Sleep Medicine Reviews 25 (2016) 4–20

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Sleep-related epileptic behaviors and non-REM-related parasomnias: Insights from stereo-EEG

Steve A. Gibbs [a], Paola Proserpio [a], Michele Terzaghi [b], Andrea Pigorini [c], Simone Sarasso [c], Giorgio Lo Russo [a], Laura Tassi [a], Lino Nobili [a, *]

[a] Centre for Epilepsy Surgery "C. Munari", Centre of Sleep Medicine, Department of Neuroscience, Niguarda Hospital, Milan, Italy
[b] Unit of Sleep Medicine and Epilepsy, C. Mondino National Neurological Institute, Pavia, Italy
[c] Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan, Milan, Italy

ARTICLE INFO

Article history:
Received 2 February 2015
Received in revised form
13 April 2015
Accepted 7 May 2015
Available online 19 May 2015

Keywords:
Cyclic alternating pattern
Dissociated state
Epilepsy
Frontal lobe seizure
Hypermotor seizure
Local sleep
Nocturnal frontal lobe epilepsy
Parasomnias
Sleep-related seizure
Stereo-EEG

SUMMARY

During the last decade, many clinical and pathophysiological aspects of sleep-related epileptic and non-epileptic paroxysmal behaviors have been clarified. Advances have been achieved in part through the use of intracerebral recording methods such as stereo-electroencephalography (S-EEG), which has allowed a unique "in vivo" neurophysiological insight into focal epilepsy. Using S-EEG, the local features of physiological and pathological EEG activity in different cortical and subcortical structures have been better defined during the entire sleep-wake spectrum. For example, S-EEG has contributed to clarify the semiology of sleep-related seizures as well as highlight the specific epileptogenic networks involved during ictal activity. Moreover, intracerebral EEG recordings derived from patients with epilepsy have been valuable to study sleep physiology and specific sleep disorders. The occasional co-occurrence of NREM-related parasomnias in epileptic patients undergoing S-EEG investigation has permitted the recordings of such events, highlighting the presence of local electrophysiological dissociated states and clarifying the underlying pathophysiological substrate of such NREM sleep disorders. Based on these recent advances, the authors review and summarize the current and relevant S-EEG literature on sleep-related hypermotor epilepsies and NREM-related parasomnias. Finally, novel data and future research hypothesis will be discussed.

Introduction

In the last decade many clinical and pathophysiological aspects of sleep-related epileptic and non-epileptic paroxysmal behaviors have been clarified. Expert recommendations and diagnostic tools have been proposed to help physicians [1–5] and reviews have been published on the mutual influence and the interrelationship between epilepsy and sleep [6–13]. The diagnostic challenges of sleep-related epileptic and non-epileptic behaviors like non-rapid eye movement (NREM) parasomnias have also been described [3,4,14–18]. Because of the authors' expertise in sleep medicine, electrophysiology and epilepsy surgery, this article will adopt a different approach and highlight the clinical and pathophysiological insights into sleep-related epileptic and non-epileptic paroxysmal behaviors that were gained from the use of stereo-electroencephalography (S-EEG) recordings during the presurgical evaluation of drug-resistant focal epilepsy.

Every year, a small percentage of patients with drug-resistant focal epilepsy undergo S-EEG recordings before possible epilepsy surgery. The data obtained from such recordings has permitted a better understanding of the interplay between sleep and epilepsy. Moreover, as NREM-related parasomnias are relatively common, co-existence with drug-resistant focal epilepsy can sometimes occur, thus providing an exceptional opportunity to capture and study NREM parasomnias with S-EEG. In this article, we aim to summarize the current S-EEG literature, first in sleep-related epilepsies and then in NREM arousal parasomnias. Novel unpublished S-EEG data will be presented along with research hypotheses on the pathophysiology of both disorders.

* Corresponding author. Centre of Epilepsy Surgery "C. Munari", Centre of Sleep Medicine, Department of Neuroscience, Niguarda Hospital, Piazza Ospedale Maggiore 3, 20162 Milano, Italy. Tel.: +39 02 6444 2867; fax: +39 02 6444 2868.
E-mail address: lino.nobili@ospedaleniguarda.it (L. Nobili).

http://dx.doi.org/10.1016/j.smrv.2015.05.002

Abbreviations

CAP	cyclic alternating pattern
CPG	central pattern generators
CSWS	continuous spike-wave discharges during slow-wave sleep
EEG	electroencephalography
ED	epileptiform discharge
EZ	epileptogenic zone
FCD	focal cortical dysplasia
IEDs	interictal epileptiform discharges
IPG	inferior parietal gyrus
hd-EEG	high-density EEG
MME	minor motor events
MRI	magnetic resonance imaging
NFLE	nocturnal frontal lobe epilepsy
NREM	non-rapid eye movement
PAs	paroxysmal arousals
PET	positron emission tomography
REM	rapid eye movement
S-EEG	stereo-electroencephalography
SMA	supplementary motor area
SPECT	single photon emission computed tomography
TLE	temporal lobe epilepsy
VIM	ventralis intermedius nucleus of the thalamus

Stereo-electroencephalography: definition and uses

S-EEG methodology is based on the stereotactic placement of a number of intracerebral multilead electrodes to obtain long-term EEG recording in a 3-D arrangement (Fig. 1) [19]. Its main goal is to define the spatial and temporal organization of seizures of focal origin [19–21]. S-EEG allows the anatomical, electrical and clinical characterization of the epileptogenic zone (EZ), an area of cortex operationally defined as the site necessary and sufficient for the initiation and early organization of the epileptic seizure [22]. As a clinical tool, a S-EEG exploration is proposed to patients with drug-resistant epilepsy when non-invasive tests have failed to adequately localize the EZ [19–21]. Each S-EEG exploration is personalized and tailored to patient characteristics, such as cerebral and vascular anatomy, seizure semiology and previous scalp EEG lateralizing and localizing features [19]. The collected electro-clinical data are then reviewed by an epileptologist and discussed with the neurosurgeons and neuroradiologists to confirm or invalidate the pre-implantation EZ localization hypothesis and, once the EZ has been confidently localized, epilepsy surgery can become an effective therapeutic option [23–25].

S-EEG is also used as a research tool. Indeed, S-EEG recordings can overcome the limits of non-invasive electrophysiological tools such as the standard scalp EEG (international 10–20 system) and high-density EEG (hd-EEG) which have high temporal resolution but often lack the spatial resolution to show circumscribed electrophysiological activity of midline and deep brain structures [26–28]. By providing direct access to the cortex as well as the deeper structures, S-EEG recordings in epileptic patients allow an anatomically precise “in vivo” study of localized cortical structures and neural networks. Such studies have helped define the clinical concept of the epileptogenic network [29,30] and enabled the characterization of the frontal and extra-frontal networks involved in sleep-related epilepsies [31–36]. S-EEG has also provided novel human data on the local pathological, paraphysiological and physiological activity of different cortical and subcortical structures during the different states of the sleep-wake cycle [37–52].

Sleep-related seizures: insights from stereo-electroencephalography

The frequency of sleep-related epilepsy, defined as « seizures occurring exclusively or predominantly during sleep » represents up to 12% of people with epilepsy, the majority of which are affected by focal epilepsy [11,53,54]. Moreover, focal seizures occurring during sleep are known to predominantly originate from the frontal lobe [55,56]. Patients with almost exclusively sleep-related hypermotor seizures are said to be affected by nocturnal frontal lobe epilepsy (NFLE) [14,57], a heterogeneous syndrome regrouping familial, sporadic, idiopathic, cryptogenic and symptomatic cases [33,57–59]. NFLE is generally considered a benign epileptic syndrome due to the relative ease of controlling seizures with antiepileptic drugs. However, severe and drug-resistant forms have been described [33,57,60,61]. NFLE has been extensively studied as the archetype syndrome of sleep-related hypermotor manifestations, first with scalp and sphenoidal EEG [57,62,63] and following a few case reports [64,65], more comprehensively with intracranial and S-EEG recordings [31–33]. Because autosomal dominant and sporadic NFLE may show similar clinical and electroencephalographic features [33,57,66], it is assumed that semiologic findings in symptomatic forms of NFLE should theoretically apply to genetic and idiopathic cases. The anatomo-electro-clinical features of sleep-related epileptic paroxysmal behaviors, as studied by S-EEG, will be reviewed here.

Sleep-related epileptic clinical manifestations in NFLE confirmed by S-EEG

Classically, NFLE is associated with frequent complex motor seizures occurring during sleep. In the space of a single night, patients may exhibit different sleep-related motor events of increasing complexity ranging from short minor motor events (MME) and paroxysmal arousals (PAs) to longer lasting major attacks.

Major attacks, can include hyperkinetic automatisms, such as bimanual/bipedal activity, kicking, thrashing, rocking, axial and pelvic movements, or asymmetric tonic or dystonic postures usually lasting 20–30 s [33,57,59,66]. Rarely, patients also present epileptic nocturnal wandering, a form of nocturnal semi-purposeful and prolonged ambulatory behavior that is often associated with vocalization, unintelligible language and/or a frightened facial expression [33,36,67,68]. PAs are characterized by sudden and brief arousals (5–10 s) sometimes accompanied by stereotyped movements, brief dystonic postures, vocalization, frightened expression and/or fear. Occasionally, PAs occur more gradually, resembling a physiologic awakening with eye opening and slight head elevation [65]. After the attack, patients quickly go back to sleep [33,57]. MME are even shorter (2–4 s) movements, often stereotyped, involving the axial musculature, the head or the limbs [69]. Both PAs and MME may go unnoticed by the bed partner or family members [33,70,71]. Auras are rarely reported as patients are sleeping but have been described during diurnal events and can be helpful in localizing the EZ, mostly when seizures originate outside the frontal lobe [31,34].

In contrast to the relatively well-recognized patterns of temporal lobe seizures, the semiology of NFLE manifestations (and frontal lobe seizures in general) is much more challenging to characterize. The spread of ictal activity can be both multi-lobar and multidirectional leading to highly variable clinical features [14,34,36,57,72]. Interictal and ictal electrophysiogical activities are often not detectable on scalp EEG recordings due to the inaccessibility of much of the frontal lobes to surface electrodes or masked

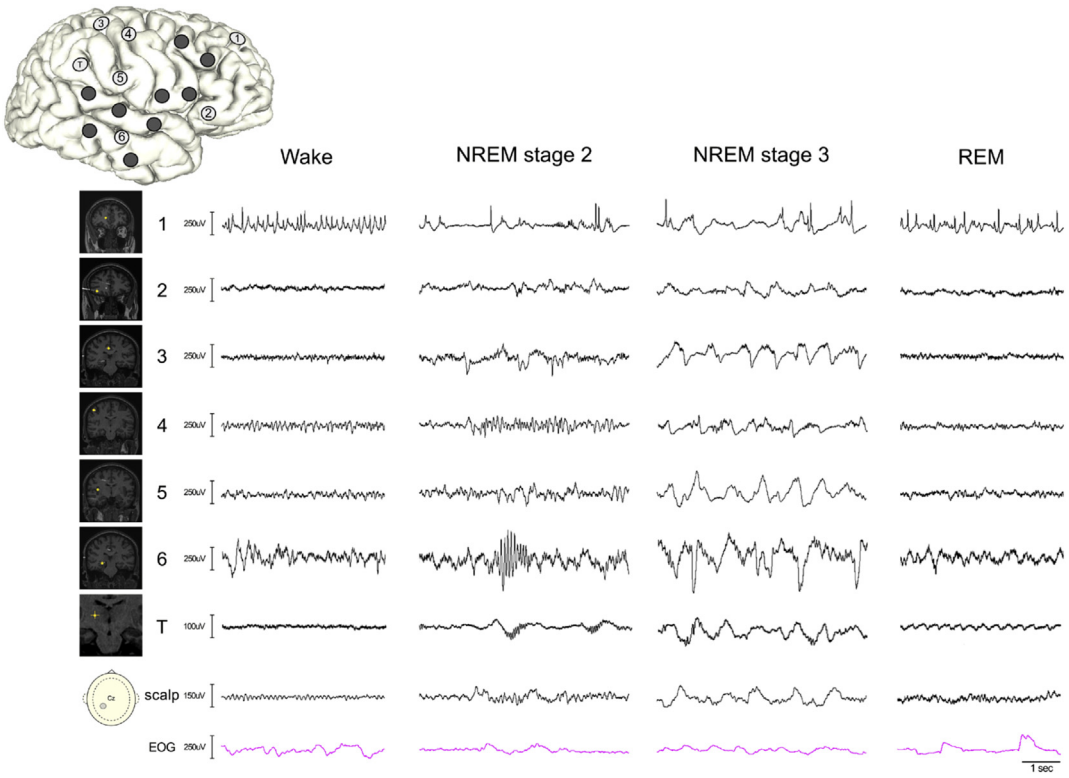

Fig. 1. Stereo-EEG recording through the sleep-wake cycle. An S-EEG recording exploring the right fronto-centro-parieto-temporal regions also including the insula and the hippocampus. Each light and dark grey circle marks one cortical entry point of the depth electrodes. Underneath the reconstructed cortical surface, each yellow dot on the brain MRI coronal images indicates the EEG lead positions inside the brain. The epileptogenic zone in this patient was located near the (1) anterior cingulate gyrus and expressed EEG activity compatible with a type II focal cortical dysplasia (FCD). Contact (1) demonstrates the typical firing pattern of the type II FCD during the sleep-wake cycle with high amplitude spikes and bursts of low voltage fast activity more frequently recorded during NREM sleep stage 2. All other selected contacts expressed physiologic cortical activity: (2) lateral orbital gyrus, (3) middle portion of the cingulate gyrus, (4) post–central gyrus, (5) long gyri of the insula, (6) hippocampus, (T) ventralis intermedius nucleus of the thalamus. Notice that the selected contacts possess distinct electrical signatures in terms of frequency and amplitude during wakefulness and REM sleep, that become more homogenous during NREM sleep stage 3. Also, wakefulness and REM sleep share similar features except for thalamus activity. (scalp) scalp electrodes P3-Pz according to the international 10-20 system, (EOG) electrooculogram. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

by movement artifacts related to seizures. This is often accompanied by a low incidence of significant magnetic resonance imaging (MRI) findings, even in symptomatic cases [33,57]. Furthermore, contradictory studies on ictal frontal semiology based solely on MRI-visible epileptogenic lesions have lead to confusing electrico–clinical correlations since in many cases, the cerebral networks involved in producing the ictal signs engage structures distant from the seizure onset zone [36]. Altogether, these characteristics can make it very difficult to identify the spatiotemporal evolution and anatomo-electro-clinical correlations of frontal lobe seizures without the use of invasive EEG recordings [34,36,73].

S-EEG correlates of NFLE

When analyzing seizure semiology, it is important to conceptualize the clinical expression of the epileptic discharge as a reflection of excessive activation (or inhibition) of a specific brain network, rather than simply being the consequence of an epileptic discharge haphazardly propagating to neighboring cerebral cortex [36]. S-EEG recordings in patients with sleep-related seizures have shown that the increasing complexity of the ictal motor behavior reflects a different duration and propagation pattern of the ictal epileptic discharge within the frontal lobe [64,72]. Studies of frontal lobe epilepsy with S-EEG have revealed that the most highly integrated ictal behaviors arise from the rostral prefrontal regions [33,34,36,72–74], while the more elementary motor signs are on the other hand associated to the more caudally located ictal discharges [33,36,73]. Moreover, the possible electroclinical involvement of extra-frontal regions (temporal, parietal and insular lobe) during seizures of frontal onset underlines the existence of specific brain circuits for the production of particular semiologic features [34–36,75]. Indeed, it is expected that seizures with comparable semiology should reflect neuronal activity in the same brain circuit, and that seizure onset remote from a particular brain circuit must reach it preferentially along predefined routes to produce a stereotyped inter-individual response [36,76].

For seizure semiology purposes, the frontal lobe can be divided into partially overlapping cortical regions representing a continuum of clinical features that follow a rostrocaudal hierarchical organization of the frontal lobe [36]. Fig. 2 summarizes the anatomo-electro-clinical features observed in sleep-related paroxysmal behaviors. Elementary motor signs such as clonic movements and the classic Jacksonian march originate from the primary motor cortex [77,78]. A somatosensory or nonspecific aura is often present [36]. The most frequent sequence consists of clonic activity starting unilaterally in the face, then spreading to the arm of the same side, followed by speech arrest, and eye blinking [79]. The presence of tonic or dystonic contractions and/or posturing were also shown to arise from precentral and/or premotor regions as well as the post–central gyrus and the central cingulate gyrus [33,34,36,73]. One of the main characteristics of these types of seizure is the preservation of consciousness [79].

Asymmetric proximal and/or axial tonic posture and anarchic motor behaviors arise from the premotor area and posterior part of the dorso-lateral pre-frontal regions as well as the posterior mesial part of the superior frontal gyrus (involvement of supplementary

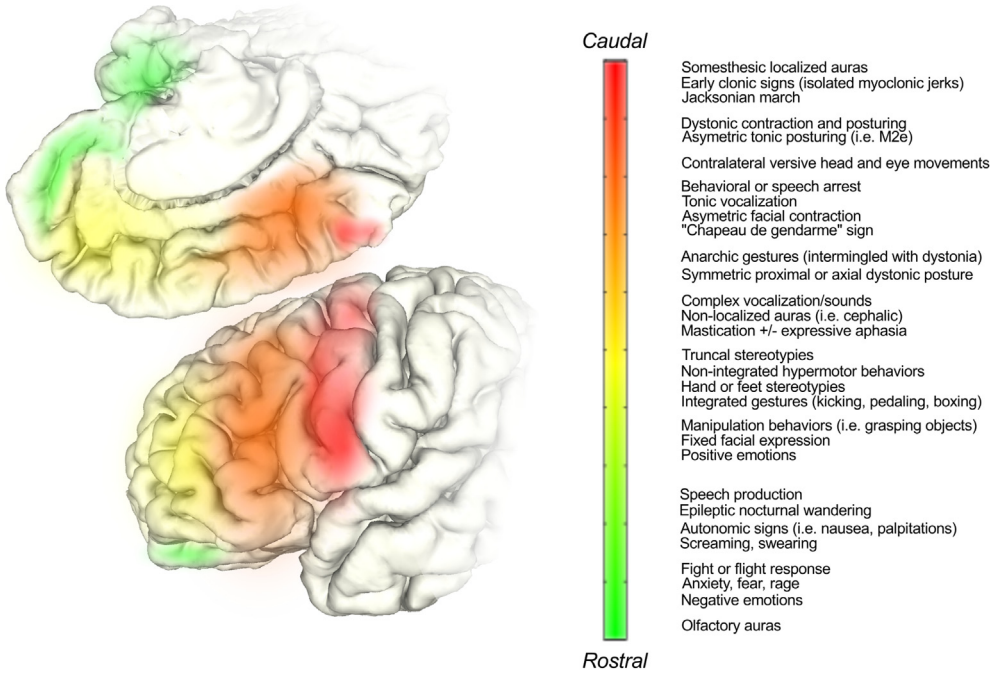

Fig. 2. Schematic representation of the rostrocaudal continuum of frontal lobe seizure manifestations derived from S-EEG recordings. Although the boundaries between color-coded subgroups are fluid and overlapping, S-EEG has permitted the identification of specific regional electroclinical patterns. Caudal manifestations are characterized by simple motor manifestations such as asymmetric clonic and dystonic movements that become more symmetric, complex and integrated as the more anterior portions of the frontal lobe are involved. Rostral involvement is characterized by very integrated, almost normal behaviors commonly associated with emotional expressions. Of note, the antero-mesial portion of the temporal lobe is frequently involved alongside the orbito-frontal cortex. Furthermore, clinical features of rostrocaudal extremes almost never occur together. Figure created using anatomo-electroclinical data from [33,34,36,72,73]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

motor area (SMA) and pre-SMA) and paracentral lobule [34,36,73,80]. These cortical areas as well as the anterior cingulate gyrus have been shown to produce ictal pouting ("chapeau de gendarme" sign) [81]. Involvement of anterior frontal regions gives rise to more integrated gestural motor behaviors, distal stereotypies, manipulation/utilization and fixed facial expression when the rostral prefrontal ventrolateral regions and the rostral cingulate gyrus are involved early [34,36,73]. Indeed, these areas have been shown to be essential for organizing and controlling goal-directed behaviors and emotional responses [82]. Hyperkinetic integrated gestures and complex motor behaviors (i.e., kicking, pedaling, boxing) may arise from the activation of the anterior dorso-lateral frontal area and fronto-polar region but are mostly the result of the involvement of the rostral part of the anterior cingulate cortex [33,34,36,73]. The activation of the orbital and medial-prefrontal networks include negative emotions, fearful behavior with occasional hyperkinetic attempts to fight or escape and affective expressions that rapidly involved the paralimbic system (ventromedial prefrontal cortex ± anterior temporal structures and amygdala) [31,36,68,74,83].

On the other hand, some stereotypic sleep-related behaviors seem to be independent of epileptic discharges and do not seem to result from direct activation of cortical areas [65,70]. Complex automatisms similar to those observed in sleep-related seizures have been described in patients with non-epileptic fits such as in syncope related to cervical tumors [84,85]. "Primitive" functional motor and emotional patterns such as masticatory automatisms, fear and sadness, copulatory behaviors and pelvic thrusting, swaying, pedaling and even walking can sometimes be observed without a clear S-EEG "epileptic" activation [86]. Indeed, these manifestations attributed to the frontal lobe have been hypothesized by Tassinari et al. to be the result of a release of inhibition on the innate behavioral automatisms and survival behaviors under the control of central pattern generators (CPG) [87]. By disrupting the neomammalian functions, the paleomammalian and reptilian brains would take over, releasing these behaviors [88]. Accordingly, when neocortical activity is disrupted by seizure activity, "primitive" functional motor and emotional patterns may emerge [86,87].

Sleep-related hypermotor seizures: always a frontal onset?

As discussed above, hypermotor seizures, sleep-related or not, have been shown to arise from various regions of the frontal lobe [33,72,89] and are considered the hallmark of frontal lobe seizures (hence the name NFLE). However, over the past decade many case reports and case series, including some by our group have challenged this idea, demonstrating that other sites of seizure onset may trigger tonic/dystonic or hyperkinetic behaviors. According to our patient database, approximately 30% of patients with pharmaco-resistant sleep-related hypermotor seizures investigated with S-EEG have a seizure onset outside the frontal lobe [54]. Most of the published sleep-related extra-frontal seizure cases exhibit a temporal [31,83,90,91] or an insular-opercular [31,32,35,92–94] onset although cases of parietal lobe, posterior cingulate cortex and even occipital lobe onset have been reported [34,75,95–97]. Carefully planned S-EEG studies have shown that in the majority of these extra-frontal cases, long delays (3–38s) between the electrical and the clinical onset are recorded [35,91,98]. Clinically, such delays might help identify an extra-frontal onset as tonic/dystonic or hyperkinetic behaviors in frontal lobe cases usually appear very early after the start of the epileptic discharge [99]. The long delays observed in extra-frontal onset also support the view that the observed motor behaviors arise from the ictal involvement or dysfunction of the frontal lobe structures [34,97]. Although the spread of epileptiform activity frequently reaches the frontal lobe before the complex motor behaviors appear [32,34,90], studies suggest that a perturbation or deactivation of frontal lobe structures by the epileptic discharge is sufficient to produce these

behaviors, possibly through the release of subcortical motor systems including CPG [87,97].

From a clinical point of view, as most extra-frontal cases are of temporal or insular origin, clinical manifestations and auras such as epigastric rising, acoustic sensations and/or déjà vu in temporal lobe onset [31,100], as well as laryngeal and throat sensations, dysarthria, hypersalivation, diffuse or bilateral cutaneous paresthesia of unpleasant or electrical character in opercular and/or insular onset [94,101] should be sought out. Although few cases have been reported, hypermotor seizures of parietal lobe onset have been shown to produce auras such as focal paresthesia, vertigo or a falling sensation [97,102].

Finally, by reviewing the published extra-frontal cases of sleep-related hypermotor seizures studied with S-EEG, extra-frontal epileptic networks communicating with specific regions of the frontal lobe can be recognized. For example, post–central regions are strongly connected to the precentral and premotor regions. Therefore, seizures arising from the post–central gyrus can produce clonic signs and tonic posture if the epileptic activity spreads more anteriorly [36,96,97]. A seizure onset in the posterior cingulate cortex, connected to the mesial and lateral parietal lobe as well as the paracentral lobule, supplementary motor area and anterior cingulate cortex can lead to mild agitation with bilateral asymmetric proximal/axial tonic postures [34,75]. The temporal pole, more than any other temporal lobe regions, seems to favor propagation of ictal activity towards the orbito-frontal cortex as well as the anterior cingulate cortex [90,91,103]. A temporal seizure onset can therefore produce the classic hyperkinetic manifestations accompanied by integrated gestural motor behaviors [31,36,73]. Since this system is also strongly connected with the amygdala complex, negative emotions are often present [33,36,74,83]. The insular cortex, which shares extensive connections with many brain regions, including the perisylvian regions (all operculae), most of the frontal and temporal lobes as well as some connections with the parietal and occipital lobes [104,105] can exhibit greater behavioral manifestations than most other structures, behaving as a great mimicker [94]. Published case series of sleep-related seizures with insular onset demonstrate a pattern of clinical manifestations that can be broadly divided in two main patterns: hyperkinetic automatisms and dystonic asymmetric posturing [35]. Because the insula has rich and reciprocal intrainsular projections [106], both patterns seem to be possible in any part of the insular cortex. Indeed, some authors have tried to subdivide insular ictal manifestations according to insular anatomy without much success [32,35,106]. In the future, a classification according to functional and structural connectivity [105–107] of the insula with its surrounding regions might provide better semiologic localization.

In summary, this section highlights the fact that in the last decade a significant portion of sleep-related hypermotor epilepsy cases were shown to arise outside the frontal lobe. Although the classical manifestations of sleep-related seizures described in the preceding sections are indeed manifestations of frontal lobe activation, inhibition or at least perturbation, the term NFLE currently seems misleading [4]. In view of these recent S-EEG findings, it might be time for a reappraisal of both the term and definition of NFLE in order to provide a more accurate definition of this syndrome.

Paroxysmal arousal, minor motor events and sleep instability

In 2003, the first S-EEG recording of a patient with PAs was published [64]. Besides major attacks, the patient presented stereotyped PAs characterized by head and trunk elevation with frightened expression. Occasionally she would sit up on the bed and rapidly fall asleep again. S-EEG recordings showed that these attacks arose from the SMA and that the increasing complexity of the motor behaviors (from minor to major events) reflected different duration, amplitude, and spread of the discharge to the surrounding areas. Successively, other patients with PAs were published where the clinical features were variable; indeed, in one patient, the elevation of the head and trunk could occur either suddenly or more slowly, resembling a physiological awakening [65]. S-EEG showed that all types of PAs (including those resembling normal awakenings) occurred during NREM sleep and were correlated with a discharge of polyspikes, followed by a low-voltage fast discharge, and localized over the dorsolateral cortex of the superior and middle frontal gyrus, the SMA or the frontal CG. The sum of these observations suggests that PAs are closely associated with epileptiform discharges (EDs) but the same ED can produce variable clinical features depending on the site of the discharge and other variables such as the level of arousal, arousal fluctuation, and body position during the ED [7,65,70,86]. Further S-EEG studies could be useful in clarifying the relationship between these modulating factors, the epileptic discharges and the motor and behavioral output.

While all PAs recorded with S-EEG were associated with EDs, the same cannot be said of MME. Defined in the previous section, MME are known to occur quasi-periodically during long stretches of NREM sleep, mostly during phases of unstable sleep, more precisely in relation with the phase A of the cyclic alternating pattern (CAP) [7,69]. MME may occur very frequently during sleep (reported range: 61–561) and, when excessive, lead to sleep fragmentation (increased CAP rate), loss of total NREM sleep time and increase daytime sleepiness, at least in patients with drug-resistant sleep-related seizures [64,71]. In earlier descriptions, MME had been assumed to represent the early phase in the continuum of sleep-related epileptic manifestations [67,69]. This was also recognized in some NFLE cases by S-EEG recording [64,65]. However, because MMEs resemble physiologic sleep-related movements and scalp EEG is frequently normal during their occurrence [64,67,70], it remained unclear whether MME were always the clinical corollary of ED. Using S-EEG data from NFLE patients, Terzaghi et al. showed that more than two thirds of MMEs were indeed related to ED, discharges that were frequently undetectable on scalp EEG [70]. Interestingly, in an individual patient, the same highly stereotyped MME could occur in either the presence or absence of an S-EEG-recorded ED. On the other hand, a local ED could be correlated with different MME patterns over the course of one night. In a second S-EEG analysis, Terzaghi et al. studied the relationship between MME, ED and arousal fluctuation in NFLE patients. They showed that the MME as well as the recorded ED shared a close relationship with arousal fluctuations as depicted by analysis of the CAP [71], preferably occurring during the phase A [7,12]. These results suggest that the organized cyclic oscillatory state represented by the phase A of the CAP could not only favor the co-occurrence of MME and ED but also create a reciprocal facilitating effect [71]. In view of these findings, ED-related MME should probably not be considered true epileptic manifestations but be construed as a motor manifestation in relation with sleep instability and somewhat facilitated, in a nonspecific way, by the presence of the ED itself. As such, the presence of MME without major attacks during a home-video, video-EEG or a polysomnography (PSG) recording should not suffice to make a diagnosis of NFLE, even in the presence of interictal epileptiform discharges (IEDs). We suggest that MME could represent a behavioral release, often stereotyped in the individual patient, provoked by the arousal [7]. The ED would act as an internal trigger increasing arousal fluctuations that in turn would enhance and modulate the occurrence of physiological movements (MME) or different types of sleep disturbances [7,15,18,44,65,70]. Conversely, the resulting sleep instability (increased CAP rate)

could facilitate the occurrence of epileptic discharges in a bi-directionally influenced system (Fig. 3) [7,18]. Importantly, the removal of the EZ can, not only eliminate major attacks but also reduce sleep instability, which consequently, can decrease MME and daytime sleepiness [33,44,108].

The neurophysiology of sleep-related hypermotor seizures and the usefulness of focal cortical dysplasia as a model of sleep-related epilepsy

During the sleep-wake process, epileptic activity is modulated by a multiplicity of self-governed oscillations whose temporal and spatial scales dynamically evolve [109]. The activation of ictal and interictal activity by these oscillations is a well-known feature of many epileptic syndromes in both children and adults [6]. As a general rule, the occurrence of IEDs and seizures tend to be slightly reduced during REM sleep as compared to wakefulness whereas unstable NREM sleep periods, such stage changes and the CAP, are considered facilitators of both [7,41,42,109,110]. Of clinical importance is the fact that during the phase A of the CAP the interictal discharges can spread ipsilaterally and contralaterally from the primary focus [7], whereas during REM sleep the discharges seem to focalize maximally, especially in temporal lobe epilepsy (TLE) [39–41]. Moreover, sleep may bring out IEDs that are not present on wake scalp EEG recordings [110–112].

Nevertheless, it is imperative to note that most studies assessing the role of sleep on ictal and interictal activity have been performed using scalp EEG and conventional sleep stage scoring. Although sleep-related seizures can be diagnosed fairly easily during video-EEG recordings, it is well known that scalp EEG lacks in sensitivity to evaluate the relationship between sleep stages and IEDs because

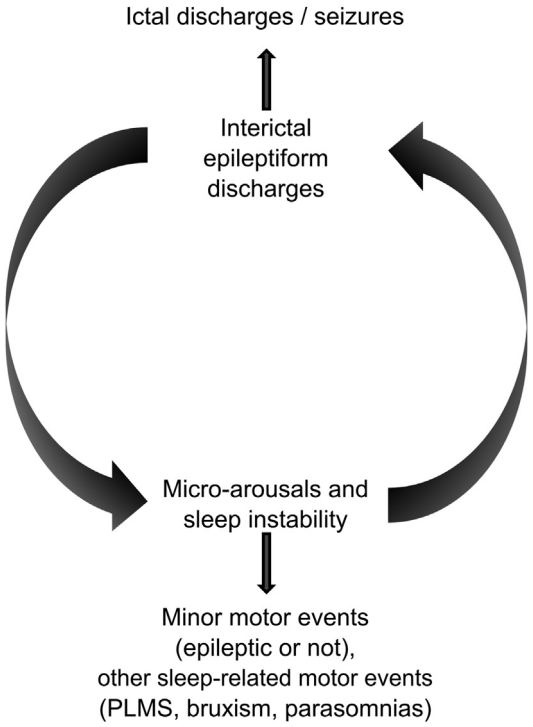

Fig. 3. The vicious circle of sleep-related epileptic discharges. Interictal epileptic discharges (IEDs) occurring during sleep act as an internal trigger that facilitates the occurrence of micro-arousals and increase sleep instability. This instability increases and/or modulates the occurrence of minor motor events and other sleep disturbances, which in turn facilitates the production of IEDs and sleep-related seizures by sustaining sleep instability. (PLMS) periodic limb movements of sleep. Modified from [188].

many intracranially-detected IEDs are absent on scalp EEG both during wakefulness and sleep [27,113,114]. As evidenced in Fig. 4, large IEDs discrepancies can be appreciated during simultaneous recordings of scalp EEG and S-EEG during different phases of the sleep-wake cycle. Furthermore, although clinically relevant, conventional sleep scoring rules simply provide a general categorization of scalp EEG activity without providing a deep understanding of the complex mechanisms underlying the interrelationship between sleep and the epileptic activity [109,115,116].

The use of intracerebral EEG recordings during sleep can partially circumvent these limitations allowing the study of local electrical fields as well as single neurons with depth electrodes and micro-wires, respectively [38,43,49–52,116]. For example, S-EEG has enabled the characterization of the peculiar electrophysiological features of a common epileptogenic lesion, the type II focal cortical dysplasia (FCD) or Taylor-type, known to significantly increase the risk of sleep-related seizures with respect to other histopathological substrates, regardless of its location inside the brain [117]. Type II FCD can therefore be considered a human in vivo model of sleep-related epilepsy, offering a unique opportunity to explore the interrelationship between sleep oscillatory properties and epileptic activity. Indeed, the influence of the sleep-wake process on type II FCD is clearly seen when inspecting the particular firing patterns of the dysplasia during sleep and wake using S-EEG. During wakefulness, type II FCD produce characteristic rhythmic and subcontinuous spike- and polyspike- and wave discharges that alternate with occasional short bursts of fast discharges ("brushes"), interrupted by electrical flattening (Figs. 1 and 6-A). In NREM sleep, fewer spike-and-wave discharges are seen, replaced by considerably more frequent short bursts of low voltage fast discharges inside the dysplasia that tend to recur pseudo-periodically, often spreading over the surrounding non-lesional areas and sometimes developing into a seizure (Figs. 1 and 6-B) [118–120]. In occasional cases, a rhythmic pattern reminiscent of the electrophysiological behavior of neurons of the thalamic reticular nucleus, the pacemakers of sleep spindles that lead to the typical 4-s periodicity of neocortical spindles, can be observed (Fig. 6). Interestingly, connexin 43, a membrane protein forming the hexametric structures of the gap junctions known to mediate these oscillations in the reticular nucleus [121] are reported to be abnormally rearranged in FCD type IIb [122], suggesting a possible mechanisms as to why some FCD may intrinsically behave like the reticular nucleus circuitry during NREM sleep [120]. Since many MRI-negative cases of sleep-related hypermotor seizures are associated with type II FCD, it has been suggested that the propensity of some type II FCD to manifest during sleep might be partly related to its size [123]. Indeed, smaller type II FCD might not be able to recruit sufficient non-dysplastic cortex for seizure propagation during wakefulness due to a low critical mass of neurons and therefore hijack the sleep oscillatory mechanisms during the night in order to manifest itself [123,124].

From the sleep-wake EEG firing pattern of FCD, it can be hypothesized that the frequent rhythmic and subcontinuous spike-and polyspike-and-wave discharges produced by the FCD during wakefulness and REM sleep denotes the strong influence of cortical and subcortical networks on the FCD (Fig. 6). REM sleep has clearly been shown to represent a much more integrated state than NREM sleep as it is able to sustain long-range, complex patterns of activation, similar to the functional connectivity observed during wakefulness [125]. Therefore, during wakefulness and REM sleep, a small FCD should be relatively integrated into the brain networks and modulated by it, receiving inputs from other brain regions. We speculate that the pattern of semi-continuous interictal spikes observed during wakefulness might indicate a state of reduced probability for low voltage fast discharges and seizure development. Accordingly, experimental studies have shown that interictal spikes

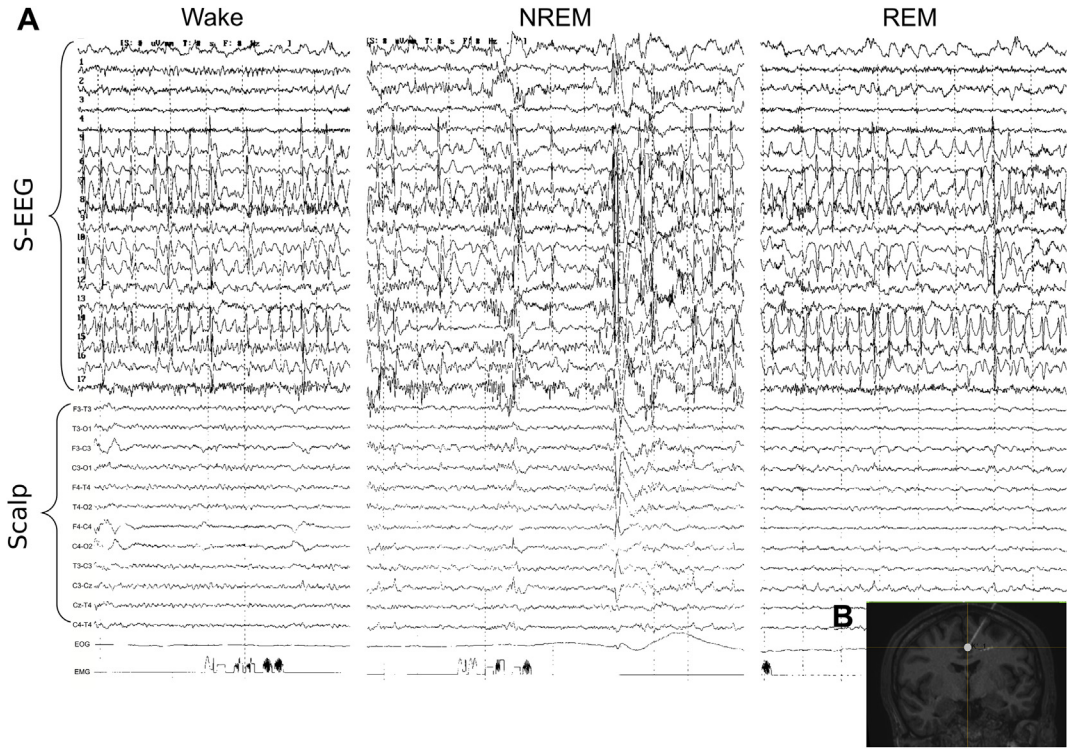

Fig. 4. A) Simultaneous stereo-EEG (upper panel) and scalp EEG (lower panel) during wakefulness (Wake), NREM sleep stage 2 and REM sleep. B) The epileptogenic zone was located medially in the left central cingulate gyrus (crosshair and dot). In all phases of the sleep-wake cycle, large discrepancies in interictal epileptiform discharges (IEDs) frequency between S-EEG and scalp EEG are observed. The IEDs recorded with S-EEG, contrary to scalp EEG findings, are more numerous during wakefulness and REM sleep than during NREM sleep. However, during NREM sleep, individual IEDs become more widespread and of greater amplitude increasing their visibility on scalp EEG. (EOG) electrooculogram, (EMG, chin) electromyogram.

in focal epilepsies set off a period of inhibition that transiently reduces tissue excitability [126–128]. Indeed, by studying the S-EEG data of patients with drug-resistant epilepsy secondary to type II FCD, de Curtis and coworkers have shown that neocortical excitability is phasically inhibited during periodic interictal spiking [129].

During light and deep NREM sleep, an important transformation of the firing pattern of the FCD occurs (Figs. 1 and 6). This change is probably related to the well-known dramatic EEG changes that accompany the transition from wakefulness to NREM sleep, changes that signal a re-arrangement of functional connectivity between brain regions [130–132]. The progressive appearance of prominent, high amplitude slow delta waves on the scalp sleep EEG is induced by a significant cortical change in the neuronal firing mode, which leads to the intra-cortical recording of high-amplitude slow oscillations and sleep spindles [133,134]. These EEG recorded slow waves reflect, at the single neuron level, the slow oscillations of the membrane potential. Steriade et al. showed that this activity consists of regularly repeated sequences of depolarization (up-state or activated state) and hyperpolarization (down-state or silent state) [133,135] Intracellular recordings in both anesthetized and naturally sleeping cats have shown that cortical neurons exhibit periods of intensive bursts of synaptic activity [136,137], spending most of their time in a depolarized, wakefulness-like up-state that is periodically interrupted by hyperpolarized, silent down-states [138]. This neuronal behavior translates into a highly homogeneous EEG pattern (both on scalp and S-EEG) during deep slow wave sleep, a pattern characterized by a stable production of slow waves (non-CAP phase), especially in the first part of the night (Fig. 1). S-EEG sampling of different cortical regions have confirmed that the spatially homogeneous and stable slow waves are linked to spatially synchronized local neuronal up- and down-states (Fig. 5-A) [50]. Interestingly, animal intracerebral recording studies have shown that neuronal up- and down-states can play a strong role in precipitating epileptic activity and seizures in a predisposed subject [124,139]. As seen in Fig. 5-G, EDs during NREM sleep occur exclusively during the up-state phase of the slow wave [139,140]. Moreover, pre-ictal discharges in anesthetized cats were shown to develop in continuity with slow oscillations before evolving into an electrographic seizure [141], suggesting that slow wave sleep is a favorable substrate for seizure development in certain susceptible patients. A recent S-EEG study has confirmed these findings by showing that high amplitude widespread slow waves that correlated with the phase A1 of the CAP on scalp EEG, are specific modulators of epileptic activity [116]. Unexpectedly, the investigators observed that epileptic spikes and high frequency oscillations, contrary to physiologic EEG activity, do not occur at the peak of the up-state but during the transition from the “up-” to the down-state of the slow wave, suggesting that the transition towards disfacilitation could facilitate the production of ED by briefly increasing neuronal hypersynchronization through inhibitory mechanisms [116,142].

That being said, seizures generally do not occur during NREM sleep stage 3 where the highest level of neuronal slow oscillation and synchronization is expected. Why is it so? One interesting possibility is that the slow oscillation characterized by up- and down-state alternation may profoundly affect the way cortical circuits process incoming information [130,143]. Indeed, during NREM sleep, a progressive loss of effective connectivity [144] occurs between brain regions due to the presence of disfacilitation (i.e., temporal absence of network activity) associated with neuronal hyperpolarization achieved through functional deafferentation [139,143]. We therefore hypothesize that the change in the FCD's firing pattern during NREM sleep is related to a reduced modulation of the FCD by the surrounding cortex. By facilitating locally regulated processes during homogeneous slow wave sleep, a regional increase in synaptic effectiveness and in local

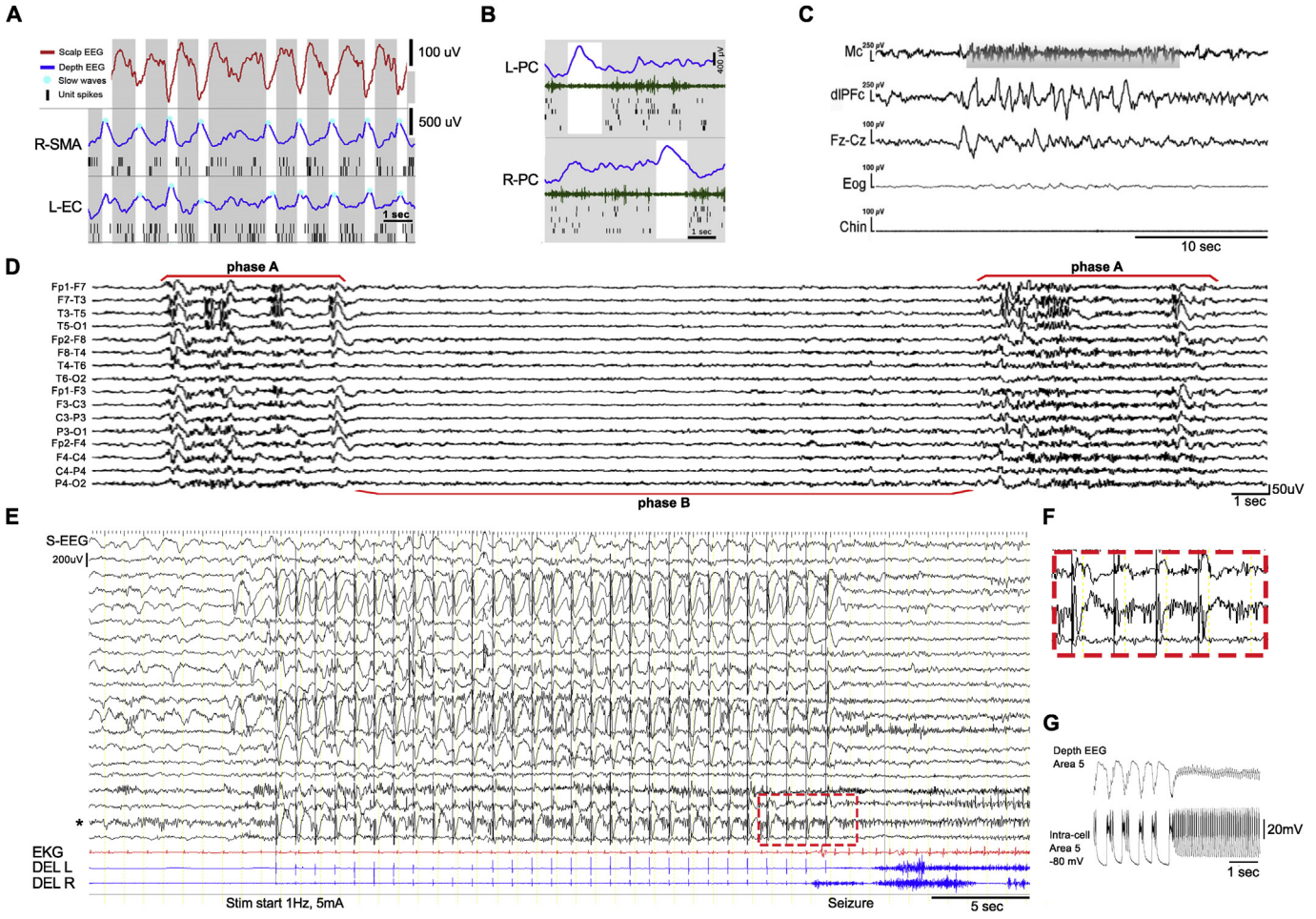

Fig. 5. Slow wave oscillations and seizure development: from intracellular recordings to scalp EEG. A) Simultaneous scalp EEG, intracerebral EEG and single-unit activity in two distant brain regions during deep NREM sleep in one individual showing that global slow waves can occur in unison across the brain (see reference [50] for complete figure). The extracellular recording (black lines, unit spikes) reveal an OFF period where unit spiking activity cease almost entirely, likely corresponding to a down state of the slow oscillations. Positive peaks in scalp EEG (red) tightly correspond to negative peaks of depth EEG (blue) and to ON periods with rigorous spiking, in accordance with a depolarized up state. Rows (top to bottom) depict activity in scalp EEG (at Cz), right supplementary motor area (R-SMA), left entorhinal cortex (L-EC). Cyan dots show individual slow waves detected automatically in each channel separately. Gray and white vertical bars mark ON and OFF periods occurring in unison across multiple brain regions. Modified from [50]. B) An example of a spatially heterogeneous state of local neuronal slow oscillation expressed by local sleep slow waves occurring at different times. White shadings mark local down-states. Intracerebral EEG (blue), multiunit activity (dark green) and single-unit spikes (black lines) in the left and right posterior cingulate gyrus (LPC and RPC). Modified from [50]. C) A sample of S-EEG recording during NREM sleep showing a local activation in the motor cortex (Mc, grey shadowed area) characterized by fast EEG activity that continues for tens of seconds while a sleep EEG with slow waves prevails in the dorso-lateral prefrontal cortex (dlPFc). (Fz–Cz) scalp electrode, (EOG) electrooculogram, (Chin) chin electromyography. Modified from ref [37]. D) The cyclic alternating pattern (CAP) during NREM sleep stage 2 on scalp EEG in a patient with sleep-related seizures. Interictal epileptiform discharges occur preferably during sequences of transient electrocortical activations (Phase A) that are distinct from background EEG activity (Phase B). For reviews see [7,115,189] E) S-EEG montage during NREM sleep showing an example of repeated low frequency electrical stimulations of 5 mA delivered at 1 Hz boosting slow wave oscillation, which favors seizure initiation in the epileptogenic zone. The asterisk marks the channel closest to the epileptogenic zone. (EKG) electrocardiogram, (DEL L/R) left and right deltoid electromyography. F) Box highlight of the previous S-EEG montage showing fast epileptiform discharges developing in continuity with up-state of the cortical slow oscillations and leading to a clinical seizure. This activity is reminiscent of the G) field potential during a fragment of an electrographic seizure obtained during the slow (sleep-like) oscillation in area 5 of an anaesthetized cat. Modified from [140]. For further explanation see reference [139]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

synchronization would allow the FCD to produce its characteristic bursts of low voltage fast activity, crucial for seizure initiation (Fig. 6) [122,145,146]. However, the presence of homogeneous slow wave sleep would also act as a seizure-preventing mechanism by disrupting the effective connectivity between the FCD and other cortical regions thus preventing long range information processing [132,143,147]. In short, a highly disfacilitated and locally-modulated state such as the stable NREM sleep stage 3 would favor the production of unregulated low voltage fast discharges inside the EZ while simultaneously segregating it from global brain dynamics.

It is well known that most sleep-related seizures occur in NREM sleep during periods of unstable sleep such as stage changes and the CAP (Fig. 5-D) [7]. During these intervals of the sleep-wake cycle, brain activity is in a transitional unbalanced state, showing fluctuating levels of synchronization, both spatially and temporally. On scalp EEG, this translates into the CAP phases [148,115]. S-EEG sleep studies have confirmed that this sleep state is one of electrophysiological heterogeneity where simultaneous wake-like and sleep-like activity can be observed at different timescales, from milliseconds using depth electrodes with microwires (Fig. 5-B) [50] to seconds using S-EEG recordings (Fig. 5-C) [37]. Using simultaneous S-EEG and single-unit extracellular recording from multiple brain regions in epileptic patients undergoing presurgical evaluation, Nir and colleagues showed than the up- and down-states and their corresponding EEG slow waves are frequently a local rather than a global phenomena (Fig. 5-B) [50]. Locally expressed sleep slow waves, occurring while other cortical areas simultaneously produce an activated EEG patterns have also been confirmed by

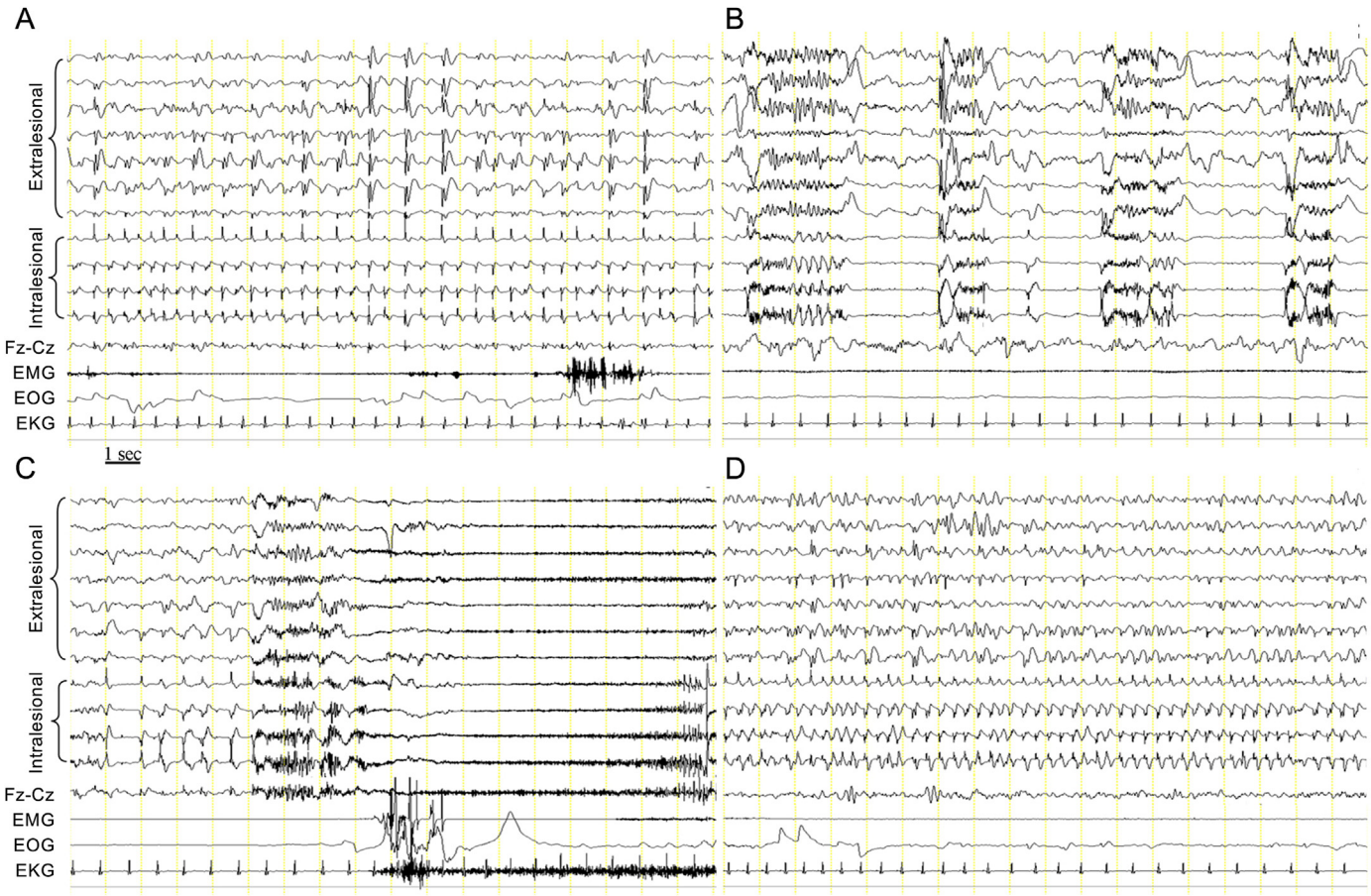

Fig. 6. S-EEG recordings of a patient with type IIb focal cortical dysplasia (FCD) during wakefulness and sleep. The four EEG panels (A–D) are divided in extra- and intralesional bipolar channels. The intralesional contacts are within the type IIb FCD. A) Pathognomonic activity of FCD during wakefulness with rhythmic and subcontinuous spike- and polyspike-and-wave discharges and occasional repetitive "brushes" inside the lesion. B) During NREM sleep, FCD activity is composed of pseudo-periodic bursts of low voltage fast discharges that spread to non-lesional areas. C) The onset of a seizure during stage II NREM sleep. D) Return of a rhythmic pattern of spike- or polyspike and wave during REM sleep, similar to wakefulness. Fz-Cz: scalp activity on the anterior vertex; EMG: electromyography (chin); EOG: electro-oculogram; EKG: electrocardiogram. Modified from [120].

concurrent S-EEG series of overnight recordings. Indeed, local wake-like EEG patterns during NREM sleep can be observed across different cortical areas, mostly during the CAP phase [38]. As an example, a number of abrupt increases in higher frequency EEG activity, including alpha and/or beta rhythm over the motor cortex have been found to occur during NREM sleep even in the absence of any sign of overt motor behavior. Simultaneously, many other cortical areas including the dorsolateral prefrontal cortex were characterized by the presence of slow waves (Fig. 5-C) [37,38]. Accordingly, it is the presence of functional heterogeneity in the cortical networks, represented by the lack of spatial slow wave homogeneity [50,149], that seems to represent the necessary condition for seizure initiation during sleep (Fig. 5-B and −C) [139,141]. Altogether, these findings suggest that circumscribed bursts of low voltage fast activity inside the FCD only propagates and develop into a full blown seizure when the EZ (re)integrates collective brain dynamics during periods of functional heterogeneity [7,124,150]. Of note, such a state occurs spontaneously every night (phase A of the CAP) [115] and can also be triggered through intracerebral electrical stimulations, a technique used to induce seizures during the presurgical evaluation (Fig. 5-E) [151,152].

To date, several research groups have used intracerebral EEG or S-EEG data to study the local physiological aspects of sleep while carefully excluding pathological epileptic activity [37,49–52]. In the future, we believe the use of advanced S-EEG signal analysis to study local aspects of sleep in relation to interictal and ictal activity could offer greater insights into the pathophysiology of sleep-related seizures.

NREM parasomnias: insights from stereo-electroencephalography

The increasing use of digital intracranial EEG recordings for the presurgical evaluation of patients with drug-resistant epilepsy [25] has opened a physiological window on human sleep and enabled the study of local aspects of sleep regulation. S-EEG recordings have allowed to overcome the intrinsic spatial limitations of scalp EEG techniques, thus confirming animal findings that showed, at the local scale, that sleep-like and wake-like EEG patterns may co-exist in different human cortical areas [50,149]. Recognition of this phenomenon has partially changed (at least at the electrophysiological level) the classical definition of wake and sleep as separate, discrete states.

Traditionally, sleep is described in terms of global behavioral state since central specialized networks are known to actively regulate the sleep-wake cycle and the different vigilance states [153–155]. Wakefulness and sleep states are considered stable and, between them, a predictable cycle is usually observed. From a behavioral and a neurophysiological perspective, an unambiguous separation is normally subserved by a widely distributed neural system that possesses functionally distinct but integrated components [156]. However, the cerebral cortex, strongly influenced by

this neural system, does not respond in a global ON/OFF manner. As previously stated, sleep defined on the basis of EEG activity does not arise simultaneously in all cortical areas since the boundaries between wakefulness and sleep have been shown to be somewhat fluid and overlapping [38,52,157–159]. Hence, wakefulness and sleep do not seem to be two mutually exclusive states [149,157,160]. The presence of simultaneous local dissociated electrophysiological states during sleep and wakefulness has been corroborated by S-EEG recordings of human sleep [37,49,50,52]. These observations suggest that the co-existence of wake-like and sleep-like electrophysiological activity is a possible property of the brain [38]. Accordingly, the paradigm of "local sleep" [161] is paramount to understanding the pathophysiology of NREM-related parasomnias since it also accounts for the occurrence of pathological dissociated states across different brain structures [157].

Pathophysiology of NREM-related parasomnias

Parasomnias are sleep disorders characterized by undesirable behavioral or experiential phenomena occurring during NREM, REM or during transitions to and from sleep. Disorders such as confusional arousals, sleep terrors and somnambulism (sleep-walking) are classified under the term "NREM-related parasomnias" because they arise from stage 3, and occasionally stage 2 of NREM sleep. All three share common features and are considered part of a continuum of paroxysmal behavioral patterns rather than biologically distinct entities [3]. They encompass a wide range of emotional and motor behaviors of increasing complexity and duration, characterized by misperception and relative unresponsiveness to external stimuli, mental confusion, automatic behaviors and variable retrograde amnesia [162]. Historically, somnambulism and other NREM parasomnias have been attributed to a host of pathological, psychological and paranormal phenomena [163] but as with epilepsy, it was the emergence of EEG and the creation of the first sleep laboratory in the 1960s that helped define and characterize these conditions [164,165]. During this period, it was recognized that somnambulism and related disorders were not related to dream enactment but occurred following incomplete arousals from slow-wave sleep [166,167]. Indeed, all NREM parasomnias seem to share a common pathophysiology that relies on the breakdown of the boundaries between the wakefulness and sleep regulatory systems during slow-wave sleep [157,162,167].

In this context, NREM parasomnias are conceptualized as disorders of arousal, and single episodes have long been assumed to represent a simultaneous admixture of wakefulness and NREM sleep [167]. During an event, subjects are neither fully awake (impaired conscious awareness) nor fully asleep (partial ability to interact with others and the immediate environment) [168]. Indeed, the association of abrupt motor activity with diffuse, rhythmic, high-voltage bursts of delta activity on the scalp EEG in patients with arousal parasomnias suggest the dissociation between mental and motor arousal [164,167]. Although no robust alterations in overall sleep architecture and the sleep-wake cycle are observed in subjects with NREM parasomnias, they have been shown to present NREM sleep instability with an increased CAP rate [169,170], hypersynchronous delta waves [166], irregular build-up of slow-wave activity [171,172] and unique EEG characteristics prior to and during somnambulistic episodes, such as rhythmic and synchronous delta activity predominant in the anterior regions, sometimes intermixed with faster rhythms [173,174].

Obviously, because of its invasive nature, S-EEG cannot be used to study sleep physiology or sleep disorders in otherwise healthy individuals. Nevertheless, drug-resistant focal epilepsy and NREM parasomnias can rarely coexist in a single patient providing an opportunity to study these sleep disorders during a presurgical S-EEG investigation. In recent years, we have had the chance to capture three NREM parasomnia episodes during S-EEG presurgical evaluation. Two of these cases have been previously published as case reports [45,46]. In 2009, Terzaghi et al. published a S-EEG recording of a confusional arousal captured during a S-EEG exploration of the right fronto-parietal brain regions. During the event, local fast wake-like EEG activations in the motor and cingulate cortices contrasted with the persistence or increase of bursts of sleep-like delta waves in the frontal and parietal associative cortices [45]. Later, a second confusional arousal was reported with similar findings of dissociated simultaneous wake-like and sleep-like activity in a S-EEG exploration that also included the limbic cortex. In this case, the persistence of delta activity in the hippocampal and frontal associative cortices was also found to be in sharp contrast with the presence of a local activation of the motor, cingulate, insular and temporopolar cortices and the amygdala [46]. Along with sleep-like slow waves, the hippocampus also exhibited regular sleep spindles during the entire duration of the event. Interestingly, S-EEG investigation ruled out the presence of epilepsy in this patient, eliminating the possibility of an influence of the epileptic substrate on local slow wave generation and thus pointing more directly to a dysfunctional and independent action of the systems involved in NREM sleep and wakefulness regulation. A third episode of confusional arousal was recently captured in our laboratory and was discussed in a recent review article on the boundaries of wake and sleep [159]. The patient, a 17 y-old boy with an 11-y history of pharmacoresistant focal epilepsy was admitted to our center for S-EEG recording in June 2012. The patient had an unremarkable brain MRI. A right temporo-parietal-occipital S-EEG exploration was undertaken, which also included electrodes in the frontal and central operculae, the anterior and posterior hippocampus and the insula. As part of a feasibility study on thalamic stimulation in epilepsy, the nucleus ventralis intermedius of the thalamus (VIM), close to the sheet-like reticular thalamic nucleus, had also been sampled by one distal electrode contact (Fig. 7-B). The recorded epileptic activity in this patient was compatible with typical FCD EEG activity and located in the posterior portion of the insula. The S-EEG recordings also exhibited slower waves in the posterior portion of the insula that extended to the central, parietal and temporal operculae. The activity of other regions, including the mesial temporal structures was reported as physiological. During his hospitalization, video-S-EEG captured a typical episode of confusional arousal during slow wave sleep. The S-EEG recorded an increase of slow, high-amplitude delta activity that progressively became pseudo-rhythmic in all the explored heteromodal cortical regions of the inferior and superior parietal lobule, the pre-cuneus, middle occipital gyrus, the posterior cingulate gyrus, and the hippocampus. As shown in Fig. 7-A, parietal scalp EEG activity showed hypersynchronous high-voltage delta activity (higher power spectral density (Fig. 7-E)) as compared to a physiological NREM epoch recorded during the same night, and consistent with an increased number of slow waves (asterisks in Fig. 7-A) detected as in Riedner et al. [175]. This confusional arousal was not associated with ictal activity in the EZ located in the operculo-insular region, which continued to produce interictal spikes and slow waves. Unfortunately and contrary to the previous cases, no intra-cortical electrodes were located in regions shown to be activated in a wake-like manner (i.e., motor cortex and cingulate gyrus) during a NREM parasomnia. However, during the episode, EEG activity in the ventro-medial portion of the thalamus showed a slight decrease in delta power and a clear-cut emergence of beta activity (Fig. 7-A, E). This fast activity was similar in frequency and amplitude to the thalamic activity recorded during wakefulness (Fig. 1) and to previously published S-EEG thalamic wake-activity [38]. To our knowledge, this S-EEG recording is the

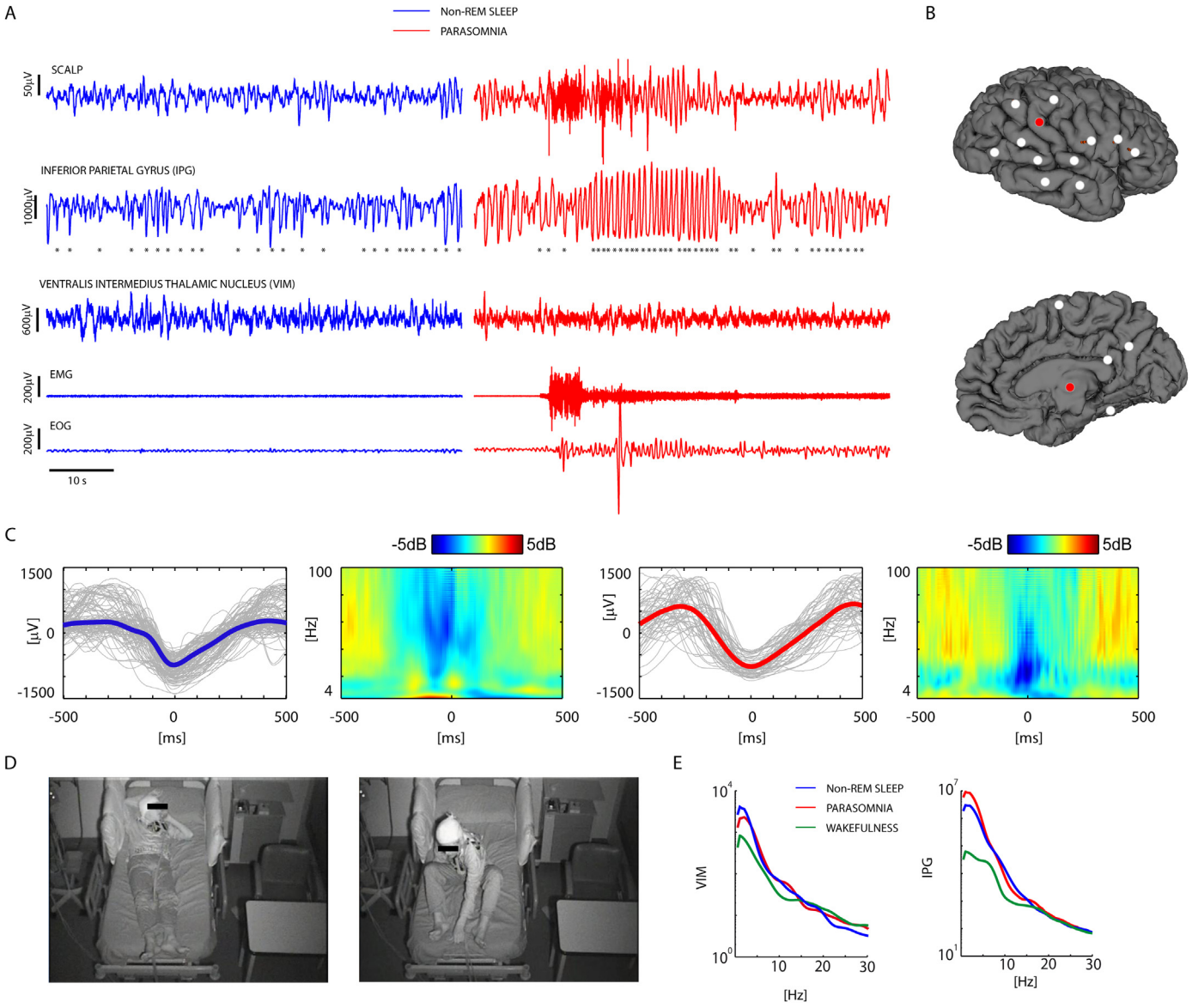

Fig. 7. Standard polygraphic and S-EEG recordings during an episode of confusional arousal compared to a NREM sleep episode of the same duration. A) Scalp EEG and S-EEG recordings from bipolar contacts located in the inferior parietal gyrus (IPG) and in the ventralis intermedius nucleus of the thalamus (VIM). Asterisks indicate detected slow waves in IPG by applying the same methods adopted by Riedner et al. [175] In blue, tracings from a 1-min NREM sleep epoch. In red, tracings from the same patient during an episode of NREM confusional arousal occurring in the same night. Scalp EEG, electromyography (EMG) and electrooculographic (EOG) recording are shown below. B) Topographic distribution of the bipolar contacts (white dots) shown on lateral (top) and medial (bottom) views of the 3D reconstruction of the patient's brain. Red dots represent the two contacts whose tracings are presented in (A). C) Wave-triggered average (individual events in grey and color coded average potential) and time-frequency analysis (EEGLAB [190] Wavelet 3 cycles) performed on the detected slow waves indicated in panel A aligned at the peak of the negative deflection. For both conditions, blue color in time-frequency plots indicates a reduction, red indicates significant increase, green indicates no change in power as compared to the time interval going from 1000 ms to 500 ms preceding the negative peak (not shown). D) Frames extracted from the video recordings corresponding to the tracings presented in panel A and B during NREM sleep (left) and the NREM confusional arousal episode (right). E) Power spectral density for VIM (left) and IPG (right) calculated over the 1-min tracings in (A) and over a recording of the same duration acquired during wakefulness (green). Modified from [159]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

first report of thalamic electrophysiological activity during a NREM parasomnia. Using simultaneous intracortical and intrathalamic S-EEG recordings, Magnin et al. have previously shown that thalamic and cortical activities are not always time-locked. During the wake–sleep transition, thalamic deactivation can precede that of the cortex by several minutes [38,49,52]. The opposite however was not observed during transition from NREM sleep stage 2 or 3 to wakefulness [49]. Our thalamic electrophysiological data suggest that thalamic activation before cortical activation is possible during arousals, at least during partial or dissociated ones. Moreover, it has been shown that NREM-related parasomnias are associated with an increased CAP rate, with hypersynchronized slow waves (phase A1 of the CAP) often accompanying the nocturnal events [170,176]. During phase A1, an increase in thalamo-cortical synchronization has been hypothesized [115,177]. Future studies, coupling intracerebral and scalp hd-EEG recordings, may further clarify the nature of the different scalp EEG phasic events.

Interestingly, the combined findings of these three cases identify specific neuronal circuits that constitute the neurophysiological substrate of most brain perfusion changes observed by Bassetti et al. during a sleepwalking event [178]. Indeed, by injecting a radiolabeled compound to visualize brain perfusion during an episode of undisturbed slow wave sleep and, on a subsequent night, during a sleepwalking episode, they highlighted a decreased regional cerebral blood of the fronto-parietal associative cortices

coexisting with an activation of the thalamus and cingulate cortex during the event [178].

Another interesting feature of S-EEG analysis during NREM parasomnias concerns the phenomenon of altered consciousness. Recent research theories on consciousness have proposed that consciousness is tied to information integration [179]. In this context, sleep represents a physiological model of decreased consciousness. As previously mentioned, the thalamocortical system during NREM sleep has been shown to breakdown into isolated regional modules thus impairing its ability to produce complex, differentiated responses and to sustain reciprocal causal interactions [130–132,143]. This behavior is likely linked to the development of neuronal slow oscillations in thalamocortical circuits during NREM sleep [133,145]. Since increased hypersynchronous high-amplitude delta waves on the scalp EEG are typical during NREM parasomnias, we therefore wondered whether the hypersynchronous slow waves recorded during the confusional arousal, a state of decreased consciousness, had the same properties as the ones occurring during physiologic slow wave sleep (i.e., they are characterized by similar neuronal behavior). Indeed, by analyzing the modulation of high frequency (>20 Hz) power associated with slow waves [180] as a local field potential proxy of the underlying brief periods of hyperpolarization and neuronal silence (down-states) during both NREM sleep and the confusional arousal, we observed that both the slow waves recorded during sleep and NREM parasomnias are underpinned by an alternation between activated up-state and a silent down-state (Fig. 7-C). This finding suggests that the local slow waves observed during a NREM parasomnia are analogous to physiologic sleep slow waves. The variable level of conscious awareness during a NREM parasomnia could therefore possibly depend on the amount and location of the local persistence of these slow waves.

In summary, because each S-EEG exploration is anatomically case-specific and cannot cover the entire cortical mantle, extrapolations from each case is necessary. However, our S-EEG findings are in line with the presence of simultaneous electrophysiologically diverse local states during physiologic sleep and that some brain networks can exhibit sleep patterns while others exhibit wake-like activities [37,45,46]. Furthermore, electrophysiological findings during NREM parasomnias parallel the functional studies consistent with the view that NREM parasomnias consist of dissociated activation of particular brain regions: specific cortical areas modify their firing pattern to produce wake-like EEG activity while most heteromodal cortices continue to produce sleep-like activity. This pattern of regional dissociation where certain cortical regions are activated while the majority of the cortical surface continues to produce slow waves is also consistent with the persistence of global slow wave activity on scalp EEG recordings [171,173]. Interestingly, these S-EEG findings could help explain some of the classic behavioral features of NREM parasomnias: the activation of the amygdalo–temporo–insular areas disengaged from the control of the prefrontal cortex could explain the motor and emotional activation, such as fear and wandering, whereas the deactivation of the hippocampal and frontal associative cortices would explain the amnesia for the event, loss of insight and disinhibited behaviors [38]. Moreover, in our third S-EEG recorded patient, the explored postero-lateral regions of the occipital cortex, the visual association areas, produced the same high amplitude delta activity as the parietal lobe and hippocampus although the patient was moving in bed with his eyes open, visually following the technician (Fig. 7-D). Although no electrode explored the primary visual cortex, this region if behaving as other previously explored primary cortices, should generate a wake-like activity during the parasomnia. As the occipito-parieto-temporal cortex is the site of visual information processing, we hypothesize that the continued production of sleep-like activity throughout the episode hinders the brain to efficiently handle the inputs of the primary visual area. This could contribute to the characteristic clumsiness and occasional sleepwalking-related injuries such as walking into walls or hitting furniture [181]. Finally, as the behavioral manifestations of NREM parasomnias can show great variations both within and across predisposed patients [182], the presented S-EEG data most likely represent an electrophysiological continuum that could explain the range of behavioral complexity and mnesic characteristics. For example, a lower threshold for local cortical networks arousability (hippocampus, frontal cortex) in adults might explain the higher proportion of episode recall in adult sleepwalkers compared to children [162].

The fundamental cause of the “pathological” state dissociation in NREM parasomnias is still unknown but genetic and maturational factors are likely to play a major role [162]. The identification with S-EEG of local dissociated states during physiological sleep seems to suggest an adaptive role of this phenomenon. Indeed, the coexistence of wake-like and sleep-like EEG patterns allows some animals, such as birds and aquatic mammals, to continue swimming, flying or monitoring the environment while obtaining some sleep [183–185]. In an evolutionary perspective, a lower arousal threshold of local cortical networks during NREM sleep in humans may have been selected, because it increases the probability of survival, i.e., prioritizing the activation of motor cortices before multimodal frontal associative cortices in case of a sudden awakening in the face of danger. However, a balance between rapid, global awakenings and sleep preservation needs be achieved to avoid repeated nocturnal arousals, and to ensure that homeostatically regulated sleep processes do occur. In subjects with NREM parasomnias, we hypothesize that a pathological increased arousability of local neuronal networks (motor and limbic) would contrast with an increased compensatory sleep preserving pressure in other cortical areas. This “dysregulated survival reflex” would therefore put in contrast structures wishing to preserve global sleep (subcortical specialized networks and cortical areas with high homeostatic sleep pressure) to the previously cited brain regions having an increased arousability or lower arousal threshold.

One limitation of studying NREM-arousal parasomnias with S-EEG is that patients must present a dual diagnosis of epilepsy and parasomnias. This reality can limit the cortical areas studied and confound the results if the sampled regions are not free of epileptic contamination. The findings described above, derived from three patients with NREM-related parasomnias, were carefully reviewed to exclude contacts with pathological activity. Moreover, our cohort includes a subject in whom the diagnosis of epilepsy was excluded following S-EEG [46]. Since we obtained similar results in all three patients, epileptic or not, we are confident in the generalizability of our findings. Nonetheless, since the use of S-EEG for future study of the pathophysiology of NREM parasomnias relies on serendipity and cannot be carefully planned, future electrophysiological studies might instead benefit from the use of high-density scalp EEG and advanced signal analysis methods [186,187]. Moreover, studying the local aspects of physiologic sleep and network connectivity in patients with epilepsy undergoing S-EEG recording might offer greater insight into specific aspects of NREM parasomnias such as the association of regional neuronal slow oscillations and altered consciousness.

Conclusion

Sleep is associated with many types of paroxysmal behaviors that have always been intertwined due to their clinical similarities. Although the intimate relationship between sleep and these

behaviors are complex, EEG and recent technological advances have helped to clarify their occurrence, differential diagnosis and their pathophysiology. Intra-cerebral EEG recordings have offered a unique opportunity to investigate simultaneously several cortical and subcortical structures across the entire vigilance spectrum, from active wakefulness to deep sleep. S-EEG recordings in patients with drug-resistant epilepsy have greatly improved our understanding of frontal and extra-frontal lobe networks implicated in sleep-related seizures as well as the influence of sleep on specific pathophysiological and histopathological substrates. Intracerebral EEG recordings derived from patients with epilepsy have also been valuable for the study of sleep physiology and specific sleep disorders such as NREM parasomnias. It is our hope that future S-EEG using advanced signal analysis methods will further contribute to understanding both disorders as well as their relationship with sleep physiology.

Practice points

- Sleep-related epilepsies
  1) Stereo-EEG is a valuable clinical tool to localize the epileptogenic zone in sleep-related drug-resistant epilepsies when non-invasive tests have failed to do so.
  2) Patients with sleep-related hypermotor seizures may exhibit many types of stereotypic motor events of increasing complexity ranging from short minor motor events (MME), and paroxysmal arousals to longer major attacks.
  3) S-EEG studies show that frontal lobe seizures follow a rostrocaudal continuum: the most highly integrated ictal behaviors arise from the rostral prefrontal regions, while the more elementary motor signs are associated with more caudally located ictal discharges.
  4) Paroxysmal arousals are strongly correlated to epileptiform discharges but the same discharge can produce variable clinical features depending not only on the cortical location but also on other variables such as the level of arousal and body position at the time of the event.
  5) In patients with NFLE, S-EEG has shown that epileptiform discharges often not detected on scalp EEG can favor the occurrence of MME and non-epileptic manifestations through an increase in arousal fluctuations (increased CAP rate).
  6) S-EEG recordings suggest that the MME observed in suspected cases of NFLE should not be considered true epileptic manifestations but a consequence of an unstable sleep (increased CAP rate) since one third of these events are not related to an epileptic discharge. As such, their presence with or without epileptiform discharges is not sufficient for the diagnosis of NFLE.
  7) Approximately 30% of patients with sleep-related hypermotor seizures have an extra-frontal onset, most frequently a temporal or operculo-insular onset, which then activates or perturbs frontal networks.
  8) Type II focal cortical dysplasia is the most common histopathological substrate of drug-resistant sleep-related hypermotor seizures, regardless of its location inside the brain.
  9) Sleep-related seizures can develop in continuity with the up-state phase of the slow wave oscillations and is favored by the presence of a spatially heterogeneous slow wave sleep state.
- NREM arousal parasomnias
  1)S-EEG recordings during the sleep-wake cycle suggest that the co-existence of wake-like and sleep-like electrophysiological activity is a possible property of the human brain. Hence, wakefulness and sleep do not seem to be two mutually exclusive states.
  2) S-EEG recordings of NREM-related parasomnias have confirmed the co-existence of simultaneous wake-like and sleep-like activity in different brain regions during an episode. The variable level of conscious awareness during a NREM parasomnia could possibly depend on the amount and location of the local persistence of these slow waves.
  3) Local slow waves characteristics and morphology during a NREM parasomnia are analogous to those observed during slow wave sleep, reflecting an alternation of neuronal up- and down-state.
  4) S-EEG findings of dissociated local wake-like and sleep-like activity are compatible with the classic clinical features of NREM parasomnias, such as motor and emotional activation along with clumsiness, disinhibited behavior, loss of insight and amnesia of the event.

Research agenda

- Sleep-related epilepsies
  1) Improve our understanding of seizure-induced alteration of consciousness during seizures using S-EEG recordings and advanced signal analysis methods.
  2) Clarify the triggers of paroxysmal arousals and minor motor events as well as the sleep-related variables such as the level of arousal, body position and cortical release phenomenon that influence them.
  3) Compare global scalp EEG findings of the CAP, namely phase A1, A2 and A3, with simultaneous local intracerebral events on S-EEG to clarify the relationship between scalp slow waves, local slow waves and epileptic activity.
  4) Provide a greater understanding of the interplay between local sleep-related slow oscillations and epileptiform activity in clinically relevant models of sleep-related epilepsy such as patients with type II focal cortical dysplasia.
- NREM arousal parasomnias
  1) Considering that capturing a NREM-related parasomnia with S-EEG is a rare event, the use of high-density scalp EEG and advanced signal analysis methods should offer greater insights in global brain dynamics during an event.
  2) Studying the local regulatory processes of physiologic sleep should increase our understanding of the pathophysiology of NREM-related parasomnias and its clinical correlates.
  3) Clarify the underlying mechanisms that relate to the alteration of consciousness in physiological sleep and in dissociated states such as NREM parasomnias with the use of S-EEG and advanced EEG signal analysis methods.

Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgments

The authors wish to thank their colleagues at the Claudio Munari Center for Epilepsy Surgery, Niguarda Hospital. SAG is supported by a research fellowship grant from the Fonds de Recherche du Québec en Santé (FRQ-S). SS gratefully acknowledges the support of the James S. McDonnell Foundation Scholar Award 2013. AP gratefully acknowledges the support of EU grant FP7-ICT-2011-9, n. 600806 "Corticonics". LN and PP gratefully acknowledge the support of the Italian Minister of Health - Targeted Research Grant RF-2010-2319316.

References

[1] Derry CP, Davey M, Johns M, Kron K, Glencross D, Marini C, et al. Distinguishing sleep disorders from seizures: diagnosing bumps in the night. Arch Neurol 2006;63:705–9.
[2] Manni R, Terzaghi M, Repetto A. The FLEP scale in diagnosing nocturnal frontal lobe epilepsy, NREM and REM parasomnias: data from a tertiary sleep and epilepsy unit. Epilepsia 2008;49:1581–5.
[3] Derry CP, Harvey AS, Walker MC, Duncan JS, Berkovic SF. NREM arousal parasomnias and their distinction from nocturnal frontal lobe epilepsy: a video EEG analysis. Sleep 2009;32:1637–44.
[4] Bisulli F, Vignatelli L, Provini F, Lugaresi E, Tinuper P. Parasomnias and nocturnal frontal lobe epilepsy (NFLE): lights and shadows – controversial points in the differential diagnosis. Sleep Med 2011;12:S27–32.
[5] Bisulli F, Vignatelli L, Naldi I, Pittau F, Provini F, Plazzi G, et al. Diagnostic accuracy of a structured interview for nocturnal frontal lobe epilepsy (SINFLE): a proposal for developing diagnostic criteria. Sleep Med 2012;13:81–7.
[6] Foldvary-Schaefer N, Grigg-Damberger M. Sleep and epilepsy: what we know, don't know and need to know. J Clin Neurophysiol 2006;23:4.
*[7] Parrino L, Halasz P, Tassinari CA, Terzano MG. CAP, epilepsy and motor events during sleep: the unifying role of arousal. Sleep Med Rev 2006;10:267–85.
[8] Hofstra WA, de Weerd AW. The circadian rhythm and its interaction with human epilepsy: a review of literature. Sleep Med Rev 2009;13:413–20.
[9] Eriksson SH. Epilepsy and sleep. Curr Opin Neurol 2011;24:171–6.
[10] Van Golde EGA, Gutter T, de Weerd AW. Sleep disturbances in people with epilepsy; prevalence, impact and treatment. Sleep Med Rev 2011;15:357–68.
[11] Derry CP, Duncan S. Sleep and epilepsy. Epilepsy Behav 2013;26:394–404.
[12] Halász P. How sleep activates epileptic networks? Epilepsy Res Treat 2013:425697.
*[13] Nobili L, Proserpio P, Combi R, Provini F, Plazzi G, Bisulli F, et al. Nocturnal frontal lobe epilepsy. Curr Neurol Neurosci Rep 2014;14:424.
[14] Provini F, Plazzi G, Montagna P, Lugaresi E. the wide clinical spectrum of nocturnal frontal lobe epilepsy. Sleep Med Rev 2000;4:375–86.
[15] Nobili L. Nocturnal frontal lobe epilepsy and non-rapid eye movement sleep parasomnias: differences and similarities. Sleep Med Rev 2007;11:251–4.
[16] Tinuper P, Provini F, Bisulli F, Vignatelli L, Plazzi G, Vetrugno R, et al. Movement disorders in sleep: guidelines for differentiating epileptic from non-epileptic motor phenomena arising from sleep. Sleep Med Rev 2007;11:255–67.
[17] Zucconi M, Ferini-Strambi L. NREM parasomnias: arousal disorders and differentiation from nocturnal frontal lobe epilepsy. Clin Neurophysiol 2000;111:S129–35.
[18] Pincherle A, Proserpio P, Didato G, Freri E, Dyljgeri S, Granata T, et al. Epilepsy and NREM-parasomnia: a complex and reciprocal relationship. Sleep Med 2012;13:442–4.
[19] Cardinale F, Cossu M, Castana L, Casaceli G, Schiariti MP, Miserocchi A, et al. Stereoelectroencephalography: surgical methodology, safety, and stereotactic application accuracy in 500 procedures. Neurosurgery 2013;72:353–66.
[20] Munari C, Hoffmann D, Francione S, Kahane P, Tassi L, Lo Russo G, et al. Stereo-electroencephalography methodology: advantages and limits. Acta Neurol Scand Suppl 1994;152:56–67. discussion 68–9.
[21] McGonigal A, Bartolomei F, Régis J, Guye M, Gavaret M, Trébuchon-Da Fonseca A, et al. Stereoelectroencephalography in presurgical assessment of MRI-negative epilepsy. Brain 2007;130:3169–83.
[22] Kahane P, Landré E, Minotti L, Francione S, Ryvlin P. The Bancaud and Talairach view on the epileptogenic zone: a working hypothesis. Epileptic Disord 2006;8:S16–26.
[23] Rosenow F, Luders H. Presurgical evaluation of epilepsy. Brain 2001;124:1683–700.
[24] Engel Jr J. Overview of surgical treatment for epilepsy. Treat. Epilepsy. 3rd ed. Oxford, UK: Blackwell Publishing Ltd.; 2009. p. 743–56.
[25] Kahane P, Dubeau F. Intracerebral depth electrode electroencephalography (stereoencephalography). Curr. Prat. Clin. Electroencephalogr. Fourth. Philadelphia: Wolters Kluwer Health; 2014. p. 393–441.
[26] Lantz G, Grave de Peralta R, Spinelli L, Seeck M, Michel CM. Epileptic source localization with high density EEG: how many electrodes are needed? Clin Neurophysiol 2003;114:63–9.
[27] Tao JX, Ray A, Hawes-Ebersole S, Ebersole JS. Intracranial EEG substrates of scalp EEG interictal spikes. Epilepsia 2005;46:669–76.
[28] Gavaret M, Badier JM, Marquis P, McGonigal A, Bartolomei F, Regis J, et al. Electric source imaging in frontal lobe epilepsy. J Clin Neurophysiol 2006;23:358–70.
[29] Spencer SS. Neural networks in human epilepsy: evidence of and implications for treatment. Epilepsia 2002;43:219–27.
[30] Bartolomei F, Wendling F, Chauvel P. [The concept of an epileptogenic network in human partial epilepsies]. Neurochirurgie 2008;54:174–84.
[31] Mai R, Sartori I, Francione S, Tassi L, Castana L, Cardinale F, et al. Sleep-related hyperkinetic seizures: always a frontal onset? Neurol Sci 2005;26(Suppl 3):s220–4.
[32] Ryvlin P, Minotti L, Demarquay G, Hirsch E, Arzimanoglou A, Hoffman D, et al. Nocturnal hypermotor seizures, suggesting frontal lobe epilepsy, can originate in the insula. Epilepsia 2006;47:755–65.
[33] Nobili L, Francione S, Mai R, Cardinale F, Castana L, Tassi L, et al. Surgical treatment of drug-resistant nocturnal frontal lobe epilepsy. Brain 2007;130:561–73.
[34] Proserpio P, Cossu M, Francione S, Gozzo F, Lo Russo G, Mai R, et al. Epileptic motor behaviors during sleep: anatomo-electro-clinical features. Sleep Med 2011;12(Suppl. 2):S33–8.
[35] Proserpio P, Cossu M, Francione S, Tassi L, Mai R, Didato G, et al. Insular-opercular seizures manifesting with sleep-related paroxysmal motor behaviors: a stereo-EEG study. Epilepsia 2011;52:1781–91.
*[36] Bonini F, McGonigal A, Trebuchon A, Gavaret M, Bartolomei F, Giusiano B, et al. Frontal lobe seizures: from clinical semiology to localization. Epilepsia 2014;55:264–77.
[37] Nobili L, Ferrara M, Moroni F, De Gennaro L, Russo GL, Campus C, et al. Dissociated wake-like and sleep-like electro-cortical activity during sleep. Neuroimage 2011;58:612–9.
*[38] Nobili L, De Gennaro L, Proserpio P, Moroni F, Sarasso S, Pigorini A, et al. Local aspects of sleep: observations from intracerebral recordings in humans. Prog Brain Res 2012;199:219–32.
[39] 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.
[40] Rossi GF, Colicchio G, Polla P. Interictal epileptic activity during sleep: a stereo-EEG study in patients with partial epilepsy. Electroencephalogr Clin Neurophysiol 1984;58:97–106.
[41] Montplaisir J, Laverdiere M, Saint-Hilaire JM, Rouleau I. Nocturnal sleep recording in partial epilepsy: a study with depth electrodes. J Clin Neurophysiol 1987;4:383.
[42] Malow BA, Lin X, Kushwaha R, Aldrich MS. Interictal spiking increases with sleep depth in temporal lobe epilepsy. Epilepsia 1998;39:1309.
[43] Staba RJ, Wilson CL, Bragin A, Jhung D, Fried I, Engel J. High-frequency oscillations recorded in human medial temporal lobe during sleep. Ann Neurol 2004;56:108–15.
[44] Nobili L, Sartori I, Terzaghi M, Stefano F, Mai R, Tassi L, et al. Relationship of epileptic discharges to arousal instability and periodic leg movements in a case of nocturnal frontal lobe epilepsy: a stereo-EEG study. Sleep 2006;29:701–4.
*[45] Terzaghi M, Sartori I, Tassi L, Didato G, Rustioni V, LoRusso G, et al. Evidence of dissociated arousal states during NREM parasomnia from an intracerebral neurophysiological study. Sleep 2009;32:409–12.
[46] Terzaghi M, Sartori I, Tassi L, Rustioni V, Proserpio P, Lorusso G, et al. Dissociated local arousal states underlying essential clinical features of non-rapid eye movement arousal parasomnia: an intracerebral stereo-electroencephalographic study. J Sleep Res 2012;21:502–6.
[47] Moroni F, Nobili L, Curcio G, De Carli F, Fratello F, Marzano C, et al. Sleep in the human hippocampus: a stereo-EEG study. PLoS One 2007;2(9):e867.
[48] Le Van Quyen M, Staba R, Bragin A, Dickson C, Valderrama M, Fried I, et al. Large-scale microelectrode recordings of high-frequency gamma oscillations in human cortex during sleep. J Neurosci 2010;30:7770–82.
[49] Magnin M, Rey M, Bastuji H, Guillemant P, Mauguiere F, Garcia-Larrea L. Thalamic deactivation at sleep onset precedes that of the cerebral cortex in humans. Proc Natl Acad Sci U A 2010;107:3829–33.
*[50] Nir Y, Staba RJ, Andrillon T, Vyazovskiy VV, Cirelli C, Fried I, et al. Regional slow waves and spindles in human sleep. Neuron 2011;70:153–69.

* The most important references are denoted by an asterisk.

[51] Andrillon T, Nir Y, Staba RJ, Ferrarelli F, Cirelli C, Tononi G, et al. Sleep spindles in humans: insights from intracranial EEG and unit recordings. J Neurosci 2011;31:17821–34.
[52] Sarasso S, Proserpio P, Pigorini A, Moroni F, Ferrara M, De Gennaro L, et al. Hippocampal sleep spindles preceding neocortical sleep onset in humans. NeuroImage 2014;86:425–32.
[53] Young GB, Blume WT, Wells GA, Mertens WC, Eder S. Differential aspects of sleep epilepsy. Can J Neurol Sci J 1985;12:317–20.
[54] Losurdo A, Proserpio P, Cardinale F, Gozzo F, Tassi L, Mai R, et al. Drug-resistant focal sleep related epilepsy: results and predictors of surgical outcome. Epilepsy Res 2014;108(5):953–62.
[55] Crespel A, Baldy-Moulinier M, Coubes P. The relationship between sleep and epilepsy in frontal and temporal lobe epilepsies: practical and physiopathologic considerations. Epilepsia 1998;39:150–7.
[56] Herman ST, Walczak TS, Bazil CW. Distribution of partial seizures during the sleep–wake cycle: differences by seizure onset site. Neurology 2001;56:1453–9.
*[57] Provini F, Plazzi G, Tinuper P, Vandi S, Lugaresi E, Montagna P. Nocturnal frontal lobe epilepsy. A clinical and polygraphic overview of 100 consecutive cases. Brain 1999;122(Pt 6):1017–31.
[58] Scheffer IE, Bhatia KP, Lopes-Cendes I, Fish DR, Marsden CD, Andermann F, et al. Autosomal dominant frontal epilepsy misdiagnosed as sleep disorder. Lancet 1994;343:515–7.
[59] Oldani A, Zucconi M, Asselta R, Modugno M, Bonati MT, Dalpra L, et al. Autosomal dominant nocturnal frontal lobe epilepsy. A video-polysomnographic and genetic appraisal of 40 patients and delineation of the epileptic syndrome. Brain 1998;121(Pt 2):205–23.
[60] De Marco EV, Gambardella A, Annesi F, Labate A, Carrideo S, Forabosco P, et al. Further evidence of genetic heterogeneity in families with autosomal dominant nocturnal frontal lobe epilepsy. Epilepsy Res 2007;74:70–3.
[61] Heron SE, Smith KR, Bahlo M, Nobili L, Kahana E, Licchetta L, et al. Missense mutations in the sodium-gated potassium channel gene KCNT1 cause severe autosomal dominant nocturnal frontal lobe epilepsy. Nat Genet 2012;44:1188–90.
[62] Tinuper P, Cerullo A, Cirignotta F, Cortelli P, Lugaresi E, Montagna P. Nocturnal paroxysmal dystonia with short-lasting attacks: three cases with evidence for an epileptic frontal lobe origin of seizures. Epilepsia 1990;31:549–56.
[63] Montagna P, Sforza E, Tinuper P, Cirignotta F, Lugaresi E. Paroxysmal arousals during sleep. Neurology 1990;40:1063–6.
[64] Nobili L, Francione S, Mai R, Tassi L, Cardinale F, Castana L, et al. Nocturnal frontal lobe epilepsy: intracerebral recordings of paroxysmal motor attacks with increasing complexity. Sleep 2003;26:883–6.
[65] Nobili L, Sartori I, Terzaghi M, Tassi L, Mai R, Francione S, et al. Intracerebral recordings of minor motor events, paroxysmal arousals and major seizures in nocturnal frontal lobe epilepsy. Neurol Sci 2005;26(Suppl 3):s215–9.
[66] Scheffer IE, Bhatia KP, Lopes-Cendes I, Fish DR, Marsden CD, Andermann E, et al. Autosomal dominant nocturnal frontal lobe epilepsy. A distinctive clinical disorder. Brain 1995;118(Pt 1):61–73.
[67] Montagna P. Nocturnal paroxysmal dystonia and nocturnal wandering. Neurology 1992;42:61.
[68] Plazzi G, Tinuper P, Montagna P, Provini F, Lugaresi E. Epileptic nocturnal wanderings. Sleep 1995;18:749–56.
[69] Sforza E, Montagna P, Rinaldi R, Tinuper P, Cerullo A, Cirignotta F, et al. Paroxysmal periodic motor attacks during sleep: clinical and polygraphic features. Electroencephalogr Clin Neurophysiol 1993;86:161–6.
[70] Terzaghi M, Sartori I, Mai R, Tassi L, Francione S, Cardinale F, et al. Sleep-related minor motor events in nocturnal frontal lobe epilepsy. Epilepsia 2007;48:335–41.
[71] Terzaghi M, Sartori I, Mai R, Tassi L, Francione S, Cardinale F, et al. Coupling of minor motor events and epileptiform discharges with arousal fluctuations in NFLE. Epilepsia 2008;49:670–6.
[72] Chauvel P, Kliemann F, Vignal JP, Chodkiewicz JP, Talairach J. The clinical signs and symptoms of frontal lobe seizures. Phenomenology and classification. Adv Neurol 1995;66:125–6.
[73] Rheims S, Ryvlin P, Scherer C, Minotti L, Hoffmann D, Guenot M, et al. Analysis of clinical patterns and underlying epileptogenic zones of hypermotor seizures. Epilepsia 2008;49:2030–40.
[74] Biraben A, Taussig D, Thomas P, Even C, Vignal JP, Scarabin JM, et al. Fear as the main feature of epileptic seizures. J Neurol Neurosurg Psychiatry 2001;70:186–91.
[75] Enatsu R, Bulacio J, Nair DR, Bingaman W, Najm I, Gonzalez-Martinez J. Posterior cingulate epilepsy: clinical and neurophysiological analysis. J Neurol Neurosurg Psychiatry 2014;85:44–50.
[76] O'Muircheartaigh J, Richardson MP. Epilepsy and the frontal lobes. Cortex 2012;48:144–55.
[77] Penfield W, Jasper H. Epilepsy and the functional anatomy of the human brain. 1954. Boston: Little.
[78] Chauvel P, Delgado-Escueta AV. Frontal lobe seizures and epilepsies57. New York: Raven Press; 1992.
[79] Salanova V, Morris HH, Van Ness P, Kotagal P, Wyllie E, Lüders H. Frontal lobe seizures: electroclinical syndromes. Epilepsia 1995;36:16–24.
[80] Kellinghaus C, Lüders HO. Frontal lobe epilepsy. Epileptic Disord 2004;6:223–39.
[81] Souirti Z, Landré E, Mellerio C, Devaux B, Chassoux F. Neural network underlying ictal pouting ("chapeau de gendarme") in frontal lobe epilepsy. Epilepsy Behav 2014;37:249–57.
[82] Szczepanski SM, Knight RT. Insights into human behavior from lesions to the prefrontal cortex. Neuron 2014;83:1002–18.
[83] Nobili L, Francione S, Cardinale F, Lo Russo G. Epileptic nocturnal wanderings with a temporal lobe origin: a stereo-electroencephalographic study. Sleep 2002;25:669–71.
[84] Ambrosetto G, Montagna P, Vetrugno R, Cortelli P. Paroxysmal bipedal activity during syncope related to carotid body tumor. Epilepsy Behav EB 2009;15:388–90.
[85] Gasparini S, Ferlazzo E, Cianci V, Leonardi CG, Vazzana F, Africa E, et al. Gestural automatisms during syncope related to cervical malignancy. Epilepsy Behav 2011;20:566–8.
[86] Gardella E, Rubboli G, Francione S, Tassi L, Lo Russo G, Grillner S, et al. Seizure-related automatic locomotion triggered by intracerebral electrical stimulation. Epileptic Disord 2008;10:247–52.
[87] Tassinari CA, Cantalupo G, Hogl B, Cortelli P, Tassi L, Francione S, et al. Neuroethological approach to frontolimbic epileptic seizures and parasomnias: the same central pattern generators for the same behaviours. Rev Neurol Paris 2009;165:762–8.
[88] MacLean PD. The triune brain in evolution: role in paleocerebral functions. New York: Plenum; 1990.
[89] Williamson PD, Spencer DD, Spencer SS, Novelly RA, Mattson RH. Complex partial seizures of frontal lobe origin. Ann Neurol 1985;18:497–504.
[90] Nobili L, Cossu M, Mai R, Tassi L, Cardinale F, Castana L, et al. Sleep-related hyperkinetic seizures of temporal lobe origin. Neurology 2004;62:482–5.
[91] Vaugier L, Aubert S, McGonigal A, Trebuchon A, Guye M, Gavaret M, et al. Neural networks underlying hyperkinetic seizures of "temporal lobe" origin. Epilepsy Res 2009;86:200–8.
[92] Kaido T, Otsuki T, Nakama H, Kaneko Y, Kubota Y, Sugai K, et al. Complex behavioral automatism arising from insular cortex. Epilepsy Behav 2006;8:315–9.
[93] Dobesberger J, Ortler M, Unterberger I, Walser G, Falkenstetter T, Bodner T, et al. Successful surgical treatment of insular epilepsy with nocturnal hypermotor seizures. Epilepsia 2008;49:159–62.
[94] Nguyen DK, Nguyen DB, Malak R, Leroux J-M, Carmant L, Saint-Hilaire J-M, et al. Revisiting the role of the insula in refractory partial epilepsy. Epilepsia 2009;50:510–20.
[95] Nishibayashi H, Ogura M, Taguchi M, Miki J, Uematsu Y, Itakura T. Nondominant parietotemporal cortical dysplasia manifesting as hypermotor seizures. Epilepsy Behav 2009;14:691–5.
[96] Bartolomei F, Gavaret M, Hewett R, Valton L, Aubert S, Régis J, et al. Neural networks underlying parietal lobe seizures: a quantified study from intracerebral recordings. Epilepsy Res 2011;93:164–76.
[97] Montavont A, Kahane P, Catenoix H, Ostrowsky-Coste K, Isnard J, Guénot M, et al. Hypermotor seizures in lateral and mesial parietal epilepsy. Epilepsy Behav 2013;28:408–12.
[98] Yu T, Zhang G, Wang Y, Cai L, Zhou X, Du W, et al. Surgical treatment of hypermotor seizures originating from the temporal lobe. Seizure 2013;22:862–6.
[99] Kotagal P, Arunkumar G, hammel J, Mascha E. Complex partial seizures of frontal lobe onset statistical analysis of ictal semiology. Seizure 2003;12:268–81.
[100] Ferri L, Bisulli F, Nobili L, Tassi L, Lichetta L, Mostacci B, et al. Auditory aura in nocturnal frontal lobe epilepsy: a red flag to suspect an extra-frontal epileptogenic zone. Sleep Med 2014;15(11):1417–23.
[101] Isnard J, Guenot M, Sindou M, Mauguiere F. Clinical manifestations of insular lobe seizures: a stereo-electroencephalographic study. Epilepsia 2004;45:1079–90.
[102] Gibbs SA, Figorilli M, Casaceli G, Proserpio P, Nobili L. Sleep-related hypermotor seizures with a right parietal onset. J Clin Sleep Med 2015 Mar 22. pii: jc-00064-15. [Epub ahead of print].
[103] Wang L, Mathews GC, Whetsell WO, Abou-Khalil B. Hypermotor seizures in patients with temporal pole lesions. Epilepsy Res 2008;82:93–8.
[104] Almashaikhi T, Rheims S, Jung J, Ostrowsky-Coste K, Montavont A, De Bellescize J, et al. Functional connectivity of insular efferences. Hum Brain Mapp 2014;35(10):5279–94.
[105] Cloutman LL, Binney RJ, Drakesmith M, Parker GJM, Lambon Ralph MA. The variation of function across the human insula mirrors its patterns of structural connectivity: evidence from in vivo probabilistic tractography. NeuroImage 2012;59:3514–21.
[106] Almashaikhi T, Rheims S, Ostrowsky-Coste K, Montavont A, Jung J, De Bellescize J, et al. Intrainsular functional connectivity in human. Hum Brain Mapp 2014;35:2779–88.
[107] Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A. Functional connectivity of the insula in the resting brain. NeuroImage 2011;55:8–23.
[108] Zanzmera P, Shukla G, Gupta A, Goyal V, Srivastava A, Garg A, et al. Effect of successful epilepsy surgery on subjective and objective sleep parameters–a prospective study. Sleep Med 2013;14:333–8.
[109] Ferrillo F, Beelke M, De Carli F, Cossu M, Munari C, Rosadini G, et al. Sleep-EEG modulation of interictal epileptiform discharges in adult

partial epilepsy: a spectral analysis study. Clin Neurophysiol 2000;111:916–23.
[110] Sammaritano M, Gigli JL, Gotman J. Interictal spiking during wakefulness and sleep and the localization of foci in temporal lobe epilepsy. Neurology 1991;23:4.
[111] Malow BA, Selwa LA, Ross D, Aldrich MS. Lateralizing value of interictal spikes on overnight sleep EEG studies in temporal lobe epilepsy. Epilepsia 1999;40:1587.
[112] Adachi N, Alarcon G, Binnie CD, Elwes RD, Polkey CE, Reynolds EH. Predictive value of interictal epileptiform discharges during non-REM sleep on scalp EEG recordings for the lateralization of epileptogenesis. Epilepsia 1998;39:628–32.
[113] Abraham K, Marsan CA. Patterns of cortical discharges and their relation to routine scalp electroencephalography. Electroencephalogr Clin Neurophysiol 1958;10:447–61.
[114] Clemens Z, Janszky J, Szucs A, Békésy M, Clemens B, Halász P. Interictal epileptic spiking during sleep and wakefulness in mesial temporal lobe epilepsy: a comparative study of scalp and foramen ovale electrodes. Epilepsia 2003;44:186–92.
[115] Parrino L, Ferri R, Bruni O, Terzano MG. Cyclic alternating pattern (CAP): the marker of sleep instability. Sleep Med Rev 2012;16:27–45.
[116] Frauscher B, von Ellenrieder N, Ferrari-Marinho T, Avoli M, Dubeau F, Gotman J. Facilitation of epileptic activity during sleep is mediated by high amplitude slow waves. Brain 2015 [Epub ahead of print].
[117] Nobili L, Cardinale F, Magliola U, Cicolin A, Didato G, Bramerio M, et al. Taylor's focal cortical dysplasia increases the risk of sleep-related epilepsy. Epilepsia 2009;50:2599–604.
[118] Chassoux F, Devaux B, Landre E, Turak B, Nataf F, Varlet P, et al. Stereoelectroencephalography in focal cortical dysplasia: a 3D approach to delineating the dysplastic cortex. Brain 2000;123(Pt 8):1733–51.
[119] Francione S, Nobili L, Cardinale F, Citterio A, Galli C, Tassi L. Intra-lesional stereo-EEG activity in Taylor 's focal cortical dysplasia. Epileptic Disord 2003;5(Suppl 2):S105–14.
[120] Tassi L, Garbelli R, Colombo N, Bramerio M, Russo GL, Mai R, et al. Electroclinical, MRI and surgical outcomes in 100 epileptic patients with type II FCD. Epileptic Disord 2012;14:257–66.
[121] Fuentealba P, Steriade M. The reticular nucleus revisited: intrinsic and network properties of a thalamic pacemaker. Prog Neurobiol 2005;75:125–41.
[122] Garbelli R, Frassoni C, Condorelli DF, Trovato Salinaro A, Musso N, Medici V, et al. Expression of connexin 43 in the human epileptic and drug-resistant cerebral cortex. Neurology 2011;76:895–902.
[123] Chassoux F, Landré E, Mellerio C, Turak B, Mann MW, Daumas-Duport C, et al. Type II focal cortical dysplasia: electroclinical phenotype and surgical outcome related to imaging. Epilepsia 2012;53:349–58.
*[124] Beenhakker MP, Huguenard JR. Neurons that fire together also conspire together: is normal sleep circuitry hijacked to generate epilepsy? Neuron 2009;62:612–32.
[125] Massimini M, Ferrarelli F, Murphy M, Huber R, Riedner B, Casarotto S, et al. Cortical reactivity and effective connectivity during REM sleep in humans. Cogn Neurosci 2010;1:176–83.
[126] Engel Jr J, Ackermann RF. Interictal EEG spikes correlate with decreased, rather than increased, epileptogenicity in amygdaloid kindled rats. Brain Res 1980;190:543–8.
[127] De Curtis M, Avanzini G. Interictal spikes in focal epileptogenesis. Prog Neurobiol 2001;63:541–67.
[128] Librizzi L, de Curtis M. Epileptiform ictal discharges are prevented by periodic interictal spiking in the olfactory cortex. Ann Neurol 2003;53:382–9.
[129] De Curtis M, Tassi L, Lo Russo G, Mai R, Cossu M, Francione S. Increased discharge threshold after an interictal spike in human focal epilepsy. Eur J Neurosci 2005;22:2971–6.
[130] Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G. Breakdown of cortical effective connectivity during sleep. Science 2005;309:2228–32.
[131] Boly M, Perlbarg V, Marrelec G, Schabus M, Laureys S, Doyon J, et al. Hierarchical clustering of brain activity during human nonrapid eye movement sleep. Proc Natl Acad Sci U. S. A 2012;109:5856–61.
[132] Tagliazucchi E, von Wegner F, Morzelewski A, Brodbeck V, Borisov S, Jahnke K, et al. Large-scale brain functional modularity is reflected in slow electroencephalographic rhythms across the human non-rapid eye movement sleep cycle. NeuroImage 2013;70:327–39.
[133] Steriade M, Nunez A, Amzica F. A novel slow (< 1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. J Neurosci 1993;13:3252–65.
[134] Steriade M. Grouping of brain rhythms in corticothalamic systems. Neuroscience 2006;137:1087–106.
[135] Steriade M, Contreras D, Curro Dossi R, Nunez A. The slow (<1 Hz) oscillation in reticular thalamic and thalamocortical neurons: scenario of sleep rhythm generation in interacting thalamic and neocortical networks. J Neurosci 1993;13:3284.
[136] Steriade M, Amzica F, Contreras D. Synchronization of fast (30-40 Hz) spontaneous cortical rhythms during brain activation. J Neurosci Off J Soc Neurosci 1996;16:392–417.
[137] Timofeev I, Grenier F, Steriade M. Disfacilitation and active inhibition in the neocortex during the natural sleep-wake cycle: an intracellular study. Proc Natl Acad Sci U. S. A 2001;98:1924–9.
[138] Chauvette S, Crochet S, Volgushev M, Timofeev I. Properties of slow oscillation during slow-wave sleep and anesthesia in cats. J Neurosci 2011;31:14998–5008.
[139] Timofeev I, Steriade M. Neocortical seizures: initiation, development and cessation. Neuroscience 2004;123:299–336.
[140] Boucetta S, Chauvette S, Bazhenov M, Timofeev I. Focal generation of paroxysmal fast runs during electrographic seizures. Epilepsia 2008;49:1925–40.
[141] Timofeev I, Bazhenov M, Seigneur J, Sejnowski T. Neuronal synchronization and thalamocortical rhythms in sleep, wake and epilepsy. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, editors. Jaspers Basic Mech. Epilepsies. 4th ed. USA: Oxford University Press; 2012.
[142] Avoli M, de Curtis M. GABAergic synchronization in the limbic system and its role in the generation of epileptiform activity. Prog Neurobiol 2011;95:104–32.
[143] Massimini M, Ferrarelli F, Sarasso S, Tononi G. Cortical mechanisms of loss of consciousness: insight from TMS/EEG studies. Arch Ital Biol 2012;150:44–55.
[144] Friston K. Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 1994;2:56–78.
[145] Steriade M, Timofeev I, Grenier F. Natural waking and sleep states: a view from inside neocortical neurons. J Neurophysiol 2001;85:1969–85.
[146] Massimini M, Amzica F. Extracellular calcium fluctuations and intracellular potentials in the cortex during the slow sleep oscillation. J Neurophysiol 2001;85:1346–50.
*[147] Pigorini A, Sarasso S, Proserpio P, Szymanski C, Anulfo G, Casarotto S, et al. Bistability breaks-off cortico-cortical causal interactions during non-REM sleep. NeuroImage 2015;112:105–13.
[148] Halasz P, Terzano M, Parrino L, Bodizs R. The nature of arousal in sleep. J Sleep Res 2004;13:1–23.
[149] Vyazovskiy VV, Olcese U, Hanlon EC, Nir Y, Cirelli C, Tononi G. Local sleep in awake rats. Nature 2011;472:443–7.
[150] Rummel C, Goodfellow M, Gast H, Hauf M, Amor F, Stibal A, et al. A systems-level approach to human epileptic seizures. Neuroinformatics 2013;11:159–73.
[151] Munari C, Kahane P, Tassi L, Francione S, Hoffmann D, Lo Russo G, et al. Intracerebral low frequency electrical stimulation: a new tool for the definition of the "epileptogenic area"? Acta Neurochir Suppl (Wien) 1993;58:181–5.
[152] Vignal JP, Chauvel P. Functional localization of the cortex with depth electrodes. Textb. Epilepsy Surg. First. London: Informa; 2008. p. 1068–72.
[153] Moruzzi G, Magoun HW. Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol 1949;1:455–73.
[154] Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature 2005;437:1257–63.
[155] Fuller PM, Fuller P, Sherman D, Pedersen NP, Saper CB, Lu J. Reassessment of the structural basis of the ascending arousal system. J Comp Neurol 2011;519:933–56.
[156] Fort P, Bassetti C, Luppi P. Alternating vigilance states: new insights regarding neuronal networks and mechanisms. Eur J Neurosci 2009;29:1741–53.
[157] Mahowald MW, Cramer Bornemann MA, Schenck CH. State dissociation, human behavior, and consciousness. Curr Top Med Chem 2011;11:2392–402.
[158] Ferrara M, De Gennaro L. Going local: insights from EEG and stereo-EEG studies of the human sleep-wake cycle. Curr Top Med Chem 2011;11:2423–37.
[159] Sarasso S, Pigorini A, Proserpio P, Gibbs SA, Massimini M, Nobili L. Fluid boundaries between wake and sleep: experimental evidence from Stereo-EEG recordings. Arch Ital Biol 2014;152(2–3):169–77.
[160] Pigarev IN, Nothdurft HC, Kastner S. Evidence for asynchronous development of sleep in cortical areas. Neuroreport 1997;8:2557–60.
[161] Krueger JM, Tononi G. Local use-dependent sleep; synthesis of the new paradigm. Curr Top Med Chem 2011;11:2490–2.
*[162] Zadra A, Desautels A, Petit D, Montplaisir J. Somnambulism: clinical aspects and pathophysiological hypotheses. Lancet Neurol 2013;12:285–94.
[163] Umanath S, Sarezky D, Finger S. Sleepwalking through history: medicine, arts, and courts of law. J Hist Neurosci 2011;20:253–76.
[164] Kales A, Jacobson A, Paulson MJ, Kales JD, Walter RD. Somnambulism: psychophysiological correlates. I. All-night EEG studies. Arch Gen Psychiatry 1966;14:586–94.
[165] Pressman MR. Why has sleepwalking research been "sleepwalking"? Neurology 2008;70:2274–5.
[166] Jacobson A, Kales A, Lehmann D, Zweizig JR. Somnambulism: all-night electroencephalographic studies. Science 1965;148:975–7.
[167] Broughton RJ. Sleep disorders: disorders of arousal? Enuresis, somnambulism, and nightmares occur in confusional states of arousal, not in "dreaming sleep." Science 1968;159:1070–8.
*[168] Mahowald MW, Schenck CH. Dissociated states of wakefulness and sleep. Neurology 1992;42:44–51. discussion 52.
[169] Zucconi M, Oldani A, Ferini-Strambi L, Smirne S. Arousal fluctuations in non-rapid eye movement parasomnias: the role of cyclic alternating pattern as a measure of sleep instability. J Clin Neurophysiol 1995;12:147–54.
[170] Guilleminault C, Kirisoglu C, da Rosa AC, Lopes C, Chan A. Sleepwalking, a disorder of NREM sleep instability. Sleep Med 2006;7:163–70.

[171] Gaudreau H, Joncas S, Zadra A, Montplaisir J. Dynamics of slow-wave activity during the NREM sleep of sleepwalkers and control subjects. Sleep 2000;23:755–60.
[172] Espa F, Ondze B, Deglise P, Billiard M, Besset A. Sleep architecture, slow wave activity, and sleep spindles in adult patients with sleepwalking and sleep terrors. Clin Neurophysiol 2000;111:929–39.
[173] Schenck CH, Pareja JA, Patterson AL, Mahowald MW. Analysis of polysomnographic events surrounding 252 slow-wave sleep arousals in thirty-eight adults with injurious sleepwalking and sleep terrors. J Clin Neurophysiol 1998;15:159–66.
[174] Jaar O, Pilon M, Carrier J, Montplaisir J, Zadra A. Analysis of slow-wave activity and slow-wave oscillations prior to somnambulism. Sleep 2010;33:1511–6.
[175] Riedner BA, Vyazovskiy VV, Huber R, Massimini M, Esser S, Murphy M, et al. Sleep homeostasis and cortical synchronization: III. A high-density EEG study of sleep slow waves in humans. Sleep 2007;30:1643–57.
[176] Bruni O, Ferri R, Novelli L, Finotti E, Miano S, Guilleminault C. NREM sleep instability in children with sleep terrors: the role of slow wave activity interruptions. Clin Neurophysiol 2008;119:985–92.
[177] Ferri R, Rundo F, Bruni O, Terzano MG, Stam CJ. Regional scalp EEG slow-wave synchronization during sleep cyclic alternating pattern A1 subtypes. Neurosci Lett 2006;404:352–7.
[178] Bassetti C, Vella S, Donati F, Wielepp P, Weder B. SPECT during sleepwalking. Lancet 2000;356:484–5.
[179] Tononi G. Consciousness, information integration, and the brain. Prog Brain Res 2005;150:109–26.
[180] Cash SS, Halgren E, Dehghani N, Rossetti AO, Thesen T, Wang C, et al. The human K-complex represents an isolated cortical down-state. Science 2009;324:1084–7.
[181] Schenck CH, Milner DM, Hurwitz TD, Bundlie SR, Mahowald MW. A polysomnographic and clinical report on sleep-related injury in 100 adult patients. Am J Psychiatry 1989;146:1166–73.
[182] Montplaisir J, Zadra A, Nielsen T, Petit Dominique. Parasomnias. Sleep disord. Med. Basic sci. Tech. Consid. Clin. Asp. Third. Philadelphia: Saunders Elsevier; 2009. p. 591–605.
[183] Lima SL, Rattenborg NC. A behavioural shutdown can make sleeping safer: a strategic perspective on the function of sleep. Anim Behav 2007;74:189–97.
[184] Lyamin OI, Manger PR, Ridgway SH, Mukhametov LM, Siegel JM. Cetacean sleep: an unusual form of mammalian sleep. Neurosci Biobehav Rev 2008;32:1451–84.
[185] Rattenborg NC, Lima SL, Lesku JA. Sleep locally, act globally. Neurosci Rev 2012;18:533–46.
[186] Lustenberger C, Huber R. High density electroencephalography in sleep research: potential, problems, future perspective. Front Neurol 2012;3:77.
[187] Siclari F, Bernardi G, Riedner BA, LaRocque JJ, Benca RM, Tononi G. Two distinct synchronization processes in the transition to sleep: a high-density electroencephalographic study. Sleep 2014;37:1621–37.
[188] Gibbs SA, Proserpio P, Lo Russo G, Francione S, Nobili L. [Anatomo-electro-clinical features of nocturnal epileptic motor behaviors and non-REM parasomnias: data from intracerebral recordings]. Prat Neurol FMC 2014;5:121–8.
[189] Halasz P, Kelemen A, Szucs A. The role of NREM sleep micro-arousals in absence epilepsy and in nocturnal frontal lobe epilepsy. Epilepsy Res 2013;107:9–19.
[190] Delorme A, Makeig SEEGLAB. an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004;134:9–21.