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

Alessandra Del Felice [a,*], Silvia Francesca Storti [b], Paolo Manganotti [c,d]

[a] Department of Neuroscience – SNPSRR, University of Padua, Padua, Italy
[b] Department of Computer Science, University of Verona, Strada le Grazie 15, Verona, Italy
[c] Department of Neurological and Movement Sciences, Section of Neurology, University of Verona, Piazzale L.A. Scuro 10, Verona, Italy
[d] Department of Neurophysiology, Foundation IRCCS San Camillo Hospital, Via Alberoni 70, Venezia-Lido, Italy

ARTICLE INFO

Accepted 5 December 2014

Keywords:
Brain oscillatory rhythms
Interictal epileptiform discharge (IED)
Epileptogenic zone
Electrical source imaging (ESI)
Perturbational approach

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

☆ The study was conducted at the High-density EEG Laboratory, Department of Neurological and Movement Sciences, Section of Neurology, University of Verona, Italy.

* Corresponding author at: Department of Neuroscience – SNPSRR, University of Padua, Via Giustiniani, 2, 35128 Padova, Italy. Tel.: +39 049 8212598/8213358.
E-mail address: alessandra.delfelice@unipd.it (A. Del Felice).

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

the averaged sleep and wake signals, as well as a *t*-map to compare sleep and wake spikes in the two groups (Fig. 1).

2.4. Statistical analysis

A *t*-test for parametric data (SPSS package, version 20) was applied to compare the number of spikes identified during wake and sleep. A two-dimensional *t*-map was computed from the *t*-values to check the topographical distribution of the significance. The *t*-map was thresholded at $p < 0.05$ ($|t| > 2.777$) for the neocortical TLE group and ($|t| > 2.447$) for the mesial TLE group (two-tailed).

2.5. Electrical source imaging localization

To estimate the source underlying the epileptic activity observed at the scalp, a standardized source imaging procedure, low-resolution brain electromagnetic tomography (LORETA) was applied to the averaged spikes (Pascual-Marqui et al., 1994). LORETA minimizes the squared norm of the Laplacian of the weighted 3D current density (CD) vector field. It incorporates the "smoothness assumption" by selecting the inverse solution of the measured data with the smoothest distribution in space (Ossenblok and Spekreijse, 1991). The analysis was performed using Cartool software (brainmapping.unige.ch/cartool). The solution space for the distributed source model contained 5014 points uniformly distributed over the gray matter of the Montreal Neurological Institute (MNI) average brain template and mapped onto the spherical head model with anatomical constraints (SMAC) space (Spinelli et al., 2000). From the electrical source imaging (ESI), the CD was quantified at each solution point ($\mu A/mm^3$).

Cortical sources were estimated for each condition (wake vs. sleep) based on the grand-averaged signal at different time points. The global field power (GFP) was calculated to maximize the signal-to-noise ratio (SNR), identifying, over the time, moments of high SNR corresponding to moments of high global neuronal synchronization. The GFP corresponds to the spatial standard deviation (SD) and is defined as the sum of the squared potential differences between all possible electrode pairs (Lehmann and Skrandies, 1980). In detail, two time frames were chosen to characterize spike topography: the first, from the beginning of the spike to the time point at 50% of the rising phase, was defined as an epoch characterizing a possible source of the spike generator (Lantz et al., 2003; Storti et al., 2012); in the second, an epoch at the peak of the spike was defined as indicating propagation. Finally, in order to identify the positive significant deflections of the GFP following the peak of the spike, the GFP peaks exceeding 2*SD from the mean of the GFP baseline values, that is, the signal preceding the rising phase of the spike, were displayed. The scale of the CD of the identified cortical generators was set on the rising phase and kept stable for all significant sources displayed (Fig. 2).

3. Results

Twelve individuals (six females, mean age 33.8 years, range: 18–63) were included. The mean time since diagnosis was 17.9 years (minimum to maximum: 4–41). Seven subjects received a diagnosis of mesial TLE. Table 1 presents the demographic characteristics of the study sample. The subjects slept for a mean of 1 h and 33 min (range: 54–143). In all traces, N1 and N2 sleep was scored, while brief periods of N3 sleep were scored only in six cases. A mean of 21 IEDs in wake and 39 in N2 sleep were selected (*t*-test between the two conditions; $p = 0.024$) to obtain the averaged signal, with increased spike frequency in sleep.

3.1. Topographic IED distribution

On bidimensional rendering, neocortical temporal spikes were detected in wake in the temporal antero-central derivations, dif-

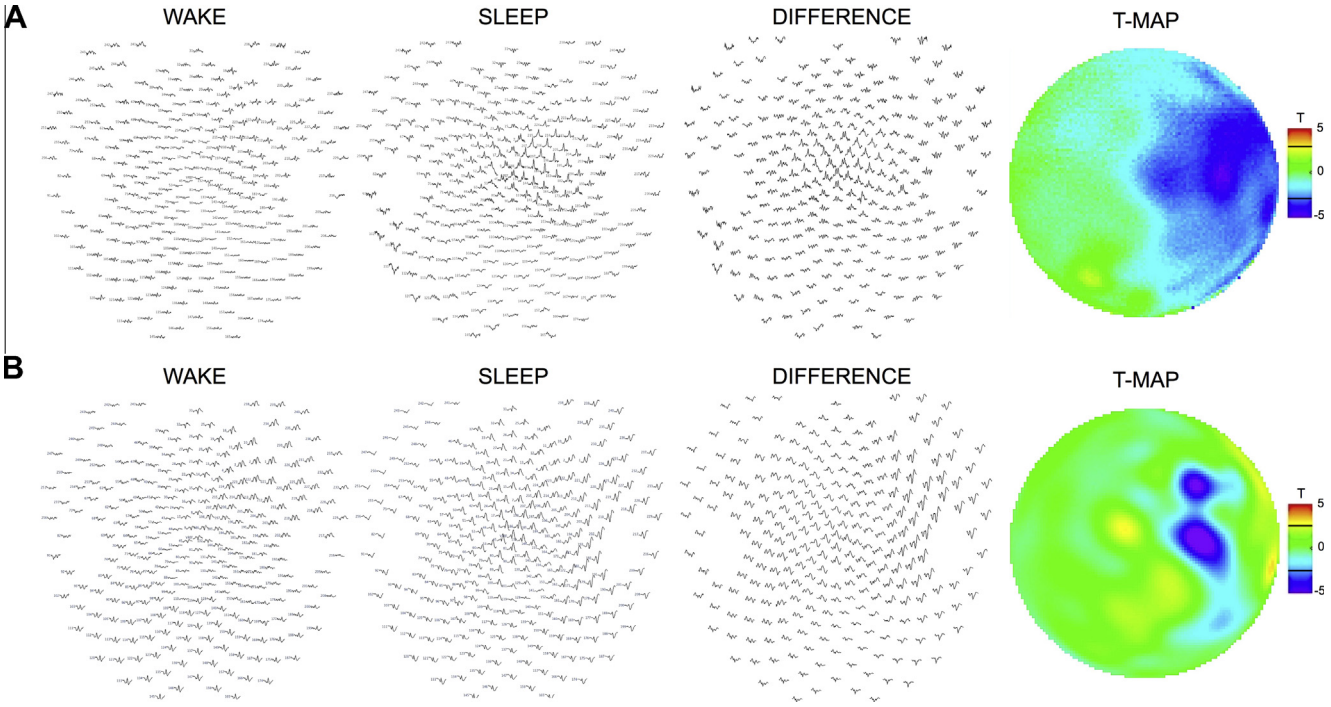

Fig. 1. Grand-averaged right temporal spike of the neocortical (A) and mesial (B) epilepsy groups in wake (W) and in sleep N2 (S) projected on a bidimensional representation of the scalp (nose pointing forward, bilateral ear spaces). The result of the subtracted digital signal (S–W) highlights an area where the spikes appear during sleep ("sleep plus area"). The statistical *t*-map comparing the two conditions confirms the presence of a temporo-posterior area of discharge spread in sleep $p < 0.05$ ($|t| > 2.447$) for the mesial-temporal lobe epilepsy group and ($|t| > 2.777$) for the neocortical epilepsy group (two-tailed). Time window of 1 s, amplitude of 4 μV/mm. *T*-map threshold level is indicated in the color bar.

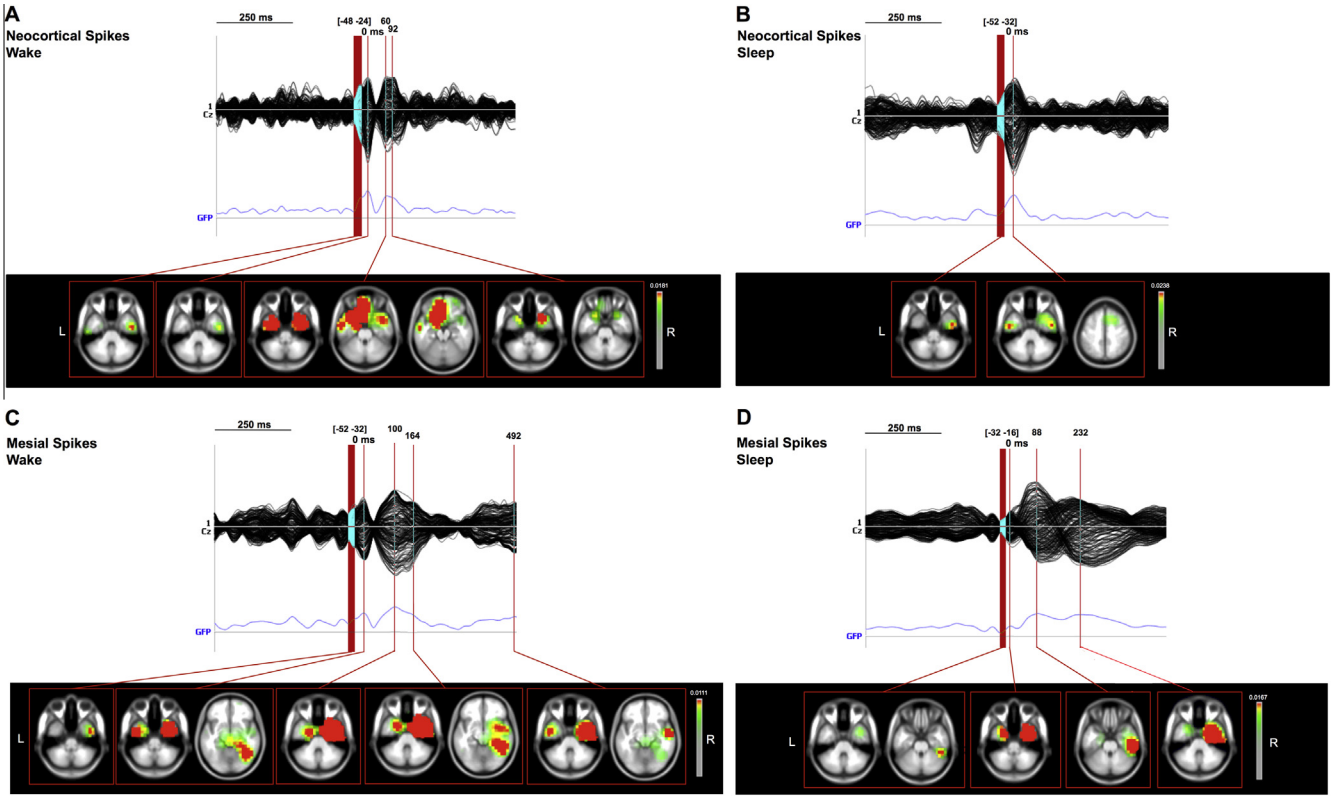

Fig. 2. Superimposed averaged EEG traces of the 256 channels on a time window of 1 s in wake and in sleep for the neocortical and mesial epilepsy groups showing the time course of cerebral oscillations around the averaged spikes. For each deflection, the cortical source generator was estimated with the LORETA algorithm and projected on MNI space. The 500 ms deflection represents the negative peak of the spike used for the averaging procedure. The GFP peaks exceeding 2*SD from the mean of the GFP baseline values were displayed. Note the low-frequency, temporally dispersed EEG activity following a spike in wake versus the high-amplitude, restricted deflections recorded in sleep. The EEG activity is mirrored by the different and temporally diversely distributed cortical sources in the two states. Note also the different source current densities in the two states. Slices were adjusted to show the maximum current density and its area.

Table 1
Demographic characteristics of the study sample.

Pt	Sex	Age	Etiology	Magnetic resonance imaging (MRI)	Drugs	Years since diagnosis
1	f	27	Post infectious	Right fronto-orbital and hippocampal hyperintensity	CBZ + VPA	6
2	m	47	Right hippocampal sclerosis	Right hippocampal volume reduction and hyperintensity	CBZ + VPA	39
3	m	18	Right temporal dysplasia	Normal	CBZ	14
4	f	20	Right hippocampal sclerosis	Right hippocampal hyperintensity	CBZ	5
5	f	21	Right hippocampal sclerosis	Bilateral hippocampal hyperintensity	CBZ	4
6	m	19	Right temporo-polar encephalocele	Right temporo-polar encephalocele	LEV, OXCBZ, LCM	4
7	m	18	Bilateral hippocampal sclerosis	Bilateral hippocampal hyperintensity	CBZ, VPA	7
8	m	43	Right temporal angioma resection	Right temporal post-surgical cavity	VPA, LTG, CLZ	29
9	f	63	Cryptogenic	Normal	CBZ + LTG	41
10	m	57	Cryptogenic	Normal	CBZ, VPA, CLZ	34
11	f	31	Post-traumatic	Right temporal malacic area	CBZ, LTG	13
12	f	41	Post-traumatic	Right temporal malacic area	CBZ, CLZ	19

fusing to more posterior and central leads in sleep (Fig. 1A). Mesial wake spikes were detectable over the right zygomatic and fronto-temporal areas; in sleep, spike distribution encompassed the whole anterior and posterior temporal leads plus the zygomatic leads (Fig. 1B). An increase in amplitude was noted in both cases. The averaged signal subtraction between sleep and wake (S–W), visualized on a bidimensional map over the scalp, produced residual focal epileptic activity for the mesial discharges restricted over the right antero-central temporal areas, also involving the zygomatic areas, with a reduced coverage as compared to both W and S. During sleep, the residual activity for the neocortical spikes persisted over the central-posterior temporal leads. The *t*-map calculated between the two conditions confirmed this aforementioned area as being peculiar to sleep, with temporo-mesial spikes concentrating over the antero-central cortical region during sleep ($p < 0.05$) and neocortical spikes over the temporal posterior areas ($p < 0.05$).

3.2. IED-induced cerebral oscillations and cortical sources

The 256-channel averaged wake and sleep traces for mesial temporal and neocortical temporal epileptic spikes were superimposed, and the magnified time and amplitude window (120 mm/s, 0.75 μV/mm) used for visualization permitted the distinction of the EEG oscillations following the spike (Fig. 2). The waking brain reacted to the spike occurrence with a series of low-amplitude, dispersed oscillations. Conversely, a much more amplified, temporally

Table 2
EEG peak latency, current density (expressed in μA/mm^3), coordinates in MNI space for each maximum (*x*, *y*, *z*), and Brodmann areas. GFP peaks exceeding 2*SD from the mean of the GFP baseline values were listed.

	ms	*x*, *y*, *z* (mm)			(μA/mm^3)	Brodmann area (BA)
Neocortical spikes						
Wake	[−48−24]	25	5	−21	0.0181	Right cerebrum, limbic lobe, uncus, gray matter, BA 28
	0	25	5	−21	0.0169	Right cerebrum, limbic lobe, uncus, gray matter, BA 28
	60	−12	8	−25	0.0562	Left cerebrum, frontal lobe, rectal gyrus, gray matter, BA 11
	92	15	15	−25	0.0215	Right cerebrum, frontal lobe, inferior frontal gyrus, gray matter, BA 47
sleep	[−52−32]	21	5	−25	0.0238	Right cerebrum, limbic lobe, uncus, gray matter, BA 28
	0	25	5	−21	0.0235	Right cerebrum, limbic lobe, uncus, gray matter, BA 28
Mesial spikes						
WAKE	[−52−32]	21	5	−25	0.0111	Right cerebrum, limbic lobe, uncus, gray matter, BA 28
	0	21	5	−25	0.023	Right cerebrum, limbic lobe, uncus, gray matter, BA 28
	100	18	8	−21	0.0384	Right cerebrum, limbic lobe, uncus, gray matter, BA 34
	164	15	12	−25	0.034	Right cerebrum, frontal lobe, inferior frontal gyrus, gray matter, BA 47
	492	21	5	−21	0.0206	Right cerebrum, limbic lobe, uncus, gray matter, BA 34
sleep	[−32−16]	25	−12	−15	0.0167	Right cerebrum, limbic lobe, parahippocampal gyrus, gray matter, hippocampus
	0	18	12	−25	0.0343	Right cerebrum, frontal lobe, inferior frontal gyrus, gray matter, BA 47
	88	28	−5	−12	0.023	Right cerebrum, limbic lobe, parahippocampal gyrus, gray matter, amygdala
	232	25	−12	−12	0.0263	Right cerebrum, sub-lobar, gray matter, amygdala

restricted, reactivity was evident when a spike perturbed the sleeping brain's ongoing oscillations.

For each subject and condition, the cortical sources correspond to the time window from the beginning of the spike to the time point at 50% of the rising phase (Lantz et al., 2003) and to the maximum negative amplitude of the averaged spike (0 ms). Subsequently, the cortical source generators were estimated for each significant deflection as identified by peaks on the GFP trace. In wake, GFP peaks exceeding the 2*SD threshold were identified at 60 and 92 ms for the neocortical temporal averaged trace, and at 100, 164, and 492 ms for the mesial temporal trace. In sleep, peaks were identified at 88 and 232 ms for mesial TLE, whereas no peak exceeding this threshold emerged for neocortical TLE. The waking brain reacted to spike perturbation with a steady interplay between cortical modules. The neocortical generated spike (uncus) (see Table 2 for source current densities and MNI coordinates) shifted 60 ms after the spike peak to the contralateral temporal and frontal lobes. After 92 ms, activation dwindled to the right frontal lobe (inferior frontal gyrus) and the left mesial temporal lobe. A similar activation pattern proper to the activity following the mesially generated spike was noted: at the peak, an activation over the contralateral temporal and ipsilateral parietal lobes was appreciated that subsequently (100 ms) massively reactivated the right temporal lobe (uncus), shifting back to the frontal (inferior frontal gyrus) and parietal ipsilateral lobes (164 ms). A final activation (492 ms) of the right temporal lobe (uncus) was detected. This sub-continuous alternating activity was largely silent during sleep. No significant neocortical spike induced peak was detectable (Table 2).

Similarly, mesial temporal spikes generated a subsequent EEG activity (deflections at 88 and 232 ms) that, after the peak-related spread (limbic lobe, parahippocampal gyrus and inferior frontal gyrus, and frontal lobe), remained restricted to the right mesial temporal lobe (limbic lobe and parahippocampal gyrus) (see Table 2 for source current densities and MNI coordinates).

4. Discussion

We were able to show how the topographical appearance of interictal epileptic spikes differs in wake and in sleep. The facilitatory effect of sleep and sleep deprivation on IEDs has been demonstrated in vivo and in vitro (Cohen and Dement, 1965; Naitoh and Dement, 1974; Shouse, 1988; Manganotti et al., 2006; Del Felice et al., 2011, 2013). To our knowledge, systematic study of differences in temporal spike scalp distribution between wake and sleep dates back to >30 years ago (Lieb et al., 1980; Rowan et al., 1982). Recent work based on invasive recordings (Asano et al., 2007; Goncharova et al., 2013) reported no influence of day- or nighttime on the spatial distribution of spiking.

Taking advantage of the high spatial resolution of 256-channel EEG, we demonstrate at the single and group levels that epileptic discharges have a wider scalp distribution during N2 sleep as compared to wake. This "sleep plus area" enucleates a scalp zone with persisting discharges, the physiological significance of which can only be speculated. We presume that a neuronal ensemble that keeps firing in both states – a sleep-facilitatory one and a waking-restricting one – could be the core of the epileptogenic focus. If true, the scalp area with persisting discharges could guide invasive EEG recording and ESI of cortical generators during presurgical workup for epilepsy.

Regions with frequent interictal spikes are often considered to be epileptogenic (Carreno and Luders, 2001), and areas of frequent interictal spikes and the seizure onset area are believed to overlap (Hufnagel et al., 2000; Carreno and Luders, 2001). Conversely, evidence for a widespread distribution of IEDs over the cortex (Lieb et al., 1980; Lange et al., 1983; Hufnagel et al., 2000) and for a lack of relationship in time between spikes and seizures (Gotman and Koffler, 1989) supports the argument that spike and seizure generation are independent processes (Gotman, 1991). Furthermore, the relation between IEDs and the seizure onset area is uncertain; therefore, the identification of a "hard core" scalp zone overlapping with the epileptogenic area could be valuable. This hypothesis will need to be validated with the surgical outcomes in people in whom such an area ("sleep plus" zone) is identified and taken into account during the planning of surgical treatment.

Our results are discordant from those of the few invasive studies that compared the possible modifications of temporal spike scalp distribution in wake and in sleep (Asano et al., 2007; Goncharova et al., 2013), in contrast to the growing number of papers comparing ESI localization accuracy with that of invasive methods (Brodbeck et al., 2011; Del Felice et al., 2014; Ding et al., 2007; Gavaret et al., 2004, 2006, 2009; Huppertz et al., 2001; Lu et al., 2012; Mégevand et al., 2014; Rikir et al., 2014; Storti et al., 2013). One reason could be the restricted coverage of invasive procedures: both stereoelectroencephalography (SEEG) and electrocorticography (ECoG) record more physiologically sound data than scalp EEG, mostly near fields, but are limited to a predefined zone. The overlap of spiking cortical areas in sleep and wake may be related to the non-complete scalp coverage with

these invasive EEG methods. EEG recording with 256 channels overcomes this constraint. The far fields recorded by surface EEG could, however, be contaminated by impedance signal distortions and so not mirror the exact deep source recorded invasively, as well as affect IEDs scalp distribution. Our data suggest a preferential spread of mesially generated temporal lobe discharges along a longitudinal axis – the electrical signal having to travel through a considerable amount of tissue with likely different impedances that smooth out the signal. By contrast, lateral temporal IEDs diffuse on an area anatomically nearer their generator, partially overcoming the problems of deeper sources and encompassing a wider scalp area.

Another finding relates to the sleep-induced spike spread: the state-dependent modulation of interplay between cortical areas. We recorded a series of EEG deflections following the spike. We adopted a restrictive selection criterion to identify deflections deemed significant, accepting only those exceeding a threshold of 2*SD from the mean value of the pre-spike baseline trace. The low-amplitude peaks observed during the 500 ms after the spike in wake were substituted by rare, high-amplitude deflections in sleep in mesial TLE and by no main deflection at all in neocortical TLE. A similar oscillatory response to TMS pulses was reported in healthy individuals (Massimini et al., 2005, 2007; Manganotti et al., 2013), in which a rebound of the EEG rhythms proper to the vigilance condition – that is, fast desynchronized alpha and beta bands in wake, and slow theta–delta bands in sleep – was elicited. When these results are integrated with our data, it appears that the brain responds to any kind of interfering stimulus with an oscillatory modality that resembles that of its vigilance state. Indeed, the time course of the EEG peaks in our study is similar to data on TEPs in healthy and epileptic subjects (Bonato et al., 2006; Massimini et al., 2007; Del Felice et al., 2011), confirming the interfering nature of IEDs and the reliability of using these elements to investigate cortical reactivity to perturbation. The reduced number of peaks identified in our traces in comparison to the aforementioned studies is likely to be due to the more selective criterion we applied for peaks inclusion. The different spatial and temporal succession of peaks in mesial and neocortical TLE probably reflects networks and/or preferential spreading pathways of the involved cortices, as recently proposed on the basis of both invasive neurophysiological (Bartolomei et al., 2010) and functional neuroimaging data (Maccotta et al., 2013).

The sleeping brain seems to respond by restraining activation to the discharging temporal lobe, inhibiting interactions with other cortical modules. This points to a breakdown in the intracortical connections in the epileptic brain during sleep, thus facilitating synchronous disengaged neuronal discharges of each area. Although we did not apply a connectivity computational model, our data are in line with recent reports of altered functional connectivity in various epilepsy types (Vessen et al., 2013; Gast et al., 2014; van Diessen et al., 2014), with a fragmented organization in the epileptic brain in sleep: a preferential, restrained connection between selected cortical zones facilitates synchronization and induces discharges.

An interesting finding that needs to be further discussed is the radical silencing of significant oscillatory-induced activity after the spike in neocortical TLE sleep. Indeed, an increased EEG synchronization in patients with mesial TLE (Bartolomei et al., 2013) has been reported, a result that is shared by previous studies, in which it was observed that mesial temporal lobe structures disclose high correlation of signals during the interictal state, as compared with a neocortical TLE control group (Bettus et al., 2008). These findings are in agreement with data using grid recordings in humans (Schevon et al., 2007), as well as in the rat-kindling model (Blumenfeld et al., 2007). They also indicate that increased interictal EEG synchrony is a property of epileptogenic structures. Our findings are proof of mesial TLE increased network synchronization and show how the IED perturbation in mesial TLE provokes a series of high-amplitude peaks that can only be generated by a neuronal ensemble coordinately discharging. Such a response is lacking in neocortical TLE, in which the immediate response to the interfering stimulus degrades into a series of lower-amplitude oscillations. Even if a certain degree of synchronization is a signature of every epileptic cortex, in this specific case we believe that deeper structures, namely, mesial temporal circumvolutions, had to give rise to higher discharges in order for these to be detected on the scalp. Conversely, neocortical structures could skip the whole subcortical circuitry to generate spikes, thus relying on less ample generators than the mesial TLE.

Nonetheless, we have to recognize that the small sample size of our study could have decreased the SNR of the EEG signals, thus reducing the sensitivity of our study. Subsequently, after adopting a strict inclusion criterion for source peaks identification, this choice possibly led to discard some peaks that remained subthreshold.

We suggest a noninvasive and pseudo-physiological method to observe cortical modularity in the epileptic brain. Cortical modularity rearranges according to the vigilance state and could determine how the epileptic spike spreads. The confinement of modules during sleep could contribute to the spread of the rhythmic signature of each of these neuronal ensembles to a more circumscribed scalp area. If we conceive of the epileptogenic zone as one of the brain's modules, then this mechanism could support the scalp diffusion of IEDs during sleep.

Acknowledgments

We thank Chiara Arcaro for the precious technical support and Emanuela Formaggio for proofreading the manuscript.

The data were analyzed with Cartool software (http://brainmapping. unige.ch/Cartool.php), developed by Denis Brunet from the Functional Brain Mapping Laboratory, Geneva, and supported by the Center for Biomedical Imaging (CIBM), Geneva, and Lausanne, Switzerland. *Conflict of interest:* None of the authors have potential conflicts of interest to be disclosed.

References

Asano E, Mihaylova T, Juhász C, Sood S, Chugani HT. Effect of sleep on interictal spikes and distribution of sleep spindles on electrocorticography in children with focal epilepsy. Clin Neurophysiol 2007;118:1360–8.

Badawy RA, Curatolo JM, Newton M, Berkovic SF, Macdonell RA. Sleep deprivation increases cortical excitability in epilepsy: syndrome-specific effects. Neurology 2006;67:1018–22.

Bartolomei F, Cosandier-Rimele D, McGonigal A, Aubert S, Régis J, Gavaret M, Wendling F, Chauvel P. From mesial temporal lobe to temporal perisylvian seizures: a quantified study of temporal lobe seizure networks. Epilepsia 2010;51:2147–58.

Bartolomei F, Bettus G, Stam CJ, Guye M. Interictal network properties in mesial temporal lobe epilepsy: a graph theoretical study from intracerebral recordings. Clin Neurophysiol 2013;124:2345–53.

Bennett DR. Sleep deprivation and major motor convulsions. Neurology 1963;13: 953–8.

Bettus G, Wendling F, Guye M, Valton L, Regis J, Chauvel P, et al. Enhanced EEG functional connectivity in mesial temporal lobe epilepsy. Epilepsy Res 2008;81:58–68.

Blumenfeld H, Rivera M, Vasquez JG, Shah A, Ismail D, Enev M, Zaveri HP. Neocortical and thalamic spread of amygdala kindled seizures. Epilepsia 2007;48:254–62.

Bonato C, Miniussi C, Rossini PM. Transcranial magnetic stimulation and cortical evoked potentials: a TMS/EEG co-registration study. Clin Neurophysiol 2006;117:1699–707.

Brodbeck V, Spinelli L, Lascano AM, Wissmeier M, Vargas MI, Vulliemoz S, Pollo C, Schaller K, Michel CM, Seeck M. Electroencephalographic source imaging: a prospective study of 152 operated epileptic patients. Brain 2011;134:2887–97.

Carreno M, Luders HO. General principles of presurgical evaluation. In: Luders HO, Comair UG, editors. Epilepsy surgery. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2001. p. 185–99.

Chatrian GE. Report on the committee on terminology. Proceedings of the general assembly. The VIIIth international £congress of electroencephalography and clinical neurophysiology. Electroencephalogr Clin Neurophysiol 1974;37:521–53.
Civardi C, Boccagni C, Vicentini R, Bolamperti L, Tarletti R, Varrasi C, Monaco F, Cantello R. Cortical excitability and sleep deprivation: a transcranial magnetic stimulation study. J Neurol Neurosurg Psychiatry 2001;71:809–12.
Cohen HB, Dement WC. Sleep: changes in threshold to electroconvulsive shock in rats after deprivation of "paradoxical" phase. Science 1965;150:1318–9.
Del Felice A, Arcaro C, Storti SF, Fiaschi A, Manganotti P. Slow spindles' cortical generators overlap with the epileptogenic zone in temporal epileptic patients: an electrical source imaging study. Clin Neurophysiol 2013;124:2336–44.
Del Felice A, Fiaschi A, Bongiovanni GL, Savazzi S, Manganotti P. The sleep-deprived brain in normals and patients with juvenile myoclonic epilepsy: a perturbational approach to measuring cortical reactivity. Epilepsy Res 2011;96(1–2):123–31.
Del Felice A, Foroni R, Manganotti P, Storti SF, Ricciardi GK, Ben Bashat D, Longhi G, Meglio M, Nicolato A. The use of electrical source imaging in targeting lesional mesial temporal epilepsy for radiosurgical treatment. Epileptic Dis 2014. http://dx.doi.org/10.1684/epd.2014.0697.
Ding L, Wilke C, Xu B, Xu X, van Drongelen W, Kohrman M, He B. EEG source imaging: correlating source locations and extents with electrocorticography and surgical resections in epilepsy patients. J Clin Neurophysiol 2007;24:130–6.
Gast H, Müller M, Rummel C, Roth C, Mathis J, Schindler K, Bassetti CL. Epileptic seizures as condensed sleep: an analysis of network dynamics from electroencephalogram signals. J Sleep Res 2014;23:268–73.
Gavaret M, Badier JM, Marquis P, Bartolomei F, Chauvel P. Electric source imaging in temporal lobe epilepsy. J Clin Neurophysiol 2004;21:267–82.
Gavaret M, Badier JM, Marquis P, McGonigal A, Bartolomei F, Regis J, Chauvel P. Electric source imaging in frontal lobe epilepsy. J Clin Neurophysiol 2006;23:358–70.
Gavaret M, Trébuchon A, Bartolomei F, Marquis P, McGonigal A, Wendling F, Regis J, Badier JM, Chauvel P. Source localization of scalp-EEG interictal spikes in posterior cortex epilepsies investigated by HR-EEG and SEEG. Epilepsia 2009;50:276–89.
Goncharova II, Spencer SS, Duckrow RB, Hirsch LJ, Spencer DD, Zaveri HP. Intracranially recorded interictal spikes: relation to seizure onset area and effect of medication and time of day. Clin Neurophysiol 2013;124:2119–28.
Gotman J. Relationships between interictal spiking and seizures: human and experimental evidence. Can J Neurol Sci 1991;18:573–6.
Gotman J, Koffler DJ. Interictal spiking increases after seizures but does not after decrease in medication. Electroencephalogr Clin Neurophysiol 1989;72:7–15.
Grosse P, Khatami R, Salih F, Kuhn A, Meyer BU. Corticospinal excitability in human sleep as assessed by transcranial magnetic stimulation. Neurology 2002;59:1988–91.
Hufnagel A, Dumpelmann M, Zentner J, Schijns O, Elger CE. Clinical relevance of quantitative intracranial interictal spike activity in presurgical evaluation of epilepsy. Epilepsia 2000;41:467–78.
Huppertz HJ, Hoegg S, Sick C, Lücking CH, Zentner J, Schulze-Bonhage A, Kristeva-Feige R. Cortical current density reconstruction of interictal epileptiform activity in temporal lobe epilepsy. Clin Neurophysiol 2001;112:1761–72.
Jovanovic UJ. General consideration of sleep and sleep deprivation. Epilepsy Res Suppl 1991;2:205–15.
King MA, Newton MR, Jackson GD, Fitt GJ, Mitchell LA, Silvapulle MJ, Berkovic SF. Epileptology of the first seizure presentation: a clinical electroencephalographic and magnetic resonance imaging study of 300 consecutive patients. Lancet 1998;352:1007–11.
Lange HH, Lieb JP, Engel Jr J, Crandall PH. Temporo-spatial patterns of pre-ictal spike activity in human temporal lobe epilepsy. Electroencephalogr Clin Neurophysiol 1983;56:543–55.
Lantz G, Spinelli L, Seeck M, de Peralta Menendez RG, Sottas CC, Michel CM. Propagation of interictal epileptiform activity can lead to erroneous source localizations: a 128-channel EEG mapping study. J Clin Neurophysiol 2003;20:311–9.
Lehmann D, Skrandies W. Reference-free identification of components of checkerboard-evoked multichannel potential fields. Electroencephalogr Clin Neurophysiol 1980;48:609–21.
Lieb JP, Joseph JP, Engel Jr J, Walker J, Crandall PH. Sleep state and seizure foci related to depth spike activity in patients with temporal lobe epilepsy. Electroencephalogr Clin Neurophysiol 1980;49:538–57.
Lu Y, Yang L, Worrell GA, He B. Seizure source imaging by means of FINE spatio-temporal dipole localization and directed transfer function in partial epilepsy patients. Clin Neurophysiol 2012;123:1275–83.
Maccotta L, He BJ, Snyder AZ, Eisenman LN, Benzinger TL, Ances BM, Corbetta M, Hogan RE. Impaired and facilitated functional networks in temporal lobe epilepsy. Neuroimage Clin 2013;2:862–72.
Manganotti P, Bongiovanni LG, Fuggetta G, Zanette G, Fiaschi A. Effects of sleep deprivation on cortical excitability in patients affected by juvenile myoclonic epilepsy: a combined transcranial magnetic stimulation and EEG study. J Neurol Neurosurg Psychiatry 2006;77:56–60.
Manganotti P, Formaggio E, Del Felice A, Storti SF, Zamboni A, Bertoldo A, Fiaschi A, Toffolo GM. Time-frequency analysis of short-lasting modulation of EEG induced by TMS during wake, sleep deprivation and sleep. Front Hum Neurosci 2013;7:767–72.
Manganotti P, Fuggetta G, Fiaschi A. Changes of motor cortical excitability in human subjects from wakefulness to early stages of sleep: a combined transcranial magnetic stimulation and electroencephalographic study. Neurosci Lett 2004;62:31–4.
Massimini M, Boly M, Casali A, Rosanova M, Tononi G. A perturbational approach for evaluating the brain's capacity for consciousness. Prog Brain Res 2009;177:201–14.
Massimini M, Ferrarelli F, Esser SK, Riedner BA, Huber R, Murphy M, Peterson MJ, Tononi G. Triggering sleep slow waves by transcranial magnetic stimulation. Proc Natl Acad Sci U S A 2007;104:8496–501.
Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G. Breakdown of cortical effective connectivity during sleep. Science 2005;309:2228–32.
Mégevand P, Spinelli L, Genetti M, Brodbeck V, Momjian S, Schaller K, Michel CM, Vulliemoz S, Seeck M. Electric source imaging of interictal activity accurately localises the seizure onset zone. J Neurol Neurosurg Psychiatry 2014;85:38–43.
Naitoh P, Dement W. Sleep deprivation in humans. In: Remoond A, editor. Handbook of electroencephalography and clinical neurophysiology. Amsterdam: Elsevier; 1974. p. 146–51.
Pascual-Marqui RD, Michel CM, Lehmann D. Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int J Psychophysiol 1994;18:49–65.
Perrin F, Pernier J, Bertrand O, Echallier JF. Spherical splines for scalp potential and current density mapping. Electroencephalogr Clin Neurophysiol 1989;72:184–7.
Pratt KL, Mattson RH, Weikers NJ, Williams R. EEG activation of epileptics following sleep deprivation: a prospective study of 114 cases. Electroencephalogr Clin Neurophysiol 1968;24:11–5.
Ossenblok P, Spekreijse H. The extrastriate generators of the EP to checkerboard onset. A source localization approach. Electroencephalogr Clin Neurophysiol 1991;80:181–93.
Rikir E, Koessler L, Gavaret M, Bartolomei F, Colnat-Coulbois S, Vignal JP, Vespignani H, Ramantani G, Maillard LG. Electrical source imaging in cortical malformation-related epilepsy: a prospective EEG-SEEG concordance study. Epilepsia 2014;55:918–32.
Rotenberg A. Prospects for clinical applications of transcranial magnetic stimulation and real-time EEG in epilepsy. Brain Topogr 2010;22:257–66.
Rowan AJ, Veldhuisen RJ, Nagelkerke NJD. Comparative evaluation of sleep deprivation and sedated sleep EEGs as diagnostic aids in epilepsy. Electroencephalogr Clin Neurophysiol 1982;54:357–64.
Schevon CA, Cappell J, Emerson R, Isler J, Grieve P, Goodman R, McKhann Jr G, Weiner H, Doyle W, Kuzniecky R, Devinsky O, Gilliam F. Cortical abnormalities in epilepsy revealed by local EEG synchrony. Neuroimage 2007;35:140–8.
Shouse MN. Sleep deprivation increases thalamocortical excitability in the somatomotor pathways, especially during seizure-prone sleep or awakening states in the feline seizure models. Exp Neurol 1988;99:664–77.
Silber MH, Ancoli-Israel S, Bonnet MH, Chokroverty S, Grigg-Damberger MM, Hirshkowitz M, Kapen S, Keena S, Kryger MH, Penzel T, Pressman MR, Iber C. The visual scoring of sleep in adults. J Clin Sleep Med 2007;3:121–31. Erratum in: J Clin Sleep Med. 2007; 3: table of contents.
Spinelli L, Andino SG, Lantz G, Seeck M, Michel CM. Electromagnetic inverse solutions in anatomically constrained spherical head models. Brain Topogr 2000;13(2):115–25.
Storti SF, Boscolo Galazzo I, Del Felice A, Pizzini FB, Arcaro C, Formaggio E, Mai R, Manganotti P. Combining ESI, ASL and PET for quantitative assessment of drug-resistant focal epilepsy. Neuroimage 2013. http://dx.doi.org/10.1016/j.neuroimage.2013.06.028.
Storti SF, Formaggio E, Franchini E, Bongiovanni LG, Cerini R, Fiaschi A, Michel CM, Manganotti P. A multimodal imaging approach to the evaluation of post-traumatic epilepsy. Magn Reson Mater Phys 2012;25:345–60.
Tononi G. Consciousness as integrated information: a provisional manifesto. Biol Bull 2008;215:16–42.
van Diessen E, Otte WM, Braun KP, Stam CJ, Jansen FE. Does sleep deprivation alter functional EEG networks in children with focal epilepsy? Front Syst Neurosci 2014;29:67.
Vaessen MJ, Braakman HM, Heerink JS, Jansen JF, Debeij-van Hall MH, Hofman PA, Aldenkamp AP, Backes WH. Abnormal modular organization of functional networks in cognitively impaired children with frontal lobe epilepsy. Cereb Cortex 2013;23:1997–2006.