkar 1997), the size of pyramidal neurons and the size and complexity of dendritic trees in prefrontal cortex (Petanjek et al. 2008), brain energy consumption measured by PET (Chugani et al. 1987), and microstructure of white matter tracts measured by diffusion tensor imaging (DTI) (Lebel et al. 2012). Healthy cortical maturation appears to follow a general pattern of early overproliferation followed by elimination, with adolescence being a critical period of reorganization (Feinberg and Campbell 2010). Gray matter matures in a regionally and temporally complex pattern (Gogtay et al. 2004) and a recent cross-sectional study demonstrated that healthy developmental declines in SWA were correlated with gray matter maturation in a regionally specific manner (Buchmann et al. 2011). A longitudinal study of gray matter volumes in early-onset schizophrenia has shown accelerated gray matter losses during adolescence that correlated with symptom severity (Thompson et al. 2001). The dramatic decline in slow wave activity during adolescence likely reflects a reduction in synaptic strength and in the

number of neurons available to participate in the synchronous slow oscillation. Given that slow wave amplitude depends on the ability of cortical neuronal populations to fire synchronously (Vyazovskiy et al. 2009), impaired neuronal integration could result in less coordinated activity, detectable as slow wave deficits. The reduction in slow waves seen in adults with schizophrenia may therefore be a product of disrupted neurodevelopment. The relationship between gray matter development and slow wave activity has not yet been examined in schizophrenia patients, however. Beyond being a marker of cortical maturation, slow waves may actively participate in the pruning of synapses (Maret et al. 2011). Neural proliferation and pruning during adolescence is a critical period for integrating complex neural circuits, and errors during this process would have severe cognitive and neural consequences.

6.2 Spindle Abnormalities in Schizophrenia

Sleep spindles are characteristic of NREM sleep and define stage N2. Spindles are waxing and waning bursts of highly synchronized 12–16 Hz oscillations, generated in the TRN and propagated throughout the cortex (Steriade 2003). In healthy humans and animals, an increase in the number and duration of spindles correlates with overnight improvements in declarative and procedural memory (Fogel and Smith 2011). Neuroimaging studies using simultaneous functional MRI and EEG showed that networks subserving memory function were activated during spindle activity, including thalamus, hippocampus, midbrain, anterior cingulate, and prefrontal cortex (Schabus et al. 2007), and spindle amplitude correlated with activity in the putamen and with gains in performance on a motor task (Doyon et al. 2011).

Several studies have found marked deficits in spindle activity in schizophrenia. Older studies using small sample sizes, manual techniques, and only 2 EEG leads (C3 and C4) had inconsistent spindle findings (Hiatt et al. 1985; Poulin et al. 2003; Van Cauter et al. 1991). Recent studies using automated detection methods, larger sample sizes, and more electrodes show more consistent deficits in schizophrenia. In the most comprehensive studies to date, medicated schizophrenia patients exhibited deficits in several spindle parameters compared to healthy controls, including power in the spindle range (13.75–15 Hz), spindle amplitude, duration, number, density (spindles/minute), and integrated spindle activity (ISA, calculated by integrating spindle activity over time) (Ferrarelli et al. 2007, 2010a). Furthermore, the spindle deficits were not present in non-schizophrenia patients receiving antipsychotics, including major depressive and bipolar patients; therefore, the effect is not explained by medication, not found in patients with other psychiatric disorders, and could be specific to the disorder. ISA was inversely correlated with positive symptoms and distinguished schizophrenia patients from psychiatric and healthy controls; therefore, spindle parameters could be a useful biological marker for schizophrenia (Ferrarelli 2013).

Given the role of spindles in learning and memory, spindle deficits could be expected to correlate with cognitive impairment in schizophrenia. Indeed, Göder et al. (2008) found that in chronically medicated patients, greater spindle density was associated with better verbal declarative memory the following morning. The study did not include a non-schizophrenia control group as it was investigating the effect of olanzapine treatment. Wamsley et al. (2012) later tested the question directly. Compared to healthy controls, medicated patients

with chronic schizophrenia showed less overnight improvement on a finger tapping motor task. Spindle number, density, and interelectrode coherence were reduced in the patient group and predicted overnight performance improvement. This impairment of sleep-dependent learning in schizophrenia is also present in daytime nap sleep (Seeck-Hirschner et al. 2010). Following a 40-min afternoon nap, visuomotor memory (mirror tracing) improved in healthy individuals and depressed patients. By contrast, medicated schizophrenia patients failed to improve and showed significantly reduced spindle density during their naps, although the correlation with performance was not significant. Manoach et al. (2010) compared the sleep and motor learning of medicated schizophrenia patients with demographically matched controls. They confirmed previous findings of spindle deficits in the patient group, reporting reductions in spindle power (13.5–15 Hz) and spindle density during the last quartile of sleep. Moreover, the patient group showed no overnight improvement on the motor task, in contrast to the control group which showed significant improvements that correlated with stage N2 duration.

Of note, spindles are also thought to block transmission of sensory information from lower brain structures to the cortex during sleep, resulting in decreased reactivity to stimuli, thereby promoting sleep continuity (Steriade et al. 1993). A failure of this gating mechanism would lead to a lower arousal threshold and more fragmented sleep. Therefore, in addition to impaired plasticity, spindle abnormalities may contribute to the common complaint of poor sleep quality and low sleep efficiency in schizophrenia.

7 The Thalamocortical Network in Sleep and Plasticity

Spindles and slow waves do not occur independently but rather participate in an important rhythmic network spanning cortical and subcortical structures. During sleep, almost all cortical neurons undergo a slow oscillation in membrane potential of <1 Hz (Steriade 2003). This underlying oscillation is a fundamental characteristic of NREM sleep and temporally groups slow waves, spindles, and hippocampal ripples, supporting synchronized activity in distant brain regions. Coordinated activity across thalamocortical networks during NREM sleep plays a crucial role in brain plasticity. One key mechanism thought to underlie hippocampal-dependent memory is the reactivation of firing patterns in hippocampal and neocortical neurons. In this view of memory consolidation, a newly encoded memory trace is initially stored in the hippocampus, and then during sleep, the temporary trace is reactivated and transferred to the cortex where enduring plastic changes occur to form long-term memories. Animal and human studies suggest that this ‘replaying’ of memory traces is mediated by hippocampal ripples which are temporally correlated with sleep spindles, and that spindles, in turn, are typically phase-locked with slow waves. This temporal coordination may facilitate synaptic plasticity by aligning hippocampal replay activity with periods of high cortical excitability during the depolarized upstate of slow waves (Mölle and Born 2011).

The slow wave and spindle deficits observed in schizophrenia therefore point to a fundamental dysfunction of the thalamocortical network. This is corroborated by findings of disrupted functional and structural thalamocortical connectivity in MRI studies. Further support for this notion comes from a recent study in a rat model of schizophrenia.

Administration of mitotoxin methylazoxymethanol acetate to pregnant rats results in offspring that exhibit physiological and cognitive dysfunction reminiscent of schizophrenia, including impaired spatial working memory. Phillips et al. (2012) reported that these animals also showed disruption of thalamocortical coordination during NREM sleep. Slow wave synchrony and propagation across the cortex were impaired, spindle phase-locking to delta waves was disrupted and hippocampal ripples were temporally uncoupled from spindles. This loss of coordination may underlie the cognitive and memory deficits seen in this rat model and in schizophrenia patients.

One possible cause of thalamocortical dyscoordination in schizophrenia is the thalamic reticular nucleus, a structural and functional hub of thalamocortical connectivity. In addition to its role as the spindle generator, the TRN is ideally placed to modulate bottom-up and top-down processes underlying higher cognitive function. It directly innervates the thalamus and receives excitatory inputs from thalamocortical and cortico-thalamic projections (Jones 2007). The TRN acts as an integrator of multiple functional modalities, amplifying relevant information and attenuating irrelevant or distracting information (Pinault 2011); as a result, the TRN has been central to theories of attention regulation (Crick 1984), sensory gating (Yingling and Skinner 1977), and self-representation (Vukadinovic 2011), all of which are impaired in schizophrenia. Evidence from molecular, animal, and human studies indicates a neurobiological dysfunction in the TRN in schizophrenia (for recent reviews, see Ferrarelli and Tononi 2011; Vukadinovic 2011).

TRN interneurons and outputs to thalamic relay nuclei are entirely GABAergic (Houser et al. 1980). The mechanism of synchronization across TRN cells is still largely unknown. GABAergic synapses between TRN neurons are one possibility; GABA receptors give rise to depolarizing currents in TRN neurons, which generate persistent spindle oscillations in these cells (Bazhenov et al. 1999; Golomb et al. 1994). Both dopamine and glutamate have been proposed to contribute to GABA hypofunction in the TRN, and the NMDAR-antagonist ketamine, which produces schizophrenia-like symptoms in humans and animals, has been shown to block thalamocortical rhythmicity (Buzsáki 1991). The GABA hypofunction observed in schizophrenia could therefore contribute to decreased spindle synchronicity, resulting in uncoordinated thalamocortical rhythms and consequently impaired plasticity.

The TRN also plays a role in embryonic development, providing axonal guidance for thalamocortical and cortical thalamic neurons (Pinault 2011). Animal studies indicate that aberrant TRN-dependent processes during critical periods of development could lead to higher-order cognitive impairments. Normally developing human and rat neonates exhibit spontaneous muscle twitches and jerks. In rats, sensory feedback from these movements triggers spindles in a somatotopic manner in primary somatosensory cortex (S1) and similar EEG bursts are observed in preterm infants (Khazipov et al. 2004); the authors hypothesize that coordinated motor-spindle activity establishes a map of the muscular system in S1 and strengthens developing thalamocortical and motor-sensory connections. Thus, spindle activity during fetal development may contribute to the development of neuronal self-representation. Importantly, an inability to correctly identify self-generated actions and thoughts may result in misattribution of mental experience to an external source and this can

manifest itself as psychosis, including auditory hallucinations. Disruption of spindle-mediated plasticity during sensorimotor development could therefore contribute to positive symptoms of schizophrenia such as hearing voices (Vukadinovic 2011).

8 Impact of Medication on Sleep and Plasticity

There is a need for new drugs to treat schizophrenia, as many of the cognitive symptoms are not improved by medication (Reichenberg and Harvey 2007). The strong link between memory and spindles and slow waves makes them an attractive target for therapy. Most medications used to treat schizophrenia are thought to exert their antipsychotic effects through antagonism of dopamine receptors, but they may also interact with acetylcholine, serotonin, and histamine receptors. A drug's relative affinity for these different receptors gives rise to a variety of side effects, including sedation (via serotonergic and histaminergic pathways), movement abnormalities (via dopaminergic pathways), and disruption of REM sleep (via anticholinergic and serotonergic actions) (Krystal et al. 2008). Both spindles and slow waves are modulated by these neurotransmitter systems and are therefore sensitive to pharmacological manipulation by antipsychotics, with the potential for cognitive benefits as well as undesirable side effects.

Animal studies suggest that current antipsychotics interact with the TRN. Phencyclidine (PCP) is an NMDA-receptor antagonist that induces schizophrenia-like behavioral symptoms in humans and animals; therefore, it is used as a pharmacological model of the disease. PCP administration in rats induced metabolic hypofunction within the TRN, which was reversed after coadministration of typical (haloperidol) or atypical (clozapine) antipsychotics with PCP (Cochran et al. 2002, 2003). PCP also induced excitotoxic lesions in the posterior cingulate and retrosplenial cortices of rats following injections into the anterior thalamus. These lesions were likely due to reduced inhibitory control of the TRN on anterior thalamic nuclei, which led to excessive activation (excitotoxicity) of corticolimbic areas. Importantly, these excitotoxic effects on the rat brain could be prevented by administering antipsychotic medications, such as haloperidol and clozapine (Olney et al. 1991; Sharp et al. 2001; Tomitaka et al. 2000). However, despite the interaction of current anti-psychotics with the TRN, they do not appear to normalize spindles in cross-sectional samples (Ferrarelli et al. 2010b). Within-subject trials are needed to confirm the effects of medication on spindle parameters.

Some recent studies have investigated the utility of drugs that influence spindle activity, with mixed success. A study in healthy individuals used zolpidem (Ambien) to increase the number of spindles during a daytime nap. The spindle increase was associated with improved verbal memory but not motor learning and was detrimental to perceptual learning (Mednick et al. 2013). Whether the decrement in perceptual learning related to increased spindles or some other effect of the drug is unclear. A recent study of medicated schizophrenic patients suggests a potential benefit of spindle enhancement, although the study may have been underpowered. Eszopiclone (Lunesta), a non-benzodiazepine hypnotic, was used to increase spindle number and density (Wamsley et al. 2013). The eszopiclone group showed significant overnight improvement on a motor learning task and the placebo group did not; however, the difference between the two groups was not significant. When the

groups were combined, spindle number and density correlated with overnight motor task improvement, as has been shown in non-intervention studies.

Olanzapine and risperidone, although primarily antagonists of the D2 receptor, are thought to increase SWS through antagonism of serotonin-2 receptors (Krystal et al. 2008). Given the benefit of SWS to learning in healthy individuals, these agents might be expected to improve memory in schizophrenia. However, this hypothesis was not supported when olanzapine was administered to schizophrenia patients who were also chronically medicated with amisulpride, another atypical antipsychotic (Göder et al. 2008). Before bedtime, patients were trained on visuomotor and verbal memory tasks and then took a single dose of either olanzapine or placebo. SWS was increased in the olanzapine group as expected, but memory performance the following morning did not differ between groups. Spindle density was significantly decreased in the olanzapine group, which could have negated any putative benefits of increased SWS.

Manipulating sleeping brain activity to improve cognitive function in schizophrenia is a promising avenue of research, but it remains to be seen which sleep parameters should be targeted and which interventions are most effective. A better understanding of the cellular dynamics and neuropharmacology of sleep spindles and slow waves could provide new insights into the mechanisms of current drug actions and more focused targets for drug development.

9 Conclusion

Brain activity during sleep reveals important clues to the biological underpinnings of schizophrenia, a widespread mental illness with devastating consequences for individuals and society. Disrupted sleep appears to contribute to cognitive deficits including memory impairment and psychotic symptoms. Abnormalities of sleep EEG draw attention to dysfunction of plastic processes including neurodevelopment, neurotransmitter pathways, and specific neuronal structures such as the thalamic reticular nucleus and thalamocortical circuits. Further investigation of sleeping brain activity in schizophrenia has the potential to uncover mechanisms and biomarkers of the disease as well as provide promising targets for drug development.

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Table 1

Diagnostic criteria for schizophrenia. Adapted from DSM-5, the American Psychiatric Association (2013)

Two or more of the following present for at least one month (less if treated)
Positive symptoms (at least one)
• Delusions
• Hallucinations
• Disorganized speaking and thinking
• Disorganized or catatonic behavior
Negative symptoms
• Affective flattening
• Diminished fluency and productivity of thought and speech (alogia)
• Lack of motivation (avolition)
Other criteria
Continuous signs of disturbance for at least 6 months
Social/occupational dysfunction in work, self-care, or interpersonal relationships

Table 2

Biological hypotheses of schizophrenia

Description	Selected reviews	Relevance to sleep and plasticity
Neurodevelopmental hypothesis		
Disturbances during critical periods of brain development results in lesions that produce the symptoms of schizophrenia. Disturbances could result from genetic or environmental factors.	Fatemi and Folsom (2009), Rapoport et al. (2012)	• Slow waves and spindles reflect and participate in cortical maturation • Slow wave and spindle deficits may indicate aberrant neural development • Disruption of thalamocortical system during development would lead to impaired slow wave- and spindle-mediated plasticity
Dysconnection hypothesis		
Abnormal modulatory activity of neurotransmitters including DA, ACh, and 5-HT results in altered regulation of NMDA-receptor-mediated plasticity. The resulting abnormal functional integration between brain regions gives rise to symptoms of schizophrenia.	Stephan et al. (2009)	• NMDAR inactivation may disrupt thalamocortical oscillations, leading to spindle and slow wave deficits that would impact sleep-dependent memory processes
Dopamine hypothesis		
Multiple environmental and genetic factors lead to increased presynaptic striatal dopaminergic function. Dysregulation of dopamine-driven circuits of stimulus salience and reward lead to the positive and negative symptoms of schizophrenia.	Howes and Kapur (2009)	• D4 receptor excess could disrupt circadian signaling and thalamocortical oscillations • COMT SNP shows impaired memory and altered responses to sleep-suppressing agents
NMDAR hypofunction hypothesis		
NMDAR antagonists produce schizophrenia-like symptoms in humans and animals, leading to the hypothesis that NMDAR hypofunction is a core pathological mechanism of schizophrenia. This hypofunction impacts other neurotransmitter systems and may result from genetic and non-genetic factors early in life.	Gilmour et al. (2012), Olney et al. (1999)	• Hypofunction of NMDARs on TRN neurons would reduce reticular inhibition of thalamocortical neurons and lead to cortical hyperactivity, giving rise to disrupted plasticity and psychotic symptoms
Genetic hypotheses		
A single genetic cause of schizophrenia is unlikely. Genetic hypotheses propose polygenic inheritance patterns, post-fertilization mutations due to genetic or epigenetic factors, or some combination of these.	Kim et al. (2011), Owen (2012)	• COMT regulates DA levels, which impact sleep-dependent plasticity in the PFC and TRN • Flies expressing DISC1 show altered sleep duration. During neurodevelopment, DISC1 is expressed in the TRN, which generates sleep spindles

ACh acetylcholine; *COMT SNP* catechol-o-methyl transferase single nucleotide polymorphism; *DISC-1* disrupted-in-schizophrenia-1; *DA* dopamine; *5-HT* serotonin; *NMDAR* N-methyl-D-aspartate receptor; *PFC* prefrontal cortex; *TRN* thalamic reticular nucleus