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Hippocampal sleep spindles preceding neocortical sleep onset in humans

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ABSTRACT

The coexistence of regionally dissociated brain activity patterns –with some brain areas being active while other already showing sleep signs– may occur throughout all vigilance states including the transition from wakefulness to sleep and may account for both physiological as well as pathological events. These dissociated electrophysiological states are often characterized by multi-domain cognitive and behavioral impairment such as amnesia for events immediately preceding sleep. By performing simultaneous intracerebral electroencephalographic recordings from hippocampal as well as from distributed neocortical sites in neurosurgical patients, we observed that sleep spindles consistently occurred in the hippocampus several minutes before sleep onset. In addition, hippocampal spindle detections consistently preceded neocortical events, with increasing delays along the cortical antero-posterior axis. Our results support the notion that wakefulness and sleep are not mutually exclusive states, but rather part of a continuum resulting from the complex interaction between diffuse neuromodulatory systems and intrinsic properties of the different thalamocortical modules. This interaction may account for the occurrence of dissociated activity across different brain structures characterizing both physiological and pathological conditions.

Introduction

Human sleep is considered a global phenomenon, coordinated by specialized and diffuse neuronal networks modulating the whole-brain activity. Specifically, global changes in cortical excitability associated with reduced activity of arousal/neuromodulatory systems of the reticular formation are interpreted as the main determinant of the electroencephalographic (EEG) synchronization characterizing the sleep state (Fuller et al., 2011; Moruzzi and Magoun, 1949).

However, recent evidence suggests that the coexistence of different brain states reflective of the local intrinsic properties of different corticothalamic modules may characterize both physiological and pathological sleep (Nir et al., 2011; Nobili et al., 2011; Terzaghi et al., 2012). Specifically, simultaneous intracerebral and multiunit recordings in humans revealed that most (~80%) of the Non-REM (NREM) sleep slow waves and spindles, the hallmarks of sleep state, occur locally, thus showing that some cortical regions can be active while others are silent (Nir et al., 2011). Similarly, during NREM sleep, Nobili et al. (2011) observed brief (up to 1 min) local activations characterized by an abrupt interruption of the sleep EEG slow wave pattern in circumscribed cortical areas (primary motor cortex) replaced by a wake-like electroencephalographic high frequency pattern (alpha and/or beta rhythm). The simultaneous occurrence of heterogeneous (wake-like and sleep-like) EEG features within the sleeping brain may also underlie some common sleep disorders as confirmed by recent studies showing the presence of dysfunctional coexistence of local cortical arousal and local cortical sleep in diffuse cortical networks in patients with NREM parasomnias (Terzaghi et al., 2009, 2012).

Notably, the physiologic wake–sleep transition also seems to be characterized by the occurrence of EEG activity regulated at the regional level as suggested by scalp recordings (De Gennaro et al., 2001b; Ferrara and De Gennaro, 2011). Other groups more directly investigated the time-course of such transitions showing evidence for an asynchronous development of electrophysiological sleep features within neocortical visual areas in monkeys (Pigarev et al., 1997). More recently Magnin et al. (2010), using intracerebral EEG recordings in epileptic patients, expanded this observation to subcortical structures showing that thalamic deactivation precedes neocortical sleep onset by several minutes. Such evidence could possibly account for some of the paradoxical phenomena characterizing the wake–sleep transition (Mavromatis, 1987; Stickgold et al., 2000). Among others, several amnestic phenomena

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characterizing the time preceding sleep onset may be explained by a dissociation between the electrophysiological activity in the hippocampus and other brain regions. To test whether the hippocampus showed sign of sleep before neocortical regions, we employed simultaneous stereotactically implanted intracerebral (Stereo-EEG, SEEG) recordings from hippocampal as well as from several neocortical sites in nine neurosurgical patients. We then analyzed the occurrence of sleep spindles – considered, together with K-complexes, the hallmarks of NREM sleep and whose appearance is taken as evidence of the onset of sleep (De Gennaro et al., 2001a)– during the transition from wakefulness to sleep.

Materials and methods

Patients

Nine neurological patients (6M, 3F; mean age: 24; age range: 8–37) with a suspected diagnosis of drug-resistant extra-temporal focal epilepsy (i.e. the epileptogenic zone was located outside the medial temporal lobe structures) and selected as potential candidates for the surgical removal of the epileptic focus participated in the study (Table 1). During the pre-surgical assessment patients underwent individual investigation with SEEG for the precise localization of the epileptogenic zone (Cossu et al., 2005). Patients were selected based on the presence of at least two electrode contacts localized within the hippocampus. Before SEEG electrode implantation patients gave written informed consent approved by the local Ethical Committee (Niguarda Hospital, Milan, Italy). In all patients, five days after SEEG implantation, one night of sleep was recorded in order to monitor the susceptibility to seizure during sleep.

SEEG implantation procedures

Intracerebral electrodes were implanted under general anesthesia. The intra-parenchymal trajectory of these MR-compatible multilead electrodes was planned on stereo-arteriographic and 3D MR images. The procedure used was the one described by Talairach and Bancaud (1966) and later refined by Munari et al. (1994) integrated with advanced computer-aided imaging and surgical techniques (Cossu et al., 2005). The position of the intracerebral contacts (5 to 18 leads per electrode) was ascertained by 3D MR, performed a few days after implantation.

Data recording

SEEG was recorded from platinum–iridium semiflexible multilead depth-electrodes, with a diameter of 0.8 mm, 5–18 contacts 2 mm in length and 1.5 mm intercontact distance (Dixi Medical, Besancon, France) (Cossu et al., 2005). Concurrently, scalp EEG activity was recorded from two bipolar referenced platinum needle electrodes placed during surgery at 10–20 positions Fz and Cz. Electroocular activity was recorded at the outer canthi of both eyes, and submental electromyographic activity was acquired with electrodes attached to the chin. Both EEG and SEEG signals were recorded using a 192-channel recording system (Nihon-Kohden Neurofax-110) with a sampling rate of 1000 Hz. Recordings were referenced to a contact located entirely in the white matter. Data were then exported in EEG Nihon-Kohden format and converted into MATLAB (MATLAB 7.5.0, The MathWorks Inc., Natick, MA, USA) format using customized routines. For all recorded channels, bipolar montages were calculated by subtracting the signals from adjacent contacts of the same depth-electrode to minimize common electrical noise and to maximize spatial resolution (Cash et al., 2009; Gaillard et al., 2009). Finally, data were bandpass filtered (0.3–70 Hz), using third order Butterworth filters and downsampled to 200 Hz (*resample* MATLAB routine).

For all the patients, polygraphic recordings started at lights-off. Blind to SEEG traces, one of the authors (P.P.) performed sleep scoring based on AASM criteria (Iber, 2007) applied to scalp EEG data only. We recognized SO as the first N2 sleep epoch identified by the occurrence of the first sleep spindle or K-complex recorded at the Fz–Cz scalp derivation. Spindle detection analyses were then performed on SEEG from lights-off to SO except for those patients whose SO was longer than 30 min (see Table 1). In these patients (5, 6, 8 and 9), analyses were limited to the 30 min preceding SO.

In parallel, for each patient we recorded data collected during alert wakefulness (eyes open) before lights-off (mean duration ± SEM: 12.3 ± 1.5 min) and during the first NREM sleep episode following SO (mean duration ± SEM: 33.6 ± 10.9 min). These data were preprocessed using the same procedures described above.

Table 1
Demographic and clinical information for each patient. R = right; L = left; F = frontal neocortex; Ins = insula; T = temporal neocortex; P = parietal neocortex; O = occipital neocortex. *SEEG assessment in this patient excluded the presence of epilepsy (for details, see Terzaghi et al., 2012). **SEEG assessment in this patient was unrevealing (no contact showed interictal/ictal signatures). The patient underwent a second SEEG investigation (not analyzed here) establishing the epileptogenic zone in the left frontal neocortex.

Patient	Gender	Age (years)	Medication (mg/day)	SEEG				SOL (min)
				Number of bipolar contacts	Hemisphere	Sample lobe	Epileptogenic zone	
1	M	8	Oxcarbazepine 600 mg/die	20	R	F, T, P	*	10
2	M	34	Levetiracetam 2000 mg/die Clonazepam 8 mg/die	13	L	F, Ins, T, P, O	Left superior temporal circonvolution	28
3	M	32	Carbamazepine 800 mg/die Phenobarbital 100 mg/die Levetiracetam 3000 mg/die	10	R	F, P	Right orbital region	15.9
4	M	37	Carbamazepine 1000 mg/die Phenytoin 300 mg/die	10	L	F, Ins, T	Left parietal operculum	14.4
5	F	34	Topiramate 500 mg/die Carbamazepine 1000 mg/die Valproate 1300 mg/die Levetiracetam 1500 mg/die	12	R	T, P, O	Right superior occipital neocortex	30
6	F	23	Carbamazepine 200 mg/die	13	L	F, Ins, P	Left frontal operculum	30
7	M	20	Carbamazepine 800 mg/die Lamotrigine 200 mg/die	35	R	F, Ins, T, P, O	Right frontal neocortex	9.3
8	M	17	Oxcarbazepine 1500 mg/die Levetiracetam 2500 mg/die	29	L	Ins, T, P, O	Left inferior temporo-occipital neocortex	30
9	F	15	Oxcarbazepine 1200 mg/die Levetiracetam 1250 mg/die	22	R	T, P, O	**	30