ELSEVIER

Brain & Development 31 (2009) 163–168

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

# Sleep spindle alterations in patients with malformations of cortical development

Megan F. Selvitelli [a], Kaarkuzhali B. Krishnamurthy [a], Andrew G. Herzog [b], Donald L. Schomer [a], Bernard S. Chang [a,*]

[a] *Comprehensive Epilepsy Center, Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA*

[b] *Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA*

Received 3 March 2008; received in revised form 13 May 2008; accepted 17 June 2008

**Abstract**

Malformations of cortical development are disorders of altered brain anatomy and architecture that arise from abnormalities in the usual processes of cerebral cortical development. Although they often lead to epilepsy, cognitive delay, and motor impairment, little is known about their effect on sleep. Since malformations may anatomically or functionally disrupt the cerebral circuits that mediate sleep spindles, we hypothesized that these disorders would be associated with abnormal spindle characteristics. We analyzed the density, maximum frequency, laterality and distribution of sleep spindles seen in routine and long-term electroencephalographic recordings performed in ten brain malformation subjects and ten matched controls. There were no significant differences in spindle density or maximum frequency between the two groups, but malformation subjects had a significantly lower proportion of bilateral spindles and a significantly higher proportion of anterior and diffuse spindles compared to controls. In addition, unilateral malformations appeared to be associated with a skewing of unilateral spindles toward the contralateral side. Our findings suggest that brain malformations disrupt the thalamocortical circuits responsible for sleep spindle generation, and support the need for further studies on the relationships between cortical maldevelopment and sleep.


*Keywords:* Sleep spindles; Malformations of cortical development; Epilepsy

## 1. Introduction

Malformations of cortical development (MCDs) are congenital brain disorders arising during embryonic and fetal development that are characterized by abnormalities in the volume, location, or architecture of cerebral gray and white matter. Clinically, MCDs commonly cause epilepsy, cognitive delay, and motor impairment. The effect of these developmental malformations on the clinically and neurophysiologically important brain function of sleep, however, has not been well-studied.

MCDs are most readily recognized by the visible anatomical changes in gray matter [1]. However, there is now extensive evidence of functionally important disruptions in white matter connectivity associated with these disorders as well. For example, some patients with subcortical gray matter heterotopia (including subcortical band heterotopia and periventricular nodular heterotopia) have demonstrated deficits in reading fluency or processing speed that may be the result of abnormalities in cortico-cortical white matter pathways [2–4]. In addition, regions of gray matter heterotopia have been shown to be functionally co-active with the overlying

* Corresponding author. Tel.: +1 617 667 2889; fax: +1 617 667 7919.

*E-mail address:* bchang@bidmc.harvard.edu (B.S. Chang).

0387-7604/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.braindev.2008.06.006

cortex during the performance of simple tasks, suggesting the presence of aberrant cortical–subcortical white matter circuits in these disorders [5,6].

Sleep spindles are neurophysiologic signatures of stage II sleep that are easily identifiable on scalp electroencephalography (EEG) recording and depend on intact white matter connections for their normal expression. They appear to be generated by reciprocal interactions between subcortical thalamic structures and the cerebral cortex [7], and acquired lesions that may disrupt thalamocortical pathways lead to alterations in spindle characteristics [8–10].

We sought, therefore, to analyze the effect of cortical maldevelopment on the generation of sleep spindles. Here, we demonstrate that patients with brain malformations indeed have significant and specific alterations in spindle expression compared to matched controls.

## 2. Methods

### 2.1. Subjects

Patients with neuroimaging-confirmed diagnoses of MCD who had a digital routine or long-term EEG monitoring study at our institution within the past seven years demonstrating at least a single sleep spindle were eligible for inclusion in this study. Ten such subjects were identified from clinical records, clinician referrals, and a research database of brain malformation patients at our institution.

For each malformation subject, an age- and sex-matched control subject was identified by selecting a patient without epilepsy who had had an EEG study of the same type (routine or long-term monitoring), demonstrating at least a single sleep spindle, within one year's time of the malformation subject's study. This was accomplished by progressively scanning consecutive procedure log numbers in our institution's EEG database and identifying patients who were within five years of age and of the same sex as the malformation subject. The control subjects had EEGs performed for evaluation of nonepileptic events, syncope, panic attacks, or, in two subjects, a remote history of seizures (more than ten years prior). Control subjects' neuroimaging with magnetic resonance imaging (MRI) demonstrated either entirely normal brain anatomy (in five) or incidental abnormalities (cerebellar encephalomalacia (one), nonspecific T2 white matter hyperintensities (three), or quadrigeminal cistern arachnoid cyst (one)).

Detailed clinical information was recorded on all 20 subjects, including MCD type, location and laterality, if appropriate, and the use of anti-epileptic drugs (AEDs), including specifically benzodiazepines and barbiturates (because of their effect on fast EEG activity). This study was performed according to a protocol approved by the institutional review board of Beth Israel Deaconess Medical Center, Boston; due to its retrospective nature, the need for written informed consent was waived.

### 2.2. EEG methods

All EEG studies were recorded using silver-chloride, gold-plated electrodes placed according to the 10–20 International system, with recorded impedances of less than 5 kΩ at all electrodes. All routine studies utilized both bipolar and average referential montages, while long-term monitoring studies utilized either a bipolar longitudinal montage or a bipolar longitudinal/transverse montage with subtemporal (T1/T2) electrodes. Initial analog signal conditioning included a 0.0–0.1 Hz high pass filter, a 30–70 Hz low pass filter and a 60 Hz notch filter. The digital sampling rate was 200–500 per second.

### 2.3. Sleep spindle analysis

For each subject, a 30-s epoch beginning with the first noted sleep spindle was analyzed by visual inspection. Sleep spindles were defined as waveforms distinct from the background with a frequency between 12 and 16 Hz [11], duration between 0.5 and 2 s and occurring in the context of EEG activity consistent with stage II sleep (slowing of posterior dominant rhythm and presence of vertex waves). Spindle density and maximum spindle frequency were measured for each subject's 30-s epoch. Sleep spindle laterality (bilateral, left, or right) and distribution (anterior, central, posterior or diffuse) for each noted spindle were recorded; distribution and laterality were determined by visual analysis based on region of greatest sleep spindle amplitude. Two electroencephalographers, blinded to subject status and diagnosis, independently scored each record and resolved differences by consensus.

### 2.4. Statistical analysis

Differences in mean spindle density between malformation subjects and control subjects were analyzed for significance using a two-tailed Student *t*-test, while differences in mean maximum spindle frequency were analyzed using the Mann–Whitney U test as these two datasets had unequal variances. Differences in spindle laterality (unilateral or bilateral) and distribution (anterior, central, posterior, or diffuse) between malformation subjects and control subjects were analyzed using chi-squared tests. A threshold of $\alpha < 0.05$ was used in all cases for significance.

## 3. Results

The ten malformation subjects and ten control subjects were well-matched for age, sex and study type