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Scalp spindles are associated with widespread intracranial activity with unexpectedly low synchrony

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ABSTRACT

In humans, the knowledge of intracranial correlates of spindles is mainly gathered from noninvasive neurophysiologic and functional imaging studies which provide an indirect estimate of neuronal intracranial activity. This potential limitation can be overcome by intracranial electroencephalography used in presurgical epilepsy evaluation. We investigated the intracranial correlates of scalp spindles using combined scalp and intracerebral depth electrodes covering the frontal, parietal and temporal neocortex, and the scalp and intracranial correlates of hippocampal and insula spindles in 35 pre-surgical epilepsy patients. Spindles in the scalp were accompanied by widespread cortical increases in sigma band energy (10–16 Hz): the highest percentages were observed in the frontoparietal lateral and mesial cortex, whereas in temporal lateral and mesial structures only a low or no simultaneous increase was present. This intracranial involvement during scalp spindles showed no consistent pattern, and exhibited unexpectedly low synchrony across brain regions. Hippocampal spindles were shorter and spatially restricted with a low synchrony even within the temporal lobe. Similar results were found for the insula. We suggest that the generation of spindles is under a high local cortical influence contributing to the concept of sleep as a local phenomenon and challenging the notion of spindles as widespread synchronous oscillations.

Introduction

Spindles are distinct electroencephalographic (EEG) events which are the hallmark of non-rapid eye movement sleep stage 2. They are characterized by waxing and waning oscillations with a frequency between 10 and 16 Hz and duration between 0.5 and 2 s (Loomis et al., 1935; Gibbs and Gibbs, 1950; Jankel and Niedermeyer, 1985). Recent research points to the importance of spindles for memory consolidation, cortical development, and sleep stability (Khazipov et al., 2004; Schabus et al., 2004; Dang-Vu et al., 2010a; Fogel and Smith, 2011).

The "classical" thalamic model of spindle generation suggests that spindles are generated in the reticular thalamic nucleus, triggered by the depolarizing phase of the cortical slow oscillation via corticothalamic pathways. After being transferred to the dorsal thalamus, they project back to the cortex following thalamo-cortical circuits (Fuentealba and Steriade, 2005; Steriade, 2006). In humans, knowledge on spindles and their source localization is gathered from EEG (Anderer et al., 2001; Kurth et al., 2010; del Felice et al., 2013), magnetoencephalography (MEG) (Nakasato et al., 1990; Manshanden et al., 2002; Ishii et al., 2003; Urakami, 2008; Gumenyuk et al., 2009; Dehghani et al., 2011) and functional imaging studies with positron emission tomography and functional magnetic resonance imaging (Hofle et al., 1997; Laufs et al., 2007; Schabus et al., 2007; Tyvaert et al., 2008; Andrade et al., 2011; Caporro et al., 2012). These studies demonstrate that there are at least two different cortical spindle generators with a maximal source activity in the frontal and parietal neocortex (Anderer et al., 2001; Gumenyuk et al., 2009). In addition, functional imaging studies revealed that at the time of scalp spindles, a signal change is present in the frontal and parietal cortex, and in the thalamus, limbic regions, precuneus and cingulate gyrus, which would be compatible with the suggested gating sensory function of spindles and their involvement in memory and learning (Dang-Vu et al., 2010b). The results of source localization with EEG and MEG are highly dependent on the algorithms used for solving the inverse problem, whereas functional imaging studies provide an indirect estimate of neuronal activity with a poor time resolution as they primarily target hemodynamic changes.

These limitations can be overcome by intracranial EEG used in the setting of the presurgical investigation of therapy-refractory epilepsy. Only two studies looked at characteristics of spindles in a small number of subjects and over different brain regions using intracerebral depth electrodes (Andrillon et al., 2011; Peter-Derex et al., 2012). Their major findings were that spindles occur across multiple brain regions, that spindle frequencies change along a caudo-rostral axis with faster

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spindles found in the centroparietal areas and slower spindles in the frontal regions and that 55% of spindles are more local than generalized when looking at overlapping activity in the spindle frequency band in different intracranial EEG channels (Andrillon et al., 2011; Peter-Derex et al., 2012). Because scalp EEG was not simultaneously analyzed during these intracerebral EEG studies, they do not inform us about what happens in different brain regions when a spindle is recorded on the scalp. This is of great interest as it provides us with direct information of intracerebral correlates of scalp spindles, and allows us to investigate synchronization between scalp spindle events and intracerebral spindles. Recent studies using simultaneous EEG/MEG revealed that MEG spindles have low spatial coherence and exhibit low correlation with EEG spindles (Dehghani et al., 2011). The authors speculated that multiple asynchronous sources as revealed by MEG may overlap sufficiently to appear synchronously in the EEG (Dehghani et al., 2011). This is still an object of controversy and can be addressed with combined scalp and intracranial EEG. We therefore investigated the intracranial correlates of scalp spindles using combined scalp–intracranial EEG. Special attention was paid to the analysis of synchrony of intracranial spindles at the time of scalp spindles. In addition, we were interested to examine the scalp correlates of spindles in the hippocampus and insula as examples of brain structures remote from the scalp.

Material and methods

Patient selection

Forty-nine consecutive patients with pharmacoresistant temporal or extra-temporal lobe epilepsy underwent continuous intracranial EEG recordings combined with scalp EEG at the Montreal Neurological Institute and Hospital between January 2010 and February 2014 for seizure foci identification and potential surgical treatment.

We included patients for whom we had at least one continuous whole night recording which was at least 72 h post-electrode implantation in order to avoid a potential influence of anesthesia on sleep as well as the acute effect of electrode implantation. Also, to be as close as possible to the study of sleep in healthy subjects, we selected brain regions and periods of recording that were as little as possible affected by the epileptic activity always recorded in these patients. Hence, a second inclusion criterion was that patients' recordings had at least one intracranial EEG channel with no or very rare epileptic discharges and no other abnormalities, and that these channels were not within lesional tissue as assessed with MRI (see "Selection of suitable intracranial EEG channels" section). Thirdly, we only included subjects in whom epileptic activity did not interfere with spindle scoring and who had at least 5 unambiguous spindles in the scalp EEG during the first sleep cycle. Choosing a different cut-off of for instance 10 spindles would have resulted in the same number of eligible EEG recordings. In fact, only 3 patients had fewer than 50 spindles in the first sleep cycle with a minimum number of 31 spindles (see Supplementary Table 1). The spindle events were marked during the first sleep cycle in order to follow the same methodology in all subjects, as density of slow wave activity changes across the different sleep cycles, and there is evidence (Andrillon et al., 2011) that spindle density and frequency are influenced by this change in slow wave activity. Exclusion criteria were the presence of a secondarily generalized seizure during the 12 h, or the presence of a partial seizure or asymptomatic EEG seizure during the 6 h prior to the evaluated night of the sleep.

Thirty-five of the 49 patients met these selection criteria. Demographic and clinical data are provided in Supplementary Table 1. Reasons for exclusion were: recordings having no channels with no or rare epileptic discharges ($n = 4$), no channels located outside lesional tissue ($n = 2$), lack of at least five unambiguous spindle events in the first sleep cycle ($n = 2$), presence of partial or asymptomatic EEG seizures within 6 h or generalized seizures within 12 h of sleep recordings ($n = 4$), absence of a sleep recording 72 h post-implantation ($n = 1$), or the presence of epileptic discharges in the scalp EEG channels interfering with the scoring of sleep spindles ($n = 1$). In patients with several full-night recordings, the first night after 72 h post-implantation was evaluated.

This study was approved by the Research Ethics Board of the Montreal Neurological Institute and Hospital. All patients signed a Research Ethics Board approved written informed consent.

Intracranial and scalp EEG recording

An average of seven multicontact depth electrodes (range, 4–12) was implanted stereotactically through an orthogonal or oblique approach using an image-guided system (ROSA robotic neuronavigation system or Medtronic Stealth neuronavigation system). In 21 patients, implantations consisted of electrodes manufactured on site (9 contacts, 0.5 to 1 mm in length and 5 mm apart); and in 14 patients, commercially available electrodes (DIXI Medical, France: 10 to 18 contacts, 2 mm in length and 1.5 mm apart) were used. The deepest contacts were targeting the mesial aspect of the lobe explored, and the most superficial ones were targeting the neocortex. The depth electrode montages were bipolar, from one contact to the neighboring contact. Epidural electrodes were additionally placed in eight patients. Electrode locations were determined by either post-implantation CT co-registered with a pre-implantation MRI using SPM 8 software ($n = 15$), post-implantation MRI ($n = 14$), or the information from the reconstructed planned position of the electrodes from the Neuronavigation System ($n = 6$). Subdermal thin wire electrodes (Ives, 2005; Young et al., 2006) were placed at the time of implantation at positions F3, F4, Fz, C3, C4, Cz, P3, P4, Pz (33 patients) or Fz, C3, C4, Cz, Pz (2 patients) allowing for sleep staging and spindle marking. Intracerebral electrode positions were tailored for each patient and depended on the clinical hypothesis on the location of the seizure generator and propagation of ictal discharge. Fig. 1 provides an overview of the number of channels investigated in the different cortical regions. Information on the localization of the electrode contacts of each patient is provided in Supplementary Fig. 1. The EEG signal was low-pass filtered at 500 Hz, and sampled at 2000 Hz. EEGs were recorded using the Harmonie EEG system (Stellate, Montreal, Canada).

Selection of suitable intracranial EEG channels

Only bipolar intracranial channels showing no or very rare epileptic discharges as well as no other background abnormalities and artifacts were evaluated. Suitable channels were selected based on the first sleep cycle independently by two electrophysiologists. For channels for which the selection differed between the two raters, a consensus was found in a common scoring session. Ambiguous channels were discarded as we aimed to investigate physiological sleep patterns. Moreover, depth electrodes placed in lesions as revealed by MRI were excluded irrespective of whether they showed interictal epileptic discharges.

Assessment of spindles in scalp EEG recordings

Sleep was scored manually in 30 s epochs (Berry et al., 2012). The identification of spindles was done visually by a sleep expert, as it presents the generally accepted approach to reliably mark scalp spindles, and the number of needed events is still reasonable for a visual approach (Warby et al., 2014). Spindles were identified during the first NREM sleep cycle by using a time scale of 30 mm/s in all scalp EEG channels (F3–C3, C3–P3, Fz–Cz, Cz–Pz, F4–C4, C4–P4). We did not use a traditional mastoid referential montage for the scoring of sleep, as this was not feasible for all patients due to the localization of the implanted depth electrodes and the risk of infection. Conventional sleep recording with the same electrodes using a bipolar and mastoid reference montage revealed in line with the existing literature (Werth et al., 1997) that most spindles seen in the bipolar montage can be