



# Topographic deficits in sleep spindle density and duration point to frontal thalamo-cortical dysfunctions in first-episode psychosis

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## ABSTRACT

Sleep spindles are NREM sleep EEG oscillations, which are initiated within the thalamus and are regulated by thalamo-cortical circuits. Previous work from our and other research groups has shown marked spindle deficits in patients with schizophrenia (SCZ). However, the presence of spindle impairments at illness onset, including which parameters are most affected, their topographic characteristics, and their relationships with clinical symptoms have yet to be characterized. In this study we performed sleep high density (hd)-EEG recordings in twenty-seven first-episode psychosis (FEP) patients and twenty-three healthy controls (HC). Several spindle parameters—amplitude, duration, and density—were calculated and compared across groups. FEP patients showed reduced spindle duration and density, but not in spindle amplitude relative to HC. These spindle reductions were localized in a frontal area and predicted the severity of FEP patients' negative symptoms. Altogether, these findings indicate that spindle deficits are present at the beginning of psychosis, contribute to clinical symptomatology, and point to frontal thalamo-cortical dysfunctions, thus providing a potential treatment target for early interventions in SCZ and related psychotic disorders.

## 1. Introduction

Sleep spindles are waxing and waning, 12–16-Hz NREM sleep EEG oscillations, which are initiated within the thalamus and regulated by thalamo-cortical circuits (Luthi, 2014). Specifically, the spindle oscillation is generated by the thalamic reticular nucleus (TRN) in combination with the dorsal thalamus, and is then transferred to the cortex, where spindles are synchronized and amplified, while thalamo-cortical connections sustain and regulate the length of the spindle oscillation (Pratt and Morris, 2015). Thus, individual spindle parameters, including amplitude, density and duration, reflect the integrity of the underlying thalamo-cortical network, and deficits in these parameters point to dysfunctions in complementary thalamo-cortical neuronal circuits in psychiatric disorders (Ferrarelli and Tononi, 2017). Furthermore, the use of high-density (hd)-EEG ( $N \geq 64$  electrodes), allows the identification of localized, topographically specific sleep spindle impairments in these patients relative to healthy controls (Pisarenco et al., 2014).

In previous work, by performing overnight sleep hd-EEG recordings we found marked deficits in several sleep spindle parameters in chronic patients with schizophrenia (SCZ) relative to both healthy and psychiatric controls (Ferrarelli et al., 2007, 2010). A recent, elegant sleep study using archival data based on two EEG channel recordings reported spindle deficits in early course SCZ and first-degree relatives of SCZ probands relative to psychiatric and healthy comparison subjects (Manoach et al., 2014). Although promising, these findings left several

unanswered questions, including whether spindle impairments are present at illness onset, which spindle parameters are most affected, where these deficits are most prominent, and how they correlate with the clinical symptoms reported by the patients. To begin addressing these questions, here we performed sleep hd-EEG recordings and measured several spindle parameters, including amplitude, duration, and density, in first-episode psychosis (FEP) patients and healthy controls (HC).

## 2. Materials and methods

### 2.1. Participants

Twenty-seven FEP patients and twenty-three age and gender matched HC were recruited for the study. Demographic and other clinically relevant data are provided in Table 1.

### 2.2. Recruitment

FEP patients were identified and recruited from the emergency room at Western Psychiatric Institute and Clinic of the University of Pittsburgh Medical Center (UPMC), and through inpatient and outpatient services within and outside of UPMC. HC were recruited from the local community through physical and online advertisements. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional

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**Table 1**  
Clinical variables of study groups.

Clinical Variables	Healthy Controls (HC) N = 23	First-Episode Psychosis (FEP) N = 27	P Value
Age (years)	24.7 ± 5.7	23.2 ± 5.8	0.74
Gender (#/% male)	16/72%	17/68%	0.72
Mean IQ	111.2 ± 6.7	106.1 ± 15.5	0.22
PANSS Positive	–	20.4 ± 4.6	–
PANSS Negative	–	16.3 ± 5.0	–
Antipsychotic naïve/ treated <sup>a</sup>	–	15/12	–

<sup>a</sup> FEP patients who were taking antipsychotics had less than 1 month exposure at the time of the EEG recordings.

committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the University of Pittsburgh Institutional Review Board, and all participants provided written informed consent prior to completing any of the study procedures.

### 2.3. Eligibility criteria

All participants met the following inclusion criteria: 1) no major medical or neurological illness, including significant head injury, affecting central nervous system function; and 2) no DSM-IV 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 more than 2 months of lifetime antipsychotic treatment. Specifically, fifteen FEP patients were antipsychotic naïve, whereas twelve had < 1-month exposure to antipsychotic medications at the time of the sleep hd-EEG recordings. Of those patients taking antipsychotic medications, seven were on risperidone, three on olanzapine, one on quetiapine, and one on aripiprazole. Chlorpromazine equivalent doses were  $216 \pm 89.5$  (Mean ± SD). Furthermore, two patients were on benzodiazepines (Lorazepam 1 mg, Clonazepam 0.5 mg) three on mood stabilizers (Lithium 600 mg, 900 mg, and 1200 mg respectively), and ten on antidepressant medications, of which three were on Sertraline 100 mg, three on Citalopram (two on 20 mg and one on 10 mg), two on Bupropion 150 mg, one on Escitalopram 10 mg, and one on Fluoxetine 20 mg. 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. FEP patients were also administered the Positive and Negative Syndrome Scales (PANSS) to assess the severity of their clinical symptoms (Table 1). PANSS scores were obtained after FEP participants were found to be eligible for the study. A Structured clinical interview (SCI-PANSS) was used to obtain these scores. A group of clinical interviewers from the Western Psychiatric Institute with extensive experience in assessing psychotic patients performed the interview and scoring. IQ was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI). At the time of the EEG recordings, FEP patients had the following diagnoses: 1) Schizophrenia (N = 16) or Schizoaffective (N = 2) disorder; 2) Psychosis NOS (N = 4); 3) Bipolar disorder (N = 2); and 4) MDD with psychotic features (N = 3). HC had no history of major psychiatric illness and were excluded for any of the following reasons: 1) treatment with an antipsychotic medication 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; or 4) substance abuse (other than cannabis and/or alcohol) within the past month.

### 2.4. Sleep laboratory procedures

We asked each participant to avoid napping as well as to refrain from alcohol and caffeine consumption in the days before the overnight sleep EEG 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). EEG sampling rate was 200 Hz, with impedance values  $\leq 50$  k $\Omega$ . Overnight sleep recordings were scored using the American Academy of Sleep Medicine (AASM) criteria (Silber et al., 2007).

### 2.5. Sleep EEG data processing and sleep spindle analyses

Sleep hd-EEG data was processed in MATLAB (The MathWorks Inc., Natick, MA). Semi-automatic 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. Only a handful of bad channels were identified during EEG data analyses, which were equally distributed between the two study groups (FEP =  $2.2 \pm 1.2$ ; HC =  $2.6 \pm 1.0$ ); thus, no bad channel replacement was performed. 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. After artifact-contaminated channels and epochs were removed, EEG signals were average referenced, and sleep spindle activity was investigated. Specifically, an automatic algorithm was employed for the detection of several spindle parameters: amplitude, duration, and density. Briefly, artifact-free NREM sleep epochs were filtered between 11 and 16 Hz, and rectified filtered traces were used as time series for each EEG channel. The thresholds for spindle detection used in this study were two times the mean (lower threshold) and six times the mean (upper threshold). For each detected spindle (i.e., contributing to spindle density), amplitude was the maximum over the upper threshold, while the beginning and the end (i.e., spindle duration) was measured before and after this maximum when the amplitude dropped below the lower threshold. To characterize spindles in slow (12–14 Hz) and fast (14–16 Hz) ranges, spindle parameters were calculated from NREM data filtered in these two frequency bands. For additional details, refer to (Ferrarelli et al., 2007, 2010).

### 2.6. Statistical analyses

To compare demographic characteristics and sleep architecture parameters between HC and FEP patients, two-tailed unpaired t-tests were performed. Topographic differences in sleep spindles across groups were assessed with Statistical Nonparametric Mapping (SnPM), a statistical nonparametric approach that enables corrections for multiple comparisons (Nichols and Holmes, 2002). We also calculate the Cohen d to determine effect sizes of the spindle parameter deficits in FEP patients relative to HC. Cohen's d values indicate how different a parameter of interest is between groups (effect size, ES) (Cohen, 1992). Effect sizes were computed on the average values of the channels significantly different between FEP and HC groups. Finally, we performed Pearson correlation analyses between sleep spindle parameters and the positive and negative PANSS scores in all FEP patients, as well as between spindles and medication doses in the subset (N = 12) of FEP patients exposed to antipsychotic compounds.

**Table 2**  
Sleep architecture parameters of study groups.

Sleep Measures	Healthy Controls (HC)	First-Episode Psychosis (FEP)	FEP vs HC
Total sleep time (min)	428 ± 50	389 ± 88	P = 0.04
Sleep latency <sup>a</sup> (min)	15 ± 12	43 ± 53	P = 0.02
WASO <sup>b</sup> (min)	59 ± 34	77 ± 59	P = 0.1
NREM N1 (%)	8 ± 4	8 ± 6	P = 0.72
NREM N2 (%)	54 ± 6	53 ± 8	P = 0.66
NREM N3 (%)	18 ± 7	17 ± 9	P = 0.74
REM (%)	19 ± 6	21 ± 7	P = 0.22

Values given as measure ± standard deviation.

<sup>a</sup> Sleep latency is defined as the time from the beginning of the recording until the first NREM sleep stage 2 epoch.

<sup>b</sup> WASO = waking after sleep onset.

### 3. Results

#### 3.1. Sleep architecture

FEP patients had significantly increased sleep latency as well as reduced total sleep time compared to HC (Table 2). In contrast, FEP and HC subjects did not differ in waking after sleep onset (WASO) or in the percentage of time spent in both NREM, including N2 and N3, and REM sleep stages (Table 2).

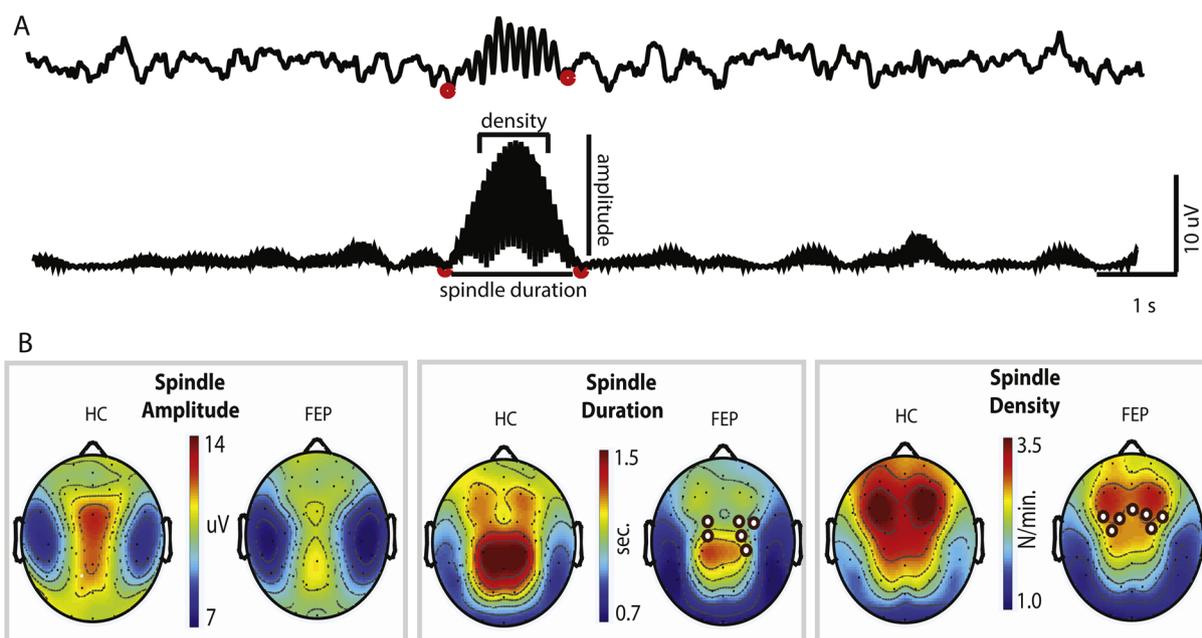
#### 3.2. Sleep spindle parameters

Several spindle parameters, including amplitude, duration, and density were computed and compared across study groups (Fig. 1A). FEP showed a significant reduction in spindle duration (N = 6 electrodes,  $p = 0.01$ , SnPM) and in spindle density (N = 7 electrodes,  $p = 0.008$ , SnPM), but not in spindle amplitude, in a frontal region relative to HC (Fig. 1B). Cohen's  $d$  yielded large effect sizes for both reduced spindle duration (ES = 0.8, CI = 0.24 to 1.40) and spindle density (ES = 0.9, CI = 0.35 to 1.50) in FEP patients vs HC. To account

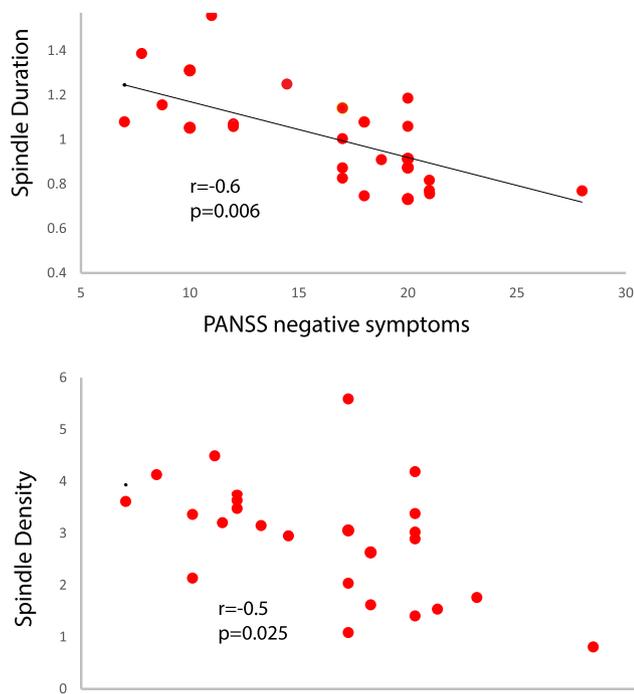
for possible medication effects on the spindle findings, we performed separate analyses for medication naïve and antipsychotic medicated FEP patients relative to HC, as well as a comparison between these naïve and medicated FEP patients. We found that both subgroups of FEP patients had reduced frontal spindle duration (N = 6 electrodes,  $p = 0.008$ , SnPM, and N = 5 electrodes,  $p = 0.02$ , SnPM respectively) and spindle density (N = 5 electrodes,  $p = 0.03$ , SnPM, and N = 6 electrodes,  $p = 0.01$ , SnPM respectively), but not amplitude, compared to HC, whereas spindle parameters did not differ between these two subgroups. Topographic analyses in the slow (12–14 Hz) and fast (14–16 Hz) range confirmed deficits in spindle duration (N = 7 electrodes,  $p = 0.009$ , SnPM, and N = 5 electrodes,  $p = 0.03$ , SnPM respectively) and spindle density (N = 5 electrodes,  $p = 0.02$ , SnPM, and N = 6 electrodes,  $p = 0.007$ , SnPM respectively), but not in spindle amplitude, in a frontal region relative to HC (Supp. Fig. 2).

#### 3.3. Correlation between sleep spindle parameters and clinical measures in FEP patients

For each of the spindle parameters significantly reduced in FEP patients (i.e., duration, density), correlation analyses were performed with PANSS positive and negative scores. As such, a significance threshold was adjusted to  $0.05/2 = 0.025$  after correction for multiple comparisons. Correlation analyses were performed between the average spindle duration or density value in the cluster of electrodes showing significant reduction in FEP patients relative to HC and PANSS scores. We found that reduced sleep spindle duration and spindle density were associated with worse PANSS negative symptoms ( $r = -0.61$ ;  $p = 0.006$ , and  $r = -0.51$ ;  $p = 0.025$  respectively, Fig. 2). In contrast, no correlation was established between spindle density or spindle duration and the PANSS positive symptoms ( $r = -0.19$ ;  $p = 0.34$ , and  $r = -0.25$ ;  $p = 0.25$  respectively). Furthermore, there was no correlation between these spindle parameters and medication doses in the antipsychotic medicated FEP subset ( $r = -0.13$ ;  $p = 0.57$ , and  $r = -0.17$ ;  $p = 0.47$  respectively).



**Fig. 1.** Deficits in sleep spindle duration and density were present in a frontal region in First Episode Psychosis (FEP) patients relative to Healthy Controls (HC). A: A spindle detection algorithm was employed to compute several spindle parameters, including amplitude, duration, and density during NREM sleep (i.e., a representative 30 s NREM sleep epoch). B: FEP patients had significantly reduced spindle duration (N = 6 electrodes,  $p = 0.01$ , SnPM) and spindle density (N = 7 electrodes,  $p = 0.008$ , SnPM), in a frontal region relative to HC.



**Fig. 2.** Deficits in sleep spindles were associated to the severity of negative symptoms in FEP patients. Top: a greater decrease in spindle duration corresponded to higher negative symptoms, assessed with the PANSS scores ( $r = -0.6$ ;  $p = 0.006$ ). Bottom: reduced spindle density was inversely correlated with the PANSS negative symptoms ( $r = -0.5$ ;  $p = 0.025$ ).

#### 4. Discussion

By performing sleep hd-EEG recordings, we investigated for the first-time topographic differences in several sleep spindle parameters between FEP patients and HC. We found that FEP patients had a significant reduction in spindle duration and density, but not in spindle amplitude, relative to HC. These spindle reductions yielded large ESs, were localized in a frontal region, and predicted the severity of FEP patients' negative symptoms.

##### 4.1. Reduced spindle duration and density, but not amplitude, are present at the onset of psychosis

In previous work, we established that chronic patients with SCZ had marked reduction in sleep spindles compared to both healthy and psychiatric controls (Ferrarelli et al., 2007, 2010). In an initial study, we found that SCZ patients had reduced spindle activity in the first NREM sleep episode relative to HC and MDD patients. In a follow-up study, we demonstrated whole night deficits in several spindle parameters, including amplitude, duration, and density, in SCZ compared to other psychiatric patients taking antipsychotic medications. Other research groups have confirmed sleep spindle impairments in chronic SCZ (Goder et al., 2015; Schilling et al., 2017; Wamsley et al., 2012), including medication naïve and un-medicated patients (Forest et al., 2007; Poulin et al., 2003). In this study, we found reduced spindle duration and density, but not amplitude, in FEP patients. These findings are important for two reasons. First, they show that focusing on the amplitude may underestimate the presence of spindle impairments, especially at illness onset. Consistent with this assumption, in a recent study Manoach and colleagues reported reduced spindle density,

whereas spindle amplitude was decreased only at trend level, in early course SCZ relative to HC (Manoach et al., 2014). Second, the present findings indicate that deficits in spindle duration and density are present at the beginning of psychosis and are likely implicated in the development and clinical manifestation of psychotic disorders. Reduced spindle duration and density also yielded large ESs, which suggests that these biological measures could help confirming clinical diagnoses, as well as contribute to revealing underlying psychopathology in psychotic patients at illness onset.

##### 4.2. Deficits in spindle duration and density are localized to a frontal region outside of C3 and C4

The reduction in spindle duration and density involved a frontal area encompassing several electrodes, which did not include C3 or C4. Other sleep EEG studies in early course in patients with SCZ focusing on these two central channels EEG studies failed to establish reduced spindle activity in SCZ relative to HC (Hiatt et al., 1985; Poulin et al., 2003; Van Cauter et al., 1991). In contrast, in a recent study Manoach et al. reported sleep spindle deficits at C4 (Manoach et al., 2014). One explanation for these inconsistent findings is that C3 and C4 are not ideally suited to reveal spindle impairments in psychosis. Consistent with this assumption, in previous sleep hd-EEG recordings we demonstrated that SCZ patients had the largest spindle deficits in a region medial to C3 and C4 (Ferrarelli and Tononi, 2011). In the present study, we showed that this frontal area is also where spindle deficits are first observed in psychotic patients at illness onset. Our findings also confirm the importance of topographic analyses in characterizing spindle impairments in SCZ and related psychotic disorders.

##### 4.3. Spindle deficits were unrelated to antipsychotic exposure and predicted worse negative symptoms in FEP patients

The majority of the FEP patients were unmedicated at the time of the sleep EEG recordings, and we found no correlation between spindle parameters and medication doses in the subset receiving antipsychotic compounds. Thus, spindle deficits were unlikely to be determined by antipsychotic medication exposure. In contrast, reduced spindle duration and density predicted worse negative symptoms in FEP patients. Negative symptoms, such as reduced initiative, blunted affect and social withdrawal, are some of the most persistent, treatment-refractory features of psychotic disorders, and tend to occur more frequently and severely in patients with chronic SCZ (Lyne et al., 2017). Furthermore, a recent study in first-episode psychosis patients found that higher baseline levels of negative symptoms significantly decreased the odds of attaining early symptom remission, even after accounting for duration of untreated psychosis, premorbid adjustments, and other possible confounds (Veru et al., 2016). The reduction in spindle duration and density could therefore be utilized as an early biological predictor of illness outcome, with greater spindle deficits associated with worse prognosis.

##### 4.4. Spindle deficits points to early thalamo-cortical dysfunctions in psychosis

Sleep spindles are generated by the interplay of the Thalamic Reticular Nucleus (TRN), which is the spindle pacemaker, with the dorsal thalamus, and TRN/dorsal thalamus circuits generate spindles in isolation, although cortical inputs can initiate and/or sustain spindle oscillations (Fuentelba and Steriade, 2005; Halassa et al., 2011; Pinault, 2004). Spindle density, which reflects the pacemaker activity of the TRN/dorsal thalamus circuits, was found to be markedly reduced in previous work in both chronic and early course patients with SCZ (Ferrarelli et al., 2007, 2010; Manoach et al., 2014), and this spindle density reduction was associated with decreased mediodorsal thalamic volumes (Buchmann et al., 2014). Here, we established that spindle

deficits are present in FEP patients, thus suggesting a thalamic dysfunction early in the course of psychosis. A reduction in spindle density and duration also suggests an altered thalamo-cortical connectivity. In vitro electrophysiological recordings have shown that the generation and maintenance of the spindle oscillation involves the reciprocal interaction between the GABAergic cells of the TRN and excitatory thalamo-cortical neurons (von Krosigk et al., 1993), while optogenetic studies in rats have demonstrated that ongoing network activity between TRN and TC neurons controls the length of sleep spindles (Bartho et al., 2014). Furthermore, several resting state neuroimaging and neurophysiological studies have reported reduced thalamo-cortical connectivity in chronic, early course, as well as un-medicated patients with SCZ (Guller et al., 2012; Woodward and Heckers, 2015; Woodward et al., 2012).

#### 4.5. Spindle-related thalamo-cortical dysfunctions in FEP implicate abnormal GABA and glutamate

A reduced binding or expression of N-methyl-d-aspartate (NMDA) glutamate receptors within the thalamo-cortical system is a likely molecular mechanism underlying spindle deficits in FEP patients. Postmortem studies have found a reduction of NMDA glutamate receptors in the thalamus and the cortex of patients with schizophrenia (Pakkenberg et al., 2009), whereas pharmacological manipulations with NMDA antagonists, including ketamine and phencyclidine (PCP), produce schizophrenia-like psychosis in healthy individuals (Bergeron and Coyle, 2012). Furthermore, it has been shown that second-generation antipsychotic medications, including clozapine, could revert a PCP-mediated blockade of NMDA receptors in the thalamus (Santana et al., 2011), while sub-anesthetic, acute ketamine treatment in mice resulted in impairments within the thalamo-cortical network (Dawson et al., 2013). Here, we found no difference in spindle parameters between antipsychotic medicated and unmedicated patients. However, the focus of the present study was to investigate spindle deficits at the beginning of psychosis in patients with no (or very limited) exposure to antipsychotics, rather than to assess the effects of these medications on spindle activity. Thus, future studies should examine the impact of antipsychotic medications on sleep spindles in psychotic patients before and after medication exposure, which could further our current understanding of the role of NMDA in spindle generation/maintenance.

Beside glutamate, an involvement of GABA neurotransmission in spindle deficits is suggested by several lines of evidence. The TRN consists entirely of  $\gamma$ -aminobutyric acid (GABA) neurons, which send diffuse, inhibitory projections to glutamatergic, excitatory thalamo-cortical neurons (Pratt and Morris, 2015). Post-mortem work has consistently shown GABA and glutamatergic abnormalities in SCZ (Hoftman et al., 2017; Rocco et al., 2016), including in the thalamus (Ibrahim et al., 2000; Thompson et al., 2009), and a recent, elegant study combining human post-mortem and transgenic mice data demonstrated profound deficits in TRN neurons in both SCZ patients and young postnatal mice relative to control groups, which confirms the presence of TRN abnormalities in SCZ and point to their occurrence in the early stages of the illness (Steullet et al., 2017). Furthermore, TRN GABA-ergic cells have greater expression of voltage-dependent transient (T-type), CaV3.3 calcium channels (Astori et al., 2011; Wei et al., 2011), and a gene encoding a T-type calcium channel (CACNA1I, which encodes CaV3.3), 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).

#### 4.6. Limitations and future directions

This study presents a number of limitations, while also paving the way for future research. First, our FEP population consisted of medication naïve or minimally treated patients experiencing their first psychotic episode, a

population that is rather difficult to engage. As such, our FEP sample was only of moderate size. Future studies are therefore needed to confirm these findings in larger groups of psychotic patients at illness onset. This work will also help establish whether spindle impairments are present in all first-episode psychosis patients or if are specific for those eventually diagnosed with SCZ. We previously found that spindle deficits were present in chronic patients with SCZ, but not in healthy and psychiatric controls. A reduction in sleep spindles was recently reported in early course SCZ (N = 15), but not in patients with other psychotic disorders (N = 11) relative to HC (Manoach et al., 2014). However, sleep EEG data were from two channels and from a relatively small sample size. Future hd-EEG studies in larger cohorts of FEP patients will help establish whether spindle deficits are specific for SCZ at illness onset. Second, given that in recent work we found that spindle deficits were associated with clinical symptoms, but not with cognitive abilities, we decided to focus on the relationships between spindle parameters with the positive and negative symptoms of FEP patients. Higher cognitive abilities, as measured by intelligent quotient (IQ), has been associated with increased spindle activity in healthy individuals (Fogel and Smith, 2011), whereas patients with SCZ tends to have lower IQ scores relative to comparison subjects (Blokland et al., 2017; Kalkstein et al., 2010). Furthermore, a recent study found that reduced spindle activity correlated with measures of executive function in early course SCZ patients (Manoach et al., 2014). Here, we found that estimated IQ was not significantly different between FEP and HC (Table 1), thus suggesting that reduced spindle activity does not simply reflect a diminished cognitive ability in SCZ. Nonetheless, future studies should include cognitive probes of sleep-dependent memory to fully establish the relationship between sleep spindles and cognitive function in psychotic patients at illness onset (Manoach et al., 2016). Third, the presence of spindle deficits in FEP patients consolidates their implication in the development and manifestation of SCZ and related disorders; however, it does not allow to establish their role as a genetic risk factor that is causally implicated in developing the illness. Longitudinal studies in individuals at clinical high risk (CHR) for psychosis are therefore needed to answer this question. Finally, it would be important to investigate whether pharmacological and/or non-pharmacological interventions, including Transcranial Magnetic Stimulation or auditory closed loop stimulation, can reliably ameliorate spindle deficits and related clinical symptoms in FEP patients (Lustenberger et al., 2016). Here, we found that spindle impairments predicted the severity of their negative symptoms, which are less likely to benefit from antipsychotic medication treatment (Rabinowitz et al., 2013). The development of novel treatment strategies enhancing sleep spindles may therefore improve some of the most treatment resistant clinical features of SCZ.

Altogether, in the present study we demonstrated that spindle deficits are present in psychotic patients at illness onset. These findings indicate that frontal thalamo-cortical dysfunctions are present at the beginning of psychosis and contribute to the severity of clinical symptoms, thus providing a potential treatment target for early interventions in SCZ and related psychotic disorders, which could eventually improve their prognosis and overall clinical outcome.

#### Conflicts of interest

Declarations of interest: none.

#### Acknowledgements

This work was supported by The Pittsburgh Foundation Emmerling Rising Star Award in Psychiatric Research (Reference No. FPG00031).

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpsychires.2019.03.009>.

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