Mechanistic insights into the interaction between epilepsy and sleep

Laurent **Sheybani** [§, 1,2,3], Birgit **Frauscher** [§, 4], Christophe **Bernard** [§, 5], Matthew C **Walker** [§, 1,2,3]

[1] Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, University College London, London, UK.
[2] National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK.
[3] NIHR University College London Hospitals Biomedical Research Centre, London, UK.
[4] Department of Neurology, Duke University Medical Center, Durham, NC, USA and Department of Biomedical Engineering, Pratt School of Engineering, Duke University, Durham, NC, USA
[5] Aix Marseille Univ, INSERM, INS, Inst Neurosci Syst, Marseille, France

[§] All authors participated equally.

Key points

- Rhythmicity in the brain molecular machinery is a novel mechanism that could determine the periodicity of epileptiform discharges and seizures.
- Multiple studies indicate an association between epilepsy and changes in sleep microarchitecture, whereas few studies have identified changes in sleep macroarchitecture, consistent with independent regulation of these processes.
- Considerable evidence shows that sleep, and particularly slow waves in sleep, is associated with increased rates of epileptiform discharges, but causality remains to be tested.
- Discrepancies between rodent models and humans, such as contradictory associations between REM sleep and seizures, can offer mechanistic insights into the interactions between sleep and epilepsy.
- Evidence indicates that epileptiform discharges during sleep can affect memory and learning.
- Contrary to the long-held assumption that interictal epileptiform discharges during rapid eye movement sleep provide the best localization of the seizure-onset zone, evidence now suggests that localization is better during non-REM sleep

Abstract

Epidemiological evidence has demonstrated associations between sleep and epilepsy, but we lack a mechanistic understanding of these associations. If sleep affects the pathophysiology of epilepsy and the risk of seizures, as suggested by correlative evidence, then understanding of these effects could provide crucial insight into the basic mechanisms that underlie the development of epilepsy and the generation of seizures. In this Review, we provide in-depth discussion of the associations between epilepsy and sleep at the cellular, network and system levels, and consider the mechanistic underpinnings of these associations. We also discuss the clinical relevance of these associations, highlighting how they could contribute to improvements in management of epilepsy. A better understanding of the mechanisms that govern the interactions between epilepsy and sleep could guide further research and the development of novel approaches to the management of epilepsy.

[H1] Introduction

The interplay between epileptic seizures and sleep has been recognized since the time of Aristotle[1]. Numerous epidemiological studies have demonstrated the link between sleep disorders and epilepsy[2], but, until recently, research on the mechanisms that underlie these interactions has been limited. Yet, understanding of these mechanisms could have important clinical consequences. Network excitability — and consequently seizure risk — changes throughout the sleep–wake cycle[3,4], consistent with the fact that seizures exhibit circadian rhythmicity (see Glossary) in most people with epilepsy[5]. Better understanding of the mechanisms that underlie this variable seizure risk should improve our understanding of the mechanisms of ictogenesis and epileptogenesis, including how network excitability shapes epileptogenic and ictogenic risks in general. This could also help to develop new drug regimens tailored to these cycles[6].

Interactions between epilepsy and sleep occur at various levels (Table 1): the cellular level (properties of individual neurons and glia, such as gene and protein expression), the network level (interactions between assemblies of neurons to generate patterns of activity) and the system level (cognition, seizure risk and associated sleep disorders). In this Review, we address the interplay between epilepsy and sleep at each of these levels, taking into account insights from basic scientific findings and clinical evidence.

Considering the relationships between sleep and epilepsy is complicated by the fact that epilepsy is not a single disease with a unique pathophysiological pathway, but encompasses various conditions that are all characterized by seizures but are heterogeneous in their clinical profiles and underlying causes. In addition, studies of people with epilepsy usually involve people who are using various antiseizure medications that independently affect sleep[2,7]. Nevertheless, certain observations hold true across different types of epilepsy, and even across species, such as periodic variations in the risk of seizures throughout the day and associations of sleep deprivation and quality with the risk of seizures[8–13]. To simplify discussion, we therefore use epilepsy as a broad term that encompasses a variety of related conditions. Similarly, we focus on the interaction between sleep and epilepsy in adults because most studies have been done in human adults and young adult animals. Though we have included findings from children where relevant, findings in adults might not directly extrapolate to children, as the spectrum of aetiologies for epilepsy differs between adults and children[14] and patterns of sleep activity also differ[15].

In this context, we highlight the challenges in research on epilepsy and sleep (BOX 1) and propose strategies to address these challenges. We conclude by discussing the implications of this complex dyad for the management of epilepsy.

[H1] Epilepsy–sleep interactions at the cellular level

[H2] Molecular machinery

In most people with epilepsy, seizures do not occur randomly but have circadian (24 h) and multidien (> 1 day) rhythmicity, and this periodicity varies between individuals[9,11,16,17]. The mechanisms that underlie such rhythmicity remain poorly understood (reviewed in detail elsewhere[5]). However, one possible explanation for the circadian rhythmicity is that the molecular architecture of neuronal networks and, consequently, network excitability change during the night and day cycle[18]. This hypothesis is supported by findings from studies of protein expression and modification across the circadian cycle. In wild-type mice, expression of >70% of synaptic transcripts and proteins oscillate during the night and day cycle[19], and phosphorylation of proteins — which is a crucial mechanism of synaptic protein regulation — is modulated by the sleep–wake cycle[20,21]. These oscillations in expression of transcripts and proteins, and in oxidative phosphorylation, which is pivotal in energy metabolism regulation[22], are all altered in experimental epilepsy (FIG. 1)[23–26].

Studies in animals and human tissue suggest that the circadian machinery itself is altered in epilepsy. Oscillations in expression of the core circadian genes *CLOCK* and *PER2* were altered in epileptogenic tissue from people with focal cortical dysplasia or tuberous sclerosis complex and in animal models (FIG. 1)[23,27,28]. In line with these findings, decreasing the expression of *CLOCK* or *BMAL1* (another core circadian gene) in mice promotes the generation of seizures[24,25,27]. These observations suggest that such alterations to the molecular mechanisms that regulate the circadian rhythm are likely to contribute to the circadian rhythmicity of seizures in epilepsy. Furthermore, oscillations in the expression of transcripts and proteins are brain region-dependent[23], suggesting that localized alterations could govern the heterogeneous circadian rhythmicity of seizures depending on the location of the epileptogenic zone[16] and could at least partially explain the diversity of epilepsy phenotypes.

Similarly, circadian changes in oxidative phosphorylation have been described in the hippocampus of mice with TLE[23]. In particular, whereas the ventral and dorsal hippocampi have different metabolic trajectories across the day in mice with epilepsy, the ventral hippocampus of mice with epilepsy has a similar metabolic pattern to that of the dorsal hippocampus[22]. In another study, the ratio of phosphorylated BMAL1 and non-phosphorylated BMAL1 at the synapse changed across the day, and phosphorylated BMAL1 increased synaptic transmission efficiency[29]. Whether this ratio is altered in animals with epilepsy and any alteration contributes to seizures remains to be tested.

Involvement of the mammalian target of rapamycin (mTOR) pathway in epilepsy[30,31] also provides evidence for a link molecular regulation of the circadian rhythm. mTOR is a protein kinase involved in intracellular signalling, and mutations in specific genes of this signalling cascade have been associated with some types of epilepsies, including tuberous sclerosis, cortical dysplasia[32] and temporal lobe epilepsy[33]. Forms of epilepsy that are associated with mutations in the mTOR pathway involve seizures that mostly occur during sleep[34,35], and this circadian periodicity is likely to be linked to the fact that mTOR has been strongly associated with circadian regulators — mTOR is involved in the circadian control of the supra-chiasmatic nucleus, a region of the hypothalamus that governs biological rhythms[36,37].

These findings raise critical questions that could be addressed in animal models of epilepsy. Such questions include whether there is a particular time window of vulnerability during fluctuations in transcript and protein expression in which the epileptic threshold is lowered, whether specific genetic or environmental factors exacerbate these fluctuations and, therefore, the risk of seizures, and whether any genes that are regulated in a circadian manner are directly involved in epileptogenesis or ictogenesis.

[H2] The glymphatic system

The glymphatic system is a perivascular pathway along which material is exchanged between the cerebrovascular fluid and interstitial fluid[38]. This system is widely thought to be a key contributor to waste clearance, particularly during sleep[38–40], though this view has been challenged by evidence that brain clearance decreases during sleep[41]. Regardless of the exact dynamics, clearance via the glymphatic system seems to fluctuate through the sleep–wake cycle, and this observation, combined with the fact that epileptic activity also fluctuates through the sleep–wake cycle[16,17] has fuelled interest in the contribution of the glymphatic system to epilepsy.

Involvement of the glymphatic system in epilepsy has been investigated in the kainate mouse model of hippocampal epilepsy. In this model, pro-epileptic kainate is locally injected into one hippocampus, leading to prolonged seizure activity (status epilepticus), a subsequent seizure-free latent period, followed by emergence of spontaneous seizures[42–44]. In this model, pharmacological enhancement of glymphatic flow shortly after kainate injection

delayed the onset of status epilepticus[45], and similar enhancement during the chronic stage of the disease suppressed seizures over the following 6 hours[45]. These observations suggest that increasing glymphatic function could have a protective role in epilepsy.

Evidence in relation to the role of the glymphatic system in epilepsy in humans is scarce. One report suggested that the function of the glymphatic system is improved after successful epilepsy surgery[46], though further testing, including a comparison with people with poor outcomes of surgery, would be needed to support a firm conclusion. Similarly, decreased glymphatic flow has been identified in a cohort of teenagers and adults with generalized epilepsy[47] and in people with temporal lobe epilepsy[48], but further studies are needed to establish a causal relationship.

In combination, these studies raise the possibility that the function of the glymphatic system can modulate the risk of seizures. In particular, the available evidence seems to indicate that a decrease in glymphatic clearance is associated with increased seizure probability. The relationship of glymphatic function to sleep could, therefore, mean that glymphatic function mediates or modulates at least some of the interactions between epilepsy and sleep.

[H1] Epilepsy–sleep interactions at the network level

[H2] Focal epilepsy and focal sleep activity

Sleep, and in particular electrophysiological hallmarks such as sleep spindles (see below), were traditionally viewed as diffuse processes in the brain, but we now know that sleep is more nuanced, as it is under subcortical and cortical regulation. Furthermore, involvement of the cortex is localized and depends upon previous regional wake activity[49–51]. This understanding has led to the concept of local sleep[52–54], in which sleep state and local network activity can vary from region to region. Consequently, sleep initiation and maintenance, sleep transitions and morning awakening can all be asynchronously instigated across different cortical brain regions[55–57]. For instance, intracranial EEG recording shows that specific brain regions transition between sleep stages up to 2 minutes before that transition is observed globally (for example, but with scalp EEG)[55]. Specifically, transitions initially occur in the lateral occipital cortex, and late transitions occur in the inferior frontal and orbital frontal gyri[55].

In alignment with these localized patterns of cortical involvement in sleep generation[55], focal epilepsies, which emerge from cortical areas, are associated with alterations in local sleep control. A striking illustration of this phenomenon comes from a study in a mouse model of temporal lobe seizures[58], in which limbic seizures had localized effects on cholinergic neurons of the basal forebrain, which stopped firing during seizures [58]. Given that these cholinergic neurons promote wakefulness[59], their decreased activity could contribute to the decreased levels of consciousness seen during temporal lobe seizures[58] and to the reduction in responsiveness to auditory stimulation in experimental epilepsy[60]. Hence, focal epilepsy can affect delimited brain regions, , which led to a pervasive sleep-like state in this study[58]. Similarly, sawtooth waves, which are a hallmark of REM sleep, are reduced in focal epilepsy[61]. This observation also suggests that epilepsy can be associated with alterations in cortically generated sleep oscillations even in REM sleep, when epileptic activity is typically low.

[H2] Epilepsy and sleep spindles

Sleep spindles are sleep-related rhythms detected with electroencephalography (EEG) that are characterized by oscillations of 10–16 Hz and last 1-2 seconds (minimum 0.5 seconds)[62]. They are a defining characteristic of NREM sleep stage 2[63] and are involved in memory

consolidation during sleep[64]. With use of scalp EEG, sleep spindles are usually detected in fronto-central regions[62], but intracranial recordings have shown that they can also be generated in other brain regions and are not always simultaneous across areas[65].

Observational studies in animal models of generalized epilepsy have suggested that spike-wave discharges (SWDs), which are to generalized epilepsies what interictal epileptiform discharges (IEDs) are to focal epilepsies, are a pathological evolution of sleep spindles[66,67] on the basis that they have a similar electrophysiological appearance and that both can be elicited by thalamic stimulation[66]. Studies of people with focal epilepsy have also shown that sleep spindles tend to disappear where IEDs are generated[68–71], in line with the hypothesis that IEDs are a pathological transformation of spindles. However, an alternative explanation could be that a third factor simultaneously induces IEDs and prevents spindle generation. For example, in an animal model of traumatic brain injury, neuroinflammatory mechanisms and expression of the complement factor C1q contribute to the emergence of IEDs and decrease sleep spindles[72].

Indeed, other evidence contradicts the general concept that IEDs are a pathological equivalent of spindles. For example, analysis of IEDs and sleep spindles in a rat model of generalized epilepsy showed that their duration and amplitude partially overlapped at 3 months but were distinct at 6 months. Similarly, SWDs occur during wakefulness and sleep, whereas sleep spindles occur only during sleep[73], suggesting that they are not two faces of the same coin. In combination, the currently available evidence indicates that the hypothesis that IEDs are generated by the neural circuits responsible for sleep spindle generation is an oversimplification[73–75], and alternative explanations should be explored to disentangle the networks that underlie sleep spindles, SWDs and IEDs.

In contrast to the suggested antagonism between IEDs and sleep spindles, emerging evidence suggests that these phenomena could in fact be mechanistically coupled (FIG. 2). In a study in rats, hippocampal IEDs were temporally associated with generation of a subsequent sleep spindle in the mesial prefrontal cortex (mPFC; FIG. 2)[76]. The proposed mechanism is that IEDs induce a period of neuronal silence — a so-called DOWN-state — in the mPFC, which is followed by rebound activity of neurons that could underlie the generation of the associated sleep spindle[76]. Such DOWN-states have also been identified during K-complexes[77], which are also typically associated with sleep spindles.

Though difficult to ascertain whether the sleep spindles coupled to IEDs were pathological or physiological, a higher rate of IED-coupled spindles (as well as a higher rate of IEDs alone) correlated with worse performance in a spatial memory task[76]. Such coupling also seems to exist in humans[78], and in a study in children, the stronger coupling was also associated with a lower intellectual quotient[79]. Therefore, the available evidence suggests that IED-triggered sleep spindles do not support normal brain function, or at least are functionally different from physiological sleep spindles. In line with this conclusion, the morphological features of sleep spindles that co-occur with IEDs tend to differ from those of physiological sleep spindles. For example, scalp-recorded sleep spindles that occur in association with a hippocampal-recorded IEDs have amplitudes that are, on average, ~9% higher than those that occur in isolation[80]. Notably, a long pause in thalamic sleep spindle generation has been described after IEDs in the thalamus[81], suggesting that the coupling between IEDs and sleep spindles could be region-specific.

How to reconcile the observations that sleep spindles are decreased where IEDs are generated[68–70] and that they are temporally associated with IEDs remains unclear [76,78]. Part of the answer could be that IED-associated sleep spindles are generally expressed at a distance from where IEDs are generated[78]. Indeed[78], analysis has shown that IED-coupled spindles are expressed an average of ~6 cm from the seizure-onset zone where IEDs are generated. Therefore, IEDs might disrupt spindle generation locally yet promote their expression at distance.

[H2] Epilepsy and low-frequency activity

Low-frequency activity in the brain during sleep includes slow oscillation, slow waves, slow wave activity and pathological focal slowing. In the literature, these terms are occasionally used interchangeably, but they are distinct[82]. Despite the similar electrophysiological appearances of slow oscillation, slow waves, slow wave activity and pathological focal slowing, the extent to which they share underlying biological mechanisms remains unclear.

A slow wave is an individual EEG event characterized by a high-amplitude fluctuation of ongoing brain activity that occurs preferentially during sleep. Hence, unlike continuous oscillations, slow waves are individual, discrete entities. To identify slow waves, electrophysiological signals are filtered within the low-frequency band, the definition of which varies across the literature but, in general, extends from 0.1 Hz to a higher range of 2–4.5 Hz[70,83,84]. They occur during sleep and are thought to contribute to the restorative function of sleep[85–88]. Slow waves during wakefulness were first described in sleep-deprived rats[54] before being detected in humans in specific conditions — under sleep pressure[89], upon stimulation of injured brain regions[90], or upon thermocoagulation of brain parenchyma[91]. In work published in 2023, intracranial recordings detected spontaneous slow waves that are typical of sleep during wakefulness in people with epilepsy[83]; whether these findings represent a physiological or pathological activity during wakefulness remains to be clarified.

Slow wave activity, which is typical during sleep, is defined as a succession of slow waves with an amplitude >75 μV[63]. Frequencies <1 Hz are generally referred to as slow oscillations[82]. In pathological focal slowing, this frequency can extend from the delta range (0.5–4 Hz) to the theta range (4.1–7 Hz) range; such slowing is a non-specific finding often observed in people with epilepsy near to or in the seizure onset zone. Whether pathological slowing shares functions of physiological slowing remains to be determined. Furthermore, though these differences in frequencies do not seem large, the order of magnitude between them is at least as large as that between alpha (~10 Hz) and gamma (~40 Hz) frequency bands, which are associated with different functions. Therefore, further work is necessary to understand whether and which different functions are associated with the different frequency bands[92].

[H3] Slow waves and sleep homeostasis

Sleep homeostasis is the concept that the waking state, NREM sleep and REM sleep are interrelated such that more synaptic usage in waking is followed by deeper sleep the following night that is characterized by more slow waves in the earlier sleep cycles and fewer in later sleep cycles. Slow wave activity is considered to be restorative of synaptic function[86]. The slope and amplitude of slow waves are both high when homeostatic sleep pressure (the need for sleep) is high, and so have been proposed as markers of homeostatic sleep pressure and synaptic strength[20,86]. Both progressively decrease during sleep and progressively increase during wakefulness (FIG. 3)[93,94]. In parallel, network excitability progressively decreases during sleep and progressively increases during wakefulness[95–97].

Epileptic activity is associated with local increases in slow wave activity during sleep (at least partially independent from pathological focal slowing)[68,98], reminiscent of increases observed during sleep after a cognitive task in wakefulness[49], suggesting that IEDs and seizures are associated with changes in homeostatic sleep pressure. In a study that included 296 children with epilepsy, a higher incidence rate of IEDs correlated with a progressive increase in the slope of slow waves during sleep[99] rather than the expected decrease (FIG. 3a), suggesting that IEDs perturb the homeostatic regulation of slow waves. Interestingly, remission of electrical status epilepticus during sleep, which is characterized by continuous epileptiform discharges during sleep, upon pharmacological treatment is associated with

normalization of the decrease in slow wave slope during sleep[100]. Hence, not only does epileptic activity disrupt the homeostatic property of slow waves, but treatment can normalize it.

[H3] Potential for slow waves to facilitate epileptic activity

During slow wave activity, the neuronal membrane potential oscillates between a depolarized UP-state, which is associated with synchronized neuronal firing, and a hyperpolarized DOWN-state, which is associated with neuronal silence (except for a recently discovered subclass of interneurons[101])[54,65,97,102,103]. The resulting synchronization, or burst firing, of neurons during sleep, and in particular during NREM sleep stage 3[104], together with increased excitability during sleep[105], could contribute to epileptiform discharges and seizures. Accordingly, IEDs, high-frequency oscillations, propagation of high-frequency oscillations, seizures and epileptic spasms correlate with the occurrence of slow waves and increased low-frequency activity (FIG. 4a)[106–113].

Although these results are mostly correlative, one study has shed light on a potential mechanism by which slow waves could promote epileptic activity[114]. This study indicated that high homeostatic sleep pressure, such as after a period of sleep deprivation, leads to an increase in intracellular chloride concentration, which causes the equilibrium potential of GABA (EGABA) to shift from hyperpolarizing to depolarizing. These changes promote high-amplitude slow wave activity, which is a marker of high homeostatic sleep pressure[86]. These findings suggest that the shift of EGABA promoted by sleep deprivation together with the associated facilitation of neuronal firing could, in turn, facilitate seizure genesis. This conclusion is in line with previous results that have linked sleep deprivation to seizures and decreased GABAergic inhibition[115], and the mechanism could explain why the risk of seizures increases after sleep deprivation in some epilepsy syndromes[116]. The finding also resonates with previous observations in humans that high-amplitude slow waves — which reflect high homeostatic sleep pressure — are more likely to be associated with epileptiform abnormalities than are low-amplitude slow waves[109,117]. Chloride regulation could be a common driver that triggers both high-amplitude slow waves and epileptiform abnormalities.

The possibility of a complementary mechanism that links low-frequency activity (0.5-4 Hz) with IEDs has also arisen from a study in which intracranial recordings from people with focal epilepsy showed that power in the high-gamma frequencies (which is a proxy of neuronal activity[118]) is coupled with oscillations in the delta frequency in the build-up to IEDs (FIG. 4b)[106]. This observation suggests that delta oscillations contribute to expression of IEDs by orchestrating bursts of high- gamma activity However, a causal relationship remains to be established.

[H3] Potential for slow waves to prevent epileptic activity

Contrary to the proposal that slow waves facilitate epileptic activity, some findings suggest that they could reduce epileptic activity. If slow waves or slow wave activity were promoting seizures and/or IEDs, then we would expect the rate of seizures and IEDs to be highest when this activity is most prominent, during NREM stage 3 sleep. However, though focal seizures, particularly those of frontal origin[16], do occur more frequently during sleep [119], they are most likely during NREM sleep stages 1 and 2[119]. Focal IEDs do seem to be more likely during NREM sleep stage 3[119], but this likelihood can vary between brain regions[120]. Furthermore, one study of ten people with focal cortical dysplasia type 2 has indicated an inverse correlation between the incidence rate of IEDs and delta power (the frequency of which overlaps with that of slow wave activity and slow waves) during NREM sleep stage 3[121], the reverse of what would be expected if slow wave activity or slow waves promote epileptic activity.

The lack of a clear association between slow wave activity or slow waves and epileptic activity weakens the hypothesis that they promote epileptic discharges and seizures, and one study has even indicated a protective effect of slow waves that occur during wakefulness. Intracranial recordings from people with focal epilepsy showed that the length of the delay between slow waves and the subsequent IED in wakefulness correlates with the extent of excitability during this subsequent IED (FIG. 4c) — a long delay was associated with higher excitability[83]. One interpretation of this finding is that slow waves have a protective function that dissipates with time. Hence, the restorative function of slow waves[85–88,122] might not be restricted to sleep but could also operate during wakefulness where, in this context, it protects against epileptic activity. A beneficial effect of slow waves is further suggested by evidence that low-frequency intracranial electrical stimulation decreases cortical excitability in people with epilepsy[123].

[H3] Timescale could determine the effects of slow waves on epilepsy

One explanation for the apparently contradictory evidence around the pro-epileptic and anti-epileptic effects of slow waves and slow wave activity is that the impact of this activity depends on the timescale (FIG. 4d). Over the short timescale of transitions from the UP-state to the DOWN-state, the strong synchronization of neurons favours IEDs (FIG. $4d_1$)[106,107,117]. However at the longer timescale, this synchronization decreases network excitability[86,88], eventually offsetting excitability during IEDs[83] and potentially preventing seizures. Indeed, burst firing of neurons, which occurs during slow waves, promotes a form of decreased network excitability called long-term depression[88,124]. We, and others[86], propose that continuous bursting of neurons promoted by slow wave activity during sleep decreases network excitability by lowering the efficacy of synaptic transmission[86–88], eventually leading to a less excitable network (FIG. $4d_{2\text{-}3}$). This hypothesis is supported by the observation that longer sleep duration is associated with a lower risk of seizures[8], as a longer duration of sleep is expected to provide extended periods of slow wave activity.

Another explanation for conflicting evidence on the effects of low-frequency activity on epileptic activity could be that slow waves in sleep and wakefulness reflect different neurobiological processes despite their morphological similarities. In this case, what we interpret as pro-epileptic and anti-epileptic waves could simply be two distinct entities. Furthermore, slow waves could have different actions in different epilepsy types, vigilance states and/or individuals.

[H2] Sleep architecture

The composition of sleep at the level of sleep spindles, slow waves, K-complexes and other sleep-related entities constitutes its microarchitecture (FIG. 5a, *left* and Glossary). The sequential distribution of the different sleep stages (NREM sleep stages 1–3 and REM), their respective durations and the duration of wake after sleep onset make up the macroarchitecture of sleep[125]. Whereas much evidence indicates interactions of epilepsy with sleep spindles and slow waves[42,68–71,117,126–128](FIG. 5a-b), little evidence indicates changes in sleep macroarchitecture in people with epilepsy. For instance, in a meta-analysis of 827 articles on sleep macroarchitecture in people with epilepsy[129], only one difference was noted — that wake after sleep onset (the time spent awake through the night after initial sleep onset) was longer in people with drug-resistant temporal lobe epilepsy than in those with frontal lobe epilepsy or in people without epilepsy (FIG. 5c)[129,130]. This increase in wake after sleep onset could explain another macroarchitectural abnormality that is occasionally seen in people with epilepsy, which is an increased duration of NREM sleep stage 1[131], as this period of light sleep typically follows periods of awakening. One other difference observed in a subsequent study was that people with drug-resistant epilepsy had a lower duration of REM

sleep[132,133]. A separate study showed that duration of REM sleep was reduced when a seizure emerged in the first 4 h of sleep[134], suggesting that decreased REM sleep duration is influenced by the recent occurrence of seizures[134]. Other studies have shown either non-systematic changes[131] or no changes in sleep macroarchitecture in epilepsy[135]. Similarly, in a study of children with epilepsy, IEDs were associated with lower rates of sleep spindles but sleep macroarchitecture remained unaltered[136]. REM sleep duration was reduced in children with drug-resistant epilepsy, but this was at least partly explained by concomitant use of benzodiazepines[136].

The fact that epilepsy is associated with marked alterations in the microarchitecture of sleep without greatly affecting the macroarchitecture (FIG. 5) could perhaps reflect the fact that epilepsy originates from cortical generators, and therefore affects cortically-generated sleep activity. The macroarchitecture of sleep relies on brainstem–cortical interactions — for example, profound changes in neural activity and neurotransmitters that are triggered by brainstem–cortical interactions underlie the different sleep stages[59,137,138]. As a result, this macroarchitecture would be more resistant to epileptic activity. Though abnormalities in sleep macroarchitecture have been found, the evidence for effects on microarchitecture is considerably more consistent and compelling.

[H1] Epilepsy–sleep interactions at the system level

[H2] Epileptic activity in sleep and wakefulness

Periodic and circadian variation in seizure incidence has been recognized for several decades[16,17,119,139]. Originally, this knowledge was based on patient reports that lacked accuracy[140], but the introduction of long-term EEG monitoring has enabled objective measurement of activity and has provided objective evidence for periodicity in the incidence of IEDs and seizures[5,9,11]. For example, intracranial recordings over a period of ≥3 months in one study showed that the risk of seizures varies over 24 hours in ≥80% of participants[141]. Such evidence has made clear that the incidence of seizures during sleep differs from that during wakefulness — overall, focal seizures are more likely to occur during sleep[119], although certain types of seizures and seizures that have specific onset zones are more likely during wakefulness[16]. Importantly, however, these population-based observations do not universally hold, as illustrated by the inter-individual variability of seizure onset timing across a 24-h period[142], and the circadian modulation of seizure risk, and modulation of risk during sleep and wake states[9,143].

One proposed mechanism for the overall increase in the risk of seizures during sleep is an increase in neuronal synchrony that is typically present during NREM sleep[104,144]; this synchrony could promote bursting activity and, consequently, epileptic discharges and seizures. Specific parameters of sleep also seem to modulate the risk. For example, a short sleep duration and variability in the time of sleep onset and waking have both been associated with an increased risk of seizures[8,145].

The overall risk of seizures is greater during sleep than wakefulness and, during sleep, epileptic activity is more likely in some stages than others. Such activity is more prominent during NREM sleep than during REM sleep[119], and generalization of seizures occurs more frequently in NREM sleep than in wakefulness[146]. Focal seizures are more likely during light sleep (NREM sleep stage 1), whereas IEDs are more likely during deep sleep (NREM sleep stage 3)[119]. As for slow wave activity, seizures, IEDs and high-frequency oscillations occur at higher rates in the first half of the night than in the second half of the night, thereby following homeostatic changes of slow wave activity (such as its amplitude)[147,148].

More fine-grained analysis has shown that sleep affects rates of epileptic activity differently in different anatomical locations. For example, the mesiotemporal region has a

greater propensity than other regions for IED production and propagation during NREM sleep, even when this region is not part of the seizure onset zone[149]. Conversely, IEDs are suppressed during REM sleep relative to wakefulness in neocortical but not mesiotemporal regions[147], possibly owing to major cholinergic innervations to neocortical regions that mediate neuronal desynchronization, resulting in suppression of epileptic activity in the neocortex. Despite the changes in rates and localization of IEDs across the circadian rhythm, their morphology does not change[120].

Despite these differences in epileptic activity in different sleep states and in different locations, once activity exceeds the seizure threshold, a seizure propagates through the underlying epileptic network irrespective of the state of vigilance. This phenomenon was shown in a study of 25 people with drug-resistant epilepsy, in which intracranial EEG recordings revealed that the contacts involved in the seizure onset zone, the propagation paths, the propagation speed, the maximum channel involvement and the seizure duration did not differ between vigilance states[150].

In combination, the observations above show that sleep and its properties, such as duration and sleep stages, are associated with varying incidence of seizures and IEDs in various brain regions. Identification of the underlying mechanisms could shed light onto the general mechanisms of ictogenesis, providing useful insight for developing therapeutic approaches.

[H2] REM sleep and epileptic activity

Epileptiform activity rarely occurs during REM sleep[119], and the occurrence of IEDs during REM sleep has been associated with a more unfavourable course of the disease[151]. REM sleep can be subdivided into phasic REM sleep, which is characterized by REM and muscular twitches, and tonic REM sleep, which is characterized by muscle atonia. Rates of IEDs are lowest during phasic REM sleep, when neural desynchronization is highest[144,152,153], supporting the idea that desynchronization prevents IEDs. In the feline penicillin epilepsy model, systemic administration of the anticholinergic drug atropine abolished REM-specific desynchronization and reversed the suppression of interictal activity during REM sleep, suggesting that acetylcholine is a major driver of desynchronization and suppression of epileptic activity during this phase of sleep[154]. Notably, overall time in REM sleep and the ratio of phasic REM sleep to tonic REM sleep are reduced in people with drug-resistant epilepsy relative to that in people with well-controlled epilepsy or who do not have epilepsy[132,133].

In contrast to the low rate of seizures and IEDs during REM sleep in humans, seizures tend to emerge from REM in the intrahippocampal rat tetanus toxin model of temporal lobe epilepsy[155], providing an opportunity to gain insight into the mechanisms of ictogenesis and epileptogenesis. In the rats, the ratio of activity in the theta range (4–12 Hz) to activity in the delta range (0.5–4 Hz) increased before seizures[155], reminiscent of changes that anticipate IEDs in humans[106,107]. This finding suggests that the increase in ratio is what leads to seizures rather than the REM state itself. Furthermore, in humans, theta activity during REM sleep differs from that in rodents, occurring in bursts rather than continuous oscillations[156]. This additional difference between human and rodent REM sleep in the pattern of theta activity could also contribute to the different seizure risk, although experimental evidence is needed to support this hypothesis. Another mechanism that could underlie the pro-epileptic nature of rodent REM sleep could be related to changes in the metabolic properties of astrocytes[157]. Induction of seizures with electrical stimulation — a procedure called kindling — leads to acidification of astrocytes during REM sleep, and these metabolic changes are known to trigger release of excitatory neurotransmitters from astrocytes[158] that could favour seizures during REM sleep[157]. However, whether this mechanism occurs in humans is not known.

Though these findings in animals are contrary to most findings in humans, they could indicate that rodent models mimic conditions or pro-epileptic mechanisms that are relevant to people with specific forms of epilepsy. Though REM-specific epilepsy is rare[159,160], seizures in neonates with epilepsy tend to occur mainly during REM sleep[161,162]. Further research is needed, but understanding why REM sleep is rarely associated with epileptic seizures in humans but frequently is in experimental models[155,163] could offer important insights into novel approaches for controlling seizures.

[H2] Cognitive effects

Cognitive difficulties in epilepsy are multifactorial, and disturbances in sleep — particularly sleep efficiency (the proportion of sleep during the period spent in bed) — can play a part[164] to a similar degree as in people without epilepsy[165]. Inferring a causative link between epilepsy-related sleep disturbances and cognitive changes is challenging, but some studies have started to provide some mechanistic insight.

Memory impairment is one of the main cognitive complaints among people with epilepsy, particularly temporal lobe epilepsy[166]. Accumulating evidence suggests that interictal epileptiform activity correlates negatively with cognitive performance during wakefulness[167], but until recently, the evidence that IEDs during sleep are associated with memory impairment has been weak[168]. However, several studies in children and adults with epilepsy have provided evidence for a direct link between IEDs, alterations in sleep physiological oscillations and cognitive dysfunction[71,79,135,169,170]. In a prospective study of 42 people aged >50 years, a higher spike rate, reduced slow wave activity power, and a higher burden of antiseizure medications were all associated with worse 24 h memory retention[169]. Another study showed that the rate of left hippocampal IEDs during NREM sleep correlated negatively with memory performance, whereas a higher rate of sleep spindles in the left hemisphere than the right hemisphere correlated positively with better verbal memory than non-verbal memory[171], in line with the role of the left and right hemispheres in verbal and non-verbal memory, respectively[172]. Given that sleep spindle rates are decreased in the epileptic hemisphere[68,69], these findings suggest that IEDs and the effects of epilepsy on sleep spindles could contribute to memory impairment[169,170,173].

Similar associations were also demonstrated in a study of children with epileptic encephalopathy with spike-wave activation in sleep, a syndrome caused by various aetiologies and characterized by a high incidence of IEDs during sleep[174]. In this study, the rate of sleep spindles was inversely correlated with the rate of IEDs, and an increase in sleep spindle rate upon treatment with antiseizure medication was associated with cognitive improvement[174]. Whether specific cognitive domains improved more than others remains to be elucidated, but this study emphasizes the relationship between IEDs, sleep spindles and cognitive function in people with epilepsy.

The effects of epilepsy on a short brain oscillation, called a ripple, with a key role in memory consolidation has also been investigated. The incidence of ripples decreases after IEDs[175], and a lower ripple rate while awake was associated with poorer performance in a memory task[175]. This observation indicates that the association between IEDs and lower ripple rate could lead to memory impairment.

Some evidence also indicates that the effects of epilepsy on slow wave sleep (the period of sleep characterized by slow wave activity) can affect cognitive function. In a study of 19 people with temporal lobe epilepsy and 17 healthy controls, the overnight duration of slow wave sleep in people with epilepsy correlated positively with the proportion of items that were forgotten in an overnight object–scene associative memory task, and this effect was independent of the number of IEDs[176]. Although the same impact of slow wave sleep on memory was not formally tested in healthy controls[176], this finding contrasts sharply with previous findings of a positive correlation between the proportion of slow wave sleep and

learning[169,177], and the fact that slow wave sleep is typically associated with memory consolidation rather than forgetting[178]. However, a similar effect was seen in a population of people with transient epileptic amnesia, a condition in which seizures are associated with transient amnesia. In this study, a long duration of slow wave sleep was associated with lower retention rate of word pairs after 12 h, whereas no correlation was observed among healthy controls[179]. One possible mechanism for these effects could be aberrant or excessive synaptic downscaling in people with epilepsy, leading to suppression of synapses that are required for memory[176]. A more complex explanation could be that the effect is mediated by pathological coupling between IEDs and sleep spindles that contribute to memory impairments, as discussed above[76,78,79].

Evidence for a role of seizures during sleep in memory impairments remains scarce. A negative effect on verbal memory has been reported in a few individuals[180,181], though other work has identified no effect on learning[177]. Although seizure forecasting is a highly active field of research[5,9,11,141,142,182], precise prediction of seizures remains challenging, making it difficult to schedule memory tasks so that memory encoding is done before a seizure. This methodological challenge could explain the lack of convincing evidence. Hence, further work is necessary to clarify the roles of seizure, as well as their type, localization and duration in their effects on memory.

[H1] Implications for management of epilepsy

The factors and evidence discussed above show that a strong relationship exists between epilepsy and sleep. This relationship is not only informative with respect to the pathophysiology of epilepsy, but studying the interactions could also provide helpful diagnostic or prognostic tools in epilepsy. We consider the implications for management of epilepsy below. The clinical implications of cycles in epilepsy, for example periodic and sleep–wake changes in network connectivity[182,183], have been reviewed elsewhere[5,142].

[H2] Sleep–wake recording

EEG is central to epilepsy diagnosis. Given that the probability of detecting IEDs varies across time, and the sleep–wake cycle in particular[9,119,184–186], a minimum duration of interictal EEG is necessary to obtain a reliable sample of the spatial distribution of IEDs, known as the IED topography. Evidence has shown that a duration of 30 min is necessary to obtain reliable sampling of IED topography, and that reliability did not differ between wake and sleep data[187].

For a long time, the topographical accuracy of EEG for localization of the epileptogenic zone was thought to vary across time and states of vigilance[188,189]. In this context, evidence had indicated that interictal epileptic biomarkers (IEDs and high-frequency oscillations) in REM sleep were most useful for localization and that their topography fits best with the clinical semiology[189]. Though use of electrical source imaging (see Glossary) has suggested IEDs that occur during REM sleep can arise from brain regions where IEDs are not detected during other states of vigilance[190] or from more restricted areas[191], whether these unique sources relate to true epileptogenic areas that should be targeted for surgery remains to be assessed. In fact, a subsequent study identified no effect of vigilance state on the accuracy of electrical source imaging[186], and other work has indicated that REM sleep does not provide new or clinically relevant localization information when compared with NREM sleep and wakefulness[147]. Indeed, one study even indicated that NREM sleep is the state of vigilance that provides the best localization of the epileptogenic zone[192] despite the fact that epileptic activity is more focally confined during REM sleep[147,190].

In fact, not all types of epileptic activity behave similarly across the sleep–wake cycle. IEDs and high-frequency oscillations seem to most accurately localize the seizure-onset

zone and the epileptogenic zone during NREM sleep[185,192,193], whereas the ratio of very-high-frequency oscillations (up to 2000 Hz) in resected and non-resected areas in people with good surgical outcomes did not differ in accuracy between sleep and wakefulness[194]. IEDs that were preceded by gamma surges had better predictive value of outcome when measured during wakefulness than during sleep[195].

The topographical reliability of seizures and IEDs between wake and sleep has also been investigated[150]. In this study, the percentage of electrodes that were recruited within the first 500 ms of seizures did not differ between wakefulness and sleep. By contrast, the number of channels that recorded an IED within 120 ms of the index IED, which indicates the speed of IED propagation, was higher during sleep than wakefulness[150]. These findings suggest that IEDs are less topographically accurate than seizures during sleep, despite their frequency being higher during sleep than wakefulness.

Altogether, the long-held belief that REM sleep provides the most accurate identification of the epileptogenic zone is currently not supported by robust evidence. The heterogeneity of findings precludes firm conclusions, and studies are needed to assess accuracy according to type of epilepsy, presumed localization, age and other features.

[H2] Modulating sleep-related phenomena

The associations between features of sleep and epileptic activity suggest that modulating sleep or epileptic activity has the potential to affect the other. For example, continuous anterior thalamic nucleus deep brain stimulation (DBS) can decrease IEDs during sleep and increase delta power during NREM sleep[196]. Though we might expect the beneficial effect of DBS to rely on the stimulation itself, an alternative mechanism could be through an increase in slow waves, suggested by the increased delta power. This study illustrates the possibility that manipulating a phenomenon that seems to protect against epileptiform discharges could help to suppress epilepsy.

An alternative to DBS is acoustic stimulation, which has been used to increase slow wave activity during sleep to improve memory[197]; given its ability to increase slow waves, which are presumed to be protective, this approach could be repurposed to decrease epileptic activity. A small study in children with various epilepsy syndromes demonstrated that scalp EEG-recorded slow waves (0.5–2 Hz) could be increased with acoustic stimulation — though no therapeutic effect was seen, this simple method could be tested in larger studies with more precise protocols[198]. Indeed, the design of neurostimulation protocols will benefit from a deeper understanding of the interactions between sleep-related phenomena and epileptic activity, and sleep-inspired brain therapy could be valuable.

The importance of considering circadian features when calibrating neuroresponsive therapies is illustrated by a study of responsive neurostimulation (RNS), a type of intracranial, electrical stimulation used in the management of epilepsy. The aim of this study was to investigate how RNS is affected by circadian variability in excitation–inhibition balance[199], which is central to the pathogenesis of epilepsy[200]. This study showed that the efficacy of RNS was greater when the excitation–inhibition balance fluctuated across the sleep–wake cycle than when it did not[199]. This observation could mean that disruption of changes in cortical excitability across sleep and wake indicate an inability to modify the excitability of that area (decreased plasticity), or could indicate a profound disruption of the excitation–inhibition balance, for example in more severe disease.

[H2] Epilepsy and the orexin system

Awakenings have been associated with epileptic activity[201]. Though it remains unclear whether awakenings promote epileptic activity or vice versa, stabilizing sleep by targeting the wake-promoting neurotransmitter orexin with an antagonist, such as lemborexant[202], is worth exploring as a therapeutic approach.

Orexin is produced in the hypothalamus and is involved in promoting wakefulness, especially for goal-directed behaviours[59]. Evidence suggests that the orexin system modulates epileptic activity[203,204]. Indeed, antagonism of orexin has anti-epileptic effects in experimental models of epilepsy[205,206], and injection of orexin has been associated with increased epileptic activity[207,208]. The role of orexin in seizures after sleep deprivation has been investigated in a rat model of epilepsy[12]. After injection of the pro-epileptic molecule pentylenetetrazol, sleep deprivation was associated with an increased concentration of orexin in the cerebrospinal fluid (CSF) and a short latency to the first seizure. Administration of an orexin antagonist was associated with a longer delay to the first seizure[12], suggesting that orexin contributes to the increased risk of seizure after sleep deprivation. Evidence in humans is scarce and comes mainly from observational studies with inconsistent findings. For example, one study showed that levels of orexin were higher in people who had recently had a seizure than in healthy controls[209]. By contrast, another study showed that orexin levels were decreased in people who had experienced a generalized tonic–clonic seizure in the previous 48 h in comparison with levels in people with a neurological condition other than epilepsy[210]. Differences between the populations , the origin of orexin samples (cerebrospinal fluid[210] or plasma[209]) and the timing of sampling might have contributed to this discrepancy.

Current knowledge suggests that the mechanism of action of orexin antagonism, beyond sleep stabilization, involves a decrease in levels of the excitatory neurotransmitter glutamate and an increase in levels of the inhibitory neurotransmitter GABA[205]. Another mechanism is indicated by the impact of orexin on the macroarchitecture of sleep, as active inhibition of REM sleep is abolished in the absence of orexin[204], leading to the emergence of REM sleep bouts early during sleep. Given that REM sleep is associated with a lower rate of seizures in humans[119] owing to neural desynchronization, this effect could reduce the risk of epileptic activity. Hence, the antiepileptic effect of orexin antagonism could rely on the promotion of a desynchronized cortical state[104,144,204].

[H1] Conclusions

Though associations between epilepsy and sleep variables have been recognized for a long time, studies of the mechanisms that underlie these interactions have emerged only recently. Studying the effects of natural changes in brain dynamics that occur during sleep holds promise for clarifying the mechanisms of epileptogenesis and ictogenesis and could help with development of therapies and therapeutic devices for the treatment of epilepsy.

However, several questions remain to be answered, including the structural basis of the numerous associations between IEDs and elements of sleep microarchitecture, how the circadian rhythmicity of molecular circuitry affects the risk of epilepsy, what makes sleep pro-epileptic, and why the risk of seizures varies in the same sleep stage between species and across brain development. We call for further research on the interactions between epilepsy and sleep, including development of manipulation protocols that will clarify whether correlative evidence equates to causative associations. We hope that by highlighting areas of controversy and posing questions, this Review will encourage further research in this increasingly active field.

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