



# Sleep spindle and slow wave abnormalities in schizophrenia and other psychotic disorders: Recent findings and future directions

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## ABSTRACT

Sleep spindles and slow waves are the two main oscillatory activities occurring during NREM sleep. Slow waves are ~1 Hz, high amplitude, negative-positive deflections that are primarily generated and coordinated within the cortex, whereas sleep spindles are 12–16 Hz, waxing and waning oscillations that are initiated within the thalamus and regulated by thalamo-cortical circuits. In healthy subjects, these oscillations are thought to be responsible for the restorative aspects of sleep and have been increasingly shown to be involved in learning, memory and plasticity. Furthermore, deficits in sleep spindles and, to lesser extent, slow waves have been reported in both chronic schizophrenia (SCZ) and early course psychosis patients. In this article, we will first describe sleep spindle and slow wave characteristics, including their putative functional roles in the healthy brain. We will then review electrophysiological, genetic, and cognitive studies demonstrating spindle and slow wave impairments in SCZ and other psychotic disorders, with particular emphasis on recent findings in early course patients. Finally, we will discuss how future work, including sleep studies in individuals at clinical high risk for psychosis, may help position spindles and slow waves as candidate biomarkers, as well as novel treatment targets, for SCZ and related psychotic disorders.

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## 1. Introduction

Schizophrenia (SCZ) is a devastating, highly disabling mental illness that affects about 1% of the population worldwide (van Os and Kapur, 2009). SCZ spectrum and related psychotic disorders are usually diagnosed based on the presence of positive (i.e., hallucinations, delusions) and/or negative (i.e., apathy, anhedonia) symptoms (First, 2013). Nonetheless, a disturbed sleep pattern has been observed since the earliest clinical descriptions of these disorders (Bleuler, 1950), and sleep disturbances are commonly experienced by psychotic patients (Kaskie et al., 2017). In the clinical setting, insomnia is a frequent, yet often overlooked symptom present in SCZ and other psychotic patients (Robertson et al., 2019). Furthermore, sleep abnormalities are associated with the severity of clinical symptoms (Yang and Winkelman, 2006), and often precede and represent an early symptom of an impending psychotic episode (Ruhmann et al., 2010). Altogether, these observations have generated significant interest in determining the putative role of sleep disturbances in the pathophysiology and

clinical manifestation of psychotic disorders (Cosgrave et al., 2018; Pocivavsek and Rowland, 2018).

Sleep spindles and slow waves are the two main oscillatory activities occurring during NREM sleep. Slow waves are 1 Hz, high amplitude oscillations that are primarily generated and coordinated within the cortex (Steriade, 2006), whereas sleep spindles are 12–16 Hz, waxing and waning oscillations that are initiated by the thalamic reticular nucleus and regulated by thalamo-reticular and thalamo-cortical circuits (De Gennaro and Ferrara, 2003). By performing overnight EEG recordings, several sleep studies from our and other research groups have demonstrated marked deficits in sleep spindles, and less consistently slow waves, in chronic patients with SCZ relative to healthy controls (HC) (Castelnovo et al., 2018). While promising, the interpretation of these findings has been complicated by several issues, including duration of illness and chronic exposure to antipsychotic medications. In contrast, sleep EEG recordings in patients with early course SCZ and related psychotic disorders allows minimizing these confounds while also assessing the presence of sleep abnormalities at illness onset. Furthermore, the use of high density (hd)-EEG ( $\geq 64$  channels) systems in early course patients affords enhanced spatial resolution, thus enabling the identification of the brain regions where slow waves and spindle parameter deficits are most prominent and

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where these deficits first arise.

In this article, we will first describe sleep spindles and slow waves, including their EEG characteristics and their putative functional roles in the healthy brain. We will then briefly review the most relevant slow wave and sleep spindle findings in patients with chronic SCZ relative to healthy controls. Next, we will focus on several recent studies investigating spindle and slow wave abnormalities in early course SCZ and other psychotic patients, including hd-EEG findings from our group. Finally, we will discuss how future work, including longitudinal studies in individuals at clinical high risk (CHR) for psychosis, could help determine the temporal relationship between sleep disturbances and psychosis, which in turn may lead to the discovery of novel treatments to mitigate, and even prevent, the development and full manifestation of SCZ and other psychotic disorders.

## 2. Sleep spindles and slow waves: EEG characteristics and putative functional roles in the healthy brain

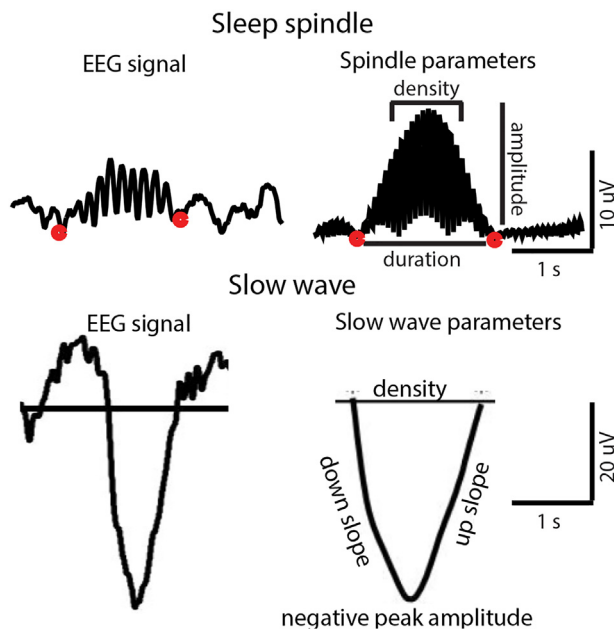
Sleep spindles are bursts of 12–16 Hz oscillatory activity that represent one of the defining EEG features of non-rapid eye movement (NREM) sleep (Fig. 1, Top). Spindles occur more frequently during NREM stage 2 (N2) and are more commonly observed in frontal-parietal and prefrontal regions (De Gennaro and Ferrara, 2003). Slow waves are large amplitude, ~1 Hz oscillations (Fig. 1, Bottom), which characterize NREM stage 3 (N3), also called slow wave sleep, and are particularly prominent in prefrontal areas (Bersagliere et al., 2018). Traditionally, spindles and slow waves were identified by visual inspection. This process was subjective, inherently relying on the individual expertise, and extremely time consuming. In contrast, over the past several years the development of spindle and slow wave detection algorithms (Mensen et al., 2016; Riedner et al., 2007; Warby et al., 2014) has provided several advantages. First, an automatic algorithm offers

the opportunity to detect spindles and/or slow waves in an objective, standardized way. Second, it allows the process to be performed in an efficient, timely manner. Third, and most important, it enables the computation of several spindle and slow wave parameters, which reflect different properties of underlying thalamo-cortical circuits. Spindle amplitude, duration, and density as well as slow wave negative peak amplitude, down-slope, up-slope, and density are some of the parameters that can be computed (Fig. 1).

In healthy individuals, slow wave activity (SWA, NREM sleep EEG power between 0.5 and 4.5 Hz), increases exponentially with the duration of prior wakefulness and decreases, also exponentially, during subsequent sleep (Massimini et al., 2009). In addition to global, wake-dependent fluctuations, SWA also shows local, use-dependent regulation. Pioneering work from Huber et al. showed that training on a visuo-motor task that targeted the right parietal cortex led to local increases in SWA over right parietal derivations (Huber et al., 2004), while several other sleep studies demonstrated that SWA is implicated in memory consolidation (Huber and Born, 2014) and executive functions (Wilckens et al., 2018). The link between sleep SWA and waking performance has been further corroborated by studies showing that boosting slow oscillations with transcranial application of oscillating potentials ameliorated declarative memories (Marshall et al., 2006), whereas a reduction in slow waves by means of acoustic stimuli prevented any sleep-dependent performance improvements (Aeschbach et al., 2008; Landsness et al., 2009). Higher spindle amplitude was associated with better general cognitive ability (Fogel and Smith, 2011), whereas increased spindle density predicted an improved performance in visuo-spatial memory (Clemens et al., 2006) and declarative learning tasks involving cued recall of word pairs (Gais et al., 2002; Schabus et al., 2004). Also, it has been shown that spindle density increased locally within brain areas implicated in a motor learning task on a brain-computer interface (Johnson et al., 2012). In another sleep study, we recently found that enhanced slow wave negative peak amplitude and down-slope was associated with better working memory performance in healthy subjects (Ferrarelli et al., 2019). Thus, while their functional role has yet to be fully established, an increasing body of evidence indicate that spindle and slow wave parameters are critically implicated in learning, memory, and plasticity (Luthi, 2014; Molle and Born, 2011; Wilckens et al., 2018).

## 3. Sleep spindle and slow wave abnormalities in patients with chronic SCZ

Over the past two decades, research on sleep spindles and slow waves in patients with SCZ has focused on two main lines of inquiry: 1) establishing abnormalities in spindle and slow wave parameters, including their topographic distribution and their relationship with underlying neuronal and molecular/genetic mechanisms; 2) investigating the links between slow wave/spindle alterations and their clinical and cognitive impairments. Deficits in spindle parameters, including power, amplitude, duration, and density, have been found by several EEG studies in chronic patients with SCZ (Baran et al., 2019; Buchmann et al., 2014; Ferrarelli et al., 2007, 2010; Schilling et al., 2017; Wamsley et al., 2012). A reduction in spindle density has been the most frequently reported impairment (Castelnovo et al., 2018). Furthermore, spindle deficits in chronic SCZ are primarily localized in fronto-parietal and prefrontal regions, as assessed with high density ( $\geq 64$  channel) hd-EEG recordings (Buchmann et al., 2014; Ferrarelli et al., 2007, 2010). Slow wave findings have been more inconsistent. A reduction in slow wave activity (SWA, 1–4 Hz NREM sleep EEG power) and density was reported in several sleep studies, which included drug free and/or drug-naïve SCZ patients (Hiatt et al., 1985; Keshavan et al., 1998; Sekimoto et al., 2011). However, other sleep studies failed



**Fig. 1.** Sleep spindles and slow waves are the two main oscillatory activities occurring during NREM sleep. Top: sleep spindles are identifiable in the EEG signal as waxing and waning, 12–16 Hz oscillations (Left). Several spindles parameters, including amplitude, duration, and density can be measured using spindle detection algorithms (right). Bottom: slow waves are large amplitude, 1 Hz EEG oscillations that characterize the deepest stage of NREM sleep (left). Slow wave down-slope, up-slope, negative peak amplitude, and density can be calculated with automated algorithms (right). Reproduce in color.

to establish slow wave abnormalities in chronic patients with SCZ relative to HC (Genzel et al., 2015; Goder et al., 2015; Manoach et al., 2010; Van Cauter et al., 1991), including two studies performing hd-EEG recordings (Ferrarelli et al., 2007, 2010). Furthermore, recent work has shown sleep abnormalities also in other psychiatric groups, including decreased fast spindle activity in adolescents with social anxiety disorder (Wilhelm et al., 2017), reduced SWA in major depressive disorder (MDD) patients (Cheng et al., 2015; Plante et al., 2012) along with an increase in slow wave amplitude and slope in treatment resistant MDD individuals who responded to acute ketamine injection (Duncan et al., 2013). Thus, future studies are needed to establish shared and unique sleep abnormalities across major psychiatric disorder patients relative to healthy comparison groups.

### 3.1. Neural origins of sleep spindles and slow wave sleep

Slow wave and sleep spindle oscillations both originate within the thalamo-cortical system. The alternation of up and down states in the slow wave oscillation corresponds to globally synchronized periods of neuronal depolarization and hyperpolarization in cortical networks. In cortical slices, slow oscillations occur in the absence of any chemical or electrical stimulation (Sanchez-Vives and McCormick, 2000). Furthermore, slow oscillations have been observed in all cortical areas, and show similar features under anesthesia, when the cortex is disconnected from the outside environment (Chauvette et al., 2011). Slow waves therefore emerge from the recurrent, synchronized interaction between cortical neurons (Sanchez-Vives et al., 2017). Via efferent pathways, the slow wave synchronizing influence then reaches the thalamus, hippocampus, and brainstem. Sleep spindles are generated by the interplay of the thalamic reticular nucleus (TRN) with the other thalamic nuclei, especially in the dorsal thalamus, and are then relayed through thalamo-cortical projections to the neocortex, with a predominance over fronto-parietal and prefrontal cortical areas. Pioneering work by Steriade et al. has demonstrated that TRN cells initiate the spindle oscillation, and that spindles occurred when reticular neurons are disconnected from the rest of the brain (Steriade et al., 1987). Computational and electrophysiological animal studies have confirmed these initial findings (Bazhenov et al., 2000; Steriade, 2006). Furthermore, by employing a combination of optogenetics and multi-electrode recording in behaving mice it was recently shown that brief drive of TRN switched the thalamocortical firing mode from tonic to bursting, which resulted in cortical spindles (Halassa et al., 2011). Thalamo-thalamic as well as cortico-thalamic loops are also involved in the coordination and maintenance of sleep spindles. In vitro recordings have shown that the spindle oscillations are synchronized by the reciprocal interaction of TRN GABA-ergic neurons and excitatory thalamic neurons (von Krosigk et al., 1993), whereas Bartho et al. has reported that ongoing network activity between thalamo-thalamic and cortico-thalamic neurons controls the length of sleep spindles (Bartho et al., 2014).

### 3.2. Neurotransmitter abnormalities

The TRN, which is the spindle pacemaker, consists entirely of gamma-aminobutyric acid (GABA) neurons (Pinault, 2004), whereas thalamo-cortical and cortical cells, which convey the spindle oscillation to the cortex and regulate slow wave parameters respectively, rely primarily on glutamatergic neurotransmission (Cosgrave et al., 2018). Thus, sleep spindle and slow wave deficits point to altered GABA and glutamate activity in SCZ. Post-mortem studies has consistently shown GABA and glutamatergic abnormalities in patients with SCZ, including in PFC (Hoftman et al., 2018; Rocco et al., 2016, 2017) and the thalamus

(Ibrahim et al., 2000; Thompson et al., 2009). GABA activity within the TRN regulates sensory auditory gating in rodents, which is disrupted by amphetamine and reversed by haloperidol (Krause et al., 2003), all findings consistent with human electrophysiological evidence of sensory processing dysfunction in SCZ (Javitt and Freedman, 2015). Additionally, treatment studies have shown that some of the therapeutic effects of clozapine as well as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) interventions in patients with SCZ are mediated by an increase in GABA neurotransmission on cortical neurons (Daskalakis et al., 2008; Kaster et al., 2015; Taylor and Tso, 2015). Pharmacological manipulations with NMDA antagonists, including ketamine and phencyclidine (PCP), produce schizophrenia-like psychosis in healthy individuals (Bergeron and Coyle, 2012), and sub-anesthetic, acute ketamine treatment in mice results in impairments within the thalamo-cortical system (Dawson et al., 2013), whereas second-generation antipsychotic medications, including clozapine, can revert a PCP-mediated blockade of NMDA receptors in both the thalamus (Santana et al., 2011) and PFC (Castane et al., 2015). Of note, while these findings suggest that abnormalities in GABA and glutamate neurotransmission, which underlie slow wave and spindle impairments, are present in patient with SCZ, future work is needed to show that pharmacological manipulations involving those neurotransmitters can ameliorate spindle and slow wave deficits in those patients.

### 3.3. Genetic basis of sleep spindle and slow wave abnormalities

Neurons of the TRN, the spindle pacemaker, express two T channel subtypes, which are encoded by the CaV3.2 (CACNA1h) and the CaV3.3 (CACNA1i) genes (Talley et al., 1999). Notably, CACNA1i has been recently implicated in schizophrenia by two large genetic studies (Irish Schizophrenia Genomics and the Wellcome Trust Case Control, 2012; Schizophrenia Working Group of the Psychiatric Genomics, 2014), while electrophysiological recordings in mice have shown that the CaV3.3 calcium channel regulate spindle occurrence in the thalamus (Astori et al., 2011), as well as that deletion of CaV3.2 and CaV3.3 lead to suppression of sleep spindle rhythmogenesis (Pellegrini et al., 2016). Another genetic study found that the Val158Met polymorphism for the catechol-O-methyl transferase (COMT) gene was strongly associated with delta and theta activity in SCZ patients (Venables et al., 2009). Altogether, these findings provided clues to genetic mechanisms linking spindle spindles, and to lesser extent SWA, with SCZ. Abnormal sleep oscillations may also be linked to the genetic risk of illness. Schilling et al. reported that, compared to healthy volunteers, fast (12–15 Hz) spindle density was reduced in patients with SCZ and their first-degree relatives compared to control groups (Schilling et al., 2017). Another study, which examined 225 SCZ probands and 201 first-degree relatives (SZR), found that both SCZ patients and SZR had enhanced frontal delta activity and increased fronto-central slow beta activity relative to HC subjects (Narayanan et al., 2014).

### 3.4. Spindle and slow wave deficits and cognitive and clinical symptoms in SCZ

Sleep oscillatory abnormalities have also been implicated in some of clinical symptoms and cognitive impairments observed in patients with SCZ. In recent work, we found that reduced spindle amplitude and density were negatively correlated with the severity of positive symptoms in chronic patients with SCZ (Ferrarelli et al., 2010; Ferrarelli and Tononi, 2011), though two other sleep studies failed to establish such correlations (Castelnovo et al., 2018). Chen et al. found that higher frontal delta activity was associated with more negative symptoms (Chen et al., 2016), and another sleep study reported that

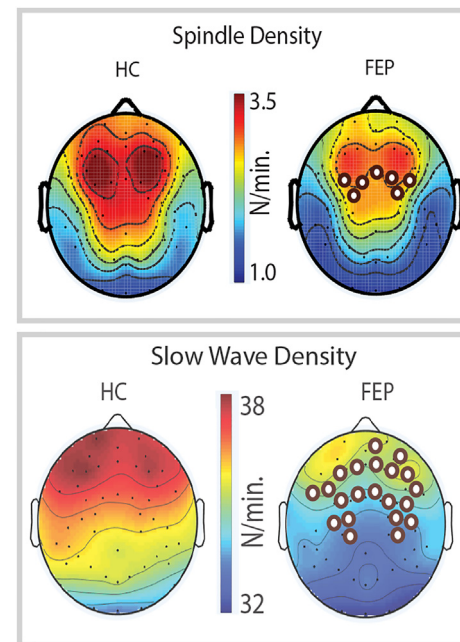


enhanced SWA in the temporal cortex correlated with stronger negative symptoms in SCZ patients (Fehr et al., 2003).

In healthy subjects, spindles have been associated with the sleep-dependent consolidation of both procedural and declarative memory (Fogel and Smith, 2011). Furthermore, several sleep studies have shown that, in chronic patients with SCZ, reduced spindle density was associated with impaired memory consolidation, assessed with a picture recognition task (Goder et al., 2015) and a motor procedural memory task (Genzel et al., 2015; Manoach et al., 2010; Wamsley et al., 2012), while a recent study has extended sleep-dependent memory consolidation deficits in SCZ to declarative memory, assessed with word-pair recall tasks (Baran et al., 2018). Based on these findings, it has been suggested that sleep spindles may represent a novel treatment biomarker for improving memory and related cognitive functions in SCZ (Manoach et al., 2016). In addition to spindles, cortical sleep slow waves, which can facilitate spindle initiation in the TRN, and high frequency hippocampal sharp-wave ripples, which occur during the troughs of the spindle oscillations, are thought to coordinate the transfer of new memories from temporary dependence on the hippocampus to longer-term representation in the cortex (Born and Wilhelm, 2012). Recent findings from animal and human studies corroborate the importance of this coordination. In mice, optogenetic induction of spindles on the rising phase of slow oscillations lead to enhanced memory consolidation, whereas spindle suppression impaired consolidation (Latchoumane et al., 2017). In older adults, reduced coupling of slow oscillations with spindles is associated with increased forgetting (Helfrich et al., 2018). Furthermore, by measuring slow wave and spindle phase/amplitude coupling in relation to overnight improvement in finger tapping motor sequence task (MST), Demanuele et al. found that spindle density and slow wave/spindle coordination predicted memory consolidation better than either parameter alone in both HC and SCZ patients (Demanuele et al., 2017). Thus, interventions that both increase spindle density and preserve or enhance slow wave/spindle coordination may be best suited to ameliorate memory in SCZ. Spindles and slow waves may also be implicated in other cognitive functions, including working memory (WM). In healthy individuals, we recently found that slow wave amplitude and slope predicted better scores in the N-back task (Ferrarelli et al., 2019), whereas decreased prefrontal (PFC) spindle density (localized in Brodmann area 10) was associated with WM worse performance in SCZ patients relative to HC (Buchmann et al., 2014).

#### 4. Sleep spindle and slow wave findings in early course/first-episode psychosis

Recent work from our and other research groups has investigated both sleep spindle and slow-wave sleep abnormalities in early course/first-episode psychosis. In one study, we conducted sleep hd-EEG recordings in first-episode psychosis (FEP) patients and HC and several spindle parameters -amplitude, duration, and density-were calculated and compared between groups. When compared to HC, FEP patients have a significant reduction in spindle duration and density, which was localized in a frontal region (Fig. 2, Top). This reduction in spindle density and duration was associated with worse PANSS negative symptom scores. in patients with SCZ (Kaskie et al., 2019b). In another sleep hd-EEG study, our group investigated several slow wave parameters, including SWA, density, negative peak amplitude, up- and down-slopes in FEP patients relative to HC. It was found that the FEP participants had a significant decrease in slow wave density in a large frontal-central area, which included the prefrontal cortex (Fig. 2, Bottom), whereas the other slow wave parameters did not differ between groups. In the subset of patients who were taking antipsychotic medications, there was no association between



**Fig. 2.** First-episode psychosis (FEP) patients had reduced sleep spindles and slow waves compared to healthy controls (HC). Reproduce in color. Slow wave and sleep parameters were calculated during N2 and N3 NREM sleep.

medication dose and slow wave density. Furthermore, the reduction in slow wave density was associated with worse positive symptoms in FEP patients (Kaskie et al., 2019a). In both of those sleep studies, slow wave and sleep parameters were calculated during N2 and N3 NREM sleep. Manoach et al. assessed sleep abnormalities in recently diagnosed adults with psychosis, non-psychotic first-degree relatives of SCZ patients and two sample groups of HC that were matched to the patients and their relatives (Manoach et al., 2014). When compared to HC and other psychotic patients, the early course patients diagnosed with SCZ showed a significant reduction in spindle-range NREM sleep EEG power, spindle amplitude, and spindle density. Relatives of SCZ patients also showed reduced spindle activity compared with controls. Across all psychotic patients, lower spindle density was linked to worse performance on all but one of the cognitive measures. A reduction in spindle amplitude was also associated with poorer cognitive scores, which however did not differ between SCZ and non-SCZ psychotic groups. Furthermore, reduced spindle amplitude correlated with lower estimated verbal IQ in the pooled data, although this effect was driven by the non-SCZ psychotic group. Another study by Tesler et al. examined sleep spindles in adolescents with early onset schizophrenia (EOS) using (hd)-EEG. It was found that the EOS group had a significant reduction in spindle density when compared to HC (Tesler et al., 2015). Topographic analysis showed a diffuse reduction of spindle density over the centro-parietal and temporal brain regions. Furthermore, reduced spindle density within these regions was inversely correlated to the severity of positive symptoms in EOS patients. Altogether, these findings indicate that sleep spindles and slow wave abnormalities are present at the beginning of psychosis, are unrelated to medication exposure, and are associated to some of the clinical and cognitive impairments commonly reported by psychotic patients.

#### 5. Future directions

While the findings reviewed above are very promising, additional work is needed to investigate the role of sleep spindle and

slow wave abnormalities in the development, full manifestation, and clinical course of SCZ and other psychotic disorders. In what follows, we will discuss how future sleep studies may contribute to achieve these goals.

- 1) Characterize spindle and slow wave abnormalities in individuals at risk for psychosis with sleep hd-EEG recording: as reported above, we recently established deficits in both spindle and slow wave in FEP patients. However, we still do not know when those sleep impairments first occur, and how they may affect the development of psychopathology in patients with SCZ. Clinical High Risk (CHR) individuals represent a unique group enriched for precursors of major psychiatric disorders, including SCZ (Bearden and Forsyth, 2018). CHR tend to have different longitudinal courses, with one subgroup showing remission of psychotic symptoms, a second subset with persistent sub-syndromal symptoms, and a third one who will transition to full-blown psychosis (Addington et al., 2015). Future sleep studies should therefore investigate the ability of spindles and slow wave to characterize the clinical course of CHR individuals, including those who will be converting to SCZ (Fig. 3). This work will eventually help to establish the relationship between sleep disturbances and psychosis, including their putative causal role in the development of SCZ and related psychotic disorders.
- 2) Examine the relationship between altered sleep oscillations and cognitive and functional impairments in CHR individuals: in addition to subdiagnostic psychotic symptoms, CHR subjects experience emergent cognitive impairment and social dysfunction. Increasing evidence from sleep studies suggest that spindles (Fogel and Smith, 2011; Schabus et al., 2008; Tamaki et al., 2008) and slow waves (Diekelmann and Born, 2010; Wilckens et al., 2018) are implicated in learning, memory consolidation, and plasticity, and recent work has linked deficits in spindles (Buchmann et al., 2014; Manoach et al., 2014; Wamsley et al., 2012) and slow waves (Demanuele et al., 2017; Gardner et al., 2014) with impaired cognitive performance in patients with SCZ. Additionally, higher spindle activity is associated with more favorable behavioral/emotional patterns, including less hyperactivity and more prosocial behaviors, in

children (Mikoteit et al., 2013), whereas fewer sleep spindles were found in autism spectrum disorder patients, and especially in a subgroup diagnosed with Asperger, compared to healthy controls (Limoges et al., 2005). Thus, future studies should assess the implication of spindle and slow wave parameters in moderating cognitive and social functioning trajectories in CHR youth.

- 3) Investigate the neural circuitry and molecular mechanisms underlying sleep abnormalities in CHR individuals relative to HC: Sleep spindles are initiated by GABA-ergic cells in the thalamic reticular nucleus (TRN), and are regulated by TRN and medio-dorsal (MD) thalamus (Ferrarelli and Tononi, 2017; Luthi, 2014). Thalamic activity is then relayed to the cortex, where spindle oscillations are synchronized (Bonjean et al., 2012). Slow waves occur primarily in prefrontal (PFC) regions, where slow wave density is most prominent, and are generated and coordinated by glutamatergic cortical pyramidal neurons (Sanchez-Vives et al., 2017). Several sleep studies from our and other research groups demonstrated that patients with SCZ, including FEP, had marked deficits in sleep spindles, and less consistently slow waves, compared to HC in frontal/prefrontal regions (Castelnovo et al., 2018). Furthermore, we recently established that reduced MD volumes correlated with decreased PFC spindle activity in patients with SCZ (Buchmann et al., 2014), whereas neuroimaging studies have shown reduced MD-PFC resting state fMRI connectivity in both chronic and early course SCZ (Woodward and Heckers, 2016). Building on these findings, future work should focus on identifying the neuronal and molecular underpinnings of sleep spindle and slow wave abnormalities, ideally even before illness onset. To begin achieving this goal, in an ongoing longitudinal sleep study we are employing a multimodal imaging approach combining sleep hd-EEG, resting state (rs)-fMRI and Magnetic Resonance Spectroscopy Imaging (MRSI) in CHR individuals (Fig. 3).
- 4) Examine the putative role of sleep oscillations as predictive, diagnostic, or prognostic biomarkers for SCZ and other psychotic disorders: biomarkers are neurobiological characteristics that are related to the pathophysiology and the clinical manifestations of psychiatric illnesses, including SCZ (Ferrarelli, 2013).

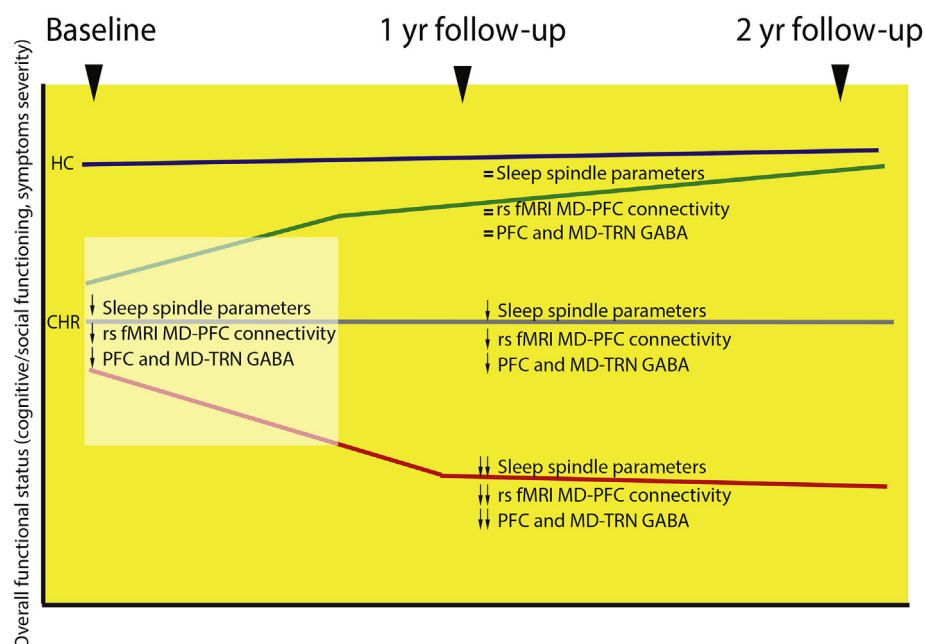


Fig. 3. Expected longitudinal changes in sleep spindle and related parameters in individuals at Clinical High Risk (CHR) for psychosis relative to HC. Reproduce in color.

While clinical symptoms can vary over the course of the illness and are assessed subjectively, biomarkers are objective measures that tend to be stable over time (Tammenga et al., 2017). Furthermore, neurophysiological biomarkers, such as sleep EEG oscillations, offer precise temporal measures of neural circuits that mediate behavioral, clinical, as well as cognitive features of SCZ (Thibaut et al., 2015). Such biomarkers could be used as predictive, diagnostic, and/prognostic measures for SCZ and related disorders (Hunter and Lawrie, 2018; Mehta and Keshavan, 2015; Pinto et al., 2017). For example, assessing spindles and slow waves during longitudinal sleep studies in CHR individuals will establish whether abnormalities in any of these sleep parameters can predict clinical outcome in these individuals, and especially progression to SCZ (Fig. 3). Furthermore, spindle deficits may represent a candidate diagnostic biomarker for SCZ. Indeed, several sleep EEG studies have reported that spindles deficits are present in both chronic, early course, and early onset SCZ, and are unrelated to antipsychotic medication exposure (Ferrarelli et al., 2007, 2010; Manoach et al., 2014; Tesler et al., 2015). Although promising, these findings will need to be replicated in larger cohorts of both psychotic, including SCZ and other psychotic disorders, and non-psychotic patients. A reduction in slow wave density was also recently observed by our group in FEP patients relative to HC. Future work performing longitudinal sleep EEG recordings in these patients will help establish whether this slow wave reduction may represent a (state) marker of acute psychosis. In patients with SCZ, sleep spindles and slow waves could also be utilized as prognostic biomarkers (i.e., biomarkers used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease of interest). For example, lower spindle/slow wave parameters at initial assessments may be associated to worse clinical prognosis, whereas higher spindles and/or slow waves may lead to better clinical outcomes.

- 5) Develop novel, early treatment interventions based on sleep neurophysiology: if sleep spindles and slow wave abnormalities are implicated in the clinical, cognitive, and social dysfunctions experienced by patients with SCZ, reversing such sleep abnormalities has a clear therapeutic potential. Slow waves and spindles can be increased using several approaches, including tones, electrical stimuli, as well as pharmacological interventions (Del Felice et al., 2015; Marshall et al., 2006; Mednick et al., 2013). Furthermore, recent studies have developed experimental procedures that allow monitoring and selectively enhancing in real time the sleep EEG oscillatory activity using auditory tones or transcranial input delivered through closed-loop stimulation (Lustenberger et al., 2016; Ngo et al., 2013). Future studies should therefore assess whether these interventions can enhance sleep spindles and slow wave deficits in patients with SCZ, and whether this enhancement leads to an improvement in their functional impairments. This work would eventually pave the way to the development of novel, early treatment interventions in SCZ based on sleep neurophysiology.

## Contributors

Fabio Ferrarelli designed the study and edited the manuscript; Ying-Yi Zhang contributed to the writing of the manuscript; Gonzalo M. Quiñones contributed to the writing of the manuscript.

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## Declaration of competing interest

All authors declare that they have no conflict of interest.

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