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REVIEW ARTICLE



Sleep and epilepsy: A snapshot of knowledge and future research lines

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Summary

Sleep and epilepsy have a reciprocal relationship, and have been recognized as bedfellows since antiquity. However, research on this topic has made a big step forward only in recent years. In this narrative review we summarize the most stimulating discoveries and insights reached by the “European school.” In particular, different aspects concerning the sleep–epilepsy interactions are analysed: (a) the effects of sleep on epilepsy; (b) the effects of epilepsy on sleep structure; (c) the relationship between epilepsy, sleep and epileptogenesis; (d) the impact of epileptic activity during sleep on cognition; (e) the relationship between epilepsy and the circadian rhythm; (f) the history and features of sleep hypermotor epilepsy and its differential diagnosis; (g) the relationship between epilepsy and sleep disorders.

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KEYWORDS

arousal, brain plasticity, circadian rhythm, clock genes, cyclic alternating pattern, disorders of arousal, epileptic spikes, epilepsy surgery, insomnia, memory, sleep apnea, sleep hypermotor epilepsy, sleep oscillations

1 | INTRODUCTION

Until the 1980s, polysomnography (PSG) was principally used to clarify diagnostic doubts about epilepsy. By exploiting the potential capacity of sleep to activate subtle or muted paroxysmal abnormalities during wakefulness, and to avoid inducing latent seizures by central nervous system stimulants (e.g. bemegride; Bancaud, Talairach, Waltegnny, Bresson, & Morel, 1969; Feuerstein, Kurtz, & Rohmer, 1966), clinical environments dedicated to electroencephalography (EEG) were converted into rudimentary and temporary sleep laboratories. However, because the patient had only to fall asleep and reach the deepest non-rapid eye movement (NREM) sleep stages, recording was limited to 30–60 min or at most an hour and a half to try to capture also a period of rapid eye movement (REM) stage. Even today, especially in the paediatric field, video-EEGs are generally scheduled in the morning after sleep deprivation in subjects with suspected epilepsy. In effect, why extend PSG monitoring throughout the night if the diagnostic uncertainties of epilepsy may be resolved after a single sleep cycle? Does it make sense to hire and pay a neurophysiology technician for an entire night? What could the complete sleep histogram ever reveal? A portion of stage N3 could be enough even in the case of NREM parasomnias. The tenacious and visionary curiosity of European sleep medicine pioneers went further, allowing us to investigate the mysterious and fruitful intertwining between sleep and epilepsy. This approach has allowed to shed light on unknown neurophysiological mechanisms, consolidate the role of sleep microstructure, and disclose the impact of ictal and interictal manifestations on daytime vigilance, cognitive functions and autonomic balance. Moreover, important clinical findings on sleep-related epilepsies (SRE) and co-morbidities with sleep disorders have been highlighted. In this review, we summarize the most stimulating discoveries and insights reached by the “European school.”

2 | THE EFFECTS OF SLEEP ON EPILEPSY

Sleep has a significant effect on epilepsy, with NREM sleep facilitating and REM sleep inhibiting epileptic activity (Ng & Pavlova, 2013; Shouse, Farber, & Staba, 2000). Evidence for the effects of sleep on epilepsy is not only present for sleep architecture but also for its microstructure. Analysis of the cyclic alternating pattern (CAP), an EEG marker of unstable sleep, has shown that epileptic activity is not uniformly increased during NREM sleep, but that enhanced epileptic activity is associated with CAP A1 subtypes that consist of recurrent EEG bursts of slow-wave activation (Parrino, Smerieri, Spaggiari, & Terzano, 2000). Subsequently, the role of slow waves known to orchestrate physiological brain rhythms was investigated in epilepsy

(Steriade, 2006). Isolated high-amplitude slow waves were found to be the main driver of interictal epileptic activity during NREM sleep (Frauscher et al., 2015a), likely mediated by EEG hypersynchronization and by the presence of a bi-stable state typical of slow oscillations (Steriade, 2006). On the other hand, in some epileptic conditions, the distribution of interictal epileptiform discharges (IEDs) follows the dynamics of spindle frequency activity throughout the night (Ferrillo, Beelke, & Nobili, 2000; Zubler, Rubino, Lo Russo, Schindler, & Nobili, 2017). In contrast, it was shown that REM sleep with (phasic) and without (tonic) rapid eye movements has distinct suppressive impact on interictal epileptic activity, with the most inhibiting effect being present during phasic REM sleep where EEG desynchronization is maximum (Campana et al., 2017; Frauscher, von Ellenrieder, Dubeau, & Gotman, 2016). Apart from these well-documented relationships, the effect of arousals on sleep and epilepsy remains a crucial issue to be investigated. In particular, it has been shown that epileptic activity (Peter-Derex et al., 2020; Terzano, Parrino, Anelli, & Halasz, 1989), as well as physiological, paraphysiological and pathological motor events share a common trait of arousal-activated phenomena (Parrino, Halasz, Tassinari, & Terzano, 2006).

In pre-surgical epilepsy evaluation as currently performed, analysis of sleep plays at most a minor role. However, in a time of increased efforts undertaken to localize the epileptogenic zone in the interictal EEG, it might be particularly beneficial to take advantage of the distinct properties of sleep. Standard EEG shows that spikes (if present) become more focally restricted during REM sleep and more widespread, revealing additional foci during NREM sleep (Ng & Pavlova, 2013; Sammaritano, Gigli, & Gotman, 1991). Furthermore, a study performing electrical source imaging with high-density EEG in six patients supported the source localizing value of REM spikes over NREM spikes (Kang et al., 2020). Finally, a recent systematic review concluded that spikes occurring during REM sleep correctly localized the epileptogenic zone in 84% of cases and that REM spikes were never false localizing (McLeod, Ghassemi, & Ng, 2020). On the other hand, capitalizing on supervised machine learning techniques, a recent study found that NREM sleep is best to identify the epileptogenic zone for both single features such as spikes or high-frequency oscillations, a novel marker of the epileptogenic zone (Frauscher et al., 2017) and the multi-feature approach (Klimes et al., 2019). One explanation that could reconcile both findings is that REM sleep is particularly useful for features relying on EEG desynchronization effects such as increased localization accuracy of spikes, whereas NREM sleep has particular value for features capitalizing on the impact of synchronization. Utilizing strengths of both states of vigilance might aid to further improve localization accuracy.

In clinical practice it is widely accepted that sleep deprivation can provoke seizures and increases the likelihood of finding specific

epileptiform abnormalities in the standard EEG, as cortical excitability increases with time awake (Huber et al., 2013). However, this statement is true only when considering specific epilepsy subtypes. It is known that sleep deprivation results more frequently in seizures in case of generalized epilepsies and in particular in juvenile myoclonic epilepsy (Xu et al., 2018). Further, sleep deprivation protocols aiming to provoke specific epileptiform anomalies in standard EEG were most useful in the context of generalized epilepsies (Renzel, Baumann, & Poryazova, 2016). In contrast, its blind use for all types of epilepsy or focal epilepsies added no further value than a subsequent repeated standard EEG. In a systematic review, Rossi et al. identified only five relevant studies based on focal epilepsy; two of the five studies showed no clear relationship between insufficient sleep and seizure risk (Rossi, Joe, Makhija, & Goldenholz, 2020). The only randomized study performed in the epilepsy monitoring unit in 84 pre-surgical epilepsy patients found no effect of sleep deprivation on seizure occurrence (Malow, Passaro, Milling, Minecan, & Levy, 2002). Interestingly, recent data obtained in focal drug-resistant epilepsy suggest that increasing sleep duration by 1.6 hr may lower the risk of seizure occurrence by 27% in the following 48 hr (Dell et al., 2021).

3 | THE EFFECTS OF EPILEPSY ON SLEEP STRUCTURE

Epilepsy is associated with changes in sleep macro- and microstructure (Sudbrack-Oliveira, Lima Najar, Foldvary-Schaefer, & da Mota Gomes, 2019). These changes are multifactorial, given that epilepsy is not only seizures but rather a complex, multidimensional condition regarding the underlying pathology, neuropsychiatric and sleep comorbidities, and effects of pharmacological and non-pharmacological treatments (Fisher et al., 2014; Liguori, Toledo, & Kothare, 2021; Romero-Osorio, Gil-Tamayo, Nariño, & Rosselli, 2018). However, apart from these manifold factors, evidence suggests that epileptic activity has a direct impact on sleep architecture, sleep continuity and sleep oscillations.

Increased wake after sleep onset is the strongest feature observed in patients with epilepsy (PWE; Crespel, Coubes, & Baldy-Moulinier, 2000; Dell et al., 2021; Parrino et al., 2012; Peter-Derex et al., 2020), especially during nights with clinical manifestations. It may result in part from the awakening effect of certain seizures, not only generalized tonic-clonic seizures but also focal, and even paucisymptomatic seizures (Awad & Lüders, 2010; Manni et al., 1997; Yildiz, Tezer, & Saygi, 2012). Seizure-associated changes in sleep parameters also include a decrease in REM sleep quantity and a delay in the first REM sleep episode (Bazil, Castro, & Walczak, 2000; Dell et al., 2021). Sleep architecture disruption is observed at the microstructural level as well. Generalized interictal discharges are associated with alterations in NREM sleep stability as evident by an increased amount of CAP rate and a longer duration of CAP cycles (Terzano, Parrino, Anelli, Boselli, & Clemens, 1992). A direct arousing effect of ictal and interictal activity has been demonstrated in focal drug-resistant epilepsy using combined intracranial EEG and PSG

recordings, which allow to explore the precise temporal relationship between epileptic discharges and arousals (Malow, Bowes, & Ross, 2000; Peter-Derex et al., 2020; Terzaghi et al., 2008). Epileptic activity also interferes with sleep oscillations. Epileptiform K-complexes may be observed in patients with generalized idiopathic or focal epilepsy, being considered as a paroxysmal response to arousing stimuli (Halász, Terzano, & Parrino, 2002; Niedermeyer, 2008). A focal deficit in sleep spindles, whose rate is negatively correlated with the spike index, was reported in childhood epilepsy with centrotemporal spikes (Kramer et al., 2021). Such a decrease in spindle activity is also observed in the region surrounding the epileptic focus in patients with drug-resistant epilepsy. Epileptic activity may also disrupt the orchestration of sleep oscillations, i.e. through abnormal coupling between hippocampal IED and remote cortical spindles (Gelinas, Khodagholy, Thesen, Devinsky, & Buzsáki, 2016). Changes in REM sleep oscillations have been reported too, with a decrease in density, duration and frequency of sawtooth waves in patients with temporal and extratemporal lobe epilepsy (Vega-Bermudez, Szczepanski, Malow, & Sato, 2005).

Epilepsy-related alterations in sleep patterns raise a number of considerations. First, it is worth underlining the bi-directional interaction between sleep instability and epileptic activity. Regardless of the causal relationship, enhanced sleep instability in PWE may also exert a negative impact on autonomic functions increasing the sympathetic tone during sleep (Tobaldini et al., 2013). Second, disruption of sleep architecture may be particularly pronounced in patients with sleep-related hypermotor epilepsy (SHE; Loddo et al., 2020; Nobili et al., 2005; Parrino et al., 2012). Third, despite the sleep alterations related to epilepsy, not all patients complain of poor sleep quality. As observed in insomnia, sleep misperception occurs frequently in PWE, although the objective-subjective mismatch remains to be explored (Ng & Bianchi, 2014). Finally, most evidence on the influence of epilepsy on sleep has been gathered from single-night hospital-based investigations many of which were performed in the epilepsy monitoring unit and not in a controlled sleep laboratory environment. Longitudinal assessment of sleep in PWE (at diagnosis and during follow-up, taking into account seizure control, co-morbidities, anti-seizure medication, etc.) is recommended to disentangle the role of epilepsy from that of confounding factors, and could benefit from ecological sleep studies using home-based devices.

4 | EPILEPSY, SLEEP, BRAIN PLASTICITY AND EPILEPTOGENESIS

Spontaneous cortical oscillations during slow-wave sleep are associated with neuronal plasticity due to rhythmic spike bursts and spike trains fired by thalamic and neocortical neurons during low-frequency rhythms characterizing this vigilance state. In vivo experimental data have shown that during slow-wave sleep oscillations, neuroplasticity changes occur at the level of both thalamic and cortical neurons, which progressively enhance their responsiveness (Steriade & Timofeev, 2003). Experimental and human studies have also shown

that the same spontaneous synchronized sleep oscillations may develop into paroxysmal epileptic activities (Steriade, Contreras, & Amzica, 1994). Finally, sleep-related epileptic transformation of physiological networks may underly plastic changes favouring epileptogenesis (Halász & Szűcs, 2020). Indeed, the normal sleep circuitry and sleep-specific oscillations (spindles, slow waves), hijacked to generate epileptic activity (Beenhakker & Huguenard, 2009; Steriade et al., 1994), may favour epileptogenesis in the most frequent (developmental) epilepsies (Halász, Bódizs, Ujma, Fabó, & Szűcs, 2019). In particular: (a) absence epilepsy with spike and wave discharges exploits the burst-firing mode of the corticothalamic system during NREM sleep (Beenhakker & Huguenard, 2009; Gloor, 1978; Steriade, McCormick, & Sejnowski, 1993); (b) in mesio-temporal epilepsy, hippocampal sharp-wave-ripples transform to epileptic spikes joining high-frequency pathological oscillations (Buzsáki, 2015; Frauscher et al., 2015b); (c) in the frame of perisylvian epileptic network centro-temporal spikes may shift into diffuse discharges as previously observed in patients with electrical status epilepticus in sleep (ESES) and Landau-Kleffner syndrome (LKS; Halász et al., 2019; Halász, Bódizs, et al., 2019; Mirandola et al., 2013; Tassinari et al., 2000).

5 | IEDs DURING NREM SLEEP: IMPACT ON COGNITION

The NREM sleep seems to play a major role in memory and cognition, regulating synaptic homeostasis (Tononi & Cirelli, 2014) and reshaping hippocampal-neocortical network necessary for long-term memory consolidation (Born & Wilhelm, 2012; Buzsáki, 2015; Diekelmann, 2014). The fact that NREM sleep may strongly activate IEDs, including those produced by the mesial temporal regions (Lambert et al., 2018), may have consequences on both synaptic plasticity and hippocampal-neocortical dialogue.

In childhood epilepsies characterized by a strong activation of IEDs during NREM sleep and cognitive alterations (LKS, continuous spike and waves during slow-wave sleep), an association between cognitive impairment and an altered overnight decrease of slow waves (a sign of altered slow wave homeostasis) has been reported, suggesting that IEDs may prevent the physiological process of synaptic downscaling. This seems to be supported by the improvement of cognitive functions in these patients after recovery of the homeostatic regulation of slow waves (Bölsterli et al., 2011, 2017).

On the other hand, IEDs occurring during sleep have been suggested to disturb the coupling between hippocampal ripples, thalamic spindles and cortical slow waves, necessary for long-term memory consolidation (Buzsáki, 1989, 2015). Indeed, recent studies, conducted during the presurgical evaluation of drug-resistant patients with focal epilepsy, showed a link between NREM sleep-related hippocampal IEDs and the impairment of long-term memory consolidation (Lambert et al., 2020, 2021). Hippocampal IED density has been shown to be negatively correlated with hippocampal spindle density (Frauscher et al., 2015b). Knowing the role of spindles on cognitive processes (Schabus et al., 2004), IEDs highly associated with spindle

frequency time course in different epileptic syndromes of childhood characterized by cognitive dysfunctions (Baglietto et al., 2001; Gibbs, Nobili, & Halász, 2019) play a negative role on cognition (Kramer et al., 2021). Finally, hippocampal IEDs have also been shown to disturb hippocampal-frontal networks, inducing spindle-like activity in the frontal region during NREM sleep, REM sleep and wakefulness (Dahal et al., 2019; Gelinis et al., 2016).

6 | CIRCADIAN RHYTHM AND EPILEPSY

Circadian rhythms are part of the internal 24-hr daily cycle of nearly all biological functions. Circadian patterns in seizure occurrence have been recognized for centuries. Advances in diagnostic technology including chronic intracranial EEG recordings have confirmed the clinical observation of different temporal patterns of epileptic activity and seizure occurrence over the 24-hr period (Baud et al., 2018; Ct, Tk, Ft, & Mj, 2015). The diurnal occurrence of seizures is influenced by several factors, including the type of epilepsy (generalized or focal) and the site of seizure onset (i.e. frontal, temporal, etc.; Khan et al., 2018; Spencer et al., 2016). Generalized seizures have a tendency to occur in the morning following sleep. In focal epilepsies, frontal lobe seizures occur predominantly during sleep, while temporal lobe seizures arise mostly in wakefulness (Hofstra et al., 2011). Of note, these studies do not allow evaluation of whether the observed preferred time of occurrence is modulated by behavioural states (wakefulness versus sleep or drowsiness), environmental conditions or independent effects of the endogenous circadian system. While demonstrating circadian patterns of seizures in humans can be challenging, strong evidence supporting a circadian modulation of seizures is derived from animal models, where rigorous study designs are feasible. In a rat model of limbic epilepsy, the presence of a distinct endogenous circadian distribution of seizures, irrespective of the sleep-wake status, has been shown, and the distribution of seizures relative to time of day resembled the one observed in human mesial temporal lobe epilepsy (Quigg, Straume, Menaker, & Bertram, 1998). Variability in cortical excitability across the circadian cycle and following sleep deprivation has also been shown in analyses of transcranial magnetic stimulation. Cortical excitability increases with time awake and appears to vary according to the epilepsy syndrome (Badawy, Curatolo, Newton, Berkovic, & Macdonnell, 2006), but is also modulated by the circadian phase with lower cortical excitability in the evening hours (Ly et al., 2016). Some studies have tried using melatonin to influence circadian rhythm and thereby improve seizure control; however, results have been variable and the role of melatonin in reducing seizures is uncertain (Brigo, Igwe, & Del Felice, 2016). Core circadian genes, *BMAL1* and *CLOCK*, which code for transcription factors, have been shown to influence excitability and seizure threshold (Gerstner et al., 2014; Li et al., 2017). *CLOCK* and *BMAL1* are also involved in the regulation of the mTOR pathways consistent with the notion that mTOR and the circadian system interact to promote epilepsy (Lipton et al., 2015; Zhang et al., 2009). Several regulator proteins bind to a complex GATOR1 to repress the activity of the

mTOR-system. Among them, *DEPDC5*, *NPRL2* and *NPRL3* are interesting, as mutations in these genes are specifically associated with SHE (Ricos et al., 2016; Scheffer et al., 2014). Further studies are needed to clarify the relationship, but this may inspire alternative future treatment options, including gene therapy or optogenetics. Variability in circadian seizure preponderance also opens the possibility for chronotherapy. An obvious treatment strategy in epilepsy to date is to treat at times of greatest occurrence of seizures based on historically highest seizure or epileptogenicity levels in relation to wakefulness, sleep, circadian or non-circadian rhythms (Ramgopal, Thome-Souza, & Loddenkemper, 2013). Such personalized antiepileptic drug-dosing regimens may improve seizure control and reduce side-effects as well as risks associated with seizures.

7 | FROM NOCTURNAL FRONTAL LOBE EPILEPSY (NFLE) TO SHE

The first description of SHE dates back to 1981, when Lugaresi and Cirignotta described five patients presenting bizarre motor behaviours or sustained dystonic postures during sleep. They named this condition “hypnogenic paroxysmal dystonia” and later “nocturnal paroxysmal dystonia” (NPD) to emphasize the complex, violent, dystonic and ballistic features of the episodes (Lugaresi & Cirignotta, 1981). In 1990, Tinuper *et al.* confirmed the epileptic nature of NPD documenting clear-cut epileptic EEG abnormalities in three patients with NPD (Tinuper *et al.*, 1990). The term “NFLE” was coined, defining NFLE as a syndrome characterized by a spectrum of motor manifestations of varying complexity and duration from the shortest episodes (paroxysmal arousals, PA) to the most prolonged events (epileptic nocturnal wanderings, ENW; Montagna, 1992; Plazzi, Tinuper, Montagna, Provini, & Lugaresi, 1995; Provini, Plazzi, & Lugaresi, 2000). A video-PSG study of 100 consecutive NFLE cases highlighted that seizure frequency was high with frequent clustering, and that PA, NPD and ENW could occur in the same patient representing the continuum of a common epileptic condition (Provini *et al.*, 1999). Subsequently, many studies showed that sleep-related seizures with hyperkinetic automatisms could have also an extra-frontal origin (Nobili *et al.*, 2004; Proserpio *et al.*, 2011; Ryvlin *et al.*, 2006). During a consensus conference in Bologna, the term NFLE was replaced by SHE to reflect the evidence that seizures are associated with sleep rather than time of day, have characteristic hypermotor features and are not always of frontal lobe origin (Tinuper *et al.*, 2016). It was also stated that although aetiology remains unknown in the majority of patients, it may include structural anomalies such as focal cortical dysplasia and genetic mutations such as *CHRNA4*, the first recognized epilepsy gene, identified in a large kindred of autosomal dominant SHE (Scheffer *et al.*, 1995; Steinlein *et al.*, 1995). Other genes have since then been recognized including *KCNT1* and *DEPDC5* (Heron *et al.*, 2012; Picard *et al.*, 2014).

Reviewing the anatomo-electroclinical data of patients with SHE also clarified seizure pattern subtypes arising from the frontal lobe, and showed that the most highly integrated ictal behaviours tend to

emerge from the anterior prefrontal regions, while more elementary motor signs are associated with posterior regions of the frontal lobe (Bonini *et al.*, 2014; Gibbs, Proserpio, *et al.*, 2019). Although sometimes impressive in nature, these seizure manifestations have a cortical correlate that include complex frontal networks as well as subcortical circuitry (Pelliccia *et al.*, 2022; Rheims *et al.*, 2008; Tassinari *et al.*, 2005; Zalta *et al.*, 2020). Distinguishing a frontal from an extra-frontal onset can be challenging especially in patients with normal brain magnetic resonance imaging. However, certain clues can be useful, including non-motor seizure semiology (auras), seizure duration and latency between the first detectable movement, usually an awakening, and the onset of hypermotor manifestations (Gibbs *et al.*, 2018; Gibbs *et al.*, 2019). Diagnosis of SHE is based primarily on clinical history and seizure description consisting of obvious and disruptive hypermotor events. Three diagnostic categories are available: (a) witnessed SHE (possible), based on the description of clinical features; (b) video-documented (clinical) SHE, based on the evaluation of a video-recorded hypermotor episode; and (c) video-EEG-documented (confirmed) SHE, requiring the video-polygraphic recording of stereotyped events and ictal or interictal epileptiform abnormalities. Because the presence of clear-cut ictal or interictal epileptiform abnormalities is only observed in a minority of patients, the absence of EEG correlated does not exclude the diagnosis of SHE (Tinuper *et al.*, 2016).

Differential diagnosis is broad, and includes disorders of arousals (DOA), sleep-related movement disorders, and REM-sleep behaviour disorder. Differentiation with DOA is often the most challenging due to clinical similarities between both entities. DOA are parasomnic events, characterized by complex, seemingly purposeful behaviours occurring during an incomplete awakening from NREM sleep (American Academy of Sleep Medicine, 2014). DOA often begin in childhood, are of variable frequency and duration and, most importantly, are not stereotypic in nature, as one event will likely be different from another (Castelnovo, Lopez, Proserpio, Nobili, & Dauvilliers, 2018). Careful history taking represents the first step for differentiating SHE and DOA, and this can be sufficient in typical cases. Different questionnaires based on clinical features have been developed as further support tool, though with variable accuracy values (Bisulli *et al.*, 2012; Derry *et al.*, 2006; Loddo *et al.*, 2021; Manni, Terzaghi, & Repetto, 2008). Video-PSG represents the “gold-standard” test for diagnosing complex sleep-related events, but the widespread availability of home-recording devices also provides a useful and affordable diagnostic instrument, especially if multiple DOA events are captured (Montini, Loddo, Baldelli, Cilea, & Provini, 2021; Nobili, 2009). However, in accordance with the current diagnostic criteria for SHE, if the recorded episodes are minor motor events or PA, the clinical diagnosis may be unreliable (Tinuper *et al.*, 2016). Indeed, recent findings demonstrate that DOAs are characterized not only by major events but also by events of lesser intensity, such as brief arousals called “simple arousal movements” (SAMs; Loddo *et al.*, 2017). These can be difficult to distinguish from minor motor events or PA in patients with SHE. Here, video-PSG is most helpful as the occurrence of at least one minor event during N3 is highly suggestive for DOA, whereas a major motor event outside N3 is significantly

indicative for SHE (Proserpio et al., 2019). Moreover, analysing specific semiological features captured on video-PSG such as duration, sleep stage at onset, limb involvement, movement progression and behaviours can be useful to differentiate seizure fragment in SHE from SAMs in DOA (Loddo et al., 2020). However, other studies suggest the existence of a possible continuum between the two conditions, mitigating the sharp dichotomy DOA versus SHE (Halász, Kelemen, & Szűcs, 2012; Mutti et al., 2020).

8 | EPILEPSY AND SLEEP DISORDERS

With a prevalence of epilepsy of 0.7% and the estimate that sleep disorders occur in every third person in his or her lifetime, it is not strange that both conditions may overlap. Sleep disorders often disappear or are successfully treated, but still a major overlap remains. In a large multicentre and long-term study in Italy, one or more comorbidities were found in 26.4% of 1006 PWE. From the 408 reported co-morbidities, 42.2% appeared to be associated by chance. Unfortunately sleep disorders are not taken as a specific disease, but many of the disorders studied are often accompanied by sleep disorders, for example depressions and other psychiatric diseases (Giussani et al., 2021). In another large study based on questionnaires, sleep disorders were mentioned in adult PWE twice as often when compared with controls (de Weerd et al., 2004). This ratio was far higher in children treated in a tertiary epilepsy centre: major complaints were reported by the parents 12 times more commonly than for healthy children in the same age range (Gutter, Brouwer, & de Weerd, 2013). In both studies, the quality of life (QoL) was lowest in the PWE combined with a sleep disorder. In unselected adults with PWE, 10% had coexisting obstructive sleep apnea (OSA); in a cohort of children and adult patients with drug-resistant epilepsies, OSA percentages were 20 and 30, respectively (Manni & Terzaghi, 2010). In general, sleep disorders seem to be prevalent in drug-resistant PWE (Bergmann et al., 2020).

The frequency of primary RLS/PLMS (restless leg syndrome/periodic leg movements) was higher in 98 patients with temporal epilepsy when compared with healthy controls (Geyer, Geyer, Fetterman, & Carney, 2017). In a review of 31 studies (Macêdo, Oliveira, Foldvary-Schaefer, & Gomes, 2017), the prevalence of insomnia was 28%–51% in PWE when a cut-off of the Insomnia Severity Index > 15 was used, and 36%–74% when insomnia was diagnosed according the DSM-IV or the International Classification of Sleep Disorders second edition (American Academy of Sleep Medicine, 2005).

It is clear that epilepsy and sleep have a bi-directional relationship. The phenomena of epilepsy, ictal and interictal, during the night and antiseizure medication (ASM) have an influence on sleep. Vice versa, sleep itself, but in particular sleep deprivation and sleep disorders, may worsen the severity of epilepsy. As such, these interactions may induce a vicious circle (Eriksson, 2011; Quigg et al., 2021) and have an even more negative influence on the QoL when compared with PWE without a sleep disorder (de Weerd et al., 2004; Gutter

et al., 2013). It is often difficult to delineate which factor is most important, the epilepsy or the sleep disorder, for example if a PWE complains of insomnia in addition to seizures. The chosen ASM (e.g. lamotrigine), may induce insomnia, but daytime as well nocturnal seizures combined with frequent interictal EEG abnormalities may also affect sleep (as outlined above). Further, if the PWE is sleepy during the day is this due to seizures during the night, co-morbid RLS/PLMS/OSA, or is it a side-effect of the administered ASM?

Recently, a consensus review on the “Standard procedures for the diagnostic pathway of SRE and co-morbid sleep disorders” was published under the auspices of the European Academy of Neurology, the European Sleep Research Society, and the European chapter of the International League Against Epilepsy (Nobili et al., 2020, 2021). SRE are classified into three groups: (a) sleep-associated epilepsies (seizures exclusively or almost exclusively from sleep) are SHE, epilepsy with centro-temporal spikes and the Panayiotopoulos syndrome; (b) sleep-accentuated epilepsies (consistent extreme potentiation of epileptiform activity during sleep) are ESES, LKS, West syndrome and Lennox–Gastaut syndrome; (c) awakening epilepsies (seizures typically occurring in the period after awakening from sleep) are juvenile myoclonic epilepsy and epilepsy with generalized tonic-clonic seizures alone. A description and value of the recommended aspects of the diagnostic pathway in patients with suspected SRE are given. They are grouped under: clinical history, questionnaires and diaries, tools for capturing the events at home: home video and tools for objective evaluation in the laboratory (e.g. video-EEG/PSG, actigraphy). Part two describes the recommendations for the diagnosis of SRE together with co-morbidity with sleep disorders. The diagnostic steps are similar to those in part 1, and include guidelines for management and therapy. The main rule for the diagnostic, management and therapeutic aspects of SRE with co-morbid sleep disorders is to simultaneously do two complete work-ups, one for the epilepsy and the other for the co-morbid sleep disorder (Nobili et al., 2021). For sleep disorders, the ICSD-3 and recent literature provide description and necessary diagnostic pathways. Further management and decisions about the treatment of epilepsy and co-morbid sleep disorders are similar to a situation when the disorders are not related to each other (Bruni et al., 2018; Geyer et al., 2017; Nobili et al., 2021; Pornsriniyom et al., 2014; Unterberger et al., 2015; Vignatelli et al., 2006), but the literature on the combination of these diseases is limited. Although not discussed in the standard for sudden unexpected death in epilepsy, knowledge of its prevalence and how to inform the patient is important for all PWE and their doctors, and particularly for patients with nocturnal seizures (Lamberts, Thijs, Laffan, Langan, & Sander, 2012).

9 | CONCLUSIONS

The impressive contribution of the “European school” in the field of sleep and epilepsy stems from a cultural background that tries to uncover all the information and secrets hidden in scalp- and intracerebral-EEG and polygraphic recordings. To determine if a

patient is or is not a carrier of an epileptic syndrome, hours can be spent analysing the traces in search of a paroxysmal anomaly or an alteration of the signal. Starting from these premises of detail and dynamism, the new frontiers of research will continue to explore the bi-directional interaction between the arousal mechanisms and epileptic susceptibility, but also the impact of epilepsy on the processes of circuit plasticity and memory consolidation that occur during or that are modulated by sleep. Overlap and differentiation between NREM parasomnias, SHE and other sleep pathologies also deserves to be revisited from different perspectives, and perhaps the time is ripe to also include SRE in the list of sleep disorders. Finally, due attention should be devoted to the biological autonomic consequences of epilepsy-related sleep alterations, and to the acute and long-term action of ASM on sleep structure.

AUTHOR CONTRIBUTIONS

Conceptualization: L.N., L.P.; B.F. and L.P.D. wrote the first draft of the chapters “The Effects of Sleep on Epilepsy” and the “Effects of Epilepsy on Sleep”; P.H. and I.L. wrote the first draft of the chapters “Epilepsy, Sleep, Brain Plasticity and Epileptogenesis” and “IEDs During NREM Sleep: Impact on Cognition”; S.E. wrote the first draft of the chapter “Circadian Rhythm and Epilepsy”; F.P., P.P., S.G. wrote the first draft of the chapter “From Nocturnal Frontal Lobe Epilepsy to Sleep Hypermotor Epilepsy”; R.M. and A.W. wrote the first draft of the chapter “Epilepsy and Sleep Disorders”; L.N. and L.P. wrote the Introduction, the Conclusions and reviewed all the chapters; all the authors have read and approved the final version of the manuscript.

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REFERENCES

- American Academy of Sleep Medicine. (2005). *The international classification of sleep disorders, (ICSD-2)* (2nd ed.). American Academy of Sleep Medicine.
- American Academy of Sleep Medicine. (2014). *International classification of sleep disorders-third edition (ICSD-3)*. American Academy of Sleep Medicine.
- Awad, A. M., & Lüders, H. O. (2010). Hypnopompic seizures. *Epileptic Disorders: International Epilepsy Journal with Videotape*, 12(4), 270–274. <https://doi.org/10.1684/epd.2010.0336>
- Badawy, R. A. B., Curatolo, J. M., Newton, M., Berkovic, S. F., & Macdonell, R. A. L. (2006). Sleep deprivation increases cortical excitability in epilepsy: Syndrome-specific effects. *Neurology*, 67(6), 1018–1022. <https://doi.org/10.1212/01.wnl.0000237392.64230.f7>
- Baglietto, M. G., Battaglia, F. M., Nobili, L., Tortorelli, S., De Negri, E., Calevo, M. G., Veneselli, E., & De Negri, M. (2001). Neuropsychological disorders related to interictal epileptic discharges during sleep in benign epilepsy of childhood with centrotemporal or Rolandic spikes. *Developmental Medicine and Child Neurology*, 43(6), 407–412.
- Bancaud, J., Talairach, J., Waltregny, P., Bresson, M., & Morel, P. (1969). Activation by Megimide in the topographic diagnosis of focal cortical epilepsies (clinical EEG and SEEG study). *Electroencephalography and Clinical Neurophysiology*, 26(6), 640.
- Baud, M. O., Kleen, J. K., Mirro, E. A., Andrechak, J. C., King-Stephens, D., Chang, E. F., & Rao, V. R. (2018). Multi-day rhythms modulate seizure risk in epilepsy. *Nature Communications*, 9(1), 88. <https://doi.org/10.1038/s41467-017-02577-y>
- Bazil, C. W., Castro, L. H., & Walczak, T. S. (2000). Reduction of rapid eye movement sleep by diurnal and nocturnal seizures in temporal lobe epilepsy. *Archives of Neurology*, 57(3), 363–368. <https://doi.org/10.1001/archneur.57.3.363>
- Beenhakker, M. P., & Huguenard, J. R. (2009). Neurons that fire together also conspire together: Is normal sleep circuitry hijacked to generate epilepsy? *Neuron*, 62(5), 612–632. <https://doi.org/10.1016/j.neuron.2009.05.015>
- Bergmann, M., Prieschl, M., Stefani, A., Heidbreder, A., Walser, G., Frauscher, B., Unterberger, I., & Högl, B. (2020). A prospective controlled study about sleep disorders in drug resistant epilepsy. *Sleep Medicine*, 75, 434–440.
- Bisulli, F., Vignatelli, L., Naldi, I., Pittau, F., Provini, F., Plazzi, G., Stipa, C., Leta, C., Montagna, P., & Tinuper, P. (2012). Diagnostic accuracy of a structured interview for nocturnal frontal lobe epilepsy (SINFLE): A proposal for developing diagnostic criteria. *Sleep Medicine*, 13(1), 81–87. <https://doi.org/10.1016/j.sleep.2011.09.003>
- Bölsterli, B. K., Gardella, E., Pavlidis, E., Wehrle, F. M., Tassinari, C. A., Huber, R., & Rubboli, G. (2017). Remission of encephalopathy with status epilepticus (ESES) during sleep renormalizes regulation of slow wave sleep. *Epilepsia*, 58(11), 1892–1901. <https://doi.org/10.1111/epi.13910>
- Bölsterli, B. K., Schmitt, B., Bast, T., Critelli, H., Heinze, J., Jenni, O. G., & Huber, R. (2011). Impaired slow wave sleep downscaling in encephalopathy with status epilepticus during sleep (ESES). *Clinical Neurophysiology*, 122(9), 1779–1787. <https://doi.org/10.1016/j.clinph.2011.01.053>
- Bonini, F., McGonigal, A., Trébuchon, A., Gavaret, M., Bartolomei, F., Giusiano, B., & Chauvel, P. (2014). Frontal lobe seizures: From clinical semiology to localization. *Epilepsia*, 55(2), 264–277. <https://doi.org/10.1111/epi.12490>
- Born, J., & Wilhelm, I. (2012). System consolidation of memory during sleep. *Psychological Research*, 76(2), 192–203. <https://doi.org/10.1007/s00426-011-0335-6>
- Brigo, F., Igwe, S. C., & Del Felice, A. (2016). Melatonin as add-on treatment for epilepsy. *The Cochrane Database of Systematic Reviews*, 8, CD006967. <https://doi.org/10.1002/14651858.CD006967.pub4>
- Bruni, O., Angriman, M., Calisti, F., Comandini, A., Esposito, G., Cortese, S., & Ferri, R. (2018). Practitioner review: Treatment of chronic insomnia in children and adolescents with neurodevelopmental disabilities. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 59(5), 489–508. <https://doi.org/10.1111/jcpp.12812>
- Buzsáki, G. (1989). Two-stage model of memory trace formation: A role for «noisy» brain states. *Neuroscience*, 31(3), 551–570. [https://doi.org/10.1016/0306-4522\(89\)90423-5](https://doi.org/10.1016/0306-4522(89)90423-5)
- Buzsáki, G. (2015). Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. *Hippocampus*, 25(10), 1073–1188. <https://doi.org/10.1002/hipo.22488>
- Campana, C., Zubler, F., Gibbs, S., de Carli, F., Proserpio, P., Rubino, A., Cossu, M., Tassi, L., Schindler, K., & Nobili, L. (2017). Suppression of interictal spikes during phasic rapid eye movement sleep: A quantitative stereo-electroencephalography study. *Journal of Sleep Research*, 26(5), 606–613. <https://doi.org/10.1111/jsr.12533>
- Castelnovo, A., Lopez, R., Proserpio, P., Nobili, L., & Dauvilliers, Y. (2018). NREM sleep parasomnias as disorders of sleep-state dissociation. *Nature Reviews Neurology*, 14(8), 470–481.

- Crespel, A., Coubes, P., & Baldy-Moulinier, M. (2000). Sleep influence on seizures and epilepsy effects on sleep in partial frontal and temporal lobe epilepsies. *Clinical Neurophysiology*, 111, S54–S59.
- Ct, A., Tk, T., Ft, S., & Mj, M. (2015). Day-night patterns of epileptiform activity in 65 patients with long-term ambulatory electrocorticography. *Journal of Clinical Neurophysiology*, 32(5), 406–412. <https://doi.org/10.1097/WNP.0000000000000183>
- Dahal, P., Ghani, N., Flinker, A., Dugan, P., Friedman, D., Doyle, W., Devinsky, O., Khodagholy, D., & Gelinas, J. N. (2019). Interictal epileptiform discharges shape large-scale intercortical communication. *Brain: A Journal of Neurology*, 142(11), 3502–3513. <https://doi.org/10.1093/brain/awz269>
- de Weerd, A., de Haas, S., Otte, A., Trenité, D. K.-N., van Erp, G., Cohen, A., de Kam, M., & van Gerven, J. (2004). Subjective sleep disturbance in patients with partial epilepsy: A questionnaire-based study on prevalence and impact on quality of life. *Epilepsia*, 45(11), 1397–1404. <https://doi.org/10.1111/j.0013-9580.2004.46703.x>
- Dell, K. L., Payne, D. E., Kremen, V., Maturana, M. I., Gerla, V., Nejedly, P., Worrell, G. A., Lenka, L., Mivalt, F., Boston, R. C., Brinkmann, B. H., D'Souza, W., Burkitt, A. N., Grayden, D. B., Kuhlmann, L., Freestone, D. R., & Cook, M. J. (2021). Seizure likelihood varies with day-to-day variations in sleep duration in patients with refractory focal epilepsy: A longitudinal electroencephalography investigation. *EClinicalMedicine*, 37(100), 934. <https://doi.org/10.1016/j.eclinm.2021.100934>
- Derry, C. P., Davey, M., Johns, M., Kron, K., Glencross, D., Marini, C., Scheffer, I. E., & Berkovic, S. F. (2006). Distinguishing sleep disorders from seizures: Diagnosing bumps in the night. *Archives of Neurology*, 63(5), 705–709. <https://doi.org/10.1001/archneur.63.5.705>
- Diekelmann, S. (2014). Sleep for cognitive enhancement. *Frontiers in Systems Neuroscience*, 8, 46. <https://doi.org/10.3389/fnsys.2014.00046>
- Eriksson, S. H. (2011). Epilepsy and sleep. *Current Opinion in Neurology*, 24(2), 171–176. <https://doi.org/10.1097/WCO.0b013e3283445355>
- Ferrillo, F., Beelke, M., & Nobili, L. (2000). Sleep EEG synchronization mechanisms and activation of interictal epileptic spikes. *Clinical Neurophysiology*, 111(Suppl 2), S65–S73. [https://doi.org/10.1016/s1388-2457\(00\)00404-1](https://doi.org/10.1016/s1388-2457(00)00404-1)
- Feuerstein, J., Kurtz, D., & Rohmer, F. (1966). Activation by means of megrimide. Indications, value and limits in the electroencephalographic diagnosis of epilepsy. *Epilepsia*, 7(3), 220–227. <https://doi.org/10.1111/j.1528-1157.1966.tb03799.x>
- Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., Engel, J., Forsgren, L., French, J. A., Glynn, M., Hesdorffer, D. C., Lee, B. I., Mathern, G. W., Moshé, S. L., Perucca, E., Scheffer, I. E., Tomson, T., Watanabe, M., & Wiebe, S. (2014). ILAE official report: A practical clinical definition of epilepsy. *Epilepsia*, 55(4), 475–482. doi:10.1111/epi.12550
- Frauscher, B., Bernasconi, N., Caldirou, B., von Ellenrieder, N., Bernasconi, A., Gotman, J., & Dubeau, F. (2015b). Interictal hippocampal spiking influences the occurrence of hippocampal sleep spindles. *Sleep*, 38(12), 1927–1933.
- Frauscher, B., Bartolomei, F., Kobayashi, K., Cimbalnik, J., van 't Klooster, M. A., Rampp, S., Otsubo, H., Höller, Y., Wu, J. Y., Asano, E., Engel, J., Kahane, P., Jacobs, J., & Gotman, J. (2017). High-frequency oscillations: The state of clinical research. *Epilepsia*, 58(8), 1316–1329. <https://doi.org/10.1111/epi.13829>
- Frauscher, B., von Ellenrieder, N., Dubeau, F., & Gotman, J. (2016). EEG desynchronization during phasic REM sleep suppresses interictal epileptic activity in humans. *Epilepsia*, 57(6), 879–888. <https://doi.org/10.1111/epi.13389>
- Frauscher, B., von Ellenrieder, N., Ferrari-Marinho, T., Avoli, M., Dubeau, F., & Gotman, J. (2015a). Facilitation of epileptic activity during sleep is mediated by high amplitude slow waves. *Brain: A Journal of Neurology*, 138(Pt 6), 1629–1641. <https://doi.org/10.1093/brain/awv073>
- Gelinas, J. N., Khodagholy, D., Thesen, T., Devinsky, O., & Buzsáki, G. (2016). Interictal epileptiform discharges induce hippocampal-cortical coupling in temporal lobe epilepsy. *Nature Medicine*, 22(6), 641–648. <https://doi.org/10.1038/nm.4084>
- Gerstner, J. R., Smith, G. G., Lenz, O., Perron, I. J., Buono, R. J., & Ferraro, T. N. (2014). BMAL1 controls the diurnal rhythm and set point for electrical seizure threshold in mice. *Frontiers in Systems Neuroscience*, 8, 121. <https://doi.org/10.3389/fnsys.2014.00121>
- Geyer, J. D., Geyer, E. E., Fetterman, Z., & Carney, P. R. (2017). Epilepsy and restless legs syndrome. *Epilepsy & Behavior: E&B*, 68, 41–44. <https://doi.org/10.1016/j.yebeh.2016.12.010>
- Gibbs, S. A., Nobili, L., & Halász, P. (2019). Interictal epileptiform discharges in sleep and the role of the thalamus in Encephalopathy related to Status Epilepticus during slow Sleep. *Epileptic Disorders: International Epilepsy Journal with Videotape*, 21(S1), 54–61. <https://doi.org/10.1684/epd.2019.1058>
- Gibbs, S. A., Proserpio, P., Francione, S., Mai, R., Cardinale, F., Sartori, I., Castana, L., Plazzi, G., Tinuper, P., Cossu, M., Russo, G. L., Tassi, L., & Nobili, L. (2019). Clinical features of sleep-related hypermotor epilepsy in relation to the seizure-onset zone: A review of 135 surgically treated cases. *Epilepsia*, 60(4), 707–717. <https://doi.org/10.1111/epi.14690>
- Gibbs, S. A., Proserpio, P., Francione, S., Mai, R., Cossu, M., Tassi, L., & Nobili, L. (2018). Seizure duration and latency of hypermotor manifestations distinguish frontal from extrafrontal onset in sleep-related hypermotor epilepsy. *Epilepsia*, 59(9), e130–e134. <https://doi.org/10.1111/epi.14517>
- Giussani, G., Bianchi, E., Beretta, S., Carone, D., DiFrancesco, J. C., Stabile, A., Zanchi, C., Pirovano, M., Trentini, C., Padovano, G., Colombo, M., Cereda, D., Tinti, L., Scanziani, S., Gasparini, S., Bogliun, G., Ferrarese, C., Beghi, E., & PRO-LONG Study Group. (2021). Comorbidities in patients with epilepsy: Frequency, mechanisms and effects on long-term outcome. *Epilepsia*, 62(10), 2395–2404. <https://doi.org/10.1111/epi.17022>
- Gloor, P. (1978). Generalized epilepsy with bilateral synchronous spike and wave discharge. New findings concerning its physiological mechanisms. *Electroencephalography and Clinical Neurophysiology. Supplement*, 1(34), 245–249.
- Gutter, T., Brouwer, O. F., & de Weerd, A. W. (2013). Subjective sleep disturbances in children with partial epilepsy and their effects on quality of life. *Epilepsy & Behavior: E&B*, 28(3), 481–488. <https://doi.org/10.1016/j.yebeh.2013.06.022>
- Halász, P., Kelemen, A., & Szűcs, A. (2012). Physiopathogenetic interrelationship between nocturnal frontal lobe epilepsy and NREM arousal parasomnias. *Epilepsy Research and Treatment*, 12, 693. <https://doi.org/10.1155/2012/312693>
- Halász, P., Bódis, R., Ujma, P. P., Fabó, D., & Szűcs, A. (2019). Strong relationship between NREM sleep, epilepsy and plastic functions—A conceptual review on the neurophysiology background. *Epilepsy Research*, 150, 95–105. <https://doi.org/10.1016/j.eplepsyres.2018.11.008>
- Halász, P., Kelemen, A., Rosdy, B., Rásonyi, G., Clemens, B., & Szűcs, A. (2019). Perisylvian epileptic network revisited. *Seizure*, 65, 31–41. <https://doi.org/10.1016/j.seizure.2018.12.003>
- Halász, P., & Szűcs, A. (2020). Sleep and epilepsy link by plasticity. *Frontiers in Neurology*, 11, 911. <https://doi.org/10.3389/fneur.2020.00911>
- Halász, P., Terzano, M. G., & Parrino, L. (2002). Spike-wave discharge and the microstructure of sleep-wake continuum in idiopathic generalised epilepsy. *Clinical Neurophysiology*, 32(1), 38–53. [https://doi.org/10.1016/s0987-7053\(01\)00290-8](https://doi.org/10.1016/s0987-7053(01)00290-8)
- Heron, S. E., Smith, K. R., Bahlo, M., Nobili, L., Kahana, E., Licchetta, L., Oliver, K. L., Mazarib, A., Afawi, Z., Korczyn, A., Plazzi, G., Petrou, S., Berkovic, S. F., Scheffer, I. E., & Dibbens, L. M. (2012). Missense mutations in the sodium-gated potassium channel gene KCNT1 cause severe autosomal dominant nocturnal frontal lobe epilepsy. *Nature Genetics*, 44(11), 1188–1190. <https://doi.org/10.1038/ng.2440>
- Hofstra, W. A., Gordijn, M. C. M., van der Palen, J., van Regteren, R., Grootemarsink, B. E., & de Weerd, A. W. (2011). Timing of temporal

- and frontal seizures in relation to the circadian phase: A prospective pilot study. *Epilepsy Research*, 94(3), 158–162. <https://doi.org/10.1016/j.eplepsyres.2011.01.015>
- Huber, R., Mäki, H., Rosanova, M., Casarotto, S., Canali, P., Casali, A. G., Tononi, G., & Massimini, M. (2013). Human cortical excitability increases with time awake. *Cerebral Cortex (New York, N.Y.: 1991)*, 23(2), 332–338. <https://doi.org/10.1093/cercor/bhs014>
- Kang, X., Boly, M., Findlay, G., Jones, B., Gjini, K., Maganti, R., & Struck, A. F. (2020). Quantitative spatio-temporal characterization of epileptic spikes using high density EEG: Differences between NREM sleep and REM sleep. *Scientific Reports*, 10(1), 1673. <https://doi.org/10.1038/s41598-020-58,612-4>
- Khan, S., Nobili, L., Khatami, R., Loddenkemper, T., Cajochen, C., Dijk, D.-J., & Eriksson, S. H. (2018). Circadian rhythm and epilepsy. *The Lancet. Neurology*, 17(12), 1098–1108. [https://doi.org/10.1016/S1474-4422\(18\)30335-1](https://doi.org/10.1016/S1474-4422(18)30335-1)
- Klimes, P., Cimbalnik, J., Brazdil, M., Hall, J., Dubeau, F., Gotman, J., & Fraitacher, B. (2019). NREM sleep is the state of vigilance that best identifies the epileptogenic zone in the interictal electroencephalogram. *Epilepsia*, 60(12), 2404–2415. <https://doi.org/10.1111/epi.16377>
- Kramer, M. A., Stoyell, S. M., Chinappen, D., Ostrowski, L. M., Spencer, E. R., Morgan, A. K., Emerton, B. C., Jing, J., Westover, M. B., Eden, U. T., Stickgold, R., Manoach, D. S., & Chu, C. J. (2021). Focal sleep spindle deficits reveal focal thalamocortical dysfunction and predict cognitive deficits in sleep activated developmental epilepsy. *The Journal of Neuroscience*, 41(8), 1816–1829. <https://doi.org/10.1523/JNEUROSCI.2009-20.2020>
- Lambert, I., Roehri, N., Giusiano, B., Carron, R., Wendling, F., Benar, C., & Bartolomei, F. (2018). Brain regions and epileptogenicity influence epileptic interictal spike production and propagation during NREM sleep in comparison with wakefulness. *Epilepsia*, 59(1), 235–243. <https://doi.org/10.1111/epi.13958>
- Lambert, I., Tramon-Negre, E., Lagarde, S., Pizzo, F., Trebuchon-Da Fonseca, A., Bartolomei, F., & Felician, O. (2021). Accelerated long-term forgetting in focal epilepsy: Do interictal spikes during sleep matter? *Epilepsia*, 62(3), 563–569. <https://doi.org/10.1111/epi.16823>
- Lambert, I., Tramon-Negre, E., Lagarde, S., Roehri, N., Giusiano, B., Trebuchon-Da Fonseca, A., Carron, R., Benar, C.-G., Felician, O., & Bartolomei, F. (2020). Hippocampal interictal spikes during sleep impact long-term memory consolidation. *Annals of Neurology*, 87(6), 976–987. <https://doi.org/10.1002/ana.25744>
- Lamberts, R. J., Thijs, R. D., Laffan, A., Langan, Y., & Sander, J. W. (2012). Sudden unexpected death in epilepsy: People with nocturnal seizures may be at highest risk. *Epilepsia*, 53(2), 253–257. <https://doi.org/10.1111/j.1528-1167.2011.03360.x>
- Li, P., Fu, X., Smith, N. A., Ziobro, J., Curiel, J., Tenga, M. J., Martin, B., Freedman, S., Cea-Del Rio, C. A., Oboti, L., Tsuchida, T. N., Oluigbo, C., Yaun, A., Magge, S. N., O'Neill, B., Kao, A., Zelleke, T. G., Depositarior-Cabacar, D. T., Ghimbovski, S., ... Liu, J. S. (2017). Loss of CLOCK results in dysfunction of brain circuits underlying focal epilepsy. *Neuron*, 96(2), 387–401.e6. <https://doi.org/10.1016/j.neuron.2017.09.044>
- Liguori, C., Toledo, M., & Kothare, S. (2021). Effects of anti-seizure medications on sleep architecture and daytime sleepiness in patients with epilepsy: A literature review. *Sleep Medicine Reviews*, 60(101), 559. <https://doi.org/10.1016/j.smrv.2021.101559>
- Lipton, J. O., Yuan, E. D., Boyle, L. M., Ebrahimi-Fakhari, D., Kwiatkowski, E., Nathan, A., Güttler, T., Davis, F., Asara, J. M., & Sahin, M. (2015). The circadian protein BMAL1 regulates translation in response to S6K1-mediated phosphorylation. *Cell*, 161(5), 1138–1151. <https://doi.org/10.1016/j.cell.2015.04.002>
- Loddo, G., Baldassarri, L., Zenesini, C., Licchetta, L., Bisulli, F., Cirignotta, F., Mondini, S., Tinuper, P., & Provini, F. (2020). Seizures with paroxysmal arousals in sleep-related hypermotor epilepsy (SHE): Dissecting epilepsy from NREM parasomnias. *Epilepsia*, 61(10), 2194–2202. <https://doi.org/10.1111/epi.16659>
- Loddo, G., La Fauci, G., Vignatelli, L., Zenesini, C., Cilea, R., Mignani, F., Cecere, A., Mondini, S., Baldelli, L., Bisulli, F., Licchetta, L., Mostacci, B., Guaraldi, P., Giannini, G., Tinuper, P., & Provini, F. (2021). The arousal disorders questionnaire: A new and effective screening tool for confusional arousals, sleepwalking and sleep terrors in epilepsy and sleep disorders units. *Sleep Medicine*, 80, 279–285. <https://doi.org/10.1016/j.sleep.2021.01.037>
- Loddo, G., Sessagesimi, E., Mignani, F., Cirignotta, F., Mondini, S., Licchetta, L., Bisulli, F., Tinuper, P., & Provini, F. (2017). Specific motor patterns of arousal disorders in adults: A video-polysomnographic analysis of 184 episodes. *Sleep Medicine*, 41, 102–109. <https://doi.org/10.1016/j.sleep.2017.08.019>
- Lugaresi, E., & Cirignotta, F. (1981). Hypnogenic paroxysmal dystonia: Epileptic seizure or a new syndrome? *Sleep*, 4(2), 129–138.
- Ly, J. Q. M., Gaggioni, G., Chellappa, S. L., Papachilleos, S., Brzozowski, A., Borsu, C., Rosanova, M., Sarasso, S., Middleton, B., Luxen, A., Archer, S. N., Phillips, C., Dijk, D.-J., Maquet, P., Massimini, M., & Vandewalle, G. (2016). Circadian regulation of human cortical excitability. *Nature Communications*, 7(11), 828. <https://doi.org/10.1038/ncomms11828>
- Macêdo, P. J. O. M., Oliveira, P. S., Foldvary-Schaefer, N., & Gomes, M. D. M. (2017). Insomnia in people with epilepsy: A review of insomnia prevalence, risk factors and associations with epilepsy-related factors. *Epilepsy Research*, 135, 158–167.
- Malow, A., Bowes, R. J., & Ross, D. (2000). Relationship of temporal lobe seizures to sleep and arousal: A combined scalp-intracranial electrode study. *Sleep*, 23(2), 231–234.
- Malow, B. A., Passaro, E., Milling, C., Minecan, D. N., & Levy, K. (2002). Sleep deprivation does not affect seizure frequency during inpatient video-EEG monitoring. *Neurology*, 59(9), 1371–1374. <https://doi.org/10.1212/01.wnl.0000031810.15811.9e>
- Manni, R., Galimberti, C. A., Sartori, I., Politini, L., Murelli, R., & Tartara, A. (1997). Nocturnal partial seizures and arousals/awakenings from sleep: An ambulatory EEG study. *Functional Neurology*, 12(3–4), 107–111.
- Manni, R., & Terzaghi, M. (2010). Comorbidity between epilepsy and sleep disorders. *Epilepsy Research*, 90(3), 171–177. <https://doi.org/10.1016/j.eplepsyres.2010.05.006>
- Manni, R., Terzaghi, M., & Repetto, A. (2008). The FLEP scale in diagnosing nocturnal frontal lobe epilepsy, NREM and REM parasomnias: Data from a tertiary sleep and epilepsy unit. *Epilepsia*, 49(9), 1581–1585. <https://doi.org/10.1111/j.1528-1167.2008.01602.x>
- McLeod, G. A., Ghassemi, A., & Ng, M. C. (2020). Can REM sleep localize the epileptogenic zone? A systematic review and analysis. *Frontiers in Neurology*, 11, 584. <https://doi.org/10.3389/fneur.2020.00584>
- Mirandola, L., Cantalupo, G., Vaudano, A. E., Avanzini, P., Ruggieri, A., Pisani, F., Cossu, G., Tassinari, C. A., Nichelli, P. F., Benuzzi, F., & Meletti, S. (2013). Centrottemporal spikes during NREM sleep: The promoting action of thalamus revealed by simultaneous EEG and fMRI coregistration. *Epilepsy & Behavior Case Reports*, 1, 106–109. doi:10.1016/j.ebcr.2013.06.005
- Montagna, P. (1992). Nocturnal paroxysmal dystonia and nocturnal wandering. *Neurology*, 42(7 Suppl 6), 61–67.
- Montini, A., Loddo, G., Baldelli, L., Cilea, R., & Provini, F. (2021). Sleep-related hypermotor epilepsy vs disorders of arousal in adults. *Chest*, 160(1), 319–329. <https://doi.org/10.1016/j.chest.2021.01.059>
- Mutti, C., Bernabè, G., Barozzi, N., Ciliento, R., Trippi, I., Pedrazzi, G., Azzi, N., & Parrino, L. (2020). Commonalities and differences in NREM parasomnias and sleep-related epilepsy: Is there a continuum between the two conditions? *Frontiers in Neurology*, 11(600), 26. <https://doi.org/10.3389/fneur.2020.600026>
- Ng, M. C., & Bianchi, M. T. (2014). Sleep misperception in persons with epilepsy. *Epilepsy & Behavior: E&B*, 36, 9–11. <https://doi.org/10.1016/j.yebeh.2014.04.007>
- Ng, M., & Pavlova, M. (2013). Why are seizures rare in rapid eye movement sleep? Review of the frequency of seizures in different sleep

- stages. *Epilepsy Research and Treatment*, 2013, 1–10. <https://doi.org/10.1155/2013/932790>
- Niedermeyer, E. (2008). Epileptiform K complexes. *American Journal of Electroneurodiagnostic Technology*, 48(1), 48–51.
- Nobili, L., Cossu, M., Mai, R., Tassi, L., Cardinale, F., Castana, L., Citterio, A., Sartori, I., Lo Russo, G., & Francione, S. (2004). Sleep-related hyperkinetic seizures of temporal lobe origin. *Neurology*, 62(3), 482–485. <https://doi.org/10.1212/01.wnl.0000106945.68292.dc>
- Nobili, L. (2009). Can homemade video recording become more than a screening tool? *Sleep*, 32(12), 1544–1545.
- Nobili, L., Beniczky, S., Eriksson, S. H., Romigi, A., Rylvlin, P., Toledo, M., & Rosenzweig, I. (2021). Expert Opinion: Managing sleep disturbances in people with epilepsy. *Epilepsy & Behavior: E&B*, 124(108), 341. <https://doi.org/10.1016/j.yebeh.2021.108341>
- Nobili, L., de Weerd, A., Rubboli, G., Beniczky, S., Derry, C., Eriksson, S., Halasz, P., Högl, B., Santamaria, J., Khatami, R., Rylvlin, P., Rémi, J., Tinuper, P., Bassetti, C., Manni, R., Koutroumanidis, M., & Vignatelli, L. (2020). Standard procedures for the diagnostic pathway of sleep-related epilepsies and comorbid sleep disorders: A European Academy of Neurology, European Sleep Research Society and International League against Epilepsy-Europe consensus review. *Journal of Sleep Research*, 29(6), e13184. <https://doi.org/10.1111/jsr.13184>
- Nobili, L., Sartori, I., Terzaghi, M., Tassi, L., Mai, R., Francione, S., Cossu, M., Cardinale, F., Castana, L., & Lo Russo, G. (2005). Intracerebral recordings of minor motor events, paroxysmal arousals and major seizures in nocturnal frontal lobe epilepsy. *Neurological Sciences*, 26(Suppl 3), s215–s219. <https://doi.org/10.1007/s10072-005-0490-x>
- Parrino, L., De Paolis, F., Milioli, G., Gioi, G., Grassi, A., Riccardi, S., Colizzi, E., & Terzano, M. G. (2012). Distinctive polysomnographic traits in nocturnal frontal lobe epilepsy: Sleep Mechanisms in Nocturnal Frontal Lobe Seizures. *Epilepsia*, 53(7), 1178–1184. <https://doi.org/10.1111/j.1528-1167.2012.03502.x>
- Parrino, L., Halasz, P., Tassinari, C. A., & Terzano, M. G. (2006). CAP, epilepsy and motor events during sleep: The unifying role of arousal. *Sleep Medicine Reviews*, 10(4), 267–285. <https://doi.org/10.1016/j.smrv.2005.12.004>
- Parrino, L., Smerieri, A., Spaggiari, M. C., & Terzano, M. G. (2000). Cyclic alternating pattern (CAP) and epilepsy during sleep: How a physiological rhythm modulates a pathological event. *Clinical Neurophysiology*, 111-(Suppl 2), S39–S46. [https://doi.org/10.1016/s1388-2457\(00\)00400-4](https://doi.org/10.1016/s1388-2457(00)00400-4)
- Pelliecia, V., Avanzini, P., Rizzi, M., Caruana, F., Tassi, L., Francione, S., Gozzo, F., Mariani, V., d'Orto, P., Castana, L., Mai, R., Terzaghi, M., Nobili, L., & Sartori, I. (2022). Association between semiology and anatomo-functional localization in patients with cingulate epilepsy: A cohort study. *Neurology*. <https://doi.org/10.1212/WNL.000000000000200145>
- Peter-Derex, L., Klimes, P., Latreille, V., Bouhadoun, S., Dubeau, F., & Fraitser, B. (2020). Sleep disruption in epilepsy: Ictal and interictal epileptic activity matter. *Annals of Neurology*, 88(5), 907–920. <https://doi.org/10.1002/ana.25884>
- Picard, F., Makrythanasis, P., Navarro, V., Ishida, S., de Bellescize, J., Ville, D., Weckhuysen, S., Fosselle, E., Suls, A., De Jonghe, P., Vasselon, Raina, M., Lesca, G., Depienne, C., An-Gourfinkel, I., Vlaicu, M., Baulac, M., Mundwiler, E., Couarch, P., Combi, R., ... Baulac, S. (2014). DEPDC5 mutations in families presenting as autosomal dominant nocturnal frontal lobe epilepsy. *Neurology*, 82(23), 2101–2106. <https://doi.org/10.1212/WNL.0000000000000488>
- Plazzi, G., Tinuper, P., Montagna, P., Provini, F., & Lugaresi, E. (1995). Epileptic nocturnal wanderings. *Sleep*, 18(9), 749–756.
- Pornsriyom, D., Kim, H. W., Bena, J., Andrews, N. D., Moul, D., & Foldvary-Schaefer, N. (2014). Effect of positive airway pressure therapy on seizure control in patients with epilepsy and obstructive sleep apnea. *Epilepsy & Behavior: E&B*, 37, 270–275. <https://doi.org/10.1016/j.yebeh.2014.07.005>
- Proserpio, P., Cossu, M., Francione, S., Gozzo, F., Lo Russo, G., Mai, R., Moscato, A., Schiariti, M., Sartori, I., Tassi, L., & Nobili, L. (2011). Epileptic motor behaviors during sleep: Anato-electro-clinical features. *Sleep Medicine*, 12, S33–S38. <https://doi.org/10.1016/j.sleep.2011.10.018>
- Proserpio, P., Loddo, G., Zubler, F., Ferini-Strambi, L., Licchetta, L., Bisulli, F., Tinuper, P., Agostoni, E. C., Bassetti, C., Tassi, L., Menghi, V., Provini, F., & Nobili, L. (2019). Polysomnographic features differentiating disorder of arousals from sleep-related hypermotor epilepsy. *Sleep*, 1-7, zsz166. <https://doi.org/10.1093/sleep/zsz166>
- Provini, F., Plazzi, G., & Lugaresi, E. (2000). From nocturnal paroxysmal dystonia to nocturnal frontal lobe epilepsy. *Clinical Neurophysiology*, 111, S2–S8.
- Provini, F., Plazzi, G., Tinuper, P., Vandi, S., Lugaresi, E., & Montagna, P. (1999). Nocturnal frontal lobe epilepsy: A clinical and polygraphic overview of 100 consecutive cases. *Brain*, 122(6), 1017–1031.
- Quigg, M., Bazil, C. W., Boly, M., St Louis, E. K., Liu, J., Ptacek, L., Maganti, R., Kalume, F., Gluckman, B. J., Pathmanathan, J., Pavlova, M. K., & Buchanan, G. F. (2021). Proceedings of the sleep and epilepsy workshop: Section 1 decreasing seizures-improving sleep and seizures, themes for future research. *Epilepsy Currents*, 21(3), 204–209. <https://doi.org/10.1177/15357597211004566>
- Quigg, M., Straume, M., Menaker, M., & Bertram, E. H. (1998). Temporal distribution of partial seizures: Comparison of an animal model with human partial epilepsy. *Annals of Neurology*, 43(6), 748–755. <https://doi.org/10.1002/ana.410430609>
- Ramgopal, S., Thome-Souza, S., & Loddenkemper, T. (2013). Chronopharmacology of anti-convulsive therapy. *Current Neurology and Neuroscience Reports*, 13(4), 339. <https://doi.org/10.1007/s11910-013-0339-2>
- Renzel, R., Baumann, C. R., & Poryazova, R. (2016). EEG after sleep deprivation is a sensitive tool in the first diagnosis of idiopathic generalized but not focal epilepsy. *Clinical Neurophysiology*, 127(1), 209–213. <https://doi.org/10.1016/j.clinph.2015.06.012>
- Rheims, S., Rylvlin, P., Scherer, C., Minotti, L., Hoffmann, D., Guenot, M., Manguière, F., Benabid, A.-L., & Kahane, P. (2008). Analysis of clinical patterns and underlying epileptogenic zones of hypermotor seizures. *Epilepsia*, 49(12), 2030–2040. <https://doi.org/10.1111/j.1528-1167.2008.01675.x>
- Ricos, M. G., Hodgson, B. L., Pippucci, T., Saidin, A., Ong, Y. S., Heron, S. E., Licchetta, L., Bisulli, F., Bayly, M. A., Hughes, J., Baldassari, S., Palombo, F., Epilepsy Electroclinical Study Group, Santucci, M., Meletti, S., Berkovic, S. F., Rubboli, G., Thomas, P. Q., Scheffer, I. E., ... Dibbens, L. M. (2016). Mutations in the mammalian target of rapamycin pathway regulators NPRL2 and NPRL3 cause focal epilepsy. *Annals of Neurology*, 79(1), 120–131. <https://doi.org/10.1002/ana.24547>
- Romero-Osorio, Ó., Gil-Tamayo, S., Nariño, D., & Rosselli, D. (2018). Changes in sleep patterns after vagus nerve stimulation, deep brain stimulation or epilepsy surgery: Systematic review of the literature. *Seizure*, 56, 4–8. <https://doi.org/10.1016/j.seizure.2018.01.022>
- Rossi, K. C., Joe, J., Makhija, M., & Goldenholz, D. M. (2020). Insufficient sleep, electroencephalogram activation, and seizure risk: Re-evaluating the evidence. *Annals of Neurology*, 87(6), 798–806. <https://doi.org/10.1002/ana.25710>
- Rylvlin, P., Minotti, L., Demarquay, G., Hirsch, E., Arzimanoglou, A., Hoffman, D., Guénot, M., Picard, F., Rheims, S., & Kahane, P. (2006). Nocturnal hypermotor seizures, suggesting frontal lobe epilepsy, can originate in the insula. *Epilepsia*, 47(4), 755–765. <https://doi.org/10.1111/j.1528-1167.2006.00510.x>
- Sammaritano, M., Gigli, G. L., & Gotman, J. (1991). Interictal spiking during wakefulness and sleep and the localization of foci in temporal lobe epilepsy. *Neurology*, 41(2 [Pt 1]), 290–297. https://doi.org/10.1212/wnl.41.2_part_1.290
- Schabus, M., Gruber, G., Parapatics, S., Sauter, C., Klösch, G., Anderer, P., Klimesch, W., Saletu, B., & Zeithofer, J. (2004). Sleep spindles and their significance for declarative memory consolidation. *Sleep*, 27(8), 1479–1485. <https://doi.org/10.1093/sleep/27.7.1479>

- Scheffer, I. E., Bhatia, K. P., Lopes-Cendes, I., Fish, D. R., Marsden, C. D., Andermann, E., Andermann, F., Desbiens, R., Keene, D., & Cendes, F. (1995). Autosomal dominant nocturnal frontal lobe epilepsy. A distinctive clinical disorder. *Brain: A Journal of Neurology*, 118(Pt 1), 61–73. <https://doi.org/10.1093/brain/118.1.61>
- Scheffer, I. E., Heron, S. E., Regan, B. M., Mandelstam, S., Crompton, D. E., Hodgson, B. L., Licchetta, L., Provini, F., Bisulli, F., Vadlamudi, L., Geck, J., Connelly, A., Tinuper, P., Ricos, M. G., Berkovic, S. F., & Dibbens, L. M. (2014). Mutations in mammalian target of rapamycin regulator DEPDC5 cause focal epilepsy with brain malformations. *Annals of Neurology*, 75(5), 782–787. <https://doi.org/10.1002/ana.24126>
- Shouse, M. N., Farber, P. R., & Staba, R. J. (2000). Physiological basis: How NREM sleep components can promote and REM sleep components can suppress seizure discharge propagation. *Clinical Neurophysiology*, 111-(Suppl 2), S9–S18. [https://doi.org/10.1016/s1388-2457\(00\)00397-7](https://doi.org/10.1016/s1388-2457(00)00397-7)
- Spencer, D. C., Sun, F. T., Brown, S. N., Jobst, B. C., Fountain, N. B., Wong, V. S. S., Mirro, E. A., & Quigg, M. (2016). Circadian and ultradian patterns of epileptiform discharges differ by seizure-onset location during long-term ambulatory intracranial monitoring. *Epilepsia*, 57(9), 1495–1502. <https://doi.org/10.1111/epi.13455>
- Steinlein, O. K., Mulley, J. C., Propping, P., Wallace, R. H., Phillips, H. A., Sutherland, G. R., Scheffer, I. E., & Berkovic, S. F. (1995). A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. *Nature Genetics*, 11(2), 201–203. <https://doi.org/10.1038/ng1095-201>
- Steriade, M. (2006). Neuronal substrates of spike-wave seizures and hypersarrhythmia in corticothalamic systems. *Advances in Neurology*, 97, 149–154.
- Steriade, M., Contreras, D., & Amzica, F. (1994). Synchronized sleep oscillations and their paroxysmal developments. *Trends in Neurosciences*, 17(5), 199–208. [https://doi.org/10.1016/0166-2236\(94\)90105-8](https://doi.org/10.1016/0166-2236(94)90105-8)
- Steriade, M., McCormick, D. A., & Sejnowski, T. J. (1993). Thalamocortical oscillations in the sleeping and aroused brain. *Science (New York, N.Y.)*, 262(5134), 679–685. <https://doi.org/10.1126/science.8235588>
- Steriade, M., & Timofeev, I. (2003). Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. *Neuron*, 37(4), 563–576. [https://doi.org/10.1016/s0896-6273\(03\)00065-5](https://doi.org/10.1016/s0896-6273(03)00065-5)
- Sudbrack-Oliveira, P., Lima Najar, L., Foldvary-Schaefer, N., & da Mota Gomes, M. (2019). Sleep architecture in adults with epilepsy: A systematic review. *Sleep Medicine*, 53, 22–27. <https://doi.org/10.1016/j.sleep.2018.09.004>
- Tassinari, C. A., Rubboli, G., Gardella, E., Cantalupo, G., Calandra-Buonaura, G., Vedovello, M., Alessandria, M., Gandini, G., Cinotti, S., Zamponi, N., & Meletti, S. (2005). Central pattern generators for a common semiology in fronto-limbic seizures and in parasomnias. A neuroethologic approach. *Neurological Sciences*, 26(Suppl 3), s225–s232. <https://doi.org/10.1007/s10072-005-0492-8>
- Tassinari, C. A., Rubboli, G., Volpi, L., Meletti, S., d'Orsi, G., Franca, M., Sabetta, A. R., Riguzzi, P., Gardella, E., Zaniboni, A., & Michelucci, R. (2000). Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. *Clinical Neurophysiology*, 111(Suppl 2), S94–S102. [https://doi.org/10.1016/s1388-2457\(00\)00408-9](https://doi.org/10.1016/s1388-2457(00)00408-9)
- Terzaghi, M., Sartori, I., Mai, R., Tassi, L., Francione, S., Cardinale, F., Castana, L., Cossu, M., LoRusso, G., Manni, R., & Nobili, L. (2008). Coupling of minor motor events and epileptiform discharges with arousal fluctuations in NFLE. *Epilepsia*, 49(4), 670–676. <https://doi.org/10.1111/j.1528-1167.2007.01419.x>
- Terzano, M. G., Parrino, L., Anelli, S., Boselli, M., & Clemens, B. (1992). Effects of generalized interictal EEG discharges on sleep stability: Assessment by means of cyclic alternating pattern. *Epilepsia*, 33(2), 317–326. <https://doi.org/10.1111/j.1528-1157.1992.tb02322.x>
- Terzano, M. G., Parrino, L., Anelli, S., & Halasz, P. (1989). Modulation of generalized spike-and-wave discharges during sleep by cyclic alternating pattern. *Epilepsia*, 30(6), 772–781. <https://doi.org/10.1111/j.1528-1157.1989.tb05337.x>
- Tinuper, P., Bisulli, F., Cross, J. H., Hesdorffer, D., Kahane, P., Nobili, L., Provini, F., Scheffer, I. E., Tassi, L., Vignatelli, L., Bassetti, C., Cirignotta, F., Derry, C., Gambardella, A., Guerrini, R., Halasz, P., Licchetta, L., Mahowald, M., Manni, R., ... Ottman, R. (2016). Definition and diagnostic criteria of sleep-related hypermotor epilepsy. *Neurology*, 86(19), 1834–1842. <https://doi.org/10.1212/WNL.0000000000002666>
- Tinuper, P., Cerullo, A., Cirignotta, F., Cortelli, P., Lugaresi, E., & Montagna, P. (1990). Nocturnal paroxysmal dystonia with short-lasting attacks: Three cases with evidence for an epileptic frontal lobe origin of seizures. *Epilepsia*, 31(5), 549–556.
- Tobaldini, E., Nobili, L., Strada, S., Casali, K. R., Braghieri, A., & Montano, N. (2013). Heart rate variability in normal and pathological sleep. *Frontiers in Physiology*, 4, 1–11. <https://doi.org/10.3389/fphys.2013.00294>
- Tononi, G., & Cirelli, C. (2014). Sleep and the price of plasticity: From synaptic and cellular homeostasis to memory consolidation and integration. *Neuron*, 81(1), 12–34. <https://doi.org/10.1016/j.neuron.2013.12.025>
- Unterberger, I., Gabelia, D., Prieschl, M., Chea, K., Hofer, M., Högl, B., Luef, G., & Frauscher, B. (2015). Sleep disorders and circadian rhythm in epilepsy revisited: A prospective controlled study. *Sleep Medicine*, 16(2), 237–242. <https://doi.org/10.1016/j.sleep.2014.09.021>
- Vega-Bermudez, F., Szczepanski, S., Malow, B., & Sato, S. (2005). Sawtooth wave density analysis during REM sleep in temporal lobe epilepsy patients. *Sleep Medicine*, 6(4), 367–370. <https://doi.org/10.1016/j.sleep.2005.02.005>
- Vignatelli, L., Bisulli, F., Naldi, I., Ferioli, S., Pittau, F., Provini, F., Plazzi, G., Vetrugno, R., Montagna, P., & Tinuper, P. (2006). Excessive daytime sleepiness and subjective sleep quality in patients with nocturnal frontal lobe epilepsy: A case-control study. *Epilepsia*, 47(Suppl 5), 73–77. <https://doi.org/10.1111/j.1528-1167.2006.00882.x>
- Xu, L., Guo, D., Liu, Y.-Y., Qiao, D.-D., Ye, J.-Y., & Xue, R. (2018). Juvenile myoclonic epilepsy and sleep. *Epilepsy & Behavior: E&B*, 80, 326–330. <https://doi.org/10.1016/j.yebeh.2017.11.008>
- Yildiz, F. G., Tezer, F. I., & Saygi, S. (2012). Temporal relationship between awakening and seizure onset in nocturnal partial seizures. *Journal of the Neurological Sciences*, 315(1–2), 33–38. <https://doi.org/10.1016/j.jns.2011.12.009>
- Zalta, A., Hou, J.-C., Thonnat, M., Bartolomei, F., Morillon, B., & McGonigal, A. (2020). Neural correlates of rhythmic rocking in prefrontal seizures. *Clinical Neurophysiology*, 50(5), 331–338. <https://doi.org/10.1016/j.neucli.2020.07.003>
- Zhang, E. E., Liu, A. C., Hirota, T., Miraglia, L. J., Welch, G., Pongsawakul, P. Y., Liu, X., Atwood, A., Huss, J. W., Janes, J., Su, A. I., Hogenesch, J. B., & Kay, S. A. (2009). A genome-wide RNAi screen for modifiers of the circadian clock in human cells. *Cell*, 139(1), 199–210. <https://doi.org/10.1016/j.cell.2009.08.031>
- Zubler, F., Rubino, A., Lo Russo, G., Schindler, K., & Nobili, L. (2017). Correlating interictal spikes with sigma and delta dynamics during non-rapid-eye-movement-sleep. *Frontiers in Neurology*, 8, 288. <https://doi.org/10.3389/fneur.2017.00288>

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