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Slow Rhythms and Sleep Spindles in Early Infancy

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Abstract

Objective—To investigate the slow rhythm and its relationship to spindling in early infancy.

Methods—We analyzed sleep MEG recordings containing sleep spindles, taken from 7 normal, healthy subjects at conceptional age 46–63 weeks in 21 sessions.

Results—We show that the sleep MEG in early infancy contains a slow rhythm, centered at approximately 0.2 Hz, which showed a striking association with spindling. The slow rhythm grouped sleep spindles, which were clock-like with a recurrence rate of approximately 0.1 Hz.

Conclusions—The association of the 0.2 Hz oscillation and low delta rhythms with spindling was so strong as to suggest that they may play a critical role during brain development in the genesis of sleep spindles.

Significance—Infant brain rhythms exhibit relatively simple, regular behavior, allowing the relationships between them to be more easily discerned.

Keywords

magnetoencephalography; slow rhythm; sleep spindles

INTRODUCTION

In a series of seminal papers, Steriade and coworkers [23–25] demonstrated in cats the crucial importance of a large oscillation of frequency 0.25 Hz or slower, which they simply called the slow rhythm. The slow rhythm gives rise to alternating periods of depolarization and hyperpolarization, referred to as up states and down states, respectively. They showed that brain activity was strongly suppressed during the down state and that higher frequency rhythms were grouped by the slow waves. Since the initial report of the slow rhythm, numerous studies have investigated its underlying cellular mechanisms [4, 5, 11, 19], demonstrated its role in synchronizing brain activity [13, 17, 29, 30], and provided evidence of its potential functional significance [6, 10, 15, 16].

The slow rhythm is the dominant component of the EEG/MEG in non-REM sleep. A defining characteristic of the slow wave is its ability to modulate faster rhythms, especially sleep spindles. Sleep spindles are distinctive bursts of 12–15 Hz oscillations that occur

primarily during stage 2 sleep. They are a hallmark of sleep, signaling the transition from wakefulness to sleep and loss of consciousness. A number of studies indicate that slow wave and spindle activity in non-REM sleep provide the necessary conditions for plastic modifications underlying memory formation [7, 18, 21, 22] and coordinated information transfer between different parts of the brain.

In infants, sleep spindles appear at age 6–8 weeks, and have been proposed as markers for the development and integrity of the CNS early in life [20, 26]. They are believed to promote and signify the formation of thalamocortical networks by providing endogenous signals with repetitive and synchronized activity [12], and may play a role in the development of sensorimotor coordination [14]. Although the development of sleep spindles has been characterized previously, the slow rhythm and its relationship to spindling in early infancy have not been investigated.

METHODS

We analyzed sleep MEG recordings containing sleep spindles, taken from 7 normal, healthy subjects at conceptional age 46–63 weeks in 21 sessions (Table 1), each lasting 2–4 hours. Three subjects were studied serially. The experimental protocol was approved by the institutional review board, and informed consent was obtained from all subjects. The recordings were made in a magnetically-shielded room, using a 37-channel SQUID biomagnetometer (Magnes II, 4D Neuroimaging, Inc.). The 37 detection coils are arranged in a hexagonal array, covering a 14 cm circular area. The dewar is floor-standing with an inverted sensor array, which allows the subject's head to rest directly on the sensor. The signal passband was 0.1–100 Hz, using an electronic 8-pole Butterworth filter. The recordings were further band-limited using a 30 Hz digital low-pass filter. The right hemisphere of each infant was positioned on the sensor the same way for each recording (see Figure 4) with the center channel proximate to EEG 10–20 location C4. Several 10–15 minute recordings were taken from each subject, commencing when the infants were asleep and relatively motionless and continuing until they awakened. Data with movement artifact were excluded.

Although infant sleep recordings are less amenable to classification than adult sleep recordings, the recordings can be classified into four patterns [2]: 1) a low amplitude, irregular pattern, which predominates during active-REM sleep, 2) a high amplitude slow pattern, which predominates during quiet (non-REM) sleep, 3) a mixed pattern that is intermediate between the first two patterns, often occurring during indeterminate sleep and transitions between states, and 4) the trace' alternant pattern, characterized by bursts of high amplitude slow wave activity, separated by periods of lower amplitude mixed activity. The trace' alternant pattern is present only in the first month of life and thus was rare in our data. Also, the low amplitude, irregular pattern was less common than the mixed and high amplitude slow patterns in the analyzed recordings, in part because movement artifact was more frequent during this pattern.

To identify the characteristic frequencies of and the correlations between the slow rhythm and spindle bursts, we computed power spectra and cross-spectra using Welch's method. A

data window of 63 s with 50 percent overlap applied to a mean data length of 732.5 s provided a frequency interval of 0.016 Hz. Power spectra were computed from a channel that showed high cross-correlation between spindling (12–15 Hz) and slow rhythms (< 0.3 Hz). Typically, these were the channels with strongest spindle power and largest slow rhythms, and were located centrally. To quantify the rate of spindle recurrence, we isolated the spindles by applying a 12–15 Hz Butterworth filter and computed the power spectrum of its Hilbert envelope. We also computed the cross-spectrum between the Hilbert envelope of the sleep spindles and the low frequency MEG.

Time-frequency analysis was performed using a 2-s window with 75% overlap, which provided a 0.5 Hz frequency interval and a 0.5 s time interval. This was sufficient to resolve the spindle bursts and to show the increase in delta power during spindling.

To demonstrate the grouping of sleep spindles by the slow rhythms we constructed histograms of the slow wave phase at the onset of each spindle burst. Using a channel with high spindle amplitude, we determined the times of spindle onset, as described in the following paragraph. The instantaneous phase of the slow rhythms was determined by applying a Hilbert transform. To isolate the 0.2 Hz rhythm, the signal was band-pass filtered at 0.15–0.35 Hz. The Rayleigh test was applied to the phase histograms to test the null hypothesis that the phase distribution was uniform [3]. In each session the slow rhythm was taken from the channel that showed highest cross-correlation between the spindling (12–15 Hz) and slow (< 0.3 Hz) rhythms. Averaged waveforms were constructed by triggering on the spindle onsets.

Sleep spindles were identified from the Hilbert envelope of the 12–15 Hz band-pass filtered data. The onset of a spindle was declared when the amplitude rose above twice the mean spindle amplitude, and the cessation was declared when the amplitude fell below this threshold. We also required that 1) the spindle amplitude remained above the threshold for at least 0.5 sec, 2) the spindle onsets were separated by at least 3 sec, and 3) the mean amplitude during the spindle was at least 3 times greater than that during the interval from the cessation of the preceding spindle to the onset of the spindle. The last condition was necessary to accurately identify sleep spindles at earlier conceptional ages when the signal-to-noise ratio was low.

RESULTS

During the high amplitude slow pattern, spectral analysis revealed distinct peaks at approximately 0.2 Hz and 13 Hz, corresponding to the slow rhythm and sleep spindles, respectively (Figure 1a and 1b). Table 1 shows for each session the oscillation frequencies of the slow rhythm and sleep spindles, and the characteristic rate of sleep spindle recurrence. Given the potential for intersubject differences in brain maturation, the data showed good consistency. Two of the three subjects with serial data showed a modest increase in the rate of spindle recurrence with conceptional age. No trends were seen for the other frequencies.

In addition to periods of sporadic spindling, the recordings showed long episodes of continual, highly regular spindling. The 0.2 Hz and low delta rhythms showed a striking

association with these episodes. It was often not possible to capture the onset or termination of these episodes because they were similar to or longer in duration than the recording time, but the amplitudes of the 0.2 Hz and low delta rhythms showed an abrupt increase prior to (10.0 ± 2.5 s; $n=3$) the onset of spindling and an abruptly decrease simultaneous with or following (8.3 ± 3.0 s; $n=8$) the cessation of spindling. This could be seen directly by passing the recordings through narrow-band filters to isolate the 0.2 Hz rhythm and the sleep spindles (Figure 2). A time-frequency plot (Figure 3) showed that the onset of spindling was also accompanied by increased power throughout the low delta band (< 2 Hz). Prior to the genesis of spindling, typically at around conceptional age 46–48 weeks, the power spectra do not show a 0.2 Hz peak.

The characteristics of the sleep spindles were notable in several respects. Unlike other infant brain rhythms, they gave rise to relatively narrow peaks in the power spectrum with an oscillation frequency virtually identical to that of adult sleep spindles. Second, they were conspicuously clock-like (Figure 2a, 3) with a characteristic rate of recurrence of about 0.1 Hz (Figure 1c and Table 1). Lastly, they were focal and showed a dipolar topography (Figure 4), compatible with a source in the vicinity of the central sulcus. In contrast, the topography of the slow rhythm was not dipolar and could not be localized.

Sleep spindles were grouped by the slow rhythm; i.e., they showed a propensity to occur at a specific phase of the rhythm. This could be seen by plotting a histogram of the slow wave phase at the onset of each spindle burst, as shown in Figure 5. Applying the Rayleigh test [3], the phase distribution was highly non-uniform with mean -0.0 ± 75.0 degrees ($n=731$; $p=3.1 \times 10^{-5}$). This is consistent with prior studies [17], which showed that spindling most often occurred shortly after the transition from the down state to the up state and not at the peak of the up state, reflecting rebound excitation due to release of inhibition.

DISCUSSION

Our data show that the characteristics and interrelationships of the major sleep rhythms are markedly different in the developing infant than in the adult. The slow rhythm observed here is much slower than the 0.7–0.9 Hz slow rhythms typically seen in adult slow wave sleep [17]; however, its frequency is compatible with that of the slow rhythms described in the original reports by Steriade and co-workers. We also note that Vanhatalo and co-workers have observed 0.02–0.2 Hz infraslow EEG signals in adults and in premature infants [27, 28]. Second, the grouping of sleep spindles by the slow rhythms is stronger in the infant than in the adult [17]. Infant sleep spindles were commonly clock-like with a recurrence frequency (0.10 Hz) approximately equal to half that of the slow wave oscillation frequency. The spindling recurrence frequency in adults is typically 0.3 Hz [1, 8, 9]. Lastly, the strong linkage between low delta activity and spindling in infant sleep patterns stands in stark contrast to adult sleep patterns, where delta and spindling exhibit a negative correlation. Adult stage 2 sleep is characterized by spindling and relatively infrequent slow waves, while stage 3 and especially stage 4 sleep are characterized by large slow waves and a decrease in spindling. Further studies are needed to ascertain how the character of the rhythms and relationships between them evolve as the brain matures.

The very low frequencies of slow and infraslow rhythms make them difficult to record using EEG and MEG. The 0.2 Hz oscillation frequency of the slow rhythm observed here lies just above the 0.1 Hz cutoff frequency of the high-pass filter of our magnetometer; therefore, we cannot rule out the importance of rhythms with even lower frequencies. It is possible, for example, that the 0.2 Hz oscillation is a harmonic of a lower frequency oscillation, although it seems unlikely that rhythms associated with spindling would have frequencies less than the 0.1 Hz spindling recurrence frequency. Also, the limited frequency resolution at low frequencies makes it difficult to recognize and separate the 0.2 Hz slow oscillations from other slow rhythms, including low delta activity. Several characteristics of the 0.2 Hz oscillations suggest that they are distinct from the low delta background. First, the oscillations give rise to spectral peaks that stand out above the broad delta background. Second, sleep spindles are grouped by the rhythm, which is a signature characteristic of the slow rhythm.

Several studies suggest that adults show two types of sleep spindles: classical fast (12–15 Hz) spindles originating in the centroparietal area and slow (9–12 Hz) spindles originating frontally. Our spindles are compatible with fast spindles. The topography was compatible with a source in the vicinity of the central sulcus and the frequency was the same as that of adult fast spindles. The spatiotemporal characteristics of the infant sleep spindles were remarkably well defined. The peak frequencies of the spindles were very similar across subjects, ranging from 13.0–14.0 Hz for all but one subject, and the topographies were highly dipolar and stationary. No evidence for slow spindles was seen, implying that they develop later. This is compatible with the hypothesized role of fast sleep spindles in sensorimotor coordination, which presumably develops early in infancy.

Infant studies are difficult to perform due to the inability of the subject to cooperate and sensitivity of MEG to movement artifact. Although the study could have been performed using EEG, MEG is convenient for neonatal studies because the application of electrodes is time-consuming and can arouse the baby. Magnetic source imaging was not performed; however, analysis of MEG topography was useful for demonstrating the stationarity and approximate location of the sources. Most MEG systems are unsuitable for neonatal studies because they designed to accommodate the much larger head of an adult. The floor-standing, inverted-array MEG system used in this study, however, is nearly ideal for mapping signals from a hemisphere of a neonate. The subject's head rests directly on the sensor surface, which minimizes the source-to-sensor distance.

CONCLUSIONS

Our findings provide evidence that slow rhythms may play a critical role during early brain development in the formation of sleep spindles. The infant brain is fertile ground for the study of brain rhythms. Compared to adult brain rhythms, infant rhythms typically exhibit behavior that is simpler and more regular, allowing relationships between them to be more easily discerned. It is also possible in the infant to follow the development of brain rhythms from their genesis.

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Figure 1.

Grand-averaged spectra (20 session average) for the high amplitude slow (HAS; solid line) and the mixed (dashed line) infant MEG patterns. The total duration of the recordings was 15,059 s for the HAS pattern and 3468 s for the mixed pattern. a) Semi-log MEG power spectrum, showing increased power in the delta band (<4 Hz) and the sigma band (12–15 Hz) for the HAS pattern. b) Linear plot of low frequency portion of the spectrum in a), showing a well-defined peak at about 0.2 Hz for the HAS pattern. c) Power spectrum of the Hilbert envelope of the sleep spindles, exhibiting a characteristic frequency of 0.1 Hz for the HAS pattern.

Figure 2.

MEG recording from (a and b) subject 2 at CA 53 weeks and (c and d) subject 4 at CA 52.5 weeks showing that the cessation of spindling coincides (to within about 10 s) with a diminution of the slow rhythm. The recording was processed using two different filters: a and c) 12–15 Hz band-pass filtered to isolate the spindle bursts, b and d) 0.35 low-pass filtered to isolate the slow rhythm.

Figure 3.
Time-frequency analysis from subject 2 at CA 47.5 weeks showing the onset of spindling.
Power from three neighboring channels was averaged to construct the plot.

Figure 4.

a) Sigma-band (12–15 Hz) filtered, 37-channel superimposition MEG tracing of a typical sleep spindle. b) During spindling the MEG topography is dipolar, implying a focal source. The topography is compatible with a source location in the vicinity of the central sulcus with a horizontal orientation.

Figure 5.

a) Histograms of the slow wave phase at the onset of the spindle bursts, depicting the phase locking of the 0.2 Hz slow rhythms with spindling. Data from all sessions were combined. b) Averaged tracings of the isolated rhythms obtained by using the spindle onsets as a trigger. Sleep spindles tend to occur near zero phase.

Table 1

Oscillation frequencies of the 0.2 Hz slow rhythm and sleep spindles, and the characteristic rate of spindle recurrence. The rate of spindle recurrence was taken to be the frequency of the spectral peak of the Hilbert envelope of the sleep spindles (Fig. 1c). The data in the last 3 columns are in units of Hz.

Subject	CA (wk)	0.2 Hz peak	Spindling	Spindle recurrence
1	49	0.24	13.75	0.08
1	52	0.22	13.75	0.10
1	54	0.22	13.50	0.11
1	56.5	0.22	13.75	0.11
1	57.5	0.21	13.50	0.10
2	47.5	0.21	13.50	0.10
2	48.5	0.22	13.75	0.08
2	50	0.21	13.75	0.10
2	52	0.22	13.50	0.13
2	53	0.24	13.50	0.11
3	48.5	0.24	11.75	0.14
4	51.5	0.22	13.25	0.08
4	52.5	0.22	13.00	0.08
4	53.5	0.24	13.50	0.08
4	54.5	0.22	13.00	0.10
4	58.5	0.22	13.50	0.10
4	62.5	0.21	14.00	0.11
5	57.5	0.21	13.50	0.10
6	56	0.19	13.25	0.10
7	50.5	0.19	13.50	0.08
Average	53.3 ± 3.9	0.22 ± 0.01	13.43 ± 0.47	0.10 ± 0.02