

Experimental observation of a theoretically predicted nonlinear sleep spindle harmonic in human EEG



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HIGHLIGHTS

- We analyze EEG data to examine the properties of a spindle harmonic oscillation.
- The harmonic occurs at twice the frequency of the spindle, scales nonlinearly in power, and is accompanied by high bicoherence.
- The spindle harmonic is consistent with predictions made by a theoretical neural field model of the brain explaining the generation of the harmonic.

ABSTRACT

Objective: To investigate the properties of a sleep spindle harmonic oscillation previously predicted by a theoretical neural field model of the brain.

Methods: Spindle oscillations were extracted from EEG data from nine subjects using an automated algorithm. The power and frequency of the spindle oscillation and the harmonic oscillation were compared across subjects. The bicoherence of the EEG was calculated to identify nonlinear coupling.

Results: All subjects displayed a spindle harmonic at almost exactly twice the frequency of the spindle. The power of the harmonic scaled nonlinearly with that of the spindle peak, consistent with model predictions. Bicoherence was observed at the spindle frequency, confirming the nonlinear origin of the harmonic oscillation.

Conclusions: The properties of the sleep spindle harmonic were consistent with the theoretical modeling of the sleep spindle harmonic as a nonlinear phenomenon.

Significance: Most models of sleep spindle generation are unable to produce a spindle harmonic oscillation, so the observation and theoretical explanation of the harmonic is a significant step in understanding the mechanisms of sleep spindle generation. Unlike seizures, sleep spindles produce nonlinear effects that can be observed in healthy controls, and unlike the alpha oscillation, there is no linearly generated harmonic that can obscure nonlinear effects. This makes the spindle harmonic a good candidate for future investigation of nonlinearity in the brain.

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1. Introduction

One of the key indicators of sleep stage 2 is the presence of sleep spindles – short bursts of 12–15 Hz EEG activity lasting around 0.5–1 s, as shown in Fig. 1 (Contreras et al., 1997; Niedermeyer and

Lopes da Silva, 1999). Much new research focuses on the roles spindles may play in learning and memory formation (Schabus et al., 2004; Clemens et al., 2005; Saletin et al., 2011), but the mechanisms of spindle generation still require some clarification.

Neural field theory has proved to be a powerful technique for constructing relatively simple physiological models of the brain that reproduce a wide variety of EEG and many other experimental results. We have developed a neural field corticothalamic model of the brain (Robinson et al., 2001, 2002, 2004, 2005; Rowe et al.,

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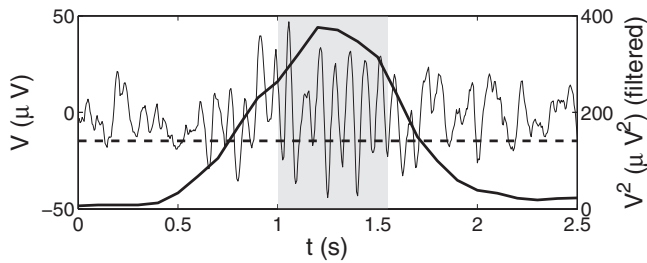


Fig. 1. EEG time series from Cz electrode (thin line) showing an automatically identified sleep spindle, occurring in the gray shaded area. The DC component has been removed from the data. The squared and downsampled time series is the bell-shaped curve (thick line) displayed using the vertical axis on the right side. The dashed horizontal line is the detection threshold.

2004) and used it to investigate the alpha rhythm (Robinson et al., 2003; O'Connor and Robinson, 2004), age-related changes to the physiology of the brain (van Albada et al., 2010), evoked response potentials (Rennie et al., 2002), and other phenomena (Robinson et al., 2003; Breakspear et al., 2006; Rowe et al., 2004). Our model produces sleep spindles due to mutual feedback between thalamic relay nuclei and the thalamic reticular nucleus, which has also been proposed on physiological grounds as a mechanism for sleep spindle generation (von Krosigk et al., 1993; Steriade and Sejnowski, 1993; McCormick and Bal, 1997).

Using our model, we recently predicted the existence of a sleep spindle harmonic arising from nonlinear effects in the thalamic relay nuclei within the above feedback loop (Abeyesuriya et al., 2014). In that study, we also verified the existence of the spindle harmonic in sample experimental data, and made testable predictions to verify the nonlinear origin of the spindle harmonic. In the present work, we analyze normal healthy adult human EEGs to test the predicted properties of the spindle harmonic. In particular, we test the predictions that the frequency of the spindle harmonic should be almost exactly double the frequency of the sleep spindle, and that the power in the spindle harmonic should scale quadratically with the power of the sleep spindle oscillation.

A nonlinear relationship between the spindle and its harmonic would lead to phase relationships between the two peaks, which can be measured by examining the bicoherence. Bicoherence at the spindle frequency itself has been observed in previous studies, most notably in Akgül et al. (2000) which found strong bicoherence at the spindle frequency. That study presented EEG power spectra that showed some evidence of a spindle harmonic, although this was not discussed there. Other studies have observed bicoherence at the spindle frequency as well, with both Fourier (Venkatakrishnan et al., 2010; Morimoto et al., 2006; Hayashi et al., 2007) and wavelet analysis (Li et al., 2011). A spindle harmonic has been observed under anesthesia in opiate-dependent patients (Wolter et al., 2006), which was recognized as being an oscillation associated with spindle activity occurring at twice the spindle frequency, but it was not identified as a harmonic and its properties were not investigated.

In Section 2, we outline the processing required to observe the sleep spindle harmonic using full-night polysomnograms, review our model predictions, and outline the procedures used to analyze the experimental data. Results are provided in Section 3, and the interpretation and significance of our findings are discussed in Section 4.

2. Method

In this section, we review the methods used to process and analyze the sleep spindle data to quantify the spindle harmonic, and the theoretical predictions made by our model that we test in Section 3.

2.1. Recording and isolating spindles

Polysomnograms (PSGs) from 9 healthy controls (age 25–36, 8 male 1 female) were gathered overnight, as described in D'Rozario et al. (2013). Recordings were made using an Alice-4 system (Respironics, Murraysville PA, USA) at the Woolcock Institute of Medical Research, with 6 EEG channels sampled at 200Hz and electrodes positioned according to the International 10–20 system. For this study, only the Cz electrode was examined, referenced to M1. A notch filter at 50Hz (as provided by the Alice-4 system) was used to remove mains voltage interference. No other hardware filters were used.

Sleep EEG power spectra are often calculated from relatively long time series (such as 30 s epochs), which combine periods with and without spindles. This type of spectrum is shown in Fig. 2 for a healthy control subject in S2 sleep. A strong peak is evident at ≈ 13 Hz, corresponding to spindle activity, but the contribution from spindle activity is combined with a contribution from background S2 sleep, which is relatively smooth. This makes the spindle peak weaker relative to the background activity because the spindle is only present some of the time. In order to investigate the EEG properties of spindles themselves, it is necessary to separate the sleep spindles from background sleep periods before calculating the power spectrum. Doing so increases the relative strength of the spindle peak, and also reveals weaker features that are otherwise obscured.

An automated spindle detection algorithm is used to identify spindle events in the EEG data. Detection is accomplished by first selecting 30 s epochs in the data that have been manually scored as sleep stages 2–4. A 11–16 Hz bandpass FIR filter is applied to the Cz electrode voltage for each epoch. The filtered data are then squared and downsampled to 10 Hz by taking a centered average with a window length of 1 s. An example of the resulting signal is shown in Fig. 1. This processed signal is large when sleep spindles are present.

Next, the epochs are concatenated and the median \tilde{V} and standard deviation σ of the squared downsampled voltage are computed. The threshold voltage V_t for spindle detection in the downsampled time series is set to $\tilde{V} + 3\sigma$, and is therefore different for each subject, taking into account differences in physiology and in recording setup. The threshold voltage for the subject in Fig. 1 is shown as a horizontal line. If more than 10 consecutive points in the downsampled time series have a voltage exceeding

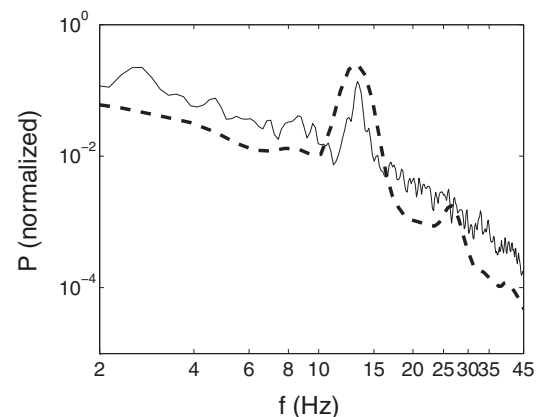


Fig. 2. Comparison of normalized EEG power spectra for 30 seconds of typical S2 sleep when spindle activity was present (solid line), and the power spectrum after isolating spindle activity (dashed line). The spectrum after isolating spindles exhibits a larger, wider spindle peak, and also shows a secondary peak at approximately double the frequency of the first. From Abeyesuriya et al. (2014) with permission from Elsevier.

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