Localization of Sleep Spindles, K-Complexes, and Vertex Waves With Subdural Electrodes in Children

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Purpose: To describe for the first time in children the localization of sleep spindles, K-complexes, and vertex waves using subdural electrodes.

Methods: We enrolled children who underwent presurgical evaluation of refractory epilepsy with subdural grid electrodes. We analyzed electroencephalogram data from subdural electrodes and simultaneous recording with Cz scalp electrode. Sleep spindles, K-complexes, and vertex waves were identified and localized based on their morphology on the subdural electrodes.

Results: Sixteen patients (9 boys; age range, 3–18 years) were enrolled in the study. The inter-rater reliability on identification and localization of maximal amplitude was high with an intraclass correlation coefficient of 0.85 for vertex waves, 0.94 for sleep spindles, and 0.91 for K-complexes. Sleep spindles presented maximum amplitude around the perirolandic area with a field extending to the frontal regions. K-complexes presented maximum amplitude around the perirolandic area with a field extending to the frontal regions. Vertex waves presented maximum amplitude around the perirolandic areas.

Conclusions: In our series of pediatric patients, sleep spindles, K-complexes, and vertex waves were localized around the perirolandic area.

Key Words: Intracranial EEG recording, K-complex, Pediatric, Sleep spindles, Subdural electrodes, Vertex waves.

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Sleep spindles, vertex waves, and K-complexes are the hallmark graphoelements of nonrapid eye movement sleep. Most studies on their localization rely on data from scalp EEG, which is sensitive to artifact and partly blind to signals arising from deep cortical regions (Werth et al., 1997; Zeitlhofer et al., 1997). In addition, synchronized discharges of 6 cm^2 of brain cortex are usually required to generate a detectable potential on scalp electrodes (Cooper et al., 1965). Therefore, scalp EEG may not be precise enough for the accurate localization of sleep spindles, vertex waves, and K-complexes. Sleep graphoelement localization with magnetoencephalography has yielded variable results (Gumenyuk et al., 2009; Ishii et al., 2003; Manshanden et al., 2002; Numminen et al., 1996; Shih et al., 2000).

Another approach to the localization of sleep graphoelements is the use of intracranial electrodes during presurgical evaluation for refractory epilepsy. Intracranial electrodes detect discharges from smaller brain areas and are more precise for localization (Carreño and Lüders, 2001; Rosenow and Lüders, 2001). In a study of 13 patients with coregistration of scalp EEG and depth electrodes, sleep spindles were detected mainly in the frontal, parietal, and, less frequently, in the temporal lobe (Andrillon et al., 2011). In another series of 13 patients evaluated with depth electrodes, spindles appeared in most of the recorded neocortical areas with a gradient of spindle density: higher in the central-parietal area and lower in the frontal area (Peter-Derex et al., 2012). In a series of 6 patients, the preferential localization of K-complexes was the anterior and superior frontal cortices (Wennberg, 2010) (Table 1). Similar studies on sleep graphoelement localization using intracranial recordings are not available in children.

We aimed to address these gaps. The specific objective of this study was to describe the localization of sleep spindles, K-complexes, and vertex waves with subdural electrode arrays in children.

METHODS

Protocol Approval

This study was approved by the Institutional Review Board of Boston Children's Hospital. All patients and/or their families consented to participate in the study and signed the specific informed consent form.

Study Design

We performed a prospective descriptive study.

Patients

We prospectively collected information on all patients who underwent a presurgical evaluation for refractory epilepsy in the Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital during the period from August 2008 to February 2010.

Placement of Electrodes

A comprehensive presurgical evaluation with scalp electrodes, neuropsychological evaluation, and neuroimaging techniques identified the cortical areas of surgical interest. Chronic intracranial recordings were performed with subdural electrodes with different arrays of grids and strips to cover the cortical areas of potential

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TABLE 1. Comparison of Our Findings to the Main Studies on Localization of Sleep Elements With Intracranial Recordings

Author and Year	Number of Patients	Age Range, Years	Display to Record Sleep Elements	Sleep Element Studied	Localization
Andrillon et al. (2011)	13	19–52	Intracranial depth electrodes and scalp EEG with 4 scalp electrodes: C_3, C_4, Pz and Fz. The intracranial electrodes covered a limited area that was different in every patient	Sleep spindles	Frontal lobe: 1.8 spindles/min
			Sleep recordings were conducted 48–72 hours after surgery at a minimal interval of 12 hours from identifiable seizures		Supplementary motor area: 1.2
			Automatic detection of spindles		Orbitofrontal cortex: 2.2 Anterior cingulate: 1.6 Presupplementary motor area: 1.5 Lateral frontal: 1.8 Parietal lobe: 1.3 spindles/min Posterior cingulate: 1.1 Posterior parietal: 2.2 Temporal lobe: 1.2 spindles/min Temporal gyrus: 2.1 Parahippocampal gyrus: 1.3 Hippocampus: 1.1 Entorhinal cortex: 0.74 Amygdala: 0.89
Peter-Derex et al. (2012)	13	17–50	Depth electrodes. The intracranial electrodes covered a limited area that was different in every patient	Spindles	Spindles appear in most recorded neocortical areas
			Automatic detection of spindles after visual inspection by human readers		Gradient of density with a higher pole in the central-parietal area and a lower pole in the frontal area
			Sleep recordings were carried out one week after the implantation of electrodes		
Wennberg, 2010	6	27–43	Simultaneous scalp EEG and 4–6 intracranial macroelectrodes with additional 4 depth electrodes in some patients. The intracranial electrodes covered a limited area that was different in every patient	K-complexes	K-complexes are maximal in the anterior and superior frontal cortices
			Detection of K-complexes by visual inspection		
This study	16	3–21	Large cortical coverage with subdural electrodes and Cz scalp electrode. The intracranial electrodes covered a limited area that was different in every patient	Sleep spindles	Sleep spindles: Maximum amplitude around the perirolandic area with a field extending to the frontal regions
			Manual detection of sleep spindles	K-complexes	K-complexes: Maximum amplitude around the perirolandic area with a field extending to the frontal regions
				Vertex waves	Vertex waves: Maximum voltage around the perirolandic areas

epileptogenicity in each patient (Table 2; Fig. 1). For the purpose of this study, scalp Cz and ear reference electrodes were recorded simultaneously with the intracranial subdural electrode recordings.

The individual placement of subdural electrode contacts was ascertained by postimplantation-computerized tomography scan. Specific subdural electrode coverage included the perirolandic area in 13 patients, the temporal area in 2, and the posterior quadrant in 1.

EEG Analysis

The signals from the subdural electrodes and the scalp Cz electrode were recorded simultaneously. Sleep and wakefulness stages were recognized based on the typical morphology in the scalp Cz and intracranial electrodes. All EEG data were analyzed by two independent board-certified clinical neurophysiologists (A.L.P. and M.V.) blinded to the clinical course of the patient.

TABLE 2. Patient Demographics, Localization of the Subdural Electrodes, and Localization of the Sleep Elements

P	Age, Years	Gender (M/F)	Epilepsy Etiology	Placement of Grids and Strips and Total Number of Electrode Contacts	Spindles	Vertex Waves	K-complexes
1	4	F	Meningioangiomatosis in the left frontal lobe (anterior pole of the left hemisphere)	Left Fr, L, Me; T, L, Me (72 electrode contacts)	Pr gyrus	Mi Fr gyrus	Mi Fr gyrus
2	8	M	Stroke in the distribution of the right middle cerebral artery	Right Fr, L, Su, In; OF; PL; T, L, A (136 electrode contacts)	Pr gyrus	Su Fr gyrus	Su Fr gyrus
3	15	M	Cortical dysplasia affecting the right temporal lobe	Right Pe, Pr, Po; FL; TMP (96 electrode contacts)	Su Pa gyrus	Su Pa gyrus	Su Pa gyrus
5	10	F	Unknown	Left OF; Pe, Pr, Po (128 electrode contacts)	Pr gyrus	Pr gyrus	Pr gyrus
6	13	M	Cortical dysplasia in the left occipital lobe	Left O, Su, In, L, Me; Ppo (56 electrode contacts)	Su Pa gyrus	Su Pa gyrus	Su Pa gyrus
7	15	M	Cortical dysplasia in the right parietal lobe	Right Pa, Su, In, L; Pr, Po; TAP (80 electrode contacts)	Su Fr gyrus	Su Fr gyrus	Pr gyrus
8	9	M	Stroke in the right frontal lobe	Right Fr, L; Pr, Su, Mi, In; TAP (72 electrode contacts)	Su Fr gyrus	Su Fr gyrus	Pr gyrus
9	3	F	Cortical dysplasia in the inferior and posterior left frontal lobe extending into the insula	Left Fr, L, Mi, In; Pr; OF; T, M, A, P (88 electrode contacts)	Su Fr gyrus	Su Fr gyrus	In Fr gyrus
10	18	F	Unknown	Left Pe, Pr, Po; T, L, Me, Su (80 electrode contacts)	Pr gyrus	Pr gyrus	Su Pa gyrus
11	9	M	Hemorrhagic stroke in the distribution of the right middle cerebral artery	Right Pe, Pr, Po; O, L, Su, In; T, L, Me, P (64 electrode contacts)	Pr gyrus	Pr gyrus	Su Fr gyrus
12	11	M	Cortical dysplasia in the medial aspect of the right frontal lobe	Right Fr, L, Me, Su, Mi, In; Pe, Pr, Po (96 electrode contacts)	Su Fr gyrus	Su Fr gyrus	Su Fr gyrus
13	17	F	Left mesial temporal sclerosis	Left T, A, P, Me (56 electrode contacts)	In Fr gyrus		
15	8	F	Cortical dysplasia in the right perisylvian region	Right Pe, Pr, A, F; T, Me, In, De; Su, De (128 electrode contacts)	Su Fr gyrus	Su Fr gyrus	Mi Fr gyrus
16	17	M	Unknown	Right T, A, P, Me (112 electrode contacts)	Mi Fr gyrus		

A, anterior; F, female; Fr, frontal; In, inferior; KC, K-complex; L, lateral; M, male; Me, mesial; Mi, middle; OF, orbito-fronto; O, occipital; P, patients; Pe, perirolandic; Pr, precentral gyrus; Po, postcentral gyrus; Pa, parietal; P, posterior; T, temporal; Su, superior; VW, vertex waves.

They independently identified the sleep graphoelements in the entire recording.

To reduce in-patient variability from 1 sleep graphoelement to the next, 15 consecutive samples of every sleep graphoelement (sleep spindles, K-complexes, and vertex waves) were analyzed in each patient. The samples were collected consecutively after the intracranial recordings were available regardless of previous occurrence of seizures. Sleep graphoelements were identified, timed, and localized by their occurrence on the subdural electrodes.

The sleep graphoelements were defined according to the AASM scoring manual as follows (Iber et al., 2007): (1) sleep spindles: train of distinct waves with frequency 11 to 16 Hz (most commonly 12–14 Hz) with a duration >0.5 seconds, (2) K-complexes: a well-delineated negative sharp wave immediately followed by a positive component standing out from the background EEG with a total duration >0.5 seconds, (3) vertex waves: sharply contoured waves with duration <0.5 seconds distinguishable from the background activity.

Neuroimaging and Three-Dimensional Reconstruction

Based on the information of the intracranial electrodes, the foci of maximum amplitude of the sleep graphoelements were identified and displayed in a three-dimensional map (Fig. 2). We used the information from the preoperative structural magnetic resonance imaging and the postoperative computerized tomography scan to generate a cortical surface map using FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/). In the cases where the computerized tomography and the magnetic resonance imaging scan results were not congruent because of postoperative deformation of the cortex, the electrode was projected tangentially along the axis of deformation.

During the process of creation of a cortical surface map, two patients were excluded because FreeSurfer could not localize the subdural electrodes. This was likely related to certain assumptions that FreeSurfer makes about the shape of a human brain and may be unable to process the brains of patients who have previously undergone resective surgery with gross anatomical changes.

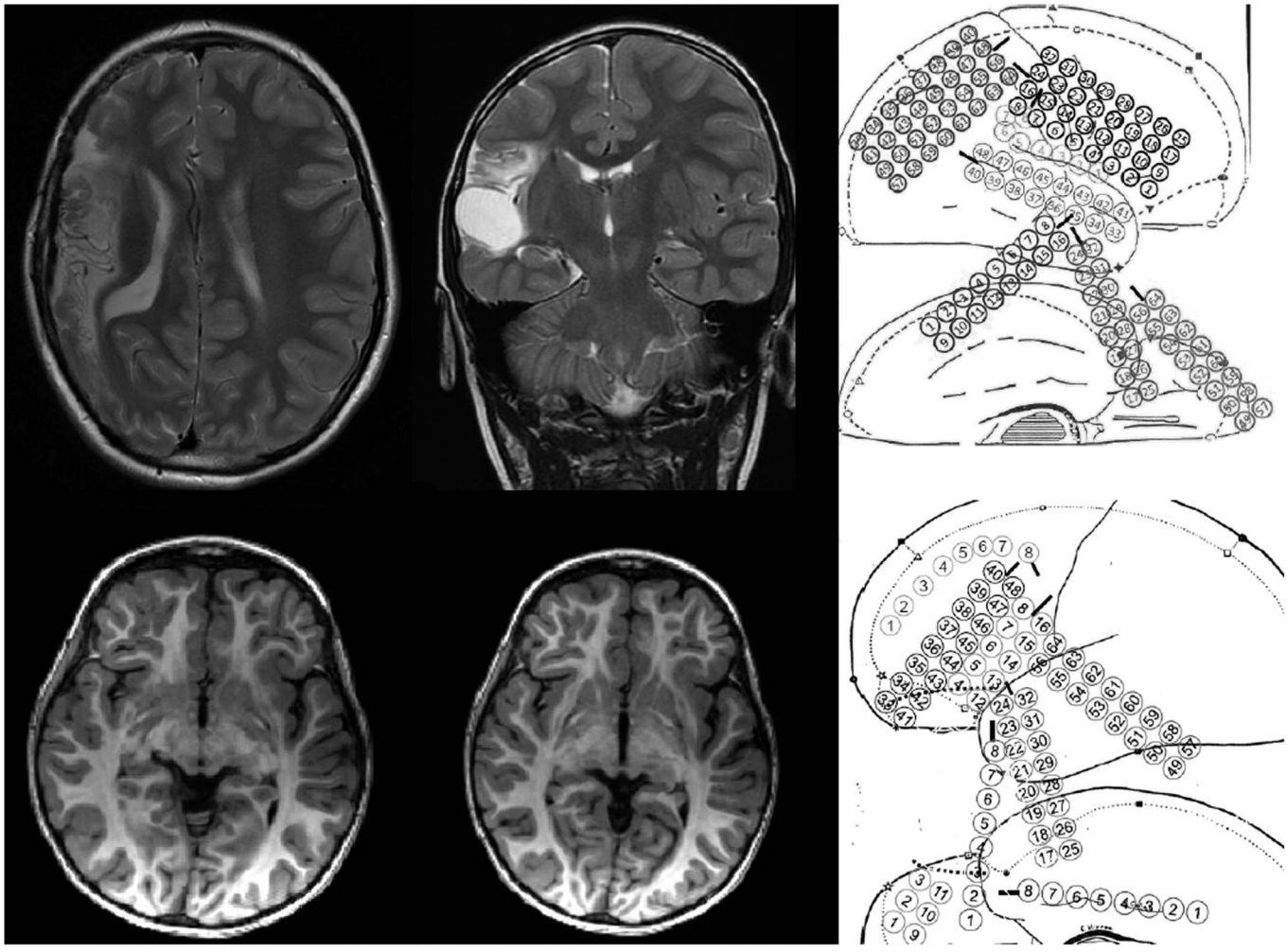

FIG. 1. Examples of lesions and grid coverage in our patient population. Patient 2 had a stroke in the distribution of the left middle cerebral artery (upper row, axial view T2-weighted image and coronal view T2-weighted image), and grids and strips covered a wide area around it (upper row, electrode scheme). Patient 9 had a cortical dysplasia affecting the left frontal lobe (lower row, axial views in T1-weighted images), and grids and strips covered a wide area around it (lower row, electrode distribution scheme).

Statistical Analysis

Intraclass correlation coefficients were used to assess the amount of agreement between observers relative to the variance in the population with values between zero (no agreement) and one (perfect agreement). Analyses were performed using SPSS 19 (SPSS Inc, Chicago, IL). We described the localization of the maximum amplitude of the sleep graphoelements for every patient without further statistical analyses.

RESULTS

Patient Population

We initially collected data on 19 patients who underwent intracranial EEG recording during the study period. Three cases were excluded for the following reasons: one patient required intense sedative medication that may have modified the sleep graphoelements on the EEG, one patient did not tolerate placement of the scalp electrode because of behavioral problems, and one patient had an increase in the frequency and duration of seizures and epileptiform discharges after placement of intracranial electrodes, which were judged to be too frequent to allow a clean recording of sleep graphoelements.

Demographic Features

Sixteen patients (9 boys) were included in the study. Their mean (range) age was 11.4 (3–18) years. Table 2 summarizes the main demographic characteristics of our study population and the distribution of lesions and electrode coverage. Figure 1 shows two examples of the lesions and the corresponding electrode coverage.

Detection of Sleep Elements

The morphology of the sleep elements was similar to that of the sleep elements described in the literature (Iber et al., 2007). The interrater reliability for recognition of sleep elements and localization of their maximal amplitude was high with an intraclass correlation

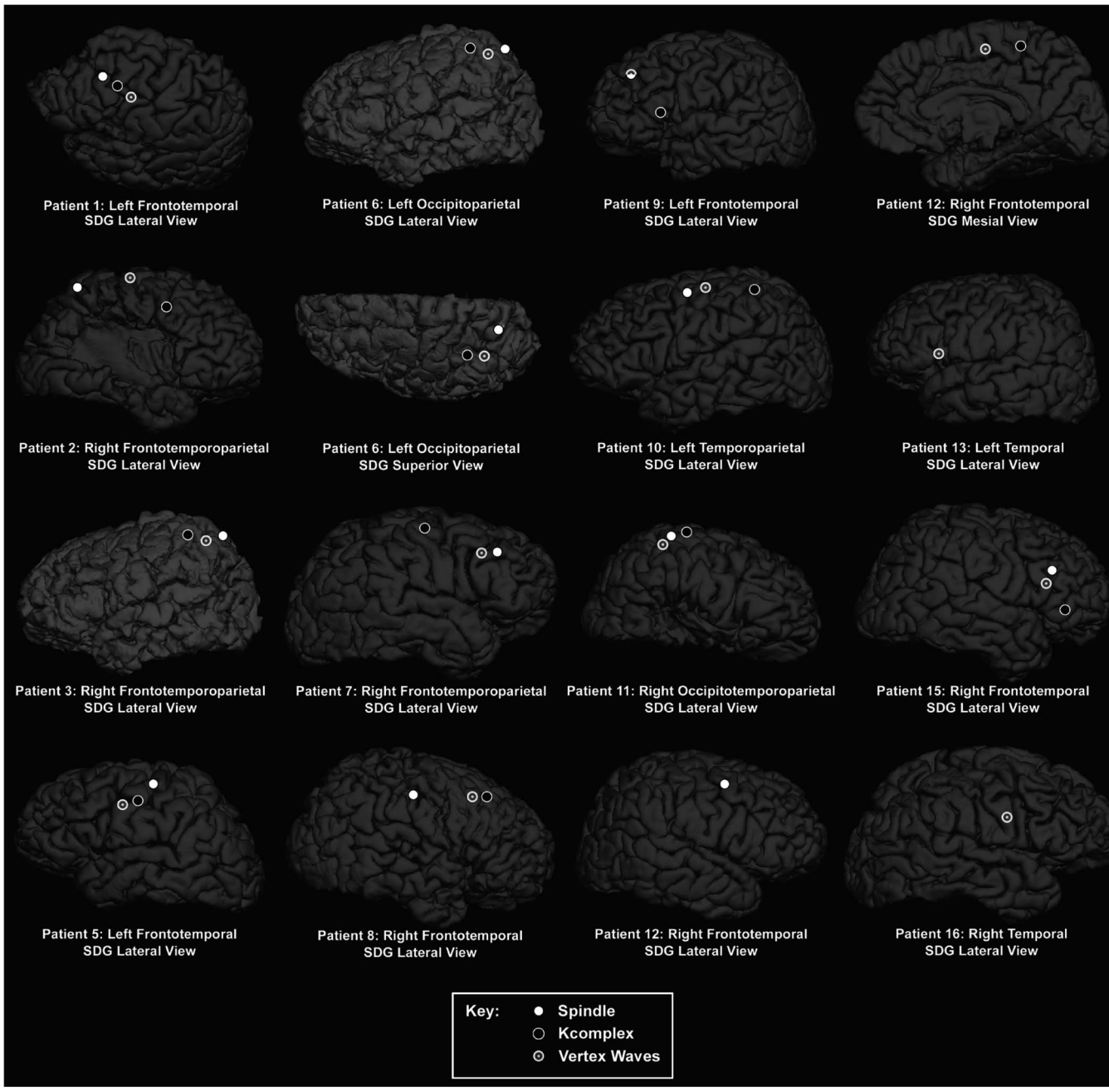

FIG. 2. Localization of the main foci of sleep graphoelements. The areas of maximal amplitude of the specific sleep graphoelements were recognized for every patient and displayed in a three-dimensional reconstruction of their brains (see text for details). Sleep spindles, K-complexes, and vertex waves tend to cluster around the perirolandic area in children.

coefficient of 0.85 for vertex waves, 0.94 for sleep spindles, and 0.91 for K-complexes.

Localization of Sleep Elements

Sleep spindles not associated with K-complexes presented maximum amplitude around the perirolandic area with a field extending to the frontal regions. K-complexes presented maximum amplitude around the perirolandic area with a field extending to the frontal regions. Vertex waves presented maximum amplitude around the perirolandic areas. The precise localization of the sleep elements is detailed in Fig. 2 and Table 3.

DISCUSSION

In our series of pediatric patients, sleep spindles, K-complexes, and vertex waves were localized around the perirolandic areas.

TABLE 3. Localization of the Main Sleep Elements in Our Series

Sleep Element	Localization	
Sleep spindles	Precentral gyrus	5
	Superior frontal gyrus	5
	Inferior frontal gyrus	2
	Superior parietal cortex	2
K-complexes	Superior frontal gyrus	3
	Superior parietal gyrus	4
	Precentral gyrus	2
	Inferior frontal gyrus	2
	Middle frontal gyrus	1
Vertex waves	Superior frontal gyrus	6
	Precentral gyrus	3
	Superior parietal gyrus	2
	Middle frontal gyrus	1

In two patients with exclusive temporal coverage, sleep spindles, K-complexes, and vertex waves were not identified.

Localization of Sleep Graphoelements

Sleep spindles, K-complexes, and vertex waves are hallmark graphoelements of nonrapid eye movement sleep, but the specific circuits that generate them remain poorly specified (Cash et al., 2009). To better understand the generators and circuits that give rise to the different sleep graphoelements, the first step would be to accurately localize them on the cortical surface.

Previous studies on the localization of sleep elements have mainly relied on scalp EEG (Werth et al., 1997; Zeitlhofer et al., 1997), magnetoencephalography (Gumenyuk et al., 2009; Ishii et al., 2003; Manshanden et al., 2002; Numminen et al., 1996; Shih et al., 2000), or depth electrodes (Andrillon et al., 2011; Peter-Derex et al., 2012).

Localization of Sleep Graphoelements With Scalp EEG

Localization of sleep graphoelements with scalp EEG demonstrates maximal spindle activity in the centroparietal midline area with spindles of slower frequency (<14 Hz) distributed more anteriorly than higher-frequency spindles (>14 Hz) (Zeitlhofer et al., 1997). K-complexes and slow waves are poorly localized and travel through the cortex, more frequently in an anteroposterior direction (Massimini et al., 2004). In a study of patients with epilepsy, sleep spindles and vertex waves attained a maximal amplitude at the parietal region (Velasco et al., 2002). A limitation of all scalp EEG studies is that the signals recorded in the head surface represent the summation of the electrical activity of broad brain areas, which makes localization inaccurate (Cooper et al., 1965).

Localization of Sleep Graphoelements With Magnetoencephalography

Sleep spindles are mainly localized to the precentral and/or postcentral areas (Gumenyuk et al., 2009), the frontal and parietal lobes (Shih et al., 2000), centroparietal region (Manshanden et al., 2002), and frontal and parietal lobes (Ishii et al., 2003). K-complexes are maximal at the frontal and parietal lobes (Numminen et al., 1996). Magnetoencephalography has widespread and high-density coverage of scalp activity, which is a major methodological difference with EEG localization. Unfortunately, studies that used magnetoencephalography yielded highly variable localizations of the sleep graphoelements among different series.

Localization of Sleep Graphoelements With Depth Electrodes

Sleep spindles are maximal in the frontal, parietal, and the temporal lobes (Andrillon et al., 2011). However, sleep spindles appeared in most neocortical areas in some studies (Peter-Derex et al., 2012). In addition, depth electrodes provide information on only a limited area of brain tissue (Sperling, 2001).

Localization of Sleep Graphoelements With Subdural Electrodes

We evaluated electrical activity in the brain using subdural electrodes, which provide a good balance between a precise localization (similar to depth electrodes) and a relatively large area of brain cortex sampled (similar to scalp EEG). A similar previous approach used a 10-20 electrode coverage in the scalp but only 4 to 6 subdural electrodes per patient (Wennberg, 2010). Some of our patients presented maximum amplitude in the mesial aspect close to the central sulcus. This activity would appear in the midline electrodes on scalp EEG without additional localizing information.

Pathophysiological Correlation

Even if our approach was limited because of the reasons outlined below, our results suggest that the localization of sleep spindles, K-complexes, and vertex waves may be more restricted in children than in adults, probably reflecting an incomplete myelination of the neuronal circuits implicated in their generation and spread. This hypothesis should be evaluated in subsequent studies with intracranial recordings from a larger series of children.

Strengths and Limitations

There have been no previous studies on the localization of sleep spindles, K-complexes, or vertex waves using subdural electrode arrays in children. This study is the first comprehensive study on localization of sleep graphoelements in children.

Our findings may be less spatially precise than that achieved with deep electrodes, but in contrast subdural electrodes provide a wider coverage of the cortical surface than depth electrodes. The patients underwent EEG recording with subdural electrodes. Therefore, most of the scalps were not available for the placement of scalp electrodes. The recognition of sleep graphoelements was based on their morphology in scalp and subdural electrodes. Even if the limited coverage of the scalp EEG with only Cz could have missed graphoelements generated distally from the central area, recognition of graphoelements on subdural electrodes, as previously performed in literature (Peter-Derex et al., 2012; Wennberg, 2010), overcame this limitation. It can be argued that the limited coverage of subdural electrodes could have missed sleep graphoelements that might have occurred in uncovered areas or that it was insufficient to map the distribution of the sleep graphoelements. However, limited coverage of the brain is a recurrent limitation in studies with intracranial electrodes because every individual patient will only have the intracranial coverage that is clinically indicated (Andrillon et al., 2011; Peter-Derex et al., 2012; Wennberg, 2010). The subdural coverage allowed the localization and determination of the maximum amplitude in each patient in our series. In addition, scalp topography studies suggest that human sleep spindles, K-complexes, and vertex

waves are maximal at midline regions (Cash et al., 2009; Ferrarelli et al., 2007; Wennberg, 2010); and hence, most sleep graphoelements were probably captured by our method.

Subdural electrodes had a different location in individual subjects. There was a good coverage of cortical areas, but in an individual patient, the subdural contacts were limited to a restricted cortical area. Sleep graphoelements may have extended beyond the coverage provided by the grid placement. The best answer to our research question "what is the localization of the different sleep grapho-elements on the cortical surface in children?" would come from a study with intracranial electrodes in both hemispheres for every patient. This ideal research study is not ethically feasible, and intracranial coverage is limited to the area of clinical interest for the specific patient. The intracranial coverage area in our study was extensive and should be evaluated in comparison with previous studies that evaluated even smaller areas. A previous study that was similar with simultaneous recording of scalp and intracranial EEG used an ample scalp coverage of 10-20 international electrode placement but only 4 to 6 subdural electrodes (Wennberg, 2010). We covered a much larger intracranial area at the expense of reduced scalp coverage. We did not find any sleep graphoelement represented in the Cz electrode that did not appear in the subdural electrodes. It is possible that there were independent sleep elements on the subdural electrodes that went unrecognized because they were not represented on the scalp Cz electrode. The design of our study prevented us from identifying them whether they did exist. However, sleep spindles, K-complexes, and vertex waves are thought to be maximal at midline regions (Cash et al., 2009; Ferrarelli et al., 2007), and their appearance in scalps and intracranial EEG is similar, so based on previous literature on scalp and intracranial EEG, the proportion of missed sleep graphoelements is expected to be minimal.

The physiological sleep graphoelements may have been altered by the presence of epileptiform activity and the use of antiepileptic medication (Beenhakker and Huguenard, 2009; Steriade and Amzica, 2003). Results from the analysis of EEG features of different epileptic syndromes appear to indicate that sleep spindles activate interictal epileptic discharges (Nobili et al., 1999, 2000). Conversely, epileptogenic cortex may also facilitate spindle generation (Clemens and Menes, 2000). The modification of sleep graphoelements by epileptiform activity is a limitation common to all the series with epileptic patients as study subjects (Andrillon et al., 2011). However, studies with healthy volunteers and intracranial recordings are not ethically acceptable. It is likely that areas of brain abnormality such as lesions or malformations distort, depress, and/or displace the sleep graphoelements. However, we did not find differences in the distribution of the sleep graphoelements between patients with different underlying pathologies and localization of the interictal discharges (data not shown).

Previous studies recognized spindles mainly based on automatic methods of sleep analysis that rely mainly on frequency and amplitude (Andrillon et al., 2011; Peter-Derex et al., 2012). Although these methods provide a robust and rapid method for detection of spindles, we believe that the detection by a board-certified clinical neurophysiologist that considers not only frequency and amplitude, but also morphology of the waves remains the gold standard in their detection.

CONCLUSIONS

In our series of pediatric patients, sleep spindles, K-complexes, and vertex waves were localized around the perirolandic areas, providing the first data on localization of sleep graphoelements with subdural electrodes in children.

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REFERENCES

Andrillon T, Nir Y, Staba RJ, et al. Sleep spindles in humans: insights from intracranial EEG and unit recordings. *J Neurosci* 2011;31:17821–17834.

Beenhakker MP, Huguenard JR. Neurons that fire together also conspire together: is normal sleep circuitry hijacked to generate epilepsy? *Neuron* 2009;62: 612–632.

Carreño M, Lüders H. General principles of presurgical evaluation. In: Lüders H, Comair Y, eds. *Epilepsy surgery*. Philadelphia: Lippincott Williams & Wilkins, 2001:185–199.

Cash SS, Halgren E, Dehghani N, et al. The human K-complex represents an isolated cortical down-state. *Science* 2009;324:1084–1087.

Clemens B, Menes A. Sleep spindle asymmetry in epileptic patients. *Clin Neurophysiol* 2000;111:2155–2159.

Cooper R, Winter AL, Crow HJ, Walter WG. Comparison of subcortical, cortical and scalp activity using chronically indwelling electrodes in man. *Electroencephalogr Clin Neurophysiol* 1965;18:217–228.

Ferrarelli F, Huber R, Peterson MJ, et al. Reduced sleep spindle activity in schizophrenia patients. *Am J Psychiatry* 2007;164:483–492.

Gumenyuk V, Roth T, Moran JE, et al. Cortical locations of maximal spindle activity: magnetoencephalography (MEG) study. *J Sleep Res* 2009;18: 245–253.

Iber C, Ancoli-Israel S, Chesson A, Quan SF, eds. *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications*. Westchester: American Academy of Sleep Medicine, 2007:59.

Ishii R, Dziewas R, Chau W, et al. Current source density distribution of sleep spindles in humans as found by synthetic aperture magnetometry. *Neurosci Lett* 2003;340:25–28.

Manshanden I, De Munck JC, Simon NR, Lopes da Silva FH. Source localization of MEG sleep spindles and the relation to sources of alpha band rhythms. *Clin Neurophysiol* 2002;113:1937–1947.
Massimini M, Huber R, Ferrarelli F, et al. The sleep slow oscillation as a traveling wave. *J Neurosci* 2004;24:6862–6870.
Nobili L, Ferrillo F, Baglietto MG, et al. Relationship of sleep interictal epileptiform discharges to sigma activity (12–16 Hz) in benign epilepsy of childhood with rolandic spikes. *Clin Neurophysiol* 1999;110:39–46.
Nobili L, Baglietto MG, Beelke M, et al. Spindles-Inducing mechanism modulates sleep activation of interictal epileptiform discharges in the Landau-Kleffner syndrome. *Epilepsia* 2000;41:201–206.
Numminen J, Makela JP, Hari R. Distributions and sources of magnetoencephalographic K-complexes. *Electroencephalogr Clin Neurophysiol* 1996;99:544–555.
Peter-Derex L, Comte JC, Mauguiere F, Salin PA. Density and frequency caudorostral gradients of sleep spindles recorded in the human cortex. *Sleep* 2012;35:69–79.
Rosenow F, Lüders H. Presurgical evaluation of epilepsy. *Brain* 2001;124:1683–1700.
Shih JJ, Weisend MP, Davis JT, Huang M. Magnetoencephalographic characterization of sleep spindles in humans. *J Clin Neurophysiol* 2000;17:224–231.
Sperling MR. Depth electrodes. In: Lüders HO, Comair YG, eds. *Epilepsy surgery*. Philadelphia: Lippincott Williams & Wilkins, 2001:597–611.
Steriade M, Amzica F. Sleep oscillations developing into seizures in corticothalamic systems. *Epilepsia* 2003;44(suppl 12):9–20.
Velasco M, Eugenia-Diaz-de Leon A, Marquez I, et al. Temporo-spatial correlations between scalp and centromedian thalamic EEG activities of stage II slow wave sleep in patients with generalized seizures of the cryptogenic Lennox-Gastaut syndrome. *Clin Neurophysiol* 2002;113:25–32.
Wennberg R. Intracranial cortical localization of the human K-complex. *Clin Neurophysiol* 2010;121:1176–1186.
Werth E, Achermann P, Dijk DJ, Borbely AA. Spindle frequency activity in the sleep EEG: individual differences and topographic distribution. *Electroencephalogr Clin Neurophysiol* 1997;103:535–542.
Zeitlhofer J, Gruber G, Anderer P, et al. Topographic distribution of sleep spindles in young healthy subjects. *J Sleep Res* 1997;6:149–155.