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Reduced frontal slow wave density during sleep in first-episode psychosis

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ABSTRACT

Background: Sleep disturbances are commonly reported in psychotic patients and often contribute to the manifestation and severity of their symptoms. Slow waves characterize the deepest stage of NREM sleep, and their occurrence is critical for restorative sleep. Slow wave abnormalities have been reported in patient with schizophrenia, especially when experiencing an exacerbation of psychosis. However, their presence and delineation, with an emphasis on topography, in first-episode psychosis patients (FEP) have not yet been characterized.
Methods: We performed sleep high density (hd)-EEG recordings in twenty FEP patients and twenty healthy control subjects (HC). Slow wave activity (SWA) and several other slow wave parameters, e.g. density, amplitude, up- and down-slopes, were calculated at each electrode location and compared across groups. Additionally, the association between slow wave characteristics and clinical symptoms was assessed.
Results: FEP patients showed a reduction selectively in slow-wave density relative to HC, and this reduction was significant in a large frontal area, including channels overlying the prefrontal cortex. Furthermore, slow wave density was inversely correlated with the severity of FEP positive symptoms.
Conclusions: Abnormalities in slow waves are present at the beginning of psychosis, occur in frontal-prefrontal regions that are highly dysfunctional in psychotic patients, and are associated with their positive symptom severity. Building on these findings, future work will help establish the direction of these associations (i.e., if clinical symptoms precede, coincide, or follow SW deficits), which will determine whether ameliorating slow wave sleep deficits is a viable treatment target in early psychosis.

1. Introduction

In the clinical setting, sleep disturbances are common for patients with acute psychosis and often represent a key motivating factor for seeking mental health treatment (Reeve et al., 2015). Furthermore, increasing evidence indicates that sleep abnormalities play a significant role in the development and full-blown manifestation of psychosis (Kamath et al., 2015). Sleep deprivation in healthy subjects, or self-reported decreases in sleep quality, can induce psychosis-like symptoms, including hallucinations and paranoid delusions (Petrovsky et al., 2014). Moreover, sleep disturbances are present in individuals at clinical high risk for psychosis (Keshavan et al., 2004; Lunsford-Avery et al., 2013). In addition, both objective and subjective measures of disrupted sleep can predict greater next-day auditory hallucinations, paranoid thoughts, and delusions of control in patients with SCZ (Mulligan et al., 2016). However, it remains unclear which aspects of sleep are implicated in the ontogenesis and clinical appearance of psychotic disorders.

The vast majority of sleep EEG studies have focused on differences in the sleep architecture of healthy and psychotic individuals, with inconsistent findings (Chan et al., 2017). Overall, patients with SCZ display shorter total sleep time, longer sleep onset latency, lower sleep efficiency, decreased duration and latency of REM sleep, and reduced slow wave sleep duration compared to healthy control (HC) subjects. Recent work has shifted towards an emphasis on specific electrophysiological characteristics of EEG activity during sleep, including slow waves (Castelnovo et al., 2017). Slow waves are large amplitude, negative-positive deflections, which are most prominent during the deepest NREM sleep stage (N3), also called slow wave sleep, and are thought to be primarily involved in the restorative function of sleep (Mander et al., 2017; Tononi and Cirelli, 2014).

In patients with chronic SCZ, deficits in slow wave activity (SWA, NREM sleep EEG power at 0.5–4 Hz) have been inconsistently found, with several sleep studies reporting negative findings. In contrast, a reduction in slow wave density has been the most commonly reported finding (Castelnovo et al., 2017). A decrease in slow wave density has been found in acutely ill, hospitalized patients (Ganguli et al., 1987; Hiatt et al., 1985; Keshavan et al., 1998; Sekimoto et al., 2011), but not in more stable, outpatient participants (Ferrarelli et al., 2010; Goder et al., 2015). While numerous studies have investigated slow wave

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abnormalities in chronic patients, preciously little is known about slow wave abnormalities at illness onset, including which specific slow wave parameter is most altered. In a recent study, newly diagnosed patients with schizophrenia had a reduction in spectral power across a broad frequency range, encompassing 0.5 to 8 Hz (Manoach et al., 2014). However, this study did not investigate slow wave parameters beside SWA and was limited by sparseness of the EEG recording channels, such that a precise topographical pattern of slow wave characteristics could not be determined. It is also unknown how slow wave changes at the beginning of psychosis relate to the clinical symptomatology of these patients.

In the present study, we performed sleep high-density (hd)-EEG (N = 64 electrodes) recordings and measured several slow wave parameters, including power, down-slope, up-slope, negative peak amplitude, and density in first-episode psychosis (FEP) and healthy comparison (HC) subjects. We anticipated that slow wave density would be the most affected parameter in these patients, in line with findings in chronic patients experiencing an acute exacerbation of psychosis. We also expected that, in FEP patients, slow wave impairments would be observed in frontal-prefrontal areas, where slow waves are usually more prominent (Bersagliere et al., 2018; Riedner et al., 2007). Finally, based on the assumption that reduced slow waves were implicated in the manifestation of the first psychotic episode and that positive symptoms were predominant at illness onset(Castro-Fornieles et al., 2007; Rosen et al., 2012), we predicted that the positive symptoms would be most strongly associated with decreased slow wave density in FEP patients.

2. Methods

2.1. Participants

Twenty FEP patients and twenty HC subjects were recruited for the study. As shown in Table 1, where demographic and other clinically relevant are provided, FEP patients were slightly younger and included more women than HC, although none of these parameters was significantly different between groups. FEP subjects were reassessed six months after baseline to determine a diagnosis of schizophrenia or other psychotic disorder, based on the Structured Clinical Interview for DSM-IV (First, 2013).

2.2. Recruitment

FEP were identified and recruited from the emergency room at Western Psychiatric Institute and Clinic of UPMC, and through inpatient and outpatient services within and outside of UPMC. HC were recruited from the local community through physical and online advertisements.

Table 1
Clinical variables of study groups.

Clinical measures	Healthy controls	First-episode psychosis	p-Value
Number of subjects	N = 20	N = 20	.
Sex (# female)	N = 4	N = 8	0.17
Age (years)	24.7 ± 5.7	22.9 ± 5.4	0.25
Parental SES	49.0 ± 12.7	44.5 ± 13.4	0.3
Med. naïve/treated[a]	N/A	N = 12/8	
Daily medication dose (CPZ equivalent)	N/A	80.2 ± 116.2	
Antipsychotic type (N)	N/A	Risperidone (5) Olanzapine (2) Quetiapine (1)	
SAPS	N/A	21.6 ± 10.2	
SANS	N/A	18.4 ± 7.5	
PANSS positive scores[b]	N/A	21.0 ± 4.8	
PANSS negative scores[b]	N/A	16.4 ± 5.4	

Measures given as mean ± standard deviation, unless otherwise specified.
[a] All patients had been treated for <2 months at the time of the sleep EEG recordings.
[b] Collected in 14 out of 20 patients.

This study was approved by the University of Pittsburgh Institutional Review Board, and all participants provided written informed consent prior to completing study procedures.

2.3. Eligibility criteria

All participants met the following inclusion criteria: 1) aged 12–40; 2) no major medical (including pregnancy) or neurological illness (including significant head injury) affecting CNS function; and 3) no DSM-IV intellectual developmental disorder. The Wechsler Abbreviated Scale of Intelligence (WASI) was administered to aid in identifying an intellectual developmental disorder. FEP patients were included if they: 1) were experiencing their first psychotic episode, defined by report of symptoms and/or history of treatment, and 2) had no >2 months of lifetime antipsychotic treatment. Specifically, twelve first-episode psychosis patients were antipsychotic naïve, whereas eight had <2-months exposure to antipsychotics at the time of the sleep hd-EEG recordings. Patients were excluded for any of the following reasons: 1) had a psychotic illness with a temporal relation to a substance use disorder; 2) co-morbidity of DSM-IV psychoactive substance dependence within the past 6 months; 3) substance abuse (other than cannabis and/or alcohol) within the past month; or 4) a temporal relationship between illness onset and head injury. All FEP patients were administered the Scale for the Assessment of the Positive and Negative Symptoms (SAPS and SANS) (Andreasen, 1990), to assess the severity of their clinical symptoms (Table 1). A subset of patients (14 out of 20) also completed the Positive and Negative Syndrome Scales (PANSS) (Kay et al., 1987). SAPS, SANS, and PANSS assessments were repeated after six months, when clinical diagnosis was ascertained. HC had no history of major psychiatric illness and were excluded for any of the following reasons: 1) treatment with an antipsychotic at any time; 2) first-degree family history of schizophrenia spectrum disorder and/or mood disorder with psychotic features; or 3) current medication affecting brain structure or function.

2.4. Sleep laboratory procedures

We asked each participant to avoid napping and refrain from alcohol and caffeine consumption in the days before the overnight sleep recordings. Participants were also asked about their sleep habits, including their usual bedtime and wake-up time, and they were invited to come to the lab accordingly. Specifically, participants were told to arrive at the sleep laboratory at least 1.5 h prior to their usual bedtime. Upon arrival, they were fitted with a high-density electroencephalography (hd-EEG) net, and two electrodes were applied to the chin to record electromyography (EMG). Data from a 64-channel EEG montage were collected using the Geodesic System 400 (Electrical Geodesics Inc., EGI). Overnight sleep recordings were scored using the American Academy of Sleep Medicine (AASM) criteria (Silber et al., 2007). We collected only one overnight sleep EEG recording. However, to mitigate the impact of the first night effect EEG recordings in the lab were performed at each participant's usual bedtime.

2.5. Sleep hd-EEG data processing

Whole night sleep hd-EEG data was processed in MATLAB (The MathWorks Inc., Natick, MA). Signals were filtered using 0.5 Hz high-pass and 40 Hz low-pass filters, then down-sampled to 128 Hz and re-referenced to the average of all channels. The sleep recording was then divided into 6-s epochs. Semiautomatic artifact rejection procedures were utilized to remove channels and epochs with high-frequency noise or other persistent artifacts (i.e. low frequency drift due to poor channel contact or sweating). Specifically, thresholds were automatically calculated for low (1–4 Hz) and high (20–30 Hz) frequency ranges for each channel. Spectral power in these ranges across all 6-s NREM epochs were plotted and visually inspected for

each channel. Channels with artifacts affecting a majority of the recording were removed. Additional spectral-based and topographic procedures were used to identify and remove channels with distinctly greater power relative to neighboring channels. Overall, >80% of the data recorded for each participant and >90% of the channels were retained after this procedure.

Spectral power density was computed using Welch's modified periodogram method in 2-s Hamming windows (50% overlap) to decompose EEG time series signals into the frequency domain in the 0.5–40 Hz range. To characterize slow wave activity (SWA, 0.5–4 Hz), we employed an in-house algorithm for the automatic detection of several slow wave parameters (Supp. Fig. 2A). Each EEG signal was referenced to the average of the two mastoid channels and band-pass filtered at 0.5–4.0 Hz. Then, slow waves were detected as negative deflections between two zero crossings. Slow waves are defined based on period and amplitude. However, in previous work we have shown that the amplitude of slow waves is affected by scalp location and time of night, such that it is maximal in frontal-prefrontal areas and at the beginning of the night, whereas it is smaller in posterior areas and at the end of the night. Thus, in this study slow waves were selected based on their period. Specifically, only waves with 0.25- to 1.0-s consecutive zero crossings detected in artifact-free NREM epochs were considered slow waves. Four slow wave parameters were computed: down slope (DS), defined as the amplitude of the most negative peak divided by the time from the previous (first) zero crossing; negative peak amplitude (NPA), defined as the most negative amplitude following the first zero crossing; up slope (US), defined as the amplitude of the most negative peak divided by the time until the next (second) zero crossing; and slow wave density, defined as the number of slow waves detected per minute of NREM sleep. These slow wave parameters were investigated by our group in a previous sleep study in chronic patients with schizophrenia (Ferrarelli et al., 2010). For additional details, refer to (Ferrarelli et al., 2010; Riedner et al., 2007).

2.6. Statistical analyses

To compare demographic characteristics, sleep architecture, and EEG power between FEP patients and HC, unpaired *t*-tests were performed. Topographic differences in slow waves across groups were assessed with Statistical Nonparametric Mapping (SnPM), a statistical approach that enables corrections for multiple comparisons (Nichols and Holmes, 2002). Finally, we performed correlation analyses between slow wave density and the SAPS, SANS, as well as positive and negative PANSS scores, in FEP patients.

3. Results

3.1. Sleep architecture parameters

FEP patients had significantly increased sleep latency as well as reduced total sleep time and sleep efficiency compared to HC (Table 2).

Table 2
Sleep architecture parameters of study groups.

Sleep measures	Healthy controls	First-episode psychosis	p value
Total sleep time (min)	429 ± 51	385 ± 81	0.04
Sleep onset latency[a] (min)	15 ± 12	47 ± 58	0.01
WASO[b] (min)	52 ± 34	75 ± 54	0.17
NREM N1 (min, %)	26 ± 11 (8%)	24 ± 17 (6%)	0.30
NREM N2 (min, %)	230 ± 27 (54%)	207 ± 69 (53%)	0.25
NREM N3 (min, %)	81 ± 35 (19%)	74 ± 34 (18%)	0.45
REM (min, %)	81 ± 28 (20%)	80 ± 30 (19%)	0.60
Sleep efficiency (%)	89.0 ± 8	82.0 ± 12	0.01

Measures given as mean ± standard deviation, unless otherwise specified.
[a] Sleep onset latency is defined as the time from the beginning of the recording until the first NREM sleep stage 2 epoch.
[b] WASO = wake after sleep onset.

These findings are consistent with prior literature in first-episode psychosis, as reported by a recent sleep review (Davies et al., 2017). However, FEP and HC subjects did not differ in time or percentage spent in both NREM and REM sleep stages or in waking after sleep onset (WASO).

3.2. Sleep EEG power analyses

There were no differences in NREM sleep EEG power spectra, including slow wave activity (SWA, 0.5–4 Hz), between FEP and HC (Supp. Fig. 1A). Similarly, topographic analyses showed no differences in SWA between groups (Supp. Fig. 1B).

3.3. Slow wave parameter analyses

We found that FEP patients had significantly decreased slow wave density compared to HC subjects in a large frontal-central area, including the prefrontal region, which was significant after correction for multiple comparisons (Fig. 1, N = 21 electrodes, p = 0.007, SnPM). In contrast, slow wave DS, US, and NPA did not differ across study groups. We also found no topographic differences in the mean slow wave frequency or the average peak-to-peak slow wave amplitude between FEP patients and HC (Supp. Fig. 4). A reduction in slow wave density (N = 21 electrodes, p = 0.006, SnPM), but not in other slow wave parameters, was confirmed in FEP patients even when employing the amplitude criterion (≥75 μV) traditionally used to identify slow waves (Supp. Fig. 3). The decrease in slow wave density in FEP patients compared to HC subjects remained significant (N = 18 electrodes, p = 0.009, SnPM, data not shown), when analysis was restricted to the subpopulation of unmedicated patients (N = 12). Furthermore, in the subset of FEP on antipsychotic medications (N = 8), we found no correlation between medication dose, calculated as chlorpromazine equivalents, and slow wave density (r = −0.11, p = 0.85). We also established that a reduction of slow wave density was present in all FEP patients regardless of their six-month diagnoses. Specifically, both schizophrenia and non-schizophrenia patients had similarly decreased slow wave density (33.3 ± 4.6 and 34.0 ± 2.7 respectively) relative to healthy comparison subjects (36.6 ± 1.2).

3.4. Correlation between slow wave parameters and clinical measures in FEP patients

In FEP patients, correlation analyses with clinical symptoms were performed using the average value of the cluster of channels showing significantly reduced slow wave density after SnPM to correct for multiple comparisons. Correlation analyses revealed that reduced slow wave density was associated with worse positive symptoms, as assessed with the SAPS (r = −0.6, p = 0.02, Fig. 2), whereas there was no significant correlation with the negative symptoms (SANS, r =

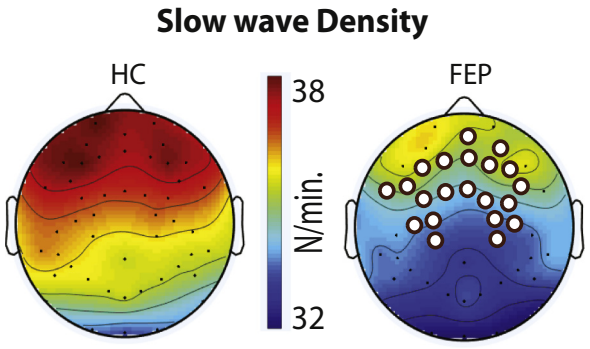

Fig. 1. FEP patients had a reduction in slow wave density in a large frontal-central area (N = 21, electrode locations indicated by open circles), which included the prefrontal region, relative to HC.

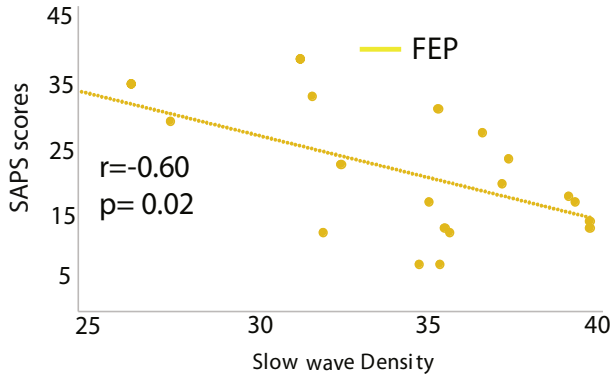

Fig. 2. Reduced slow wave density was associated with worse positive symptoms (i.e., higher SAPS scores) in FEP patients.

-0.1, $p = 0.8$). These findings were confirmed in a subset of patients (14 out of 20) who completed the PANSS scores, such that slow wave deficits were associated with higher PANSS positive symptoms ($r = -0.55$, $p = 0.03$, Supp. Fig. 5), but not with the PANSS negative symptoms ($r = -0.07$, $p = 0.85$).

4. Discussion

This is the first study to utilize sleep hd-EEG recordings to investigate topographic differences in SWA and several other slow wave parameters between first episode psychosis (FEP) patients and healthy controls (HC). FEP participants had a decrease in slow wave density, but not in SWA or other slow wave parameters, compared to HC subjects. This reduction in slow waves involved a large frontal-central area, including the prefrontal cortical region, where slow waves are usually more prominent. Furthermore, reduced slow wave density predicted the severity of the FEP positive symptoms, thus reflecting the intensity of their psychotic episode.

4.1. Slow wave density, but not SWA or other slow wave parameters, were reduced in FEP patients

Sleep EEG studies in acutely ill (Hiatt et al., 1985) and hospitalized individuals with chronic SCZ (Keshavan et al., 1998) have reported reduced slow wave density. In contrast, slow wave density deficits were not observed in stable, chronic outpatients with SCZ relative to HC (Ferrarelli et al., 2007; Ferrarelli et al., 2010; Tekell et al., 2005). Previously, it was unknown whether there are also slow wave density changes in early psychosis. We are the first to show that in FEP patients there is a significant reduction in slow wave density relative to HC. This would suggest that slow wave density abnormalities are only present early in the disease course or during acute psychosis. Importantly, the reduction in slow wave density was not a result of antipsychotic medication since it was still observed in the subset of unmedicated FEP patients. It is more likely that the changes in slow wave density occurred as part of the disease process.

In contrast, we failed to detect any differences in SWA or any other slow wave parameters, e.g. NPA, up and down slopes, between FEP patients and HC. It should be noted that a recent study in early course psychosis reported a reduction in broadband frequencies encompassing the slow oscillation, delta and theta frequency bands (0.5–8 Hz) (Manoach et al., 2014). This discrepancy could be due in part to the focus of the Manoach et al. study only on N2 sleep, which is primarily characterized by sleep spindles. In contrast, we also investigated N3, where slow waves are most prominent. It is also possible that SWA reduction is restricted to a subset of early course patients, a finding in line with reports in chronic SCZ (Manoach and Stickgold, 2009).

Overall, these results support the conclusion that in FEP patients there is an overall reduced ability to generate slow waves during sleep. However, the slow waves that are present in FEP patients maintain characteristics, e.g. SWA and NPA, like the slow wave oscillations observed in HC.

4.2. Slow wave density was reduced in a frontal-prefrontal region in FEP

With the benefit of hd-EEG recordings across 64 channels, we established that FEP patients have reduced slow wave density specifically in a frontal-central area, encompassing the prefrontal region. Frontal cortical areas, especially the prefrontal cortex, seem especially vulnerable to gray matter volume loss, metabolic disruption, as well as alterations in functional connectivity in SCZ (Vidal et al., 2006). It is perhaps unsurprising then that the greatest reductions in slow waves occurred in similar frontal areas in FEP. While the structural data from FEP is somewhat heterogeneous, there is evidence for early frontal cortical changes. Adolescents diagnosed with SCZ demonstrate distinct frontal gray matter loss in a dorsal-to-ventral pattern over a five-year period (Vidal et al., 2006). In addition, FEP patients exhibit smaller volumes of frontal and temporal lobes at the time of hospital admission (Gur et al., 1998). When observed longitudinally, SCZ patients have faster volume decreases in frontal cortical areas than HC subjects, and this reduction is associated with greater severity of symptoms (Ho et al., 2003; Mathalon et al., 2001). There are also activity changes occurring in primarily frontal cortical areas overlapping with structural alterations early in schizophrenia. Unmedicated patients with schizophrenia experiencing predominately positive symptoms demonstrate hyperactivity of the frontal cortex, as measured by cerebral metabolic rate of glucose with 18F-FDG PET/CT (Shinto et al., 2014; Soyka et al., 2005). Such hyperactivity in frontal areas also disrupts functional connectivity within and across cortical regions. Indeed, a recent study showed there are numerous alterations in dynamic functional connectivity, including between the frontal cortex and thalamus, measured with resting state MRI in early psychosis (Du et al., 2017). Consequently, there is overlap between the regions where we observed reductions in slow wave density and the areas exhibiting morphological, metabolic, and functional changes early in psychosis. Slow wave activity during sleep might provide a readout of frontal-prefrontal dysfunction in acutely psychotic patients.

4.3. Reduced slow waves density predicted positive symptom severity in FEP

In individuals experiencing their first psychotic episode, a common clinical presentation is the occurrence of hallucinations, paranoia, and other types of delusional thinking. These positive symptoms are usually observed in patients with acute psychosis, regardless of their later clinical diagnoses (Ihara et al., 2009). In this study, we found that slow wave density was inversely correlated with the severity of the positive symptoms measured by the PANSS in all FEP patients, independent of any antipsychotic treatment. Consequently, slow wave sleep alterations could represent an early treatment target with novel therapeutics for psychosis patients. Indeed, recent studies have shown that earlier interventions yield a better long-term prognosis for schizophrenia patients (Kurachi et al., 2018).

4.4. Reduced slow waves are unlikely due to sleep disruption and may benefit from antipsychotic treatment

FEP patients had more disrupted sleep compared to HC. We think, however, that sleep disruption is unlikely to account for their slow wave density reduction for several reasons. First, while FEP patients had less total sleep relative to HC, this effect was primarily due to an increased sleep latency, rather than wake after sleep onset (WASO). Second, the amount of time spent on NREM N3, also called slow wave sleep, was not significantly different between groups. Third, slow wave density was calculated as number of slow waves per minute of NREM, rather than being cumulated over the total NREM sleep time, thus

being less affected by sleep disruption. Fourth, sleep disruption should have a global effect on slow waves, whereas in the present study SW reduction was localized to frontal-prefrontal regions. Finally, we run correlation analyses between slow wave density and WASO, a key sleep disruption parameter, and found it to be not significant ($r = -0.13$, $p = 0.85$).

The reduction in slow wave density reported here in FEP patients was not found in previous work from our group in chronically medicated, stabilized patients with schizophrenia (Ferrarelli et al., 2010). About two-thirds of the FEP participants recorded in this study were unmedicated at the time of the assessment, whereas the remaining third had a relatively short (<2 months) exposure to antipsychotic treatment. Thus, the present findings suggest that long-term treatment with antipsychotic medications is needed for ameliorating SW density along with stabilizing these patients.

4.5. Reduced slow waves suggests primarily cortical and dopamine/serotonin alterations in FEP

The molecular mechanisms regulating slow waves have yet to be fully elucidated. However, serotoninergic, glutamatergic, and especially dopaminergic neurotransmission have been implicated in slow wave regulation. In contrast, dysregulation of these systems has important effects on disrupted sleep and proneness to psychosis. Hallucinogenic drugs, e.g. the NMDA antagonist PCP and the 5-HT2A serotonin agonist 2,5-dimethoxy-4-iodoamphetamine (DOI), can elicit psychotic symptoms in healthy individuals during wakefulness (Javitt et al., 2012) and also reduce the spectral power of slow wave oscillations in the prefrontal cortex of anesthetized rats (Celada et al., 2008). The effects of DOI on oscillatory activity in rats are reversed by clozapine (Celada et al., 2008), an atypical antipsychotic which acts as antagonist of the 5-HT2A subunit of the serotonin receptor (Meltzer, 1994). Clozapine is one of the most effective antipsychotic compounds, which is usually prescribed to treatment refractory patients with schizophrenia; however, the ability of clozapine to specifically modulate slow wave density in these patients has yet to be established. Sleep deprivation results in higher plasma dopamine levels and increased dopamine turnover in the ventral striatum, as reflected by enhanced exploratory behavior and response to environmental stimuli in rats (Andersen et al., 2005). The serotonergic system displays a response to sleep deprivation that is distinct from the dopaminergic system with reductions in serotonin and its metabolite occurring mainly in the frontal and parietal cortices (Farooqui et al., 1996). These responses, which are all proxy measures in animal models of human psychosis, can be normalized by dopamine antagonists (Demontis et al., 1990). However, electrophysiological recordings combined with pharmacological manipulations of dopaminergic and/or serotonergic systems are needed to establish the implication of slow wave density changes in these effects. Sleep deprivation in rats can also reduce pre-pulse inhibition (PPI), a measure of sensorimotor gating abnormally decreased in SCZ (Braff, 2010). This reduction is reversed by D2 antagonist antipsychotic administration or after recovery sleep (Frau et al., 2008). Moreover, higher dopamine levels via pharmacological stimulation of D1/D2 receptors leads to sleep disturbances, including reduced sleep time and slow wave sleep (Isaac and Berridge, 2003). In contrast, dopamine-blocking antipsychotic medications often lead to a better clinical outcome for patients with SCZ (Cohrs, 2008), perhaps in part by ameliorating sleep problems.

4.6. Conclusions and future directions

This study was an important first step in establishing the link between distinct electrophysiological changes during sleep and clinical symptoms in FEP. Building on the present findings, future work will help establishing slow wave deficits in larger group of psychotic patients at illness onset. In addition, replicating these findings in a larger sample of patients will help to clarify the contribution of different symptom clusters, including in the cognitive domain, to these deficits (Lisman, 2012).

SW density was reduced in all FEP patients, regardless of the final diagnosis (schizophrenia vs other psychiatric disorders). However, given that most of the FEP patients were eventually diagnosed with schizophrenia (14 out of 20), we think that follow-up studies on larger subgroups of patients are needed to rule out possible differences between schizophrenia and non-schizophrenia patients, as previously reported for sleep spindles (Ferrarelli et al., 2010; Manoach et al., 2014).

Future studies should also systematically investigate how differences in daily activity may affect SW density in FEP. While it is unlikely that some of these factors, like naps or caffeine consumption, can induce topographically specific changes in slow wave incidence, it is possible that a better monitoring of certain daytime parameters, like intensity of psychotic symptoms or level of cognitive engagement, may help predict subsequent SW density deficits in FEP patients. Furthermore, due to the difficulty of recruiting and collecting sleep in these patients, here we were unable to perform back-to-back overnight EEG recordings, thus addressing the potential confound of the first-night effect in the sleep laboratory. It will therefore be important to confirm in future studies that SW deficits are stable across nights.

In the present study we found that reduced SW density was associated with the severity of psychosis in FEP patients. This slow wave reduction occurred at illness onset, while other studies in chronic SCZ patients failed to detect any slow wave abnormalities (Ferrarelli et al., 2007). Consequently, this would suggest that slow wave changes are observed early and transiently in psychotic disorders, and may represent a neurophysiological signature of acute psychosis.

Future work will help establish the direction of these associations (i.e., whether clinical symptoms precede, coincide, or follow SW deficits), which would reveal possible causation. For example, it could be that the occurrence of psychotic symptoms affects the ability to generate slow waves during sleep. Alternatively, frontal cortical changes occurring during the development of psychosis may simultaneously lead to the development of psychotic symptoms and SW impairments. Another possibility is that slow wave deficits precede the onset and determine the severity of psychosis at illness onset. Consistent with this assumption, elegant work from Feinberg et al. has shown that slow waves are a marker of adolescent brain reorganization and have suggested that disruptions to this process may result in onset of schizophrenia (Feinberg and Campbell, 2010). The present findings established reduced slow wave density in FEP, including in three adolescent subjects. Future work in larger groups of adolescent and young adult FEP patients will help better characterize the temporal relationship between reduced slow wave density and the development of psychosis. Additionally, the presence of slow wave alterations in a clinical high-risk population prior to subsequent transition to psychosis would suggest that reduced slow waves are a precipitating, and possibly even a causal factor for illness to occur.

The predominance of slow waves in frontal regions and the presence of frontal cortical abnormalities in psychotic patients at illness onset indicate that reduced SW density may represent a “read-out” for frontal dysfunction in early course psychosis. Thus, future studies investigating the relationship between slow wave deficits and working memory/executive function impairments in FEP will establish if slow waves can help revealing some of the mechanisms underlying cognitive dysfunctions in these patients.

Finally, an intriguing possibility is that treating disturbed slow wave activity during sleep could protect against transition to psychosis or prevent symptom worsening. Sleep symptoms are not a direct target for existing antipsychotic drug treatments. There have also been few studies on the impact of antipsychotic treatment on sleep. Indeed, in stable SCZ patients undergoing long-term antipsychotic treatment there are persistent reductions in sleep quality (Bosch et al., 2018). In addition, transcranial magnetic stimulation is a noninvasive intervention that has been shown by our group to specifically increase the occurrence of

slow waves during NREM sleep (Massimini et al., 2007). Consequently, TMS treatment may mitigate the severity of psychotic symptoms, thus enabling a better clinical outcome.

Altogether, by performing hd-EEG recordings during sleep, we established topographic differences in the density of slow waves between FEP and HC that was associated with positive symptom severity. These findings indicate that abnormalities in slow waves are present at the beginning of psychosis, and likely reflect a state-related biological marker of acute psychosis.

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Contributors

F.F. designed the study and wrote the protocol. R.K. conducted sleep EEGs and processed EEG data. F.F. and R.K. completed statistical analyses and wrote the first draft of the manuscript. F.F. created the figures, and K.G. made substantial revisions to the manuscript and created tables. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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