



## Sleep correlates of cognition in early course psychotic disorders

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### ABSTRACT

**Background:** Slow waves and sleep spindles, the main oscillations during non-rapid eye movement sleep, have been thought to be related to cognitive processes, and are impaired in psychotic disorders. Cognitive impairments, seen early in the course of psychotic disorders, may be related to alterations in these oscillations, but few studies have examined this relationship.

**Method:** Twenty seven untreated patients with a recently diagnosed psychotic disorder had polysomnographic sleep studies and neuro-cognitive testing.

**Results:** Reduced power in the sigma range, which reflects spindle density, was associated with impaired attention, and reasoning, but not intelligence quotient (IQ). Slow wave sleep measures were not significantly associated with any cognitive measures.

**Conclusions:** Impairments in sleep spindles may be associated with cognitive deficits in the early course of psychotic disorders. These observations may help clarify neuro-biologic mechanisms of cognitive deficits in psychotic disorders such as schizophrenia.

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### 1. Introduction

Cognitive dysfunction is part of the core pathology of psychotic disorders such as schizophrenia (Elvevag and Goldberg, 2000; Mesholam-Gately et al., 2009; Kalkstein et al., 2010) which are also characterized by significant alterations in sleep architecture (Keshavan et al., 1990; Monti and Monti, 2005; Cohrs, 2008). Cognitive impairments which are strong determinants of functional outcome in schizophrenia (Green, 1996) do not consistently respond to currently available antipsychotic treatments (Hill et al., 2010). An improved understanding of the relationship between sleep and cognition in health as well as in disease may therefore be critical for developing better approaches to treat these deficits.

Converging data suggest that sleep is critical to a number of cognitive processes such as information processing and memory consolidation (Crick and Mitchison, 1983; Maquet et al., 2000). Furthermore, different components of sleep, i.e. Rapid Eye Movement (REM) sleep and non-REM sleep (Schabus et al., 2007; Diekelmann and Born, 2010) seem to have distinct roles in memory consolidation processes (Gais et al., 2000; Maquet et al., 2000; Stickgold et al., 2000). Slow waves, a hallmark of NREM sleep (also called delta sleep), increase after motor learning in direct correlation with the improvement in post-sleep performance on the learning task (Huber, 2007). Similarly, a second hallmark of the NREM sleep, the 12–15 Hz rhythms

in the sigma band commonly referred to as sleep spindles, increase after training on a declarative learning task (Gais et al., 2002). Sleep spindles have also been associated with verbal memory consolidation (Goder et al., 2008). Decreases in delta sleep are associated with impairments in visuospatial memory (Goder et al., 2004), declarative memory (Goder et al., 2008), attention/cognitive flexibility (Goder et al., 2006) and consolidation of declarative memory (Plihal and Born, 1999). Since cognitive deficits and sleep disturbances are both part of the core pathology in schizophrenia (Keshavan et al., 1998; Elvevag and Goldberg, 2000), elucidating the relationship between cognitive deficits, delta and spindle sleep changes in psychotic disorders is likely to shed light on the pathophysiology of this illness.

Unfortunately, much of the research on cognition and sleep in schizophrenia has been conducted in chronic patients, with some exceptions (Taylor et al., 1992; Forest et al., 2007) and is potentially confounded by the use of current or past medications, and disease chronicity. Herein, we present the results of a study of cognition and sleep architecture in patients with early course psychotic disorders. We hypothesized that two components of sleep architecture i.e. sleep spindles and delta sleep, correlate with performance on tasks involving multiple domains of cognition.

### 2. Methods

#### 2.1. Participants

Twenty seven patients newly diagnosed with psychosis (18 males and 9 females) were recruited from among inpatients and outpatients of Western Psychiatric Institute and Clinic, Pittsburgh. The subjects'

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age was in the range of 18 and 44 years (mean  $27.2 \pm 7.3$ ). The duration of psychosis was 100.6 weeks (S.D. = 91.33 weeks), consistent with our previously published data in the larger sample (mean 95.7 weeks; Keshavan et al., 2003). Approaches to determination of illness duration, and other clinical characteristics of this sample are detailed elsewhere (Keshavan et al., 2003). All of the 27 patients were antipsychotic-naïve at the time of their sleep study and neuropsychological testing. Diagnoses were confirmed following structured clinical interviews for DSM diagnoses (SCID) interviews (First et al., 2002) by experienced clinicians using DSM-IV criteria. Diagnoses included schizophrenia (15), schizoaffective disorder (2), psychotic disorder, not otherwise specified ( $n=1$ ); bipolar disorder with psychotic features ( $n=2$ ); major depression with psychotic features ( $n=4$ ) and delusional disorders ( $n=3$ ). The Scales for the Assessment of Positive and Negative Symptoms, respectively (SAPS and SANS) (Andreasen, 1989; Andreasen, 1990) were used to estimate levels of psychopathology. None of the subjects had any significant medical illness, history of head injury with loss of consciousness >30 min, or mental retardation ( $IQ < 75$ ). All subjects gave written informed consent to the study which was approved by the University of Pittsburgh Institutional Review Board.

## 2.2. Sleep studies

Subjects underwent at least two nights of sleep EEG studies on consecutive nights. They were discouraged from napping during the day, to avoid confounding effects of naps on cognition (Seeck-Hirschner et al., 2010). A few days prior to the sleep studies, the subjects were requested to maintain a diary of their sleep wake patterns to estimate the usual time at which the subjects were to be woken up in the morning. The subjects chose the time to retire to bed. Electrodes for polysomnographic (PSG) recording were placed about one hour before bedtime. PSG was recorded on two nights to control for adaptation effect to the sleep lab. The second night of sleep was used in these analyses.

PSG was conducted using Grass Telefactor M15 bipolar Neurodata amplifiers and locally-developed collection software. The recording montage consisted of bilateral central EEG leads referenced to A1 + A2; right and left electro-oculogram referenced to A1 + A2; and bipolar electromyogram. Sleep stages were scored in 60-second epochs according to standard criteria (Rechtschaffen and Kales, 1968) by trained raters blind to clinical data. For the analyses in this study, we used the percent spent in visually scored delta (stage 3 + 4) sleep.

Methods for automated sleep analysis have been previously published (Doman et al., 1995). Briefly, EEG signals were digitized at a rate of 256 Hz. The raw digitized data were bandlimited to 64 Hz using a low pass finite impulse response (FIR) filter, then decimated to 128 Hz for quantitative analyses. Low frequency artifacts were excluded by eliminating epochs scored as wakefulness or movement time. High frequency EEG artifacts were identified and excluded in 4-second bins with a previously validated and published algorithm that uses a moving window threshold. Basically, this algorithm excludes 4-second bins whose power in the frequency range of 26.25–32 Hz exceeds the power in adjacent bins by a factor of 4 or greater. Power spectral analysis was used to quantify the frequency content of the sleep EEG from 0.25 to 50 Hz (Doman et al., 1995; Brunner et al., 1996; Vasko et al., 1997). Non-overlapping 4-second epochs were weighted with a Hamming window, and periodograms were then computed for these epochs using the Fast Fourier transform (FFT). EEG spectra for each artifact-free 4-second epoch were then aligned with 60-second visually-scored sleep stage data to exclude epochs scored as awake or REM sleep. EEG power values from artifact-free 4-second epochs at 0.25 Hz resolution were averaged into 0.5 Hz bins prior to analysis, to provide adequate resolution of frequencies while limiting the number of statistical comparisons. For this analysis, we used the frequency band from

13.5 to 15 Hz to measure the spindle density. It is to be noted that this frequency range corresponds to the sigma activity (Aeschbach and Borbely, 1993; Landolt et al., 1996) which comprises the spindles. Spectral power in the sigma range typically reflects spindle density, though these terms are not synonymous (De Gennaro and Ferrara, 2003). One study has shown that sleep spindle waveforms are sensitive to learning while quantified EEG sigma activity is not (Gais et al., 2002).

Using Period amplitude analyses (Doman et al., 1995; Tekell et al., 2005), the number of delta “counts” (the number of half-waves above and below the baseline at 0.5–2 Hz, 75–200- $\mu$ V activity) per minute was measured with a zero-crossing half-wave detector. For analyses in this study, we used average delta counts per minute of NREM sleep, thus controlling for differences in non-REM period length.

## 2.3. Neuropsychological testing

Each subject also underwent neuropsychological testing within 1–2 days of sleep studies, including tasks of attention and psychomotor speed (Trails B errors and time) (Reitan and Wolfson, 1992), reasoning and conceptual flexibility (Wisconsin card test) (Heaton and Pendleton, 1981) and intelligence quotient (the Ammon's quick IQ) (Otto and McMenemy, 1965).

## 2.4. Statistical analyses

Pearson correlations and where the data were non-normally distributed, Spearman correlations were used to examine relationships between sleep and cognitive parameters. Partial correlations were also used to examine these relationships after covarying the effect of age. Two-tailed tests were used for significance.

## 3. Results

Spindle power did not correlate with age, duration of the psychotic symptoms or the severity of SAPS positive and SANS negative symptoms (all correlation coefficients <0.25 and  $p > 0.2$ ). Similarly, delta power did not correlate with duration of symptoms or severity of positive and negative symptoms. However, there was a trend towards decreased delta sleep ( $r = -0.38$ ;  $p = 0.052$ ), delta power ( $r = -0.32$ ;  $p = 0.1$ ) and spindles ( $r = -0.27$ ;  $p = 0.16$ ) with age, which was consistent with previous studies of declines in sleep and age (Keshavan et al., 1995). Age correlated positively with percent perseverative error ( $r = 0.49$ ,  $p = 0.01$ ) and Trails B time ( $r = 0.47$ ,  $p = 0.015$ ). There were no differences between genders for cognitive

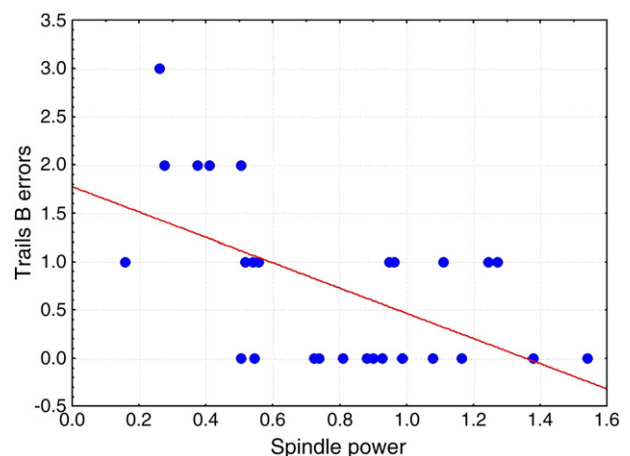


Fig. 1. Scatterplot showing the partial correlation between spindle power and trails B errors in first episode psychosis patients.

or sleep measures. Delta sleep correlated non-significantly with spindle power ( $r = 0.36$ ;  $p = 0.06$ ).

Spindle power correlated inversely with Trails B errors (Fig. 1) and time, and Wisconsin card sort perseverative errors (Table 1), but not with IQ. When these correlations were examined with diagnosis (schizophrenia and other psychoses) as a categorical covariate, the results remained significant. The correlation between spindle power and Trails B errors survived Bonferroni correction for multiple inference testing.

Average Delta counts had a trend for a correlation with IQ (partial  $r = 0.38$ ;  $p = 0.055$ ) but did not correlate with any other cognitive measure. Visually scored delta sleep showed a negative trend-worthy correlation with WCST perseverative errors (partial  $r = -0.34$ ;  $p = .09$ ) but not with any other cognitive measure.

#### 4. Discussion

Reduced sleep spindle power was associated with impaired attentional and executive function measures in patients with early course psychotic disorders. This deficit was unrelated to reduced general cognitive ability. This observation is consistent with prior evidence that spindle activity is related to the learning potential of an individual (Bodizs et al., 2005; Schabus et al., 2007). Our findings are also consistent with and expand on an earlier small study of neuroleptic naive patients with schizophrenia ( $n = 8$ ) showing a negative correlation between reaction time on the selective attention task and sleep spindle density and the duration of the delta sleep (Forest et al., 2007). In the absence of an appropriately matched-control group, we could not examine whether the spindle activity is reduced in patients with treatment naïve psychosis, but this is a key question to be addressed in future studies. In a study of medicated schizophrenia patients, Ferrarelli et al. (2007, 2010) observed reduction in spindle activity. The effect of antipsychotics on spindles remains unclear with no effects (Ferrarelli et al., 2007; Ferrarelli et al., 2010) and reductions with olanzapine being observed (Goder et al., 2008). Contrary to some earlier observations (Huupponen et al., 2002), we did not see a gender effect on spindle parameters, perhaps due to the relatively small sample size in this study.

Our data suggest that cognitive deficits may be related to spindle activity reductions in both schizophrenia and non-schizophrenia psychotic disorders. Decreased spindle activity has been observed across a range of disorders, including autism (Godbout et al., 2000), Alzheimer's (Prinz et al., 1982), normal aging (Nicolas et al., 2001), paramedian thalamic stroke (Hermann et al., 2008), and depression (Lopez et al., 2010). It is possible that reductions in spindle activity cuts across a number of conditions – physiological and pathological – and may reflect impairments in neuroplasticity across these conditions.

Examining spindle measures in early course psychosis patients is of importance to investigate developmental alterations that may characterize the early phases of these disorders. Induction of long term potentiation appears to increase spindles; synchronous neuronal activation during spindles may contribute to learning-related synaptic plasticity (Werk et al., 2005). Spindle activity decreases progressively with age (from teenage to the high sixties) (Nicolas et al., 2001), perhaps as a function of decreasing plasticity. Since cognitive function also declines during prodromal phase of schizophrenia (Seidman

et al., 2010), follow-up sleep studies during the prodromal phase may further elucidate the psychobiology of transition to schizophrenia. Spindles have been shown to increase neocortical neuroplasticity (Steriade et al., 1993; Steriade, 1999).

We have previously reported decreased delta sleep in early course schizophrenia (Keshavan et al., 1998). There is also evidence for a correlation between decrements in delta activity and attentional impairment in schizophrenia (Orzack et al., 1977). Furthermore, striking similarity between age related changes in delta activity and synaptic density has led to a view that these two are related (Feinberg, 1982; Tononi, 2009). However, in the present study, we observed only a weak, non-significant relation between cognitive performance and delta sleep. These differential correlations for spindle activity and slow wave sleep (with cognition) may reflect differences in the physiological substrate between these two sleep oscillations. For instance, slow oscillations are primarily generated by the cortex, while sleep spindles are generated by thalamo-cortical circuits (Ferrarelli et al., 2010). It is also possible that delta sleep reductions are seen only in a subgroup of schizophrenia and their relationship to cognitive deficits is subtle and may have not reached significance. The evidence that thalamocortical gamma-amino butyric acid (GABA) ergic activity has a role in spindle generation (Pangratz-Fuehrer et al., 2007) may mean that the observed relationship between spindles and cognitive abilities in the present study supports the theory of GABA dysfunction in schizophrenia (Gonzalez-Burgos et al., 2010). This view is consistent with the view that alterations in selective attentional processes in schizophrenia may be mediated by thalamo-cortical circuits (Crespo-Facorro et al., 2007; Trenado et al., 2009).

A significant strength of our study was inclusion of treatment naïve patients with early course psychosis. The difficulty in recruiting these patients in sleep studies affected our chances of working with a more homogenous group. Limitations of our study include the lack of an appropriately matched control group, the absence of visual scoring of spindles, and the use of 60 s epochs that may have limited resolution for quantification of the sleep data. Further studies are needed to document the effect of individual antipsychotic medications on sleep spindles and activity. Prospective studies throughout the course of the illness can be expected to further enhance our understanding of schizophrenia.

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#### Contributors

Matcheri Keshavan wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

#### Conflict of interest

This research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**Table 1**

Partial correlations (with age partialled out) between cognitive and sleep measures.

	Spindle power Partial $r$ ( $p$ )	Delta counts Partial $r$ ( $p$ )
Trails B time	−0.45 (0.01)	−0.24 (0.23)
Trails B errors	−0.56 (0.0038)	−0.18 (0.36)
WCST PE%	−0.48 (0.014)	−0.27 (0.18)
IQ	0.12 (0.53)	0.38 (0.055)



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