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Preliminary communication

Topographic and sex-related differences in sleep spindles in major depressive disorder: A high-density EEG investigation

D.T. Plante [a,*], M.R. Goldstein [a], E.C. Landsness [a], M.J. Peterson [a], B.A. Riedner [a], F. Ferrarelli [a,b], T. Wanger [a], J.J. Guokas [a], G. Tononi [a], R.M. Benca [a]

[a] Department of Psychiatry, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[b] Department of Clinical Sciences, "Luigi Sacco," Università degli Studi di Milano, Milan, Italy

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ABSTRACT

Background: Sleep spindles are believed to mediate several sleep-related functions including maintaining disconnection from the external environment during sleep, cortical development, and sleep-dependent memory consolidation. Prior studies that have examined sleep spindles in major depressive disorder (MDD) have not demonstrated consistent differences relative to control subjects, which may be due to sex-related variation and limited spatial resolution of spindle detection. Thus, this study sought to characterize sleep spindles in MDD using high-density electroencephalography (hdEEG) to examine the topography of sleep spindles across the cortex in MDD, as well as sex-related variation in spindle topography in the disorder.

Methods: All-night hdEEG recordings were collected in 30 unipolar MDD participants (19 women) and 30 age and sex-matched controls. Topography of sleep spindle density, amplitude, duration, and integrated spindle activity (ISA) were assessed to determine group differences. Spindle parameters were compared between MDD and controls, including analysis stratified by sex.

Results: As a group, MDD subjects demonstrated significant increases in frontal and parietal spindle density and ISA compared to controls. When stratified by sex, MDD women demonstrated increases in frontal and parietal spindle density, amplitude, duration, and ISA; whereas MDD men demonstrated either no differences or decreases in spindle parameters.

Limitations: Given the number of male subjects, this study may be underpowered to detect differences in spindle parameters in male MDD participants.

Conclusions: This study demonstrates topographic and sex-related differences in sleep spindles in MDD. Further research is warranted to investigate the role of sleep spindles and sex in the pathophysiology of MDD.

1. Introduction

Sleep spindles are waxing-waning oscillations (11–15 Hz) that are hallmarks of electroencephalographic (EEG) non-rapid eye movement (NREM) sleep. Although the functional role of sleep spindles remains unclear, there is evidence they are involved in a number of domains including maintaining disconnection from the external environment during sleep (Steriade, 2003), cortical development (Khazipov et al., 2004), and sleep-dependent memory consolidation (Fogel and Smith, 2011). Sleep spindles are heterogenous in both frequency and location, with fast spindles (13–15 Hz) occurring predominantly in central and parietal regions, whereas slow spindles (11–13 Hz) are more prominent frontally (Anderer et al., 2001; Schabus et al., 2007). Furthermore, the importance of cortical topography in the evaluation of sleep spindle activity is underscored by recent evidence that spindles may occur and be regulated locally (Andrillon et al., 2011; Nir et al., 2011).

Major depressive disorder (MDD) is associated with both decrements in subjective and objective quality of sleep (Benca et al., 1992; Peterson and Benca, 2006; Steiger and Kimura, 2010) and sleep-dependent memory consolidation (Dresler et al., 2010; Dresler et al., 2011), and thus it is not surprising that previous investigations have examined the role of sleep spindles in the disorder. Results have not been consistent among prior studies, with no difference (Goetz et al., 1983; Reynolds et al., 1985) or reductions (de Maertelaer et al., 1987; Lopez et al., 2010) in spindle activity reported in MDD. However, comparison of results across studies is difficult as ages and sexes of subjects have varied widely among studies. Also, prior investigations have typically utilized standard EEG montages in which only one or a few EEG

* Corresponding author at: Wisconsin Psychiatric Institute and Clinics, 6001 Research Park Blvd. Madison, WI 53719, USA. Tel.: +1 608 232 3328; fax: +1 608 231 9011.
E-mail address: dplante@wisc.edu (D.T. Plante).

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channels were used to detect sleep spindles, and thus topographic differences in spindle activity between groups could not be distinguished. Prior studies have also predominantly evaluated spindle density (number of spindles/unit time), and have not computed other parameters to examine spindle morphology in MDD such as amplitude and duration.

A recent investigation utilizing high-density EEG (hdEEG), which has superior spatial resolution compared to standard scalp-level EEG methods, did not demonstrate topographical differences in spindle parameters between depressed and control participants (Ferrarelli et al., 2007). However, in this study nearly half of MDD subjects were in remission, several participants were taking psychotropic medications, subjects were not sex-matched, and all-night sleep spindle measures could not be ascertained as only sleep from the first NREM period was utilized (Ferrarelli et al., 2007). This is potentially problematic as healthy women may have greater sleep spindle activity relative to men (Huupponen et al., 2002). In addition, decrements in sleep spindles in adolescent MDD have been reported to be more prominent in female MDD patients, and be more readily observed in later portions of the night (Lopez et al., 2010).

Thus, the primary aim of this study was to utilize hdEEG to examine all-night sleep spindle topography in MDD using a well-defined cohort of unmedicated, unipolar MDD subjects relative to age and sex-matched control subjects. Based on prior literature, we hypothesized that MDD subjects would demonstrate decrements in sleep spindles relative to controls, and that these decrements would be more pronounced in female MDD participants.

2. Methods

2.1. Participants

Thirty unmedicated MDD participants (19 female) were selected from a larger study on sleep homeostasis in neuropsychiatric disorders, conducted at the University of Wisconsin–Madison. MDD was diagnosed via the Structured Clinical Interview for DSM-IV Axis I disorders (SCID) (First et al., 2002b). For inclusion, subjects were required to have moderate or worse unipolar depression, defined as a score of 15 or higher on the clinician-administered 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960). Subjects had no history of psychosis, active drug/alcohol dependence, or significant neurological/medical condition. Age and sex-matched healthy comparison subjects without current or past psychiatric disorders were evaluated with the non-patient SCID (First et al., 2002a). Subjects with evidence of clinically significant sleep disordered breathing (apnea-hypopnea index >10/hr) or sleep-related movement disorder (periodic limb movement arousal index >10/hr) during overnight recording (see below) were excluded.

All subjects provided informed consent and were instructed to maintain regular sleep-wake schedules, avoid napping, and to limit the use of caffeinated and alcoholic beverages for the duration of the study. Adherence was monitored using sleep-logs and actigraphy (Actiwatch, Mini-Mitter, Bend, OR). This study was approved by the Institutional Review Board of the University of Wisconsin-Madison.

2.2. EEG recording and analysis

All subjects underwent overnight in-laboratory hdEEG recordings that utilized a 256 channel system (Electrical Geodesics Inc., Eugene, OR). During hdEEG recordings, additional monitoring with electrooculogram (EOG), sub-mental electromyogram (EMG), electrocardiogram (ECG), bilateral tibial EMG, respiratory inductance plethysmography, pulse oximetry, and a position sensor were utilized for sleep staging and to evaluate for sleep disordered breathing and sleep-related movement disorders. Participants slept undisturbed in the laboratory beginning within 1 h of their usual bedtime. Sleep hdEEG recordings were collected with vertex-referencing, using NetStation software (Electrical Geodesics Inc., Eugene, OR).

EEG signals were sampled at 500 Hz, first-order high-pass filtered in Net Station (0.1 Hz), down sampled to 128 Hz, band-pass filtered (2-way least-squares FIR, 1–40 Hz) in MATLAB (The Math Works Inc., Natick, MA), and average-referenced to the average scalp voltage computed in all channels. Semi-automatic artifact rejection allowed for removal of channels for individual epochs with high-frequency noise or interrupted contact with the scalp. To increase the signal-to-noise ratio, analyses were restricted to channels falling within a plotting radius of 0.57 specified in the topoplot function of the EEGLAB (Delorme and Makeig, 2004) plug-in for MATLAB, resulting in 173 channels overlaying the scalp. A registered polysomnographic technologist scored sleep stages in 30 s epochs using Alice® Sleepware (Philips Respironics, Murrysville, PA) utilizing a mastoid referenced montage according to standard criteria (Iber et al., 2007).

2.3. Spindle detection and analysis

Spindle detection and analysis was performed similar to prior studies in our laboratory utilizing a customized spindle detection algorithm in MATLAB (Ferrarelli et al., 2007, 2010). NREM epochs were initially filtered between 11 and 15 Hz, and rectified filtered signals were used as time series for each channel. Spindle detection occurred whenever the mean signal amplitude of each channel exceeded an upper threshold that was set at six times the mean amplitude for each channel. The peak amplitude for each spindle was defined as the local maximum above the upper threshold. The beginning and end of the spindle were defined as the points at which the amplitude of the time series dropped below a lower threshold, which was defined as two times the mean amplitude of the channel signal, occurring ≥ 0.25 s from the peak. To characterize spindles in the slow (11–13 Hz) and fast (13–15 Hz) ranges, detected spindles with a frequency falling within these ranges were grouped together.

For all detected spindles, four parameters were investigated: spindle density, duration, maximal amplitude, and integrated spindle activity (ISA). The number of detected spindles divided by NREM sleep duration defined spindle density; ISA was determined by integrating the absolute amplitude values of each spindle divided by NREM sleep duration (Ferrarelli et al., 2007, 2010). To examine topographic differences in slow and fast spindles, spindle parameters were also calculated from NREM data filtered from 11–13 Hz and 13–15 Hz, respectively.

2.4. Statistics

To evaluate the primary outcome measure of topographic differences in all-night sleep spindle parameters in MDD versus control subjects, unpaired two-tailed *t*-tests were used. Given previous reports of sex-related differences in sleep spindles among both healthy and MDD subjects (Huupponen et al., 2002; Lopez et al., 2010), and reported differences in spindle parameters related to age (Feinberg et al., 1967; Guazzelli et al., 1986; Nicolas et al., 2001; Wei et al., 1999), analyses between MDD and healthy controls stratified by sex were also performed to maintain age-matching of subjects. Slow (11–13 Hz) and fast (13–15 Hz) spindles were also evaluated separately given different topographical distributions and likely involvement of different thalamo-cortical circuits (Ferrarelli et al., 2010; Schabus et al., 2007). Statistical non-parametric