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Spatiotemporal characteristics of sleep spindles depend on cortical location

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ABSTRACT

Since their discovery almost one century ago, sleep spindles, 0.5–2 s long bursts of oscillatory activity at 9–16 Hz during NREM sleep, have been thought to be global and relatively uniform throughout the cortex. Recent work, however, has brought this concept into question but it remains unclear to what degree spindles are global or local and if their properties are uniform or location-dependent. We addressed this question by recording sleep in eight patients undergoing evaluation for epilepsy with intracranial electrocorticography, which combines high spatial resolution with extensive cortical coverage.

We find that spindle characteristics are not uniform but are strongly influenced by the underlying cortical regions, particularly for spindle density and fundamental frequency. We observe both highly isolated and spatially distributed spindles, but in highly skewed proportions: while most spindles are restricted to one or very few recording channels at any given time, there are spindles that occur over widespread areas, often involving lateral prefrontal cortices and superior temporal gyri. Their co-occurrence is affected by a subtle but significant propagation of spindles from the superior prefrontal regions and the temporal cortices towards the orbitofrontal cortex.

This work provides a brain-wide characterization of sleep spindles as mostly local graphoelements with heterogeneous characteristics that depend on the underlying cortical area. We propose that the combination of local characteristics and global organization reflects the dual properties of the thalamo-cortical generators and provides a flexible framework to support the many functions ascribed to sleep in general and spindles specifically.

Introduction

The cortical extent and spatiotemporal dynamics of spontaneous oscillatory rhythms are fundamental principles of brain organization and the object of intense investigation. This is particularly true for oscillations occurring during sleep. One such canonical oscillation is the spindle, a 0.5–2 s long burst of oscillatory activity between 9 and 16 Hz (Davis et al., 1937; De Gennaro and Ferrara, 2003). These graphoelements arise from the interaction of distinct populations of thalamic and cortical neurons (Steriade et al., 1993a) and are thought to represent a common mechanism for many functions attributed to sleep, such as memory consolidation (Diekelmann and Born, 2010; Fogel and Smith, 2011; Lüthi, 2013) and synaptic plasticity (Rosanova and Ulrich, 2005). Putative sources of spindle activity have been identified in lateral frontal and superior parietal regions (Anderer et al., 2001; Gumenyuk et al., 2009; Manshanden et al., 2002; Siclari et al., 2014; Urakami, 2008), but their presence in other regions, especially in the temporal lobe, has been subject of long-running debates (Montplaisir et al., 1981; Peter-Derex et al., 2012; Sarasso et al., 2014).

Pioneering work indicated that spontaneous spindles during natural sleep and barbiturate anesthesia are synchronized over large cortical areas (Achermann and Borbély, 1998; Contreras et al., 1997), This observation has been supported by studies combining electroencephalogram (EEG) and fMRI showing regional but widespread activation associated with spindles (Andrade et al., 2011; Schabus et al., 2007). More recent studies based on magnetoencephalography (MEG) and intracranial EEG (iEEG) in patients with epilepsy, however, have advanced the notion that spindles are a fundamentally isolated event (Andrillon et al., 2011; Dehghani et al., 2010b; Frauscher et al.,

Abbreviations: ANOVA, analysis of variance; CT, cortical tomography; ECoG, electrocorticography; EEG, electroencephalogram; FDR, false discovery rate; iEEG, intracranial EEG; LMEM, linear mixed-effects regression model; MEG, magnetoencephalography; MRI, magnetic resonance imaging; NREM, non-rapid eye movement; ReML, Restricted Maximum Likelihood

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2015; Nir et al., 2011; Sarasso et al., 2014). However, the sparse sampling and the high spatial selectivity of depth electrodes in iEEG might bias towards spatially limited phenomena, and the true spatial extent of spindles remains unknown.

In fact, the degree to which spindles manifest themselves on the scalp as local or widespread events might depend on the underlying cortical regions, which vary in terms of corticocortical and thalamocortical connectivity. This issue is linked to the observation that distant brain regions are associated with varying spindle characteristics, such as density, amplitude, and duration (Martin et al., 2013). This is particularly evident for the distinction between fast and slow spindles, with a lower peak in the spindle frequency band for more anterior electrodes (De Gennaro and Ferrara, 2003; Gibbs and Gibbs, 1950; Jobert et al., 1992).

The dichotomy between global and local events becomes less tenable if we consider the proposal that spindles represent a mixture of different types of phenomena – some which might be exquisitely focal while others are more broadly spread, depending on the degree to which thalamic pathways, core or matrix, contribute to their generation (Bonjean et al., 2012; Dehghani et al., 2010a,b). Reconciling these viewpoints may be aided by the examination of the spatial extent and the synchronization properties of sleep spindles by recording techniques that offer both fine-grained spatial resolution and broad cortical coverage, such as electrocorticography (ECoG), in which grids of electrodes are placed directly on the cortical surface.

In the current study, we investigated fundamental questions regarding the spatial properties of the sleep spindle from continuous ECoG recordings in patients with epilepsy who were candidates for resective surgery. We detected spindles in individual channels during non-rapid eye movement (NREM) sleep in eight participants and mapped their characteristics onto the underlying cortical structures. We investigated three questions: Can the sleep spindle be considered a uniform phenomenon at the cortical level based on the spatial variability of its fundamental characteristics, such as the peak frequency in the spindle frequency band, its amplitude, and its duration? Should the spindle be thought of as a local or a global phenomenon based on their spatial extent and synchronization profile? Is there a preferential direction in the propagation of these events, akin to the bias for anterior-to-posterior propagation of slow waves and K-complexes (Mak-McCully et al., 2015; Massimini et al., 2004)?

Materials and methods

ECoG recordings

Recordings were obtained from eight patients with drug-resistant epilepsy implanted semi-chronically with a grid of electrodes on the pial surface in an effort to localize the seizure origin (see patients' characteristics in Table 1). The grids consisted of platinum-iridium electrodes of 3 mm diameter spaced 10 mm apart (Ad-Tech Medical Instrument Corp., Racine, WI). One strip of electrodes positioned in the epidural space facing the skull was used as reference during the recordings. Due to the craniotomy and the risk of infection, no external electrodes was applied on the scalp. Recordings were performed with clinical EEG monitoring equipment (XLTEK, Natus Medical Inc., Pleasanton, CA) and sampled at 500 Hz, 512 Hz, or 1024 Hz. The research was approved by the local institutional review board and electrode placement was determined solely by clinical criteria.

Nights that did not have any seizures in the preceding or following 12 h were scored visually by an expert rater from the ECoG electrodes following as closely as possible the standard sleep stage classification (Iber et al., 2007), because of the absence of external electrodes. In particular, for stage N2 and N3, scoring was based on the preponderance of spindles, K-complexes and occasional slow waves in N2, and more continuous slow waves in N3. We included at least 60 min of stage N2 and N3 in the first part of the night after sleep onset (Table 1 for details regarding time of selected recordings and medication for each patient). For each patient, we obtained on average 76.43 min (range 60–112) of sleep, when spindles are most visible.

Based on the clinical reports and on visual inspection, channels exhibiting epileptic activity were excluded. On average, the percentage of excluded channels was 8.90% (range 2.50–23.75%), mostly over the postcentral areas (12 channels), the middle temporal region (10 channels), and the supramarginal gyrus (9 channels). The number of electrodes included in the analysis per patient was on average 78.75 (range 57–93). The signal of the these channels was re-referenced to the common average (Canolty et al., 2006; Hermes et al., 2015). Recordings were then filtered at 0.5 Hz (high-pass filter) and at 50 Hz (low-pass filter) and subsequently resampled to 256 Hz.

Analyses were carried out in Python 3.4 with numpy (1.9.2), scipy (0.16), and vispy (0.5). The code for the analysis can be requested from the corresponding author.

Electrode locations

Electrode positions were picked manually from the post-surgery cortical tomography (CT) scans and realigned to the pre-surgery magnetic resonance imaging (MRI) using SPM (as described in detail in Dykstra et al. (2012)). Cortical surfaces were computed with FreeSurfer (Dale et al., 1999; Fischl et al., 1999). To account for misalignment between the MRI and CT and distortion of the brain structure due to the craniotomy, the locations of the grid electrodes were projected onto the cortical surface (Fig. 1).

The coverage across all subjects shown in the bottom panel of Fig. 1 was generated by projecting a sphere with a 10 mm Gaussian window for each electrode onto the subject-specific anatomical space and realigning this subject-specific map onto the average brain surface using surface-based normalization (Fischl et al., 1999), after flipping a

Table 1
Patients' characteristics.

ID	Sex	Age	Hemi	Onset	Medications	Diagnosis	Resection	Start time	Duration
S1	M	43	R	~30	CLZ, LCS, LTG, ZNS	M.T.S.	O.F./AntTemp	23:44:38	67.5
S2	F	46	R	15	CLZ	C.D.	AntTemp	01:54:30	60.5
S3	M	29	L	18	LTG, LEV	C.D./Het.	S.T./AntTemp	00:35:22	98.5
S4	M	25	L	16	LTG, LEV, PNT, TPR	Unclear	MedTemp	00:06:14	67.0
S5	F	21	L	Unknown	LCS, LTG	Post-infarct	Temporal	00:53:11	61.5
S6	M	45	R	15	PNT	Unknown	AntTemp	01:40:42	60.0
S7	M	37	R	18	CRB, CLZ, LEV	Unknown	Prefrontal	21:16:19	112.0
S8	M	47	R	38	None	Unknown	None	23:02:21	81.5

Description of the patients' profiles. Patient population was heterogeneous in terms of age, epilepsy form, age of onset, cortical area, suggesting that no single particular aspect biased the findings. Start time of the sleep period is given in the format hour:minute:second and the duration is in minutes. Abbreviations for the medications taken during the recordings are CRB: Carbamazepine, CLZ: Clonazepam, LCS: Lacosamide, LEV: Levetiracetam, LTG: Lamotrigine, PNT: Phenytoin, TPR: Topiramate, ZNS: Zonisamide. Abbreviations for the diagnosis are C.D.: cortical dysplasia, Het.: heterotopia, M.T.S.: mesial temporal sclerosis. Abbreviations for the resection are AntTemp: anterior temporal, MedTemp: medial temporal, O.F.: orbitofrontal, S.T.: subpial transection.