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Neural oscillations during non-rapid eye movement sleep as biomarkers of circuit dysfunction in schizophrenia

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Abstract

The neurophysiology of non-rapid eye movement sleep is characterized by the occurrence of neural network oscillations with distinct origins and frequencies, which act in concert to support sleep-dependent information processing. Thalamocortical circuits generate slow (0.25–4 Hz) oscillations reflecting synchronized temporal windows of cortical activity, whereas concurrent waxing and waning spindle oscillations (8–15 Hz) act to facilitate cortical plasticity. Meanwhile, fast (140–200 Hz) and brief (< 200 ms) hippocampal ripple oscillations are associated with the reactivation of neural assemblies recruited during prior wakefulness. The extent of the forebrain areas engaged by these oscillations, and the variety of cellular and synaptic mechanisms involved, make them sensitive assays of distributed network function. Each of these three oscillations makes crucial contributions to the offline memory consolidation processes supported by non-rapid eye movement sleep. Slow, spindle and ripple oscillations are therefore potential surrogates of cognitive function and may be used as diagnostic measures in a range of brain diseases. We review the evidence for disrupted slow, spindle and ripple oscillations in schizophrenia, linking pathophysiological mechanisms to the functional impact of these neurophysiological changes and drawing links with the cognitive symptoms that accompany this condition. Finally, we discuss potential therapies that may normalize the coordinated activity of these three oscillations in order to restore healthy cognitive function.

Introduction

Sleep is a highly evolutionarily conserved process and is tightly regulated by circadian rhythms and homeostatic mechanisms (Borbély & Achermann, 1999; Tononi & Cirelli, 2006). Different sleep stages are characterized by specific neuronal network activity patterns that reflect state-dependent oscillations spanning the neocortex, thalamus and hippocampus. These oscillations do not occur in isolation, but are coordinated across different spatial and temporal scales, with the extent of coordination reflecting the strength of coupling between the networks involved. Sleep neurophysiology is therefore a sensitive indicator of distributed network function in health and disease.

Sleep disturbances are a common feature of most major psychiatric diseases, although the precise nature of sleep phenotypes varies across diagnostic categories and individuals. For example, sleep irregularities are a predictor for schizophrenia (SCZ) and mood disorders (Ford & Kamerow, 1989; Breslau *et al.*, 1996). Disrupted sleep patterns can coincide with abnormal neurophysiology during sleep (Keshavan *et al.*, 2011) and may reflect the convergence of neurodevelopmental (Lewis & Levitt, 2002; Lynall *et al.*, 2010) and circadian (Wulff *et al.*, 2012) abnormalities impacting neuronal network development, connectivity and function.

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Here, we review the basic neurophysiology of forebrain population activity during sleep, with a particular focus on non-rapid eye movement (NREM) sleep and the three major brain areas involved in generating its characteristic oscillatory patterns: the neocortex, thalamus and hippocampus (Sejnowski & Destexhe, 2000). We review known pathologies in the respective areas in SCZ and their possible impact on sleep physiology and consider the functional implications of aberrant neuronal network activity. We then describe the interaction of different brain areas during NREM sleep in the healthy brain and in relation to molecular, cellular and anatomical pathologies in SCZ. Finally, we discuss emerging diagnostic and therapeutic approaches that may help to restore normal sleep neurophysiology and could thus be beneficial in the treatment of SCZ symptoms. We hope to highlight convergent results from preclinical and clinical research and through this promote new translational approaches targeting the neurophysiology of sleep in psychiatry.

Neurophysiology of non-rapid eye movement sleep

Non-rapid eye movement sleep shows characteristic neural network oscillations that have been used to distinguish different sleep stages since studies of sleep electroencephalography (EEG) patterns during the 1960s (Rechtschaffen & Kales, 1968). The initial light stages (stages 1 and 2) of NREM sleep are identified based on the appearance of waxing and waning thalamocortical (TC) spindle oscillations at frequencies from 8 to 15 Hz. Deeper NREM sleep is dominated by slow oscillations in the range of 0.25–4 Hz (formerly stages 3

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and 4, which have now been combined into slow-wave sleep). In addition, deep brain recordings in rodents and humans have revealed fast 'ripple' oscillations (140–200 Hz) in CA1 and CA3 regions of the hippocampus during NREM sleep. Below we give a brief overview of the circuit, cellular and synaptic mechanisms involved in generating these characteristic NREM sleep oscillations, which is crucial for understanding sleep physiology deficits seen in SCZ.

Neurophysiology of (thalamo)-cortical slow-wave activity

Slow EEG oscillatory activity in the range of 0.25–4 Hz is a defining feature of deep NREM sleep (Halász, 2005) [note, however, that ultra-slow activity may also be observed under appropriate recording conditions (Tallgren *et al.*, 2005)]. This frequency range has been referred to as slow-wave and/or delta activity. The 'slow-wave' and 'delta' labels are often used interchangeably in the literature, but delta oscillations [first described in the 1930s by William Grey Walter (Walter, 1963)] appear to oscillate slightly faster (1–4 Hz). Although delta waves may share some circuit elements with slow-wave-generating networks, delta oscillations may constitute a separate physiological phenomenon, for example Steriade and colleagues showed distinct firing of thalamic cells in synchrony with delta frequency field potential oscillations (Dossi *et al.*, 1992; Amzica & Steriade, 1997a). A recent *in vitro* model of delta oscillations (which can be induced in frontal slice preparations following blockade of dopamine and acetylcholine neurotransmission) showed that intrinsically bursting cells in layer 5 are involved in generating delta activity (Carracedo *et al.*, 2013). Other recent studies have shown synchronized delta oscillations in the frontal and parietal cortices during working memory in rats and monkeys (Fujisawa & Buzsáki, 2011; Nácher *et al.*, 2013). How these wakeful delta oscillations are related to sleep oscillations in the same frequency range has so far not been addressed systematically. Alongside sustained slow oscillations during NREM sleep, individual events including K-complexes (Loomis *et al.*, 1938; reviewed in Colrain, 2005) and vertex sharp waves (Barlow, 1993) also contribute to low-frequency power.

However, macroscopic low-frequency power in cortical tissue during NREM sleep is dominated by slow waves (0.25–1 Hz), which have been linked to bistable cortical state transitions (Steriade *et al.*, 1993a,b), and may also contribute to K-complexes (Amzica & Steriade, 1997b; Cash *et al.*, 2009). Slow waves are local field potential and EEG signatures of cortical network transitions between high and low activity states: a depolarized UP state associated with neuronal spiking and a low-activity DOWN state with little firing or synaptic drive (Steriade *et al.*, 1993a,b). The membrane potentials of pyramidal cells therefore display a characteristic bimodal distribution during slow waves, with the origin of UP/DOWN state transitions focused in the deep layers of the cortex (Amzica & Steriade, 1997b; Sanchez-Vives & McCormick, 2000; Chauvette *et al.*, 2010; Beltramo *et al.*, 2013).

In sleep EEG recordings, slow waves tend to initiate in frontal areas and can propagate as travelling waves towards parietal and occipital regions in both humans and rats (Massimini *et al.*, 2004; Murphy *et al.*, 2009; Vyazovskiy *et al.*, 2009; Hangya *et al.*, 2011). Thus, single evoked slow waves or the spiking of small groups of deep layer pyramidal neurons can initiate waves of activity that reach distant cortical sites at the single-cell level (Chauvette *et al.*, 2010; Stroh *et al.*, 2013). However, slow waves at the EEG level do not always propagate and may sometimes reflect localized events affecting only small areas of the cortex; these 'local' slow waves have been particularly correlated with homeostatic sleep pressure in rats and humans (Huber *et al.*, 2004; Vyazovskiy *et al.*, 2011).

Electrophysiology and large-scale network modelling approaches suggest that both intrinsic and synaptic mechanisms contribute to slow wave generation and propagation. In one of the first detailed biophysical simulations of UP/DOWN state transitions in cortical tissue, Compte *et al.* (2003) combined data from slice experiments with large network simulations of deep layer cortical networks. They estimated a balance of excitation and inhibition during the UP state and suggested that Na^+-dependent K^+ channels [$I_{Na(K)}$] regulate UP state duration. This balance of excitation and inhibition was also confirmed experimentally (Shu *et al.*, 2003; Peyrache *et al.*, 2012). Other models came to similar conclusions, indicating that both intrinsic and synaptic properties are involved in guiding UP/DOWN state dynamics. Hill & Tononi (2005) concluded that a persistent sodium current (I_{Nap}) and hyperpolarization-activated current (I_h) are involved in the initiation of UP states, whereas K^+ channels (I_{dK}) and synaptic depression both aid in the termination of the UP state. However, a recent study has shown that the selective forebrain hyperpolarization-activated cyclic nucleotide-gated channel knockout has little influence on UP/DOWN transitions in mice (Thuault *et al.*, 2013), which questions the influence of I_h on UP state initiation and maintenance.

Others have suggested the existence of preferentially excitable cells in cortical networks that could act as initiators of UP states (Cossart *et al.*, 2003), and recently these pacemaker cells were identified through large-scale calcium imaging in slice preparations (Bon-Jego & Yuste, 2007). Concurrent single-cell recordings showed that spontaneously active 'pacemaker' cells possess a higher persistent sodium current (I_{Nap}). Recently, Destexhe (2009) proposed a simpler mechanism where cells with high adaptation create UP/DOWN state transitions in small network models, whereas other models have emphasized the importance of connectivity and inhibition for large-scale synchronization of state transitions (Chen *et al.*, 2012). Another new development is the acknowledgement of astrocyte signalling as an influence on slow waves (Fellin *et al.*, 2012).

The respective roles of the cortex and thalamus in generating slow waves are debated. *In vitro*, slow waves have been demonstrated in isolated cortical slices (Sanchez-Vives & McCormick, 2000; Timofeev *et al.*, 2000), whereas the decorticated thalamus *in vivo* failed to show slow oscillations (Timofeev & Steriade, 1996). However, the absence of slow oscillations in the decorticated thalamus may result from the absence of tonic corticothalamic glutamatergic drive; later studies showed that, *in vitro*, slow oscillatory bursting patterns are seen in both TC and thalamic reticular nucleus (TRN) cells when metabotropic glutamate receptors are tonically activated (Hughes *et al.*, 2002; Blethyn *et al.*, 2006). The low-threshold Ca^{2+} bursts fired by TC cells have been predicted to be effective at causing UP/DOWN state transitions in the cortex (Crunelli *et al.*, 2011) but, conversely, an optogenetic *in vivo* study showed that stimulation of layer V cortical neurons was more effective at eliciting global slow waves than stimulation of TC cells (Stroh *et al.*, 2013). It is likely that the intrinsic oscillatory capacities of the cortex and thalamus act synergistically to generate synchronized slow waves (Crunelli & Hughes, 2010).

As the mechanistic differences between inter-related low-frequency events have not been unequivocally resolved, we will refer to slow oscillations in the frequency range of 0.25–4 Hz as 'slow-wave activity' (SWA).

Neurophysiology of thalamocortical spindles

During NREM sleep, the occurrence of SWA is typically accompanied by brief episodes of faster oscillatory activity known as

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sleep spindles. These 0.5–3 s events are marked by high-amplitude, waxing and waning deflections in the EEG or local field potential occurring either locally or simultaneously over wide areas of the neocortex. In humans, spindles are a feature of the intermediate and deep stages of NREM sleep, although they are also seen under some types of general anaesthesia, which have commonly been used as models of sleep in animal studies. Spindles have been observed in numerous mammalian species, reptiles (De Vera *et al.*, 1994) and amphibians (Fang *et al.*, 2012); therefore, they may be a universal feature of sleep among land-dwelling vertebrates.

The mechanisms at the core of spindle oscillations are found in the thalamus where, during NREM sleep, neurons become hyperpolarized and enter a burst-firing mode. Under these conditions, the reciprocal circuit linking inhibitory TRN cells and excitatory TC cells generates rhythmic bursting activity that acts as the 'pacemaker' of the spindle oscillation. The thalamic mechanisms of spindle generation have been well characterized (McCormick & Bal, 1997); by comparison, the nature and role of cortical activity during spindles are much less clear. Whereas spindle-like events can be artificially elicited by stimulation of the TRN (Halassa *et al.*, 2011), cortical stimulation is also effective (Contreras & Steriade, 1996; Vyazovskiy *et al.*, 2009), suggesting that corticothalamic inputs may be an important influence on spindles. Indeed, thalamic spindles persist after the removal of the cortex in anaesthetized cats, but they occur in an uncoordinated manner (Contreras *et al.*, 1996); therefore corticothalamic feedback is believed to aid long-range spindle synchrony. Furthermore, the combination of *in vivo* recordings with *in silico* TC network models has led to an emerging hypothesis that corticothalamic feedback additionally contributes to the termination of spindles by desynchronizing the rhythmic activity of the TRN–TC spindle pacemaker circuit (Timofeev *et al.*, 2001; Bonjean *et al.*, 2011; Gardner *et al.*, 2013).

In humans, there is considerable variation of spindle activity across the cortical mantle. The majority of spindle epochs are restricted to small regions of the cortex, whereas global spindles are comparatively rare (Nir *et al.*, 2011). Furthermore, a number of studies have observed two types of spindles with distinct spatial and frequency distributions (Zygierewicz *et al.*, 1999; Anderer *et al.*, 2001; Mölle *et al.*, 2011). According to these findings, 'fast' spindles tend to occur at central and parietal locations, whereas 'slow' spindles are found in frontal areas and tend to occur after fast spindles. However, evidence for intraspindle changes in frequency suggests that there may be some overlap between fast and slow spindle activity (Andrillon *et al.*, 2011; Gardner *et al.*, 2013). The physiological basis and functional relevance of distinct fast and slow spindles, or of intraspindle frequency dynamics, are not yet clear.

In addition, there is an apparent dichotomy between local spindle activity recorded by magnetoencephalography and global synchronized spindle activity as evident in scalp EEG recordings (Dehghani *et al.*, 2011). It may be that EEG, which is less sensitive to local events, only registers spindles that are highly synchronized across the cortex, whereas magnetoencephalography is also able to detect localized pockets of spindle activity that do not become globally coherent. In a recent modelling study, globally synchronized spindles were linked to diffuse TC projections originating in the matrix of the thalamus (Bonjean *et al.*, 2012).

Neurophysiology of hippocampal ripples

Hippocampal population activity in rodents and humans during NREM sleep or quiet wakefulness is characterized by the synchronous emergence of sharp waves (2–4 Hz) and high-frequency ripple oscillations (140–200 Hz) termed 'sharp-wave ripple' (SWR) events (for review see Buzsáki & da Silva, 2012). SWRs were first recorded in rodents (O'Keefe & Nadel, 1978; Buzsaki *et al.*, 1992), but were later observed in non-human primates (Skaggs *et al.*, 2007) and humans (Bragin *et al.*, 1999; Clemens *et al.*, 2007). Although ripple oscillations appear to be slower in humans compared with rodents, they share similar cellular mechanisms (Quyen *et al.*, 2008): they are thought to originate as highly synchronized firing in the strongly recurrent network of CA3 and propagate down the CA1–subicular–entorhinal axis (Chrobak & Buzsáki, 1996) and are most pronounced in the pyramidal cell layer of CA1.

The precise biophysical and network mechanisms underlying SWR generation are not completely understood. For example, despite the extensive innervation of CA1 by CA3 Schaffer collaterals, pyramidal cells in CA1 can either participate or be silent during individual ripple events (Royer *et al.*, 2012). This selective activation probably stems from the large number of local interneuron cell types that exert tight control over pyramidal cell activation during ripple events (Ylinen *et al.*, 1995; Klausberger *et al.*, 2003; Klausberger & Somogyi, 2008; Cutsuridis & Taxidis, 2013). One particularly important mechanism that contributes to ripple oscillations appears to be perisomatic inhibition from parvalbumin (PV)-positive interneurons onto pyramidal cells. PV-positive basket cells (and bistratified cells) show a strong increase in firing rate during ripples, whereas other interneuron types stay nearly silent during ripple events (Klausberger *et al.*, 2003). The crucial involvement of PV-positive interneurons suggests that any basket cell dysfunction is likely to manifest in altered ripple patterns and disrupted hippocampal function during NREM sleep.

A combination of *in vivo*, *in vitro* and computational modelling studies have tried to pin down specific intrinsic and synaptic biophysical mechanisms that contribute to ripple generation and propagation along the hippocampal formation (Draguhn *et al.*, 1998; Traub & Bibbig, 2000; Maier *et al.*, 2003; Geisler *et al.*, 2005; Cutsuridis & Taxidis, 2013). The generation and propagation of ripples have been attributed to intrinsic properties of participating neurons, such as the effective membrane time constant and the balance of excitation and inhibition (Geisler *et al.*, 2005). Furthermore, some studies have emphasized the importance of axo-axonic coupling between pyramidal cells through gap junctions for ripple initiation and synchronization across the hippocampus (Traub & Bibbig, 2000). Indeed, it has been suggested that antidromic activation of axonic compartments in CA1 pyramidal cells, combined with strong perisomatic inhibition, constitutes a fundamental aspect of fast oscillations (Epsztein *et al.*, 2010; Bähner *et al.*, 2011).

In addition, various studies have identified synaptic mechanisms involved in ripple generation. It is believed that ripple generation critically depends on synaptic AMPA and GABA currents (Csicsvari *et al.*, 2000; Maier *et al.*, 2003; Wu *et al.*, 2005). A recent model integrates axo-axonic and synaptic mechanisms by demonstrating a gating mechanism of low-amplitude axonic activity that is brought to suprathreshold level through coherent synaptic inputs (Vladimirov *et al.*, 2013).

Non-rapid eye movement sleep deficits in schizophrenia and possible underlying pathologies

Overall sleep deficits in schizophrenia

Sleep disruptions have long been recognized as a symptom in SCZ. Patients with SCZ show increased sleep latency, reduced rapid eye movement latency, reduced NREM sleep and total sleep time across the whole night (Poulin *et al.*, 2003; Göder *et al.*, 2004; Keshavan

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et al., 2011). These results survived a meta analysis that included patients without neuroleptic treatment at the time of recording (Chouinard *et al.*, 2004). NREM sleep properties have been linked to the cognitive symptom cluster in SCZ (Yang & Winkelman, 2006; Wamsley *et al.*, 2012). Although some of the sleep disruptions in SCZ might stem from circadian rhythm abnormalities (Bromundt *et al.*, 2011; Wulff *et al.*, 2012), we will discuss the known pathophysiologies in SCZ and their possible impact on sleep physiology and cognitive function in SCZ.

Slow-wave activity abnormalities in schizophrenia

Given its dependence on complex interactions between cellular excitability, excitatory–inhibitory balance, local and long-range connectivity and neuronal–glial interactions, SWA is a sensitive metric of cortical function, and aberrant SWA is associated with pathological states during sleep and wake. The number of slow-wave events or delta power during sleep in patients with SCZ has been reported to be lower (Keshavan *et al.*, 1998; Hoffmann *et al.*, 2000; Göder *et al.*, 2006), although this is not the case in all studies (Keshavan *et al.*, 2011). Where a specific reduction in SWA has been reported, changes have typically been limited to occipital and temporal regions (Göder *et al.*, 2006) or to a missing frontal asymmetry of slow-wave counts in SCZ (Sekimoto *et al.*, 2007).

Several of the hallmark neuropathologies of SCZ (Pearlson & Marsh, 1999) are likely to contribute to the SWA abnormalities evident in EEG. These include enlarged ventricles (Van Horn & McManus, 1992), reduced cortical thickness (Kuperberg *et al.*, 2003), and reduced volume of association cortices (Davidson & Heinrichs, 2003) and thalamus (Konick & Friedman, 2001). At the cellular level, altered GABAergic tone reflected by reduced expression of glutamate decarboxylase (GAD) 67 (Akbarian *et al.*, 1995; Volk *et al.*, 2000) is likely to affect the proposed balance of excitation and inhibition, implicated in the initiation, maintenance and propagation of slow waves. In particular, PV-positive interneurons have consistently been linked to SCZ (Hashimoto *et al.*, 2003) and may contribute to the generation of SWA (Compte *et al.*, 2003).

Equally, cellular pathologies of excitatory pyramidal cells in frontal cortices have been reported. Early studies identified smaller somas (Rajkowska *et al.*, 1998; Pierri *et al.*, 2003) and reduced dendritic spine density in layer 2/3 pyramidal cells in SCZ (Garey *et al.*, 1998; Glantz & Lewis, 2000). Pathologies of the major output neurons of the cortex layer 5 pyramidal cells have also been identified, for example reduced basal dendrite field size (Broadbelt *et al.*, 2002; Black *et al.*, 2004).

Cellular mechanisms of disrupted SWA in patients are increasingly informed by animal models, although inter-relationships between sleep patterns and sleep neurophysiology in animal models of SCZ have only been examined very recently. One of the earliest results showed that the addition of a truncated version of disrupted in schizophrenia 1 to the *Drosophila* genome induces prolonged sleep episodes (Sawamura *et al.*, 2008). With a point mutation in a synaptic protein that leads to disrupted exocytosis, blind-drunk (Bdr) mice show a fragmented sleep phenotype linked to circadian rhythm disruptions, but EEG was not performed (Oliver *et al.*, 2012). Most recently, Phillips *et al.* (2012a) showed that fragmented NREM sleep in the methylazoxymethanol acetate (MAM-E17) rat neurodevelopmental model of SCZ is associated with reduced SWA power and reduced coherence between remote cortical areas. Interestingly, Moore *et al.* (2006) reported reduced bistability in the membrane potential of frontal pyramidal cells in MAM-E17 animals, which might provide a cellular basis for the reduced SWA observed *in vivo* in this animal model of SCZ (Phillips *et al.*, 2012a). As the density of PV-positive interneurons has been shown to be selectively reduced in the MAM-E17 model (Phillips *et al.*, 2012b), a consequent impairment in the excitation–inhibition balance may underpin this phenotype and associated cognitive deficits seen in this particular model of SCZ (Flagstad *et al.*, 2004).

Alongside fast excitatory and inhibitory transmission, neuromodulation is also likely to contribute to SWA and its pathology. For example, dopamine physiology is affected in SCZ (Davis *et al.*, 1991). As dopamine is known to introduce bistability in cortical pyramidal cells and networks (Durstewitz & Seamans, 2002; Seamans & Yang, 2004), it is conceivable that dysfunctional dopamine physiology will affect SWA generation. Indeed, dopamine transporter knockout mice display severe disruptions in sleep state control (Dzirasa *et al.*, 2006).

Given the involvement of all these observed pathologies in slow-wave sleep, SWA presents itself as a useful indicator of cortical circuit functionality in psychiatry, where spontaneous circuit dynamics during sleep are unbiased by attention and potentially less affected by the specific experimental paradigms used.

Spindle abnormalities in schizophrenia

Novel insights into sleep physiology in SCZ stem from a series of studies reporting a distinct spindle phenotype: In patients with SCZ, reductions of spindle activity have been observed during daytime naps and overnight sleep (Ferrarelli *et al.*, 2007, 2010; Manoach *et al.*, 2010; Seeck-Hirschner *et al.*, 2010), and a rat model of the disorder recapitulates this phenotype (Phillips *et al.*, 2012a).

The underlying cause of the recently discovered spindle phenotype in SCZ is unclear. However, as the key pacemaking circuit for spindles is located in the thalamus, disrupted function in this brain region could explain the deficit in spindle activity. In support of this, structural magnetic resonance imaging studies of patients have revealed thalamic abnormalities in patients with first-episode and chronic SCZ (Adriano *et al.*, 2010; Smith *et al.*, 2011). The essential role of the TRN in spindle generation, in addition to the involvement of this nucleus in functions such as sensory gating and attentional shifting, which are also impaired in SCZ, has led to a hypothesis that TRN dysfunction could underlie the spindle phenotype (Ferrarelli & Tononi, 2011). Another specific anatomical substrate of the spindle deficit could lie in the matrix pathway of the thalamus, which in a recent modelling study was shown to generate highly synchronized spindles as measured with EEG (Bonjean *et al.*, 2012). This raises the possibility that the reduced spindle power and coherence observed in EEG recordings from patients with SCZ stem from abnormalities in the TC matrix pathway.

However, the crucial role of the cortex in initiating spindles and maintaining synchrony of the oscillation across the TC network also lends possibility to a significant cortical contribution to the spindle deficit in SCZ. One of the most consistent neuropathologies found in SCZ postmortem studies is a reduction in the expression of genes associated with GABAergic signalling, including PV, GAD-67, and the GABA transporter GAT-1 (Lewis *et al.*, 2012; Jiang *et al.*, 2013). Although the functional impact of these expression changes is unclear, it is thought that widespread disruption in the functioning of these cells could lead to significant changes in the cortical excitatory–inhibitory balance (Lewis *et al.*, 2012). Furthermore, compared with cortical pyramidal cells, fast spiking cells receive particularly strong monosynaptic projections from TC cells (Cruikshank *et al.*, 2007; Bagnall *et al.*, 2011), which may underlie the strong activation and phase locking of these cells during spindle oscillations (Gardner *et al.*, 2013).

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Fast spiking cells are believed to inhibit cortical pyramidal cells in a rapid feedforward process that regulates their responses to monosynaptic TC inputs (Gabernet *et al.*, 2005). Dysfunction of fast spiking cells may therefore result in the loss of this precise feedforward inhibition and lead to unregulated pyramidal cell responses to the volleys of TC activation that occur during spindles.

Ripple abnormalities in schizophrenia

There is considerable evidence for hippocampal dysfunction in SCZ from behavioural studies and from functional and structural imaging of awake brain activity (Harrison, 2004; Tamminga *et al.*, 2010). Examples include reduced hippocampal size (Steen *et al.*, 2006), specific cellular pathologies (Weinberger, 1999) and reduced expression of GABAergic and glutamatergic molecular markers in patients (Simpson *et al.*, 1998; Deicken *et al.*, 1999). In addition, neonatal lesions of the ventral hippocampus lead to a SCZ-like phenotype in rats (Lipska *et al.*, 1993; Lipska & Weinberger, 2000).

Although the availability of non-invasive EEG recordings in humans has enabled the characterization of slow-wave and spindle activity in SCZ, little is known about the characteristics of SWRs in SCZ (in contrast to epilepsy, where hippocampal recordings are performed routinely). Instead, rodent models of SCZ have been used to study changes in hippocampal physiology during NREM sleep. In rats, the chronic injection of the *N*-methyl-D-aspartate antagonist phencyclidine does not alter core ripple properties (M.W.J., unpublished), and ripple characteristics in MAM-E17 animals (Moore *et al.*, 2006; Lodge & Grace, 2009) do not differ markedly from controls during sleep (Phillips *et al.*, 2012a).

Despite the lack of an overt ripple phenotype in these models, MAM-E17 and chronically phencyclidine-treated animals display deficits in PV expression in interneurons in the hippocampal CA1 region (Kaalund *et al.*, 2013). PV-positive interneurons in this area show phase-locked firing during ripple oscillations (Klausberger & Somogyi, 2008), which they are thought to maintain by exerting strong inhibition on pyramidal neurons, dramatically increasing their firing rates (Klausberger *et al.*, 2003; Cutsuridis & Taxidis, 2013). A study that used another animal model of SCZ, the dysbindin-1 mutant mouse, showed that reduced PV expression in the CA1 interneurons results in an impaired inhibition of CA1 pyramidal cells (Carlson *et al.*, 2011), which could affect ripple generation and maintenance.

A recent study measured ripple activity during awake and quiet rest in a forebrain-specific calcineurin knockout mouse, which has been identified as a risk gene in patients with SCZ (Suh *et al.*, 2013). They reported increased ripple power and density that coincided with over-reactivity of place cells during SWRs and less specific replay of spatial information during SWRs. This model differs from the models above in that it features increased synaptic plasticity, and higher place cell activity. It is important to note that Suh *et al.* (2013) specifically refer to ripple activity during awake rest, which might differ from ripples during NREM sleep. In our own analysis we found a higher occurrence of ripple activity specifically during awake behaviour in MAM-E17 rats (U.B. & M.W.J., unpublished data). Hence, there might be a differential effect of wake and sleep on SWR activity in SCZ.

Non-rapid eye movement sleep oscillations and cognition: implications for schizophrenia

A wealth of recent work has established the importance of NREM sleep for learning and memory in the healthy brain (Stickgold, 2005; Rasch & Born, 2013). Memory consolidation during sleep has recently been linked to the reactivation of activity patterns observed during wake behaviour. This 'replay' of neuronal activity is thought to constitute a neural correlate of memory consolidation during sleep in the hippocampus and cortex (Euston *et al.*, 2007; O'Neill *et al.*, 2010).

During wake, hippocampal place cells fire selectively in restricted regions (place fields) within an animal's environment (O'Keefe & Dostrovsky, 1971), enabling online encoding of spatial information (Rolls, 2010). When encoded, spatial memory is thought to undergo further consolidation and stabilization during sleep by reactivation, or 'replay', of firing patterns observed during online encoding (Wilson & McNaughton, 1994; Skaggs & McNaughton, 1996; Lee & Wilson, 2002; Luczak *et al.*, 2007). Replay of structured activity has also been described in the cortex (Hoffman & McNaughton, 2002; Ikegaya *et al.*, 2004). Moreover, correlated replay of activity sequences occurs simultaneously in the hippocampus and cortex (Ji & Wilson, 2007). This has been suggested to be a signature of information transfer from short-term hippocampal storage to long-term storage in the cortex (Schwindel & McNaughton, 2011).

Given that sleep physiology is impaired in SCZ it is likely that these disruptions contribute significantly to the cognitive symptoms observed (Yang & Winkelman, 2006; Manoach & Stickgold, 2009; Wamsley *et al.*, 2012). Given the strong associations between NREM sleep oscillations and replay in the cortex and hippocampus, we will describe evidence for the role of SWA, spindles and ripples in memory consolidation and how abnormal sleep physiology in SCZ could contribute to cognitive deficits. We end by emphasizing that synchronization between the cortex, hippocampus and thalamus is likely to play a crucial role in memory consolidation and evaluate connectivity deficits in SCZ in relation to NREM sleep oscillations.

Slow-wave activity has been correlated with overnight improvement in a simple episodic memory task (Mölle *et al.*, 2009), and increasing the number of slow waves during NREM sleep using transcranial stimulation augments overnight memory improvement (Marshall *et al.*, 2006). SWA has been shown to favour the reactivation of cortical neuronal spiking sequences both *in vivo* (Hoffman & McNaughton, 2002) and *in vitro* (Ikegaya *et al.*, 2004).

Indeed, some studies have linked the previously described SWA deficits in SCZ with cognitive abilities of patients (Keshavan *et al.*, 1998, 2011; Mohamed *et al.*, 1999; Forest *et al.*, 2007). Thus, although the functional consequences of reduced SWA in SCZ could also result from disrupted inter-relationships with other NREM sleep oscillations (see below), some mnemonic deficits may be direct correlates of impaired SWA.

There is also an increasing body of evidence that suggests a role for spindle oscillations in offline memory consolidation. In humans and rats, spindles increase in density after learning (Gais *et al.*, 2002; Eschenko *et al.*, 2006), and one report has shown such increases to be specific to the areas of cortex engaged by the behaviour (Johnson *et al.*, 2012). Furthermore, spindle activity predicts the degree of overnight improvement in task performance (Clemens *et al.*, 2005; Rasch *et al.*, 2009) and pharmacologically increasing spindle activity enhances the consolidation of declarative memories (Kaestner *et al.*, 2013; Mednick *et al.*, 2013). Treatments that increase NREM sleep but reduce spindles show no memory benefit (Feld *et al.*, 2013). Evidence from animal studies suggests that spindle activity is functionally related to frontal cortex replay events (Johnson *et al.*, 2010), and thus it seems possible that spindles may play a role in facilitating plasticity at synapses of neuronal assem-

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blies that have been reactivated by replay. The rhythmic TC spike volleys that occur during spindles are likely to induce Ca^{2+} entry into postsynaptic cortical cells and thus may induce long-term synaptic plasticity. This hypothesis is supported by a study, where an *in vivo* cortical spindle spiking pattern was replayed into the cortex *in vitro*, that found that this activity was able to induce long term potentiation (Rosanova & Ulrich, 2005).

The increasing evidence that spindles support offline memory consolidation raises the question of whether cognitive impairments in neuropsychiatric disorders could be a product of disrupted spindle-associated activity. Indeed, in recent studies, spindle deficits are accompanied by a reduced overnight improvement in procedural memory (Manoach *et al.*, 2010; Seeck-Hirschner *et al.*, 2010; Wamsley *et al.*, 2012), raising the possibility that reduced spindle activity in SCZ may contribute to impaired memory consolidation.

In the hippocampus, replay events occur preferentially during SWRs, and suppression of SWRs after learning impairs hippocampal memory consolidation, similar to that observed after surgically damaging the hippocampus (Girardeau *et al.*, 2009; Ego-Stengel & Wilson, 2010). Furthermore, as CA1 ripples co-occur with the replay of reward-related information in the ventral striatum (Pennartz *et al.*, 2004), it seems likely that hippocampus and sleep-dependent processing of information may go awry during affective state disorders.

Stronger ripple activity during rest observed in one animal model of SCZ (Suh *et al.*, 2013) fits with the idea that hippocampal hyperactivity could contribute to the occurrence of psychosis, and that a disruption in synaptic connectivity seen in SCZ could indeed favour the occurrence of disordered thought and delusions (Tamminga *et al.*, 2010).

Otherwise, there is only indirect evidence for hippocampal deficits in SCZ and how these might be related to hippocampal physiology during sleep remains to be investigated.

Temporal coupling between non-rapid eye movement sleep oscillations and connectivity

So far we have described the neurophysiology of neuronal activity during sleep in the neocortex, thalamus and hippocampus and how pathologies in SCZ could explain some of the neurophysiological deficits observed in these individual brain regions. However, a hallmark of NREM sleep is that these oscillations do not occur in isolation, but are correlated across a range of brain regions and timescales. The first results on how sleep activity patterns are correlated across different brain areas came from rodent research, where simultaneous recordings in the cortex and hippocampus showed the precise temporal coordination of slow waves, spindles and ripples (Siapas & Wilson, 1998; Sirota *et al.*, 2003). This coordination is remarkably similar in rodents and humans (Mölle *et al.*, 2002, 2006; Clemens *et al.*, 2007). SWA appears to act as a framework for orchestrating the synchrony of the faster spindle and ripple oscillations (Mölle *et al.*, 2002; Peyrache *et al.*, 2011). More specifically, the generation of hippocampal ripples is suppressed during the cortical DOWN state and increased during the succeeding UP state depolarization (Sirota *et al.*, 2003; Isomura *et al.*, 2006; Mölle *et al.*, 2006; Clemens *et al.*, 2007; Mölle & Born, 2009). In both rats and mice, ripple oscillations appear to be amplitude-modulated by the phase of sleep spindles, with ripple events temporally nested in individual spindle cycles (Sirota *et al.*, 2003; Phillips *et al.*, 2012a). Here, information might arrive at the cortex from hippocampal inputs during a SWR event, whereas the repetitive activation of TC inputs during a following sleep spindle could serve to consolidate this information (Peyrache *et al.*, 2011). In this model, spindles principally serve to facilitate long-term cortical plasticity, which is supported by the ability of spindle-like stimulation patterns to induce long term potentiation in the cortex *in vitro* (Rosanova & Ulrich, 2005). In addition, spindle modulation of cortical gamma activity indicates that spindles may also coordinate local processing (Ayoub *et al.*, 2012).

FIG. 1. Circuits involved in generating and synchronizing network activity during NREM sleep. The main circuits involved in generating NREM sleep neural network oscillations are found in the CTX, TH and HPC. These circuit diagrams are simplifications of the actual circuits, with an emphasis on long-range connectivity. The main elements in the CTX are deep layer (L5) pyramidal cells and local interneurons (mostly PV-positive basket cells) (Compte *et al.*, 2003; Crunelli & Hughes, 2010); the TH contains TC cells (in the reuniens and other TC nuclei) and inhibitory cells of the TRN (Steriade *et al.*, 1993c; Steriade, 2005); and the HPC is exemplified by pyramidal cells and local interneurons (fast-spiking PV-positive basket cells). Top – Sleep circuits in healthy controls. In the CTX local recurrent networks mainly found in the deep layers 5 and 6 are thought to be main drivers in generating SWA activity (blue). The CTX sends efferents to the TH where TC and TRN generate spindle activity. The UP/DOWN state transitions in the CTX (manifested as slow waves in the EEG) bias thalamic spindling to occur mainly during the UP state. Thus, spindles are 'framed' by cortical DOWN states. DOWN states can be synchronized between remote cortical areas, as illustrated by the two recorded traces on the right. Similarly, spindles can be synchronized across cortical areas as measured by EEG recordings, although magnetoencephalography recording also reveals localized spindle events. Global synchronization of spindles is thought to be carried by diffuse projections of the thalamic matrix to the CTX and intense reciprocal connections between TC and reticular cells across wider areas of the TH. Here we have illustrated two remote cortical regions with respective thalamic projection areas and their long-distance connectivity. Importantly they differ in their connectivity to the HPC. Occipital and temporal cortices provide direct input into the hippocampal formation, whereas frontal cortices only receive input from it. As hippocampal activity is biased by cortical inputs it is likely to cause ripple oscillations to mainly occur during cortical UP states. Moreover, hippocampal ripples are tightly synchronized to spindle oscillations where ripple power appears to be highest during the peaks of corticothalamic spindles. This precise temporal coupling could be organized by the strong reciprocal connections between the TH (in particular the reuniens) and HPC (mainly CA1; Vertes, 2006). Neuromodulation –here exemplified by dopaminergic projections from the VTA – might play a role in setting the correct modulatory tone for these complex network dynamics to occur. Although dopamine (DA) tone is thought to be low during sleep, frontal cortices and the HPC receive significant DA input from the VTA. Bottom – Sleep circuits in SCZ. There are various molecular, cellular and synaptic pathologies that contribute to symptoms in SCZ. Here we speculate how known pathologies, particularly of connectivity between the CTX, TH and HPC, might influence neuronal activity during NREM sleep. There is strong evidence for impaired cortico-cortical connectivity in SCZ. This will most likely influence the long-range synchronization of SWA between remote cortices (see cortical traces in blue/purple on the right). Also, cortical input into the TH seems impaired, which will most likely reduce cortical influence on spindle timing and reduce the succession of DOWN to UP state transition followed by spindles (top trace on the right). Thalamic pathologies are likely to reduce spindle amplitudes and their synchronization across wider cortical and thalamic areas, although little direct evidence on intrathalamic projections in SCZ is available (highlighted with a question mark). Equally, there appears to be reduced cortical drive from temporal and occipital cortices on the HPC, which will impair the modulation of hippocampal activity by the CTX. The HPC might show increased reciprocal connectivity and synaptic plasticity possibly leading to increased ripple activity and thus increased hippocampal outputs. More importantly, the precise temporal synchronization with TC spindles appears to be abandoned. This might be due to the impaired cortico-cortical as well impaired thalamo-hippocampal connectivity in SCZ. Also, a changed tone in neuromodulation might contribute to the desynchronization of different neural network oscillators. As an example, increased DA tone (increased D2-type receptor activation), possibly caused by an overactive HPC, might push cortical networks further away from a bistable regime, possibly destabilizing SWA activity in SCZ (Durstewitz & Seamans, 2008). CTX, cortex; HC, healthy controls; HPC, hippocampus; SCZ, schizophrenia; TC, thalmocortical; TH, thalamus; TRN; thalamic reticular nucleus; VTA, ventral tegmental area.

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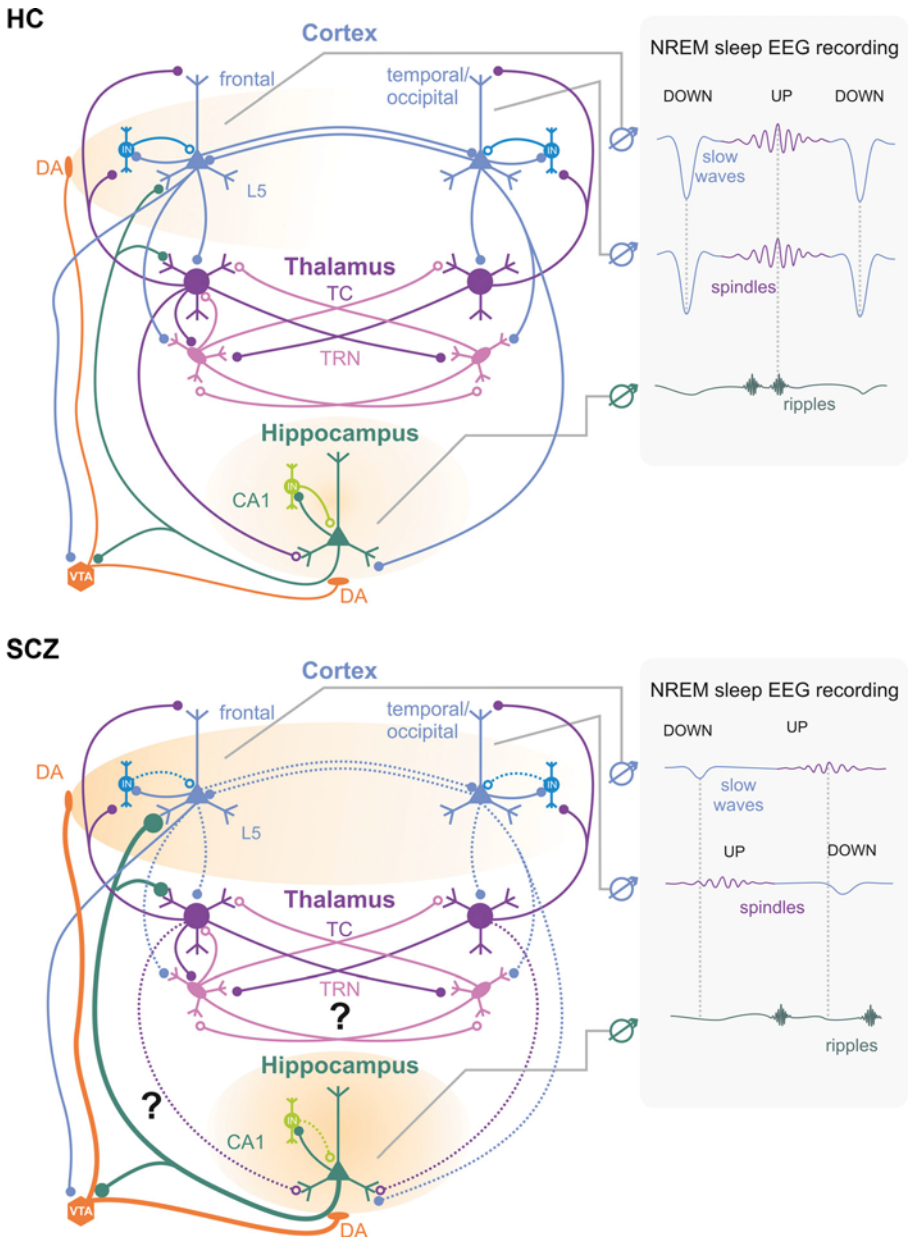
It is likely that this precise coordination of different network oscillations is essential for normal functioning of the brain. The succession and synchronization of global and local network states during sleep seems to be crucial for providing feedback to circadian and homeostatic mechanisms as well as providing the framework for the reorganization of recently acquired information and during sleep. The synchronization and modulation of these different network oscillators will depend on intact long-range connectivity between remote cortical areas, intact TC loops and adequately timed cortico-hippocampal-thalamic interaction (See Fig. 1, top for a summary of circuits involved NREM sleep physiology in healthy controls).

The integrity of long-range cortico-cortical connections is a likely determinant of the brain's propensity to generate synchronized SWA and spindles. Indeed, SWA shows a high degree of synchrony between different cortical areas (Nir *et al.*, 2011) and strongly influences the timing of spindle epochs (Mölle *et al.*, 2002). As spindles are hypothesized to be triggered by barrages of corticothalamic spikes that result from synchronous entrainment of cortical neurons by SWA, changes in the global synchrony of SWA might affect the spindle-generating propensity of the TC network. In agreement with this, individual differences in spindle power correlate with the integrity of long-range forebrain white matter tracts (Piantoni *et al.*, 2013).

Studies on connectivity in patients with SCZ have shown pathological changes in connectivity measures of all brain areas involved in generating NREM sleep oscillations, and therefore SCZ has been described as a disease of 'reduced synaptic connectivity' (McGlashan & Hoffman, 2000; Fitzsimmons *et al.*, 2013). There appear to be extensive reductions in cortico-cortical connectivity (Kubicki *et al.*, 2007), most prominently frontotemporal, frontoparietal (Burns *et al.*, 2003; Alexander-Bloch *et al.*, 2013) and fronto-occipital structural connectivity (Zalesky *et al.*, 2011). These connectivity deficits have been correlated with impaired cognitive performance (Szeszko *et al.*, 2007; Karlsgodt *et al.*, 2008; Fornito *et al.*, 2011)



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and it is tempting to speculate that this reduced connectivity will also hinder the synchronization of SWA and spindles across distant cortical areas (Phillips *et al.*, 2012a; Wamsley *et al.*, 2012).

The connectivity of the cortex to the hippocampus is also of interest. The major input region to the hippocampus, the entorhinal cortex, is reduced in size in patients with SCZ (Falkai *et al.*, 1988), which may be due to a pyramidal cell pathology (Arnold *et al.*, 1991). There is extensive evidence from resting state and structural imaging approaches for aberrant connectivity of the hippocampus to various cortical areas in SCZ (Meyer-Lindenberg *et al.*, 2005; Konrad & Winterer, 2008; Zhou *et al.*, 2008) and in individuals carrying psychosis risk allele variants (Esslinger *et al.*, 2009). More recent results show a task-dependent disconnection of frontal and anterior cingulate cortices with the hippocampus in patients (Hao *et al.*, 2009).

Thalamocortical connectivity has also been studied extensively (Andreasen *et al.*, 1998; Sim *et al.*, 2006). In particular, thalamic connectivity with frontal cortices appears to be reduced, whereas it is increased with motor and sensory cortex areas (Marenco *et al.*, 2012; Woodward *et al.*, 2012), which might be a sign of cell type-selective pathologies in thalamic nuclei (Ellison-Wright & Bullmore, 2010). A recent transcranial magnetic stimulation study has confirmed the reduced responsiveness of the thalamus of patients with SCZ in comparison to healthy individuals (Guller *et al.*, 2012b). Less is known about thalamo-hippocampal connectivity in SCZ, which is extensive in rodents and primates (Amaral & Cowan, 1980; Aggleton *et al.*, 1986; Vertes, 2006) and is likely to influence synchronization of activity between these two areas (Bertram & Zhang, 1999; Lisman *et al.*, 2010).

In the MAM-E17 model of SCZ, SWA was desynchronized between different cortical areas and the SWA modulation of spindle activity was weaker. However, there was also a desynchronization of spindle and ripple oscillations (Phillips *et al.*, 2012a); ripples precede spindle occurrence in a time range of 50 ms in the prelimbic area of the frontal cortex, but this timing relationship is lost in the MAM-E17 model. Furthermore, spindle modulation of CA1 ripple power is reduced in these animals. These deficits may contribute to cognitive impairments in the MAM-E17 model (Korotkova *et al.*, 2010) and possibly reflect impairments in long-range connections between the cortex, hippocampus and thalamus, although this awaits experimental confirmation. Preliminary results from our own analyses indicate that a similar reduction in coordination between SWA and spindles can be seen in EEG recordings from patients with SCZ (Bartsch *et al.*, 2013).

Recently, 2-deoxyglucose imaging in the ketamine model of SCZ in mice revealed abnormal connectivity between the frontal cortices and multiple thalamic nuclei, and the CA3 region of the hippocampus (Dawson *et al.*, 2013), which supports some of our claims, and illustrates the translational value of animal models for elucidating systems and circuit mechanisms of psychiatric diseases (See Fig. 1, bottom for a summary of circuit changes that possibly affect NREM sleep physiology in SCZ).

In addition to structural changes, there is a plethora of molecular changes, associated with glutamatergic synaptic transmission, that will very likely affect the precise long-range coordination of neural activity (English *et al.*, 2011). The normal succession of sleep stages also depends on global changes in tone of various neuromodulators controlling the initiation and maintenance of these global brain states (Lee & Dan, 2012). Most prominently this includes acetylcholine and noradrenaline, which have been implicated in the pathophysiology of SCZ (Yamamoto & Hornykiewicz, 2004; Raedler *et al.*, 2006), although their influences have mainly been examined in the wake state and their influence on sleep patterns in SCZ remains largely unknown.

Diagnostic and therapeutic implications

In this last section we evaluate what is known from NREM sleep deficits in SCZ in relation to possible applications in diagnosis and therapy.

Schizophrenia has been recognized as a complex genetic disorder with multiple symptom clusters, such as positive, negative and more recently cognitive dimensions. In a reflection of the multifactorial causes of SCZ the current Diagnostic and Statistical Manual (DSM V) issued by the American Psychiatric Association (APA, 2013) does not include subtypes of SCZ, but instead suggests the use of a dimensional approach where individual symptom dimensions are scored and evaluated throughout the treatment. The five main symptom dimensions are delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour and negative symptoms (i.e. diminished emotional expression or avolition). These descriptive behavioural symptom definitions are still the most significant indicators of SCZ, and the identification of unique and distinct genetic, physiological or molecular biomarkers has not reached a consistency needed for daily clinical use (Kapur *et al.*, 2012). Here the classic descriptive clinical approach might actually hinder the development of a classification rooted in biological psychiatry. Despite the significant advances of technology in neuroscience in the last two decades meta studies highlight the inconsistency in findings from imaging (Davidson & Heinrichs, 2003; Van Snellenberg *et al.*, 2006) and genome-wide association studies (Collins *et al.*, 2012). Some authors advocate a more restrictive approach in the evaluation of possible biomarkers where neurophysiology phenotypes should be linked to specific genetic backgrounds, which should result in specific 'endophenotypes' of the disease (Gottesman & Gould, 2003; Braff *et al.*, 2007). This would help to identify individual differences in patients and possibly allow more tailored psychiatric treatment. In particular, indicators that predict the later occurrence of SCZ in prodromal patients would be most useful (Yung & McGorry, 1996; Ruhrmann *et al.*, 2010).

Sleep physiology as a diagnostic measure

Sleep architecture and electrophysiology present themselves as candidate indicators of cortical, thalamic and hippocampal function in SCZ. Indeed, longitudinal studies of sleep disturbances have been shown to predict later psychopathology (Yung & McGorry, 1996; Gregory & O'Connor, 2002) and sleep disturbances are apparent in drug-naive first-episode patients (Ganguli *et al.*, 1987; Lauer *et al.*, 1997). Undifferentiated sleep abnormalities have been included as general symptoms in some longitudinal studies (Cannon *et al.*, 2008) and their inclusion adds predictive value in models of psychosis onset (Ruhrmann *et al.*, 2010). Thus, a monitoring of sleep–wake cycles in high-risk individuals could prove beneficial in detecting the onset of psychosis. The detection of sleep irregularities in high-risk individuals could be achieved through activity monitoring ('actigraphy'), which provides a simple and low-cost possibility of monitoring sleep–wake patterns in high-risk individuals and diagnosed patients (Bromundt *et al.*, 2011; Tahmasian *et al.*, 2013; Walther *et al.*, 2013).

In contrast, EEG is a powerful tool in the identification of reliable neuronal biomarker and possible endophenotypes, but most research in SCZ has so far focussed on awake EEG and event-related potentials (Leiser *et al.*, 2011). Sleep EEG promises less interference

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from daily variations in behaviour and vigilance state, and some sleep EEG features such as spindle reduction might even allow a distinction from depressive endophenotypes (Ferrarelli *et al.*, 2007). To further increase specificity, EEG could be combined with genetic analysis, functional imaging, and event-related potential or other stimulation approaches (Haraldsson *et al.*, 2004; Calhoun *et al.*, 2009; Guller *et al.*, 2012a; Arbabshirani *et al.*, 2013; Frantseva *et al.*, 2014).

Thus, sleep architecture and electrophysiology have the promise of adding a new dimension to prediction and diagnosis in psychiatry, and might even be useful to evaluate and monitor progress during treatment.

Therapies targeting sleep

At this point it is interesting to identify possible routes to normalizing abnormal sleep patterns in patients and their impact on cognitive deficits in SCZ. The effects of antipsychotics and antidepressants on sleep has been described in detail previously (Monti & Monti, 2004; DeMartinis & Winokur, 2007). Here we would like to highlight GABAergic targets as SWA, spindle and ripple oscillations critically depend on balanced excitation/inhibition and there is evidence for reduced inhibition in SCZ.

Benzodiazepines such as diazepam and Z-hypnotics (zolpidem, eszopiclone) are the current treatments of choice for sleep disorders (Sie, 2013). Benzodiazepines and Z-hypnotics are positive allosteric modulators of $GABA_A$ receptors and each compound displays a differential affinity for the different $GABA_A$ alpha subunits. Diazepam is a non-selective allosteric modulator acting on α1,2,3- and 5-containing $GABA_A$ receptors, whereas zolpidem acts selectively on α1-containing receptors (Rudolph & Knoflach, 2011), and their hypnotic effects are thought to be mediated by the activation of $GABA_A$ α1 subunits (Kralic *et al.*, 2002; Rudolph & Möhler, 2004).

GABAergic signalling is central to the spindle pacemaker mechanism, and several drugs targeting this system have been shown to alter spindle activity in humans (Aeschbach *et al.*, 1994; Dijk *et al.*, 2010; Feld *et al.*, 2013; Mednick *et al.*, 2013). Spindle occurrence is decreased in SCZ and is correlated with sleep-dependent memory consolidation impairment (Wamsley *et al.*, 2012). Following eszopiclone, Wamsley *et al.* (2013) showed an increase in spindle number and density in patients with SCZ compared with placebo, which was correlated with overnight motor sequence task improvement. A recent study from Mednick *et al.* (2013) described a positive correlation between the increase in spindle density and amelioration of declarative memory in healthy volunteers induced by zolpidem, although the effects are in contradiction to the effects of triazolam, which has been found to increase spindles but to deteriorate motor sequence task performance in healthy individuals (Morgan *et al.*, 2010).

There are also differential effects of benzodiazepines on hippocampal physiology, in particular zolpidem increases SWRs number and power in rats, whereas diazepam reduces their number as well as amplitude (Ponomarenko *et al.*, 2004; Koniaris *et al.*, 2011). These effects are believed to be mediated by the activation of α5-containing $GABA_A$ receptors. α5-$GABA_A$ is responsible for the GABAergic tonic inhibition of pyramidal cells in the CA1 (Caraiscos *et al.*, 2004) and α5 inverse agonists increase SWR occurrence *in vitro* (Papatheodoropoulos & Koniaris, 2011). Furthermore, a number of studies have shown that memory encoding in the hippocampus both in rodents (Collinson *et al.*, 2006; Braudeau *et al.*, 2011; Rissman & Mobley, 2011; Redrobe *et al.*, 2012) and humans (Atack, 2010) can be improved by a5 inverse agonists under certain conditions.

These differential effects of $GABA_A$ drugs on sleep and memory consolidation may reflect the pharmacology of these drugs (selectivity towards specific $GABA_A$ subunits) but could also be the result of the differential effects on the temporal coupling of slow waves, spindles and ripples – this remains to be investigated. Other approaches to the modulation of the excitatory–inhibitory balance during sleep may also be useful. A recent study found that spindle duration was increased in transgenic mice that overexpress SK2-type calcium-activated potassium channels (Wimmer *et al.*, 2012), which in future may allow to selectively modify specific properties of spindle oscillations.

Recently, 'electroceutical' methods of electromagnetic brain stimulation, including transcranial magnetic stimulation, direct current stimulation or deep brain stimulation (DBS), have been applied in both preclinical and clinical research (Hallett, 2000; Mayberg *et al.*, 2005; Perlmutter & Mink, 2006; Nitsche *et al.*, 2008). For example, an early case study on the use of DBS in treatment-resistant depressive patients reported that within the first week of chronic DBS, one of the first notable sustained symptom changes was a normalization of early-morning sleep disturbances (Mayberg *et al.*, 2005).

The application of stimulation during sleep is less common but some studies have shown promising results in influencing neural network oscillations during sleep. For example, direct current stimulation has been used to induce SWA during early deep NREM sleep, which enhanced overnight performance in a declarative memory task in humans (Marshall *et al.*, 2006). Hence, stimulation of SWA could potentially alleviate cognitive symptoms in SCZ that might be due to a lack of SWA. Previous applications of transcranial magnetic stimulation in the treatment of SCZ have varied widely in terms of apparatus, stimulus properties, locations and stimulation protocols (Haraldsson *et al.*, 2004). DBS is not currently used for the treatment of SCZ but a case for the hippocampus as a target for DBS treatment has been made (Mikell *et al.*, 2009).

Ultimately, the attenuation of particular NREM sleep oscillations in psychiatric patients could be normalized by appropriately timed electrical stimulation to initiate and/or prolong functional local oscillatory neural network states (slow waves, spindles or ripples). Of particular interest are closed-loop applications of electrophysiological monitoring, real-time analysis and online delivery of stimulation. Electrophysiological recordings can be analysed online to detect characteristic events like slow waves or spindles in order to trigger event-related stimulation. Examples from rat models demonstrate that closed-loop stimulation can be used to inhibit ripple oscillations, which disrupts hippocampal memory consolidation during NREM sleep (Girardeau *et al.*, 2009) and can disrupt epileptic seizures (Berényi *et al.*, 2012). In a very recent application it has been demonstrated that in-phase auditory stimulation with ongoing SWA in humans increases the amplitude and length of SWA, increases subsequent spindle oscillations and augments overnight memory consolidation in a declarative memory task (Ngo *et al.*, 2013).

Most studies use pulse-like stimulation in their paradigms but the rational design of stimulation patterns should be reconsidered based on what is known about the biophysics of neural network oscillations. Natural stimulation patterns with alternating currents have rarely been explored in transcranial magnetic stimulation/direct current stimulation/DBS but some studies have demonstrated the modulation of neuronal activity through alternating currents (Fröhlich & McCormick, 2010; Reato *et al.*, 2010; Frohlich & Schmidt, 2013). Indeed, positive feedback through alternating electric fields enhances SWA amplitude and consistency in an *in vitro* model of SWA (Fröhlich & McCor-

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mick, 2010). In the future, circuit-selective stimulation through cell-type-specific infection with light-sensitive ion channels (optogenetics) could deliver even more specific activation or inhibition of relevant circuit elements (Cardin *et al.*, 2009; Halassa *et al.*, 2011; Beltramo *et al.*, 2013). Indeed, optogenetic stimulation of the TRN in mice induces spindle-like oscillations (Kim *et al.*, 2012).

A more difficult target for intervention through stimulation would be the realignment of desynchronized oscillations in remote brain areas (Phillips *et al.*, 2012a; Wamsley *et al.*, 2012), which could only be realized through multisite recording and stimulation combined with real-time analysis. Equally important should be the reinstalling of the normal succession and amount of different sleep stages during sleep, that is normalizing sleep architecture with the aim of creating a 'healthy hypnogram'. This could be achieved by triggering appropriate stimulation patterns throughout the night to stabilize and enhance residual spontaneous activity related to specific sleep stages.

Conclusions

Non-rapid eye movement sleep neurophysiology culminates from an orchestrated array of interactions between excitatory and inhibitory neurotransmission spanning neocortical, thalamic and limbic circuits. These circuits subserve waking cognition, but are also recruited during sleep-dependent memory consolidation. As such, neurophysiological measures of brain activity during sleep provide both direct, mechanistic insights into the nature of distributed circuit dysfunction during disease and neural correlates of cognitive symptoms.

Sleep neurophysiology is to some extent less confounded by behavioural change – studying the brain 'offline' means that the observed neurophysiological changes are less likely to be secondary to changes in ongoing behaviour. However, given the dependence of NREM sleep oscillations on previous waking experience, dissociating cause from effect remains challenging, for example do changes in spindle coherence in SCZ reflect a reduced propensity for learning during wakefulness, or a cause of impaired memory consolidation? How specific to traditional diagnostic categories are the NREM sleep phenotypes seen in SCZ, or do certain sleep features span other neuropsychiatric disorders? Future studies in healthy risk allele carriers and prodromal subjects should help to resolve these issues, as should pharmacological or electroceutical manipulation of NREM sleep oscillations designed to directly enhance sleep-dependent memory processing.

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Abbreviations

DBS, deep brain stimulation; EEG, electroencephalography; MAM-E17, methylazoxymethanol acetate at embryonal day 17; NREM, non-rapid eye movement; PV, parvalbumin; SCZ, schizophrenia; SWA, slow-wave activity; SWR, sharp-wave ripple; TC, thalamocortical; TRN, thalamic reticular nucleus.

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