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Sleep affects cortical source modularity in temporal lobe epilepsy: A high-density EEG study ☆

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HIGHLIGHTS

- Sleep induces a spread of temporal interictal epileptiform discharges (IEDs) to a "sleep plus" zone, potentially signaling the epileptogenic zone and aid in the presurgical workup.
- IEDs are naturally occurring, perturbing stimuli that interfere with brain oscillations.
- Mesial and neocortical temporal lobe epilepsy (TLE) react to IEDs with different EEG patterns in sleep, suggesting a state-dependent effect on cortical modularity.

ABSTRACT

Objective: Interictal epileptiform discharges (IEDs) constitute a perturbation of ongoing cerebral rhythms, usually more frequent during sleep. The aim of the study was to determine whether sleep influences the spread of IEDs over the scalp and whether their distribution depends on vigilance-related modifications in cortical interactions.
Methods: Wake and sleep 256-channel electroencephalography (EEG) data were recorded in 12 subjects with right temporal lobe epilepsy (TLE) differentiated by whether they had mesial or neocortical TLE. Spikes were selected during wake and sleep. The averaged waking signal was subtracted from the sleep signal and projected on a bidimensional scalp map; sleep and wake spike distributions were compared by using a *t*-test. The superimposed signal of sleep and wake traces was obtained; the rising phase of the spike, the peak, and the deflections following the spike were identified, and their cortical generator was calculated using low-resolution brain electromagnetic tomography (LORETA) for each group.
Results: A mean of 21 IEDs in wake and 39 in sleep per subject were selected. As compared to wake, a larger IED scalp projection was detected during sleep in both mesial and neocortical TLE ($p < 0.05$). A series of EEG deflections followed the spike, the cortical sources of which displayed alternating activations of different cortical areas in wake, substituted by isolated, stationary activations in sleep in mesial TLE and a silencing in neocortical TLE.
Conclusion: During sleep, the IED scalp region increases, while cortical interaction decreases.
Significance: The interaction of cortical modules in sleep and wake in TLE may influence the appearance of IEDs on scalp EEG; in addition, IEDs could be proxies for cerebral oscillation perturbation.

1. Introduction

Sleep and sleep deprivation are known triggers of epileptic seizures, increasing the yield of interictal epileptiform discharges (IEDs) and inducing seizures (Bennett, 1963; Pratt et al., 1968; Jovanovic, 1991; King et al., 1998). The underlying neurophysiological mechanism is thought to be an increase in cortical

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excitability, as documented by transcranial magnetic stimulation (TMS) (Badawy et al., 2006; Civardi et al., 2001; Del Felice et al., 2011; Grosse et al., 2002; Manganotti et al., 2006). Sleep/sleep deprivation-induced modulation of the corticospinal tract has been demonstrated by measuring changes in motor evoked potentials (MEPs) in healthy individuals (Manganotti et al., 2004, 2006; Rotenberg, 2010). A modulatory sleep effect has also been observed by measuring TMS evoked potentials (TEPs) (Del Felice et al., 2011). Because they bypass the influence of the descending corticospinal tracts, TEPs seem to be more sensitive than MEPs in detecting modifications in cortical reactivity induced by sleep or sleep deprivation. In addition, cortical reactivity appears to be even more affected in a pathologically excitable cortex, namely, the epileptic brain (Badaway al., 2006; Manganotti et al., 2006; Del Felice et al., 2011).

In addition to measuring MEPs and TEPs, another approach to study brain reactivity in sleep and wake is by analyzing brain oscillatory activity in response to an external perturbation, that is, TMS. Evoked oscillations during non-rapid eye movement (NREM) sleep have a higher amplitude and reduced resonance in time and space as compared to wake when TMS is delivered to the anterior cortical areas of healthy sleeping individuals (Massimini et al., 2009). These phenomena have been interpreted as a marker of cortical integration and a possible neurophysiological signature of reduced consciousness in sleep. The theoretical reasoning underpinning this view is that consciousness relies on a high level of information and integration, otherwise defined as brain complexity (Tononi, 2008). Information translates into a high number of available states of the thalamocortical system that interacts in a complex manner with the environment, generating a state corresponding to the external situation. Integration, on the other hand, means that the brain works as if constituted by a collection of interdependent modules that interact to generate information. The neurophysiological signature of wake results in a low-amplitude highly desynchronized response. During sleep, the brain reacts with more synchronized, less diffused oscillations generated by larger neuronal populations discharging as a whole. If this model is correct, it would support the view that each cortical module maintains its own vigilance-specific oscillatory rhythm, with an extension and/or clustering of areas over which this rhythm appears during sleep, that is, for the epileptogenic zone, an extension of the scalp area on which spikes are detected.

However, unanswered questions remain regarding the appearance of IEDs during sleep: is the topographical distribution of IEDs affected by sleep and, if so, by which mechanism? It is also of interest to determine whether IEDs are endogenous stimuli that interfere with brain oscillations and its integration processes. This would provide a model to test the hypothesis for cortical modularity in epilepsy.

The aim of this study was to determine whether the localization of IEDs over the scalp differs between wake and sleep, and if such a difference exists, to determine whether a correlation with the different integration processes during sleep and wake could shape this phenomenon. The assumption that IEDs are naturally occurring endogenous stimuli interfering with brain functioning could provide a paraphysiological proxy for TMS pulses and allow the study of brain modularity in wake and sleep in people with epilepsy.

2. Materials and methods

2.1. Subjects

The study sample included people with right temporal lobe epilepsy (TLE) selected from a larger cohort of adults undergoing presurgical evaluation for epilepsy. All subjects underwent video-EEG, 256-channel EEG, and 3T magnetic resonance imaging (MRI), including the pulsed arterial spin labeling (pASL) sequence. On the day of 256-channel EEG recording, antiepileptic drugs were withheld and the subjects were partially sleep deprived (awakened at 3 a.m. to facilitate the recording of stage N2 sleep). Subjects were asked to refrain from consumption of stimulants until the recordings were completed. The local Ethics Committee approved the study protocol.

2.2. EEG recording

EEG recording was performed using 256 channels (Electrical Geodesic, Inc., Eugene, OR, USA). The net was adjusted so that Fpz, Cz, Oz, and the preauricular points were correctly placed according to the international 10/20 system. By virtue of the net's geodesic tension structure, all electrodes were evenly distributed on the scalp. The data were recorded against a vertex electrode reference (Cz) at a sampling rate of 250 Hz and band-pass-filtered at 0.5–70 Hz. Electrooculogram (EOG) channels were mounted on the left and right eye canthus, with a sampling rate of 250 Hz, band-pass-filtered at 0–100 Hz, with sensitivity below 5 mV. Sleep 256-channel EEG was routinely performed as a nap EEG recording in a sleep-deprived condition in a shielded, soundproof laboratory. The lights were switched off at 1.30 p.m.

2.3. EEG data analysis

Subjects were grouped into a mesial temporal or a lateral temporal (neocortical) subgroup according to clinical, neurophysiological, and neuroimaging data. For each subject, the peak of the spike was used as a trigger for averaging in epochs of ±500 ms. Spikes were manually selected by two experienced neurophysiologists independently. Possible discordances were to be collectively discussed, although none arose. IEDs were marked during wake (W-spikes) and during stage N2 (S-spikes) after visual scoring of the EEG traces according to the American Academy of Sleep Medicine (AASM) guidelines (Silber et al., 2007), avoiding epileptic discharges intermixed with physiological sleep figures. To facilitate IED recognition, the first EEG reading was performed on the simplified standard montage (double-banana or 10–20 monopolar). Once marked, graphoelement morphology was double-checked by visualizing the traces on the 256-channel grid and on the bidimensional scalp projection. Spike selection criteria are based on a report of the commission on terminology (Chatrian, 1974), with sharp waves being defined as transients, clearly distinguishable from background activity, with a pointed peak at conventional paper speeds and a duration of 70–200 ms, whereas spikes are defined the same as sharp waves but having a duration of 20–<70 ms. Only spikes with a minimum inter-peak interval of 20 s were selected in order to avoid possible diffusion phenomena that could have affected subsequent analysis. At visual inspection, whole segments contaminated by ocular, muscular, or movement artifacts were rejected. Single electrodes containing artifacts were manually selected and interpolated using a three-dimensional spline interpolation algorithm (Perrin et al., 1989) to keep the number of electrodes the same for all epochs. A visual rendering of the averaged superimposed 256-channel traces was provided for each subject and for each condition (mesial and lateral TLE, sleep, and wake).

Finally, a grand average for W- and S-spikes was calculated for both mesial and lateral spikes and for each condition, and the distribution of abnormalities over the scalp depicted via a bidimensional, 256-channel topographical representation. Digital signal subtraction was also applied to obtain the difference between