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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.

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 ± 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-naive 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-μV 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

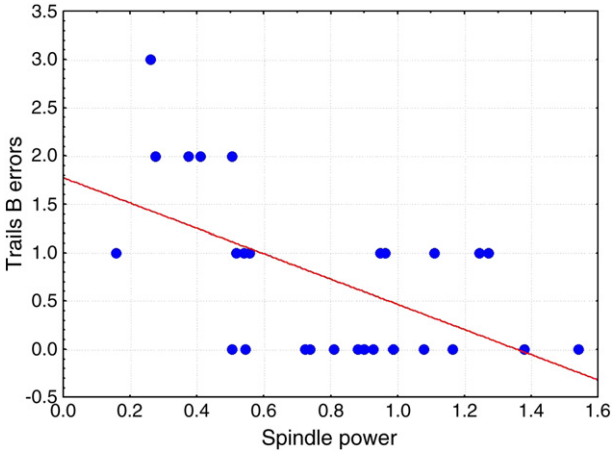

Fig. 1. Scatterplot showing the partial correlation between spindle power and trails B errors in first episode psychosis patients.