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Heterogeneity of arousals in human sleep: A stereo-electroencephalographic study

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ABSTRACT

Wakefulness, non-rapid eye movement (NREM), and rapid eye movement (REM) sleep are characterized by specific brain activities. However, recent experimental findings as well as various clinical conditions (parasomnia, sleep inertia) have revealed the presence of transitional states. Brief intrusions of wakefulness into sleep, namely, arousals, appear as relevant phenomena to characterize how brain commutes from sleep to wakefulness. Using intra-cerebral recordings in 8 drug-resistant epileptic patients, we analyzed electroencephalographic (EEG) activity during spontaneous or nociceptive-induced arousals in NREM and REM sleep. Wavelet spectral analyses were performed to compare EEG signals during arousals, sleep, and wakefulness, simultaneously in the thalamus, and primary, associative, or high-order cortical areas. We observed that 1) thalamic activity during arousals is stereotyped and its spectral composition corresponds to a state in-between wakefulness and sleep; 2) patterns of cortical activity during arousals are heterogeneous, their manifold spectral composition being related to several factors such as sleep stages, cortical areas, arousal modality ("spontaneous" vs nociceptive-induced), and homeostasis; 3) spectral compositions of EEG signals during arousal and wakefulness differ from each other. Thus, stereotyped arousals at the thalamic level seem to be associated with different patterns of cortical arousals due to various regulation factors. These results suggest that the human cortex does not shift from sleep to wake in an abrupt binary way. Arousals may be considered more as different states of the brain than as "short awakenings." This phenomenon may reflect the mechanisms involved in the negotiation between two main contradictory functional necessities, preserving the continuity of sleep, and maintaining the possibility to react.

Introduction

Three main states of vigilance are classically described in humans: wakefulness, non-rapid eye movement (NREM), and rapid eye movement (REM) sleep. They correspond to specific brain activities and different levels of perception and responsiveness. The regulation of cyclic changes and transitions between these states depends on circadian and homeostatic processes (Borbely, 1982). These processes are under the control of brainstem and diencephalon in which "sleep promoting" and "wake promoting" structures mutually inhibit each other (Saper et al., 2001, Dang-Vu et al., 2010). The transition between wake and NREM sleep is characterized by a shift of EEG cortical activity from a low-amplitude high-frequency to a high-amplitude low-frequency mode, the so-called "EEG synchronization" which leads to a deactivated state (Steriade & McCarley, 1990; Steriade et al., 1990). During REM sleep, EEG activity is desynchronized whereas muscle tone is abolished and recurrent rapid eye movements sporadically occur. The states of vigilance appear to be very different and mutually exclusive. However, many clinical situations such as parasomnia, sleep inertia, paradoxical insomnia, and sleepiness, as well as recent experimental works, suggest that transitional or intermediary states can be in fact observed (Balkin et al., 2002, Magnin et al., 2010, Vyazovskiy et al., 2011, 2014).

The pioneering works described phasic brief phenomena disrupting the continuity of sleep, the so-called arousals (Schieber et al., 1971, Halasz et al., 1979). They correspond to abrupt and short shifts toward high EEG frequencies indicating a transient intrusion of wakefulness into sleep, or at least a sudden brief elevation of the level of vigilance. According to the American Sleep Disorders Association (ASDA) criteria, arousals are defined as abrupt EEG frequency shifts occurring after at least 10 s of stable sleep and lasting 3–15 s (ASDA, 1992). These brief intrusions of wake into sleep might reflect a compromise allowing to

Abbreviations: REM, Rapid eye movement; NREM, Non-rapid eye movement; EEG, Electroencephalography; S-EEG, Stereo-electroencephalography; EKG, Electrocardiogram; EOG, Electro-oculogram; TF, Time–frequency; PMC, Primary motor cortex; PSC, Primary somatosensory cortex; DLFC, Dorso-lateral frontal cortex; DLPC, Dorso-lateral parietal cortex; MPC, Medial parietal cortex; SMA, Supplementary motor area; ACC, Anterior cingulate cortex; PCC, Posterior cingulate cortex; ASIC, Antero-superior insular cortex; PSIC, Postero-superior insular cortex; AIIC, Antero-inferior insular cortex; PIIC, Postero-inferior insular cortex; PIC, Posterior insular cortex; AIC, Anterior insular cortex.

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preserve sleep continuity and to evaluate external/inner stimulations, and to modulate brain activation level within a given sleep stage. They also offer an opportunity to characterize the brain processes involved in the transition from one vigilance state (sleep) to another (transient wakefulness). Few studies have been devoted to physiological arousals. Some of them suggest that they are constitutive of the sleep structure itself (Mathur and Douglas, 1995; Boselli et al., 1998; Mathur and Douglas, 1995). Different types of arousals may occur, providing a hierarchy in levels of activation, from slow waves, including or not K-complexes, to fast rhythms which are not clearly mentioned in ASDA arousal definition (Schieber et al., 1971; Halasz, 1998; Halasz et al., 1979).

Different patterns of cortical arousals recorded on scalp EEG might correspond to various levels of cortical activation occurring either globally or differently in various cortical areas. The latter possibility was recently assessed by Nobili et al. (2011). During NREM sleep, they observed simultaneous wake-like (fast activity) and sleep-like (slow activity) patterns in primary motor and dorsolateral prefrontal cortices, respectively. This report of the coexistence of different patterns of activation in two distinct cortical areas suggests the presence of a broader heterogeneity among a larger sample of different functional cortical areas. This heterogeneity in arousal process has also been proposed in terms of hierarchical activation, with a continuous spectrum in the arousal processing, based on behavioral, EEG, and autonomic criteria, originating from the brainstem and progressing to cortical areas (Sforza et al., 1999, 2000, Chouchou et al., 2011, Halasz et al., 2004). Most studies on arousals were focused on NREM sleep; given the dramatically different activity of the thalamus and the cortex during REM sleep (Magnin et al., 2004), it can be hypothesized that arousal processes differ between these two structures during this sleep stage. Moreover, within NREM sleep, regulation processes such as homeostasis influence not only the presence but also the pattern of activation during arousals (Sforza et al., 2004; De Gennaro et al., 2001; Terzano et al., 1985; Parrino et al., 2001). Lastly, the quality of the stimulus triggering arousal, be it internal or external and of various modalities, affects the resulting pattern of activation (Kato et al., 2004). Using intra-cerebral recordings in 8 drug-resistant epileptic patients, we analyzed EEG activity during spontaneous, i.e., for which no trigger could be identified, or nociceptive-induced arousals during NREM and REM sleep. Wavelet spectral analyses were performed to compare arousal EEG activities in the thalamus, and primary, associative, or high-order cortical areas with those recorded during sleep and wakefulness. We aimed at describing cortical patterns of activation associated with thalamic arousals, and at comparing such "micro-states" with sleep and wakefulness. We show that 1) in the thalamus, EEG activity during arousals is stereotyped with a spectral composition intermediate between wakefulness and sleep; 2) in the cortex, patterns of activity during arousals are heterogeneous, the diversity of patterns being related to several factors such as sleep stage, anatomical localization, arousal trigger, and homeostasis; 3) cortical activity during arousal differs from that of wakefulness.

Materials and methods

Patients

Eight patients suffering from focal (mostly temporal) refractory epilepsy were included in this study (Table 1). To delineate the extent of the cortical epileptogenic area and plan a tailored surgical treatment, depth EEG electrodes were implanted according to the stereotactic technique of Bancaud and Talairach (1973) (Guenot et al., 2001). The choice of cortical anatomic targets was guided by data from non-invasive investigations (clinical history, video-scalp-EEG monitoring, morphologic MRI, [18F]-fluorodeoxyglucose positron emission tomography). The most often explored areas were limbic structures (hippocampus, amygdala), sensorimotor primary, insular, cingular, and fronto-parietal dorsolateral cortices (for a complete description of the rationale of electrode implantation, see Isnard, 2004). The thalamus, and more specifically the medial pulvinar nucleus (PuM), was a target of stereotactic implantation because it might be an important relay in the propagation of epileptic discharges, given its reciprocal connections with temporal cortical areas (Rosenberg et al., 2006). Explorations of temporal neocortical areas and PuM were possible using a single multi-contact electrode, so that thalamic exploration did not increase the risk of the procedure by requiring an additional electrode track specifically devoted to the PuM activity recording. Anti-epileptic drugs were tapered down in order to increase the occurrence probability of spontaneous seizures (Table 1). In agreement with the French legislation relative to invasive investigations with a direct individual benefit, patients were fully informed about electrode implantation and stereotactic EEG recordings. The laser stimulation paradigm was submitted to, and approved by, the local ethics committee (CPP Léon Bérard – Lyon, Authorization No. 22236S). Patients gave written informed consent after being aware that nocturnal laser stimuli were not a part of the diagnostic procedure but performed for research purposes. The present work was supported by a grant from the French Sleep Research and Medicine Society.

Electrode implantation and anatomical localization of recording sites

The electrode implantation procedure was carried out using multiple contact electrodes introduced into the brain perpendicular to the

Table 1
Clinical and demographic characteristics of the patients.

Patient	Gender	Age (years)	Medication (mg/d)	Hemisphere	Selected areas for sleep study	Epileptogenic zone	MRI
1	M	20	Valproate 1500 Levetiracetam 1000 Carbamazepin 400	L	Thalamus, PSC, PMC, SMA, DLFC, DLPC, ACC, ASIC, PSIC, AIIC	Left posterior temporal neocortex	Normal
2	M	19	None	R	Thalamus, PSC, PMC, DLFC, ACC, ASIC, PSIC, AIIC, PIIC	Right temporal medial lobe	Normal
3	F	37	Carbamazepin 600 Pregabalin 75	L	Thalamus, PMC, DLFC, DLPC, MPC, SMA, ACC, PCC, ASIC, PIIC	Left temporal medial lobe	Left hippocampus atrophy
4	M	21	Carbamazepin 800 Valproate 500 Clobazam10	R + L	Thalamus, DLPC, MPC, PCC, PIIC	Right fronto-orbital cortex	Diffuse malformative aspect
5	F	23	Levetiracetam 2000 Lamotrigin 800	F	Thalamus, DLPC, PCC, MPC	Left temporal medial lobe	Left hippocampus atrophy + occipito-temporal dysplasia
6	M	26	Carbamazepin 200 Lamotrigin 200 Pregabalin 75	L	Thalamus, PMC, DLFC, SMA, ACC, ASIC, AIIC, PIIC	Left temporal medial lobe	Left hippocampus atrophy
7	F	51	Oxcarbazepin 600 Clobazam 10	R	Thalamus, PSC, DLFC, ASIC, AIIC	Right temporal neocortex	Right temporal dysplasia
8	M	21	Topiramate 200 Oxcarbazepin 900 Lamotrigin 400	R+L	Thalamus, PSC, PMC, DLFC, DLPC, MPC, PCC	Right temporal neocortex	Right fronto-temporal polymicrogyria

ACC = anterior cingulate cortex; AIIC = antero-inferior insular cortex; ASIC = antero-superior insular cortex; DLFC = dorso-lateral frontal cortex; DLPC = dorso-lateral parietal cortex; MPC = medial parietal cortex; PCC = posterior cingulate cortex; PMC = primary motor cortex; PIIC = postero-inferior insular cortex; PSC = primary somatosensory cortex; PSIC = postero-superior insular cortex; SMA = supplementary motor area.