Effect of sleep on interictal spikes and distribution of sleep spindles on electrocorticography in children with focal epilepsy

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Abstract

OBJECTIVE—To determine how sleep with central spindles alters the spatial distribution of interictal spike frequency in children with intractable focal seizures, and whether such children have spindles arising from the medial temporal region in addition to the frontal-central region.

METHODS—Seventeen children (age: 7 months – 17 years) were studied using extraoperative electrocorticography (ECoG).

RESULTS—Overall spike frequency across the subdural electrodes was greater during sleep with central spindles compared to wakefulness. In 13 children showing at least 1 spike/min in an electrode, the spatial distribution of spike frequency was similar during wakefulness and sleep; in addition, the spike frequency was greater in the seizure onset zones compared to the non-onset areas, regardless of wakefulness or sleep. Spindles were identified in the medial temporal region during sleep with central spindles in all 17 children.

CONCLUSION—Overall spike frequency may be increased by sleep with spindles, but the spatial distribution of spike frequency appears similar during wakefulness and sleep in children with intractable focal seizures.

SIGNIFICANCE—Both awake and sleep ECoG may be useful to predict seizure onset zones in children with intractable focal epilepsy. Medial temporal spindles are present in some children with focal epilepsy.

Keywords

clinical neurophysiology; pediatric epilepsy surgery; quantitative interictal intracranial EEG; hippocampus; and tuberous sclerosis complex
INTRODUCTION

Interictal spike activity is considered as one of the hallmarks of epilepsy (Gibbs et al., 1936; Rosenow and Luders, 2001). Traditionally, induction of sleep state by sleep-deprivation has been routinely used to activate interictal spike activity on scalp EEG or magnetoencephalography in patients being evaluated for epilepsy surgery (Kellaway, 1950; Crespel et al., 1998; Xiao et al., 2006). Previous studies have shown that some types of seizures preferentially occur during sleep with spindles, and association between sleep and activation of epileptiform activity on EEG has been of interest to investigators for years (Caveness et al., 1950; Terrano et al., 1991; Nobili et al., 1999; Zucconi et al., 2000; Herman et al., 2001; Steriade and Amzica, 2003).

Sleep spindle is an oscillatory waveform ranging from 12–16 Hz on EEG, intermittently emerging during non-REM sleep. The frequency of spindles may be slower in patients with epilepsy treated with antiepileptic drugs (Drake et al., 1991; Steriade and Amzica, 2003). Extraoperative intracranial electrocorticography (ECoG) recording for presurgical evaluation in epilepsy surgery provides a unique opportunity to assess electrographic activity from deep brain structures in the human. Previous studies of adults with uncontrolled focal epilepsy demonstrated that sleep spindles can be recorded intracranially (Brazier, 1968; Montplaisir et al., 1981) and that the amplitude of sleep spindles is highest in the frontal-central region (Caderas et al., 1982). Several studies in adults have documented that sleep spindles are also present in the medial temporal region predominantly during non-REM sleep (Brazier, 1968; Montplaisir et al., 1981; Malow et al., 1999). The nature of such medial temporal spindles has not been clearly understood, and its possible association with epileptic or physiological phenomenon has been proposed (Montplaisir et al., 1981; Malow et al., 1999).

Does sleep with central spindles alter the spatial distribution of interictal spike frequency in children with focal seizures? For example, does sleep alter spike frequency differentially in a certain brain region? Are sleep spindles in the medial temporal region present also in children? None of the previous studies of intracranial ECoG recording have addressed these issues. In the present study, we determined how sleep with spindles altered the spatial distribution of interictal spike frequency in children with intractable focal epilepsy and also determined whether sleep spindles are present in the medial temporal region in these children.

METHODS

Patients

The inclusion criteria of the present study included: (i) age ranging from 6 months to 17 years, (ii) epilepsy surgery using extraoperative ECoG monitoring in Children’s Hospital of Michigan, Detroit between March 2004 and March 2006, and (iii) subdural electrode placement involving the frontal-central region as well as the medial temporal region. The exclusion criteria included (i) the absence of clear-cut sleep spindles in the frontal-central region on ECoG and (ii) the lack of interictal sleep ECoG segments due to very frequent seizures during sleep. Among a consecutive series of 22 children who met the inclusion criteria, three children with epileptic spasms were excluded due to the lack of clear-cut central spindles, and other two children were excluded because of the lack of interictal sleep ECoG segments due to very frequent seizures during sleep. Thus, we studied a total of 17 children with focal seizures (age: 7 months – 17 years; 9 girls) who met the inclusion criteria and satisfied the exclusion criteria (Table 1).

All 17 subjects underwent scalp video-EEG monitoring, MRI, 2-deoxy-2-[18F]fluoro-D-glucose (FDG) PET, and chronic intracranial ECoG monitoring with subdural electrodes as part of their presurgical evaluation. On MRI, six children showed the evidence of focal cortical

Clin Neurophysiol. Author manuscript; available in PMC 2007 August 13.
dysplasia (Raymond et al, 1995); four children had multiple cortical tubers; three children had a brain tumor; one child each had a solitary tuber and focal ulegyria. In the remaining two children, MRI was normal but FDG PET scan showed cortical regions with glucose hypometabolism in the presumed epileptic hemisphere. The study has been approved by the Institutional Review Board at Wayne State University, and written informed consent was obtained from the parents or guardians of all subjects.

**Subdural electrode placement**

For extraoperative video-ECoG recording, platinum grid electrodes (10 mm intercontact distance; 4 mm diameter; Ad-tech, Racine, WI) were surgically implanted on the presumed epileptogenic hemisphere. As shown in our previous report (Asano et al, 2005), all electrode plates were stitched to adjacent plates and/or the edge of the dura mater, to avoid movement of subdural electrodes after placement. In addition, intraoperative pictures were taken with a digital camera before dural closure, to enhance spatial accuracy of electrode display on the three-dimensional brain surface reconstructed from MRI (Wellmer et al, 2002). The total number of electrode contacts in each subject ranged from 70 to 128.

**Extraoperative video-ECoG recording**

Extraoperative video-ECoG recordings were performed as shown in our previous report (Asano et al, 2003; Asano et al, 2004a). Anti-epileptic medications were discontinued or reduced during ECoG monitoring until a sufficient number of habitual seizures (typically three seizures) were captured. A ground lead and a reference electrode were placed to the contralateral mastoid by a registered EEG technician. Surface EMG recordings from the left and right deltoid muscles were added as needed. ECoG data were obtained using a Stellate HARMONIE digital system (sampling rate: 200Hz; Stellate Inc., Quebec, Canada) for 2–5 days. Clinical manifestations were assessed using synchronized digital videos with 30 frames per second.

**Visual analysis of ECoG data**

ECoG data were assessed mostly with a low frequency filter of 0.5 – 1.0 Hz and a high frequency filter of 35 – 100 Hz applied. A low frequency filter of 3.0 Hz or higher was occasionally used to assess a low-amplitude fast wave activity. While the subject quietly lay in a spine position with her/his eyes closed, minimal body movement and regular respiration noted in the video, sleep spindles in the frontal-central region (Sperling, 2003) were visually determined (Figure 1). Subsequently, sleep spindles in the medial temporal region (Malow et al, 1999), while central spindles were present, were also visually determined by the consensus of two clinical neurophysiologists (E.A. and T.M.) (Figure 1). ‘Seizure onset zones’ were defined as a single or multiple brain areas initially showing a sustained rhythmic change in the ECoG accompanied by subsequent clinically typical seizure activity, not explained by level of arousal, and clearly distinguished from background ECoG and interictal activity (Spencer et al, 1992; Asano et al, 2003). ‘Non-onset areas’ were defined as all brain regions not classified as ‘seizure-onset zone’. Seizure onset zones were determined by the consensus of two clinical neurophysiologists (Asano et al, 2004a).

**Quantitative analysis of interictal spike frequency recorded on ECoG**

Quantitative analysis of interictal spike frequency was performed on the ECoG, using Stellate SENA software, as previously described and validated (Gotman and Gloor, 1976; Asano et al, 2003; 2004a; 2005). All signals were re-montaged to an average reference (Hart et al, 1998; Asano et al, 2005). In short, three distinct 10-minute ECoG segments during quiet wakefulness as well as sleep with central spindles were selected from the video-ECoG data, based on the following criteria: at least a 3-hour interval between each segment; at least 8 hours after a secondarily generalized tonic clonic seizure and at least 2 hours after other types of
clinical seizures (Asano et al, 2003). In cases where frequent interictal spikes (greater than 30 spikes/min in an electrode) were seen and spike distribution visually appeared consistent to two clinical neurophysiologists, three distinct 5-minute segments instead of 10-minute segments were selected (Asano et al, 2004a). Subsequently, the averaged spike frequency for each intracranial electrode was obtained from the three ECoG segments. In cases where extremely frequent interictal spikes (a total of 5,000 spikes across the electrode arrays or 500 spikes in an electrode) were seen and spike distribution visually appeared consistent among three segments, a spike frequency for a single ECoG segment instead of three distinct ECoG segments was utilized for subsequent analyses.

**Imaging protocol**

FDG PET studies were performed and evaluated as previously described (Muzik et al, 1998; Juhasz et al, 2000). MRI including a T1-weighted spoiled gradient echo (SPGR) image and fluid-attenuated inversion recovery image were also obtained. Planar X-ray images (lateral and anterior-posterior images) were acquired with the subdural electrodes in place for determining the location of the electrodes on the brain surface. Three metallic fiducial markers were placed at anatomically well-defined locations on the patient’s head for coregistration of the x-ray with the MRI as previously described (von Stockhausen et al, 1997; Juhasz et al, 2000; Muzik et al, 2001). Finally, a three-dimensional brain surface view was created which corresponds to the planar X-ray image position and where the location of electrodes was directly defined on the brain surface.

**Statistical analysis**

In order to determine whether sleep with spindles altered overall spike frequency, the mean spike frequency across the whole subdural electrode arrays during wakefulness was compared to that during sleep with spindles in the frontal-central region, using the Wilcoxon Signed Ranks test. In order to determine whether the spatial distribution of spike frequency was similar between wakefulness and sleep with central spindles, the Spearman’s rank correlation was applied to each patient’s dataset of spike frequency. We subsequently determined whether sleep differentially increased spike frequency in the seizure onset zone, by comparing the mean fractional rank of spike frequency in the seizure onset zone during wakefulness to that during sleep with central spindles, using the paired t-test. In order to determine whether sleep differentially increased spike frequency in the medial temporal region, the mean fractional rank of spike frequency in the medial temporal region (including the hippocampus, amygdala, uncus and parahippocampal gyrus) during wakefulness was compared to that during sleep with central spindles, using the paired t-test. Finally, we determined whether the seizure onset zones were predicted by frequent spike activity on both awake and sleep recordings, by comparing the mean fractional rank of spike frequency in the seizure onset zone to that in the non-onset zone, using the paired t-test. A p-value cutoff of 0.05 was used to assess significance in all statistical analyses.

**RESULTS**

**Sleep with central spindles associated with increased spike frequency**

The mean spike frequency across the whole subdural electrodes was greater on sleep compared to awake recording (Table 1; N=17; p=0.009; Wilcoxon Signed Ranks test). One subjects had no spikes during wakefulness but spikes greater than 1/min only during sleep with spindles. Three subjects had either no or very rare spikes less than 1/min on both awake and sleep ECoG recordings.
Similar spatial distribution of spike frequency during wakefulness and sleep with spindles

Thirteen subjects showing at least 1 spike/min in an electrode both during wakefulness and sleep were included into statistical analysis. The remaining four subjects (patients #2, 12, 13 and 16; Table 1) were excluded, since the spatial distribution of spike frequency during wakefulness was not well formulated due to very rare or complete lack of spikes. The Spearman’s rank correlation revealed that the spatial distribution of spike frequency was quite similar between wakefulness and sleep (Figure 2; mean rho among the 13 subjects = 0.72 [range: 0.45 – 0.88]; p<0.0001 in all 13 individuals).

Lack of differential effect of sleep on the spatial distribution of spike frequency

The paired t-test failed to prove that the mean fractional rank of spike frequency in the seizure onset zones during sleep differed from that during wakefulness (p=0.2); the mean fractional rank of spike frequency in the seizure onset zone was 0.81 during sleep with central spindles and 0.84 during wakefulness in the above-mentioned 13 subjects showing at least 1 spike/min in an electrode.

Similarly, the paired t-test failed to indicate that the mean fractional rank of spike frequency in the medial temporal region during sleep with spindles differed from that during wakefulness (p=0.5); the mean fractional rank of spike frequency in the medial temporal region was 0.68 during sleep with central spindles and 0.70 during wakefulness in the above-mentioned 13 subjects showing at least 1 spike/min in an electrode.

Spikes during wakefulness and sleep similarly associated with the seizure onset zones

Regardless of wakefulness or sleep with central spindles, spike frequency was greater in the seizure onset zones compared to the non-onset areas in the above-mentioned 13 children showing at least 1 spike/min in an electrode (Figure 2; p<0.0001; paired t-test); the mean fractional rank of spike frequency in the seizure onset zones was 0.84 (95% Confidence Interval [95% CI]: 0.75 – 0.92) on awake ECoG and 0.81 (95% CI: 0.70 – 0.92) on sleep ECoG, and the mean fractional rank of spike frequency in the non-onset areas was 0.61 (95% CI: 0.51 – 0.70) on awake ECoG and 0.55 (95% CI: 0.50 – 0.61) on sleep ECoG.

Visual analysis of sleep spindles in the medial temporal region

Sleep spindles in the medial temporal region were visually identified exclusively during non-REM sleep as suggested by central spindles in all 17 subjects (Figures 1 and 2). The youngest subject showing spindles in the medial temporal region was a 7-month-old girl (Figure 2). The duration of medial temporal spindles ranged approximately from 0.5 to 2 seconds and the frequency ranged approximately 11 to 16 Hz. Such spindles in the medial temporal region appeared independent of or simultaneous to the central spindles, as described in a previous study of adults with temporal lobe epilepsy (Malow et al, 1999). According to visual assessment, more than half of medial temporal spindles appeared independent of central spindles. Medial temporal spindles appeared independent of interictal spikes arising from the hippocampus or neocortex. None of the patients had a medial temporal spindle subsequently evolving into an ictal discharge. The amplitude of medial temporal spindles was highest in the hippocampal region in all 17 children.

DISCUSSION

Sleep may alter the overall frequency but not the spatial distribution of interictal spike frequency

The present study demonstrated that overall spike frequency was increased during sleep with spindles. Previous studies also demonstrated that the frequency and spatial field of interictal
spike activity were greater during sleep with spindles compared to wakefulness in children with various forms of epilepsies including focal epilepsy, Landau-Kleffner syndrome and continuous spike-waves during slow wave sleep (Nobili et al, 1999;2000;2001;Luat et al, 2005). Previous studies describing the cyclic alternating pattern of sleep indicated that the phase A with K-complex and slow-waves may be an excitatory phase associated with increased frequency of interictal epileptiform discharges while phase B with low-voltage fast waves, including sleep spindles alone, may be an inhibitory phase (Terzano et al, 1991;Terzano et al, 1992;Zucconi et al, 2000;Eisensehr et al, 2001). A study of adults with temporal lobe epilepsy showed that the firing rate of single neurons in the hippocampus was increased during non-REM sleep compared to wakefulness (Staba et al, 2002). Yet, none of the above-mentioned studies were designed to determine whether there was a differential effect on the spatial distribution of spike frequency. In the present study, we found no evidence of a differential effect of sleep on the spike frequency in the medial temporal region or the seizure onset zones. Instead, we found that the spatial distribution of spike frequency was quite similar between wakefulness and sleep with spindles in children with focal epilepsy. Thus, we speculate that sleep with spindles may decrease the threshold of emergence of interictal spike activity diffusely rather than focally.

Children with focal epilepsy also have sleep spindles in the medial temporal region

The present study using extraoperative ECoG recording demonstrated that sleep spindles in the medial temporal region were present during non-REM sleep (suggested by central spindles) in children with focal epilepsy. This finding might suggest that spindles in the medial temporal region develop during childhood in human. Previous studies of scalp EEG revealed that sleep spindles in the central region are normally present in all healthy infants’ EEGs by 9 weeks post-term (Ellingson and Peters, 1980). It is uncertain at what age spindles in the medial temporal region begin to show up in healthy infants. Some investigators who studied adults with temporal lobe epilepsy believed that sleep spindles in the medial temporal region likely represent a physiological rather than pathological phenomenon (Malow et al, 1999), whereas other investigators believe that spindle-like activity in the medial temporal region may represent an epileptogenic phenomenon (Nakabayashi et al, 2001). In the present study, we observed that the majority of our subjects had seizure onset zones in the neocortical regions (Table 1). None of the patients had such a medial temporal spindle subsequently evolving into an ictal discharge. Medial temporal spindles appeared independent of interictal spikes arising from the hippocampus or neocortex. Thus, we speculate that medial temporal spindles visualized in the present study represented a physiological activity in most of the subjects. Yet, the observations in the present study do not suggest that medial temporal spindles are universally of physiological nature in patients with epilepsy, especially because patients with pure medial temporal lobe epilepsy were not included in the present study.

Methodological Issues

Three children with epileptic spasms showing very frequent interictal spike activity were excluded from the present study, since we were not able to identify clear-cut central spindles on ECoG, although intracranial electrodes widely covered the frontal-central region. Sleep staging of ECoG was not easy and we were not able to specify whether ECoG data were selected exactly from Stage 2 or Stage 3 sleep. On the other hand, sleep spindles were relatively easy to recognize. We recognize that an additional scalp electrode on the contralateral central region may potentially have shown sleep spindles arising from the healthy hemisphere in some children with spasms and enabled sleep staging in more detail (Malow et al, 1999). However, no additional contralateral scalp electrode was placed in the present study, since we were concerned that the children may not have tolerated further manipulation on their heads.
None of the subjects in the present study underwent bilateral subdural electrode placement, since the noninvasive pre-surgical evaluation lateralized the presumed epileptogenic zones. Thus, the present study did not assess whether sleep altered the spatial distribution of interictal spike frequency across the two hemispheres. Furthermore, neither morphology nor propagation speed of interictal spike discharge was assessed in the present study.

Factors which may affect interictal spike frequency include antiepileptic medication and post-ictal state. Previous scalp EEG and intracranial ECoG studies in adults with focal epilepsy suggested that interictal spike frequency was increased during the post-ictal period but not simply after a decrease in medication (Gotman and Marciani, 1985; Gotman and Koffler, 1989). The exclusion criteria of the present study included the lack of interictal sleep ECoG segments due to very frequent seizures during sleep, and two children were excluded from the present study because of this exclusion criterion.

**Future Direction**

The strength of the association between frequent spike activity and the seizure onset zone was similar between wakefulness and sleep with spindles in the present study. Thus, we speculate that both awake and sleep ECoG recordings may be equally good predictors of the seizure onset zones in children with intractable focal seizures, as long as spike activity of at least 1 spike/min in an electrode is visually identified. Yet, this study was not designed to answer the question: whether frequent spike activity is simply a predictor of seizure onset zones or frequent spike activity is an independent indicator of the epileptogenic zones. The logical next step in the application of quantitative interictal ECoG analysis for pediatric epilepsy surgery is to formulate a model for prediction of surgical outcome using multiple variables derived from ictal and interictal ECoG data as well as neuroimaging data.

In the present study of children with focal epilepsy, sleep spindles in the medial temporal region were visually identified and we found that the amplitude of spindles was highest in the hippocampus in all cases. The next step in the research of medial temporal spindles is to explore the clinical significance of quantitative measurements of this type of spindle, using larger samples consisting of various aged subjects with focal epilepsy of medial temporal as well as neocortical origin.

**Acknowledgements**

This work was supported by NIH grants NS47550 (to E. A.). We are grateful to Aashit Shah, M.D, Jagdish Shah, M.D., Carol Pawlak, R. EEG/EP. T. and Ruth Roeder, R.N., M.S., and the staff of the Division of Electroneurodiagnostics at Children’s Hospital of Michigan, Wayne State University for the collaboration and assistance in performing the studies described above.

**References**


Figure 1. A 15-year-old boy with uncontrolled focal seizures associated with a tumor in the left superior temporal gyrus.

(A) On interictal ECoG recording, sleep spindles were independently or simultaneously noted in the left frontal-central region (arrowheads) and the left medial temporal region (arrows). Visual assessment revealed that the amplitude of spindles in the medial temporal region was about twice as high as those in the frontal-central region. A low frequency filter of 1.0 Hz and a high frequency filter of 70Hz were applied. (B and C) A typical ictal ECoG trace is shown. A low frequency filter of 1.0 Hz and a high frequency filter of 70Hz were applied. The seizure onset zone was localized to the left superior temporal gyrus surrounding the tumor. Ictal ECoG discharges consisted of low-amplitude fast wave bursts at electrode D3. The ictal discharges...
gradually evolved into irregular rhythmic polyspike-and-wave bursts, and involved the adjacent temporal neocortices including electrodes C2, C3, C4, D2, D4 and B4. This ictal ECoG finding was consistent with his seizure semiology, which was characterized by auditory aura followed by altered consciousness, right-sided facial twitching and occasional secondary generalized tonic clonic convulsion. Medial temporal spindles were intermittently noted during the seizure (arrows), but did not participate in the ictal discharges. (D) The topography of central spindles was delineated on his own three-dimensional reconstructed surface MR image, using a method similar to that previously described (Asano et al, 2004b). To obtain reference-free topographic maps of spectral measures, all signals were re-montaged to an average reference (Hart et al, 1998;Asano et al, 2005). A total of 40 1.28-second epochs of interest were placed on sleep ECoG segments exactly showing central spindles, and an averaged amplitude spectral curve was created for each epoch. Then, a spindle magnitude (defined as the area under the averaged spectral curve within a 12–16Hz band) was determined for each electrode. Increased spindle magnitude was noted mainly in the left premotor region. Increased spindle magnitude in the medial temporal region here may be associated with the observation that some central spindles were noted simultaneously to those in the medial temporal region. (E) The topography of spindles in the medial temporal region was similarly delineated; using spindle magnitudes derived from a total of 40 1.28-second epochs of interest placed on sleep ECoG segments exactly showing spindles in the medial temporal region. (F) Fluid-attenuated inversion recovery (FLAIR) MRI images showed a well-defined hyperintense lesion in the left superior temporal gyrus but no evidence of abnormality in the left hippocampus. Lesionectomy plus additional cortical resection involving the left superior temporal gyrus, preserving the left hippocampus, resulted in seizure-free outcome (follow-up period: 27 months).
Figure 2. A 7-month-old girl with uncontrolled tonic seizures associated with cortical dysplasia involving the right temporal neocortex

(A) Scalp EEG recording showed central spindles (arrowheads) bilaterally with their fields minimally involving the temporal regions. Frequent interictal spike activity was noted in the right temporal-parietal region. (B) On interictal ECoG recording, sleep spindles were noted in the left frontal-central region (arrowhead) and the left medial temporal region (arrow). The amplitude of spindles in the medial temporal region was about equal to that in the frontal-central region on ECoG recording. Medial temporal spindles appeared independent of interictal spikes arising from the temporal neocortex (see electrodes LT3 - LT8). A low frequency filter of 1.0 Hz and a high frequency filter of 70Hz were applied. (C) A surface topography of interictal spike frequency during wakefulness is delineated on her own three-dimensional reconstructed surface MR image. (D) Interictal spike frequency during sleep with spindles is similarly delineated. The spatial distribution of spike frequency was similar between during wakefulness and sleep with spindles (rho=0.88; p<0.0001; Spearman’s rank correlation). (E) Seizure onset zones are shown as red electrodes. Cortical resection involving the left temporal-parietal-occipital region resulted in seizure-free outcome (follow-up period: 29 months).
## Table 1

<table>
<thead>
<tr>
<th>Patients</th>
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<th>Seizure onset zones determined on ECoG</th>
<th>Histology</th>
<th>Mean spike frequency across the whole subdural electrodes during wakefulness (per min)</th>
<th>Mean spike frequency across the whole subdural electrodes during sleep (per min)</th>
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