Review

Circadian rhythm and epilepsy

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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 a 24-h period. The rhythmic patterns in epileptic activity and seizure occurrence are probably related to vigilance states and circadian variation in excitatory and inhibitory balance. Core circadian genes *BMAL1* and *CLOCK*, which code for transcription factors, have been shown to influence excitability and seizure threshold. Despite uncertainties about the relative contribution of vigilance states versus circadian rhythmicity, including circadian factors such as seizure timing improves sensitivity of seizure prediction algorithms in individual patients. Improved prediction of seizure occurrence opens the possibility for personalised antiepileptic drug-dosing regimens timed to particular phases of the circadian cycle to improve seizure control and to reduce side-effects and risks associated with seizures. Further studies are needed to clarify the pathways through which rhythmic patterns of epileptic activity are generated, because this might also inform future treatment options.

Introduction

Circadian rhythms are part of the internal 24-h daily rhythm of nearly all biological functions (panel 1). The presence of circadian patterns in epilepsy has been recognised for centuries, and advances in technology, including long-term EEG recordings of neuronal activity, have confirmed and greatly advanced our knowledge about the role of circadian rhythmicity in epilepsy.[1] Better understanding of circadian rhythmicity allows the development of more accurate seizure prediction algorithms, which could be used, for example, to improve closed-loop neurostimulation techniques that reduce seizures.[2] Moreover, advances in understanding circadian influences on excitatory and inhibitory mechanisms could help to clarify the factors involved in seizure generation and inhibition of spread of epileptic activity, and could potentially lead to novel treatment approaches, including gene therapy or optogenetics as tools for controlling and monitoring neuronal activity.[3] With a third of patients with epilepsy being refractory to current treatments,[4] alternative treatment approaches are needed. For example, the use of chronotherapy (ie, therapies timed to particular phases of the circadian cycle)[5] could lead to a more personalised and tailored management strategy for patients with epilepsy. This Review describes how circadian rhythms can shape the temporal patterns of epileptic activity and seizures through control of sleep–wake states and mechanisms that are independent of the vigilance state. We also evaluate how the emerging field of chronoepileptology can contribute to novel diagnostic and management strategies, which could potentially transform our approach to treating patients with epilepsy.

Circadian rhythm-dependent and sleep–wake-dependent modulation of EEG and cortical excitability

The circadian timing system affects brain function relevant to epilepsy in two ways: the system contributes to the regulation of the timing of wakefulness and sleep and its phases (ie, slow-wave sleep and rapid-eye-movement [REM] sleep), and modulates brain function during sleep and wakefulness.[6] Consideration of these two different pathways can help with the interpretation of temporal patterns in epileptic and seizure activity (panel 2).[7–12]

During sleep, progressive synchronisation within the thalamocortical network takes place via a synchronous discharge of the thalamic reticular nucleus,[13] which enables the generation of non-REM sleep oscillations such as slow waves and sleep spindles.[14] Similar circuits are thought to be involved in the generation of spike-wave discharges in patients with generalised epilepsy.[15] Cortisol and melatonin are released in circadian patterns.[16] Cortisol concentrations are positively correlated with epileptiform activity in patients with stress-sensitive seizures, and might have a role in the circadian occurrence of seizures.[17]

Analyses of transcranial magnetic stimulation (TMS) evoked responses across the circadian cycle, and after sleep deprivation in patients with focal or generalised epilepsy have shown that cortical excitability increases with time awake and appears to vary according to the epilepsy syndrome, with bilateral changes being reported in patients with generalised epilepsy and ipsilateral changes in those with focal epilepsy.[18] Cortical excitability is also modulated by circadian phase, such that cortical excitability is more reduced in the evening hours than during the day.[12] Clinically, patients report an increase in seizure probability the morning after sleep deprivation. In healthy volunteers, cortical excitability assessed by TMS increases with time awake, but is also modulated by circadian phase.[12] Additionally, in healthy volunteers, blood oxygen level-dependent (BOLD) signal, assessed during functional MRI sessions across the circadian cycle and during sleep deprivation, depends on both circadian phase and time awake in a brain region-specific manner.[19] For example, variations in the hypothalamic BOLD signal that underly working memory performance depends on circadian-related promotion of wakefulness in the evening.[20] Diurnal changes in vigilance state and neurobehavioural performance are regulated by slow daily regulation of cortical excitation-inhibition balance, which depends on circadian timing and prior

Panel 1: Definition of terms

Circadian rhythm

A biological rhythm is considered to be a circadian rhythm if it meets three criteria: the rhythm should have an endogenous free-running (approximately) 24 h period, should be entrainable (ie, be capable of phase reset by environmental cues and synchronisation to the 24 h day), and should exhibit temperature compensation. If all these criteria are not fulfilled, the term diurnal rhythm is often used. Throughout this Review we have used the term circadian rhythm for ease of reference, even when the studies cited might refer to diurnal rhythms.

Chronotype

Refers to an individual's preferred time to sleep and perform activity, and is in part genetically determined but also changes across the lifespan. Usually three chronotypes are distinguished: morning types, who prefer early sleep times, wake up early, and are most alert early in the day; evening types, who have preferred late (delayed) sleep times and late wake-up times and feel at their best later in the day; and neutral types, who are the most common types (60–70%) are in the middle of this chronotype spectrum.

Diurnal rhythm

Diurnal rhythm is a biological rhythm that is synchronised with the day–night cycle. A diurnal rhythm may or may not be a circadian rhythm.

Multidien rhythm

Refers to rhythms with a time period covering several days.

Non-rapid eye movement (REM) sleep

Non-REM is one of the two major sleep states, and can be further subdivided in three different sleep stages (N1–N3) that repetitively occur across the entire sleep episode. Non-REM sleep is characterised by low-frequency high-amplitude synchronised EEG oscillations, sleep spindles, and K-complexes. Non-REM sleep stage N3 is equivalent to deep sleep, also referred to as slow-wave sleep.

REM sleep

REM is the other major sleep state, and is not divided into substages. REM sleep is characterised by low-amplitude mixed-frequency EEG oscillations, rapid eye movements, and low muscle tone.

Ultradian rhythm

Refers to rhythms with periods of less than 24 h; ultradian rhythm cycles can occur with a frequency of more than once per day. A prominent ultradian rhythm is the non-REM–REM cycle, which in humans has a period of approximately 90 min.

Panel 2: Basics of the circadian rhythm

Circadian rhythms can be observed in processes ranging from transcription and translation to membrane potentials, sleep–wake states, and cortical excitability. At the molecular level, circadian rhythms are generated by a transcriptional-translational feedback loop comprising a set of core clock genes, including *CLOCK, ARNTL,* cryptochromes, and their associated proteins.[7] Variations in these genes have been shown to affect both the timing and structure of human sleep and the response to sleep loss.[8] This molecular clock and associated 24 h rhythmicity is present in nearly every cell.

At the organ level, circadian rhythmicity can be described as a hierarchically organised multi-oscillator system.[7] At the top of this hierarchy is the central circadian pacemaker located in the suprachiasmatic nuclei, which generates circadian rhythms in neuronal activity and peptide release, driving endocrine rhythms (eg, melatonin) and cortisol rhythms, which provide cues for synchronising other brain and body regions.[7] The suprachiasmatic nuclei receives time-of-day information via retinal light input to allow optimal synchronisation between internal timing and daily environmental changes.[9]

The suprachiasmatic nuclei generates a 24 h rhythm in sleep–wake propensity. The circadian drive for wakefulness increases throughout the day to reach a maximum drive for wakefulness during the evening hours.[10] The peak circadian drive for sleep occurs during the early morning hours, at around the lowest core body temperature rhythm.[10] Sleep–wake propensity also depends on sleep–wake history, such that during wakefulness sleep propensity increases and dissipates during sleep.[10] This sleep–wake process is known as the homoeostatic process which refers to the capability of the brain to compensate for sleep loss by increases in sleep intensity, as indexed by high amplitude synchronised EEG oscillations and sleep duration.[11] The interaction between these two opposing processes (ie, the sleep–wake-dependent increase and decrease of sleep propensity and the paradoxical circadian sleep–wake propensity rhythm) regulates timing and structure of sleep and consolidation of the sleep–wake cycle,[11] as well as cortical excitability.[12]

sleep–wake history.[6] These results in healthy controls and patients with epilepsy highlight the important influence of circadian rhythm and sleep–wake history and vigilance states on the cortical inhibitory and excitatory balance.

Circadian rhythm and 24-h distribution of seizures and epileptic activity

The propensity of epileptic seizures to occur in temporal patterns has been known since the Babylonian era, and by the end of the 19th century, seizures were classified as
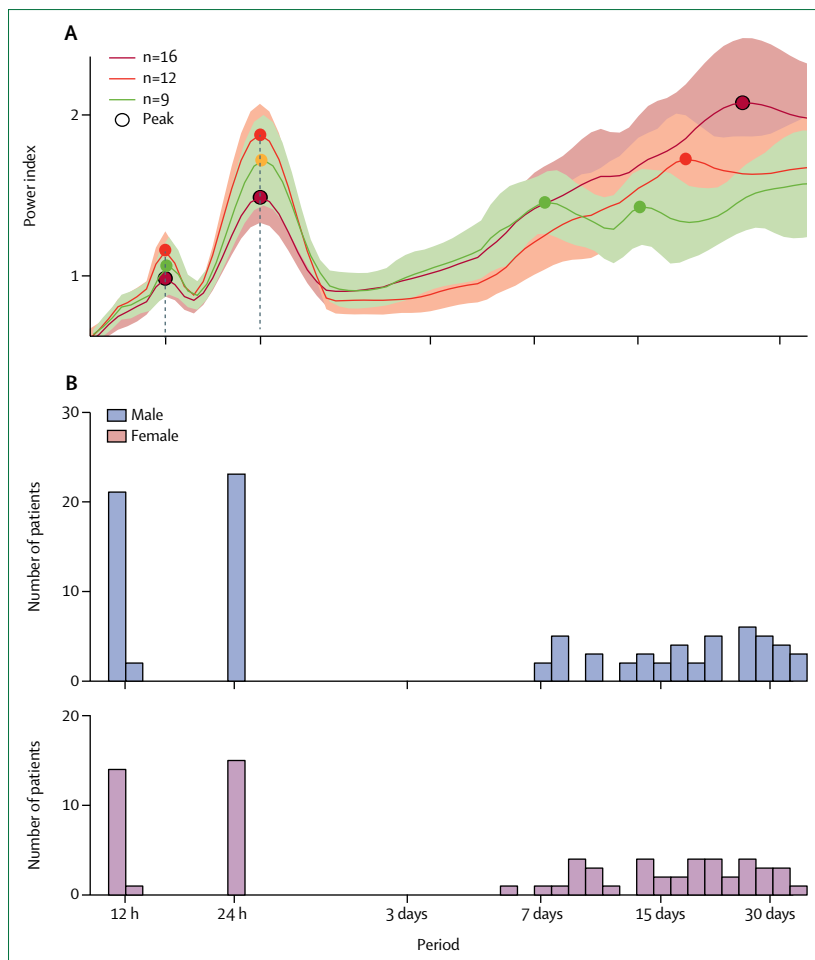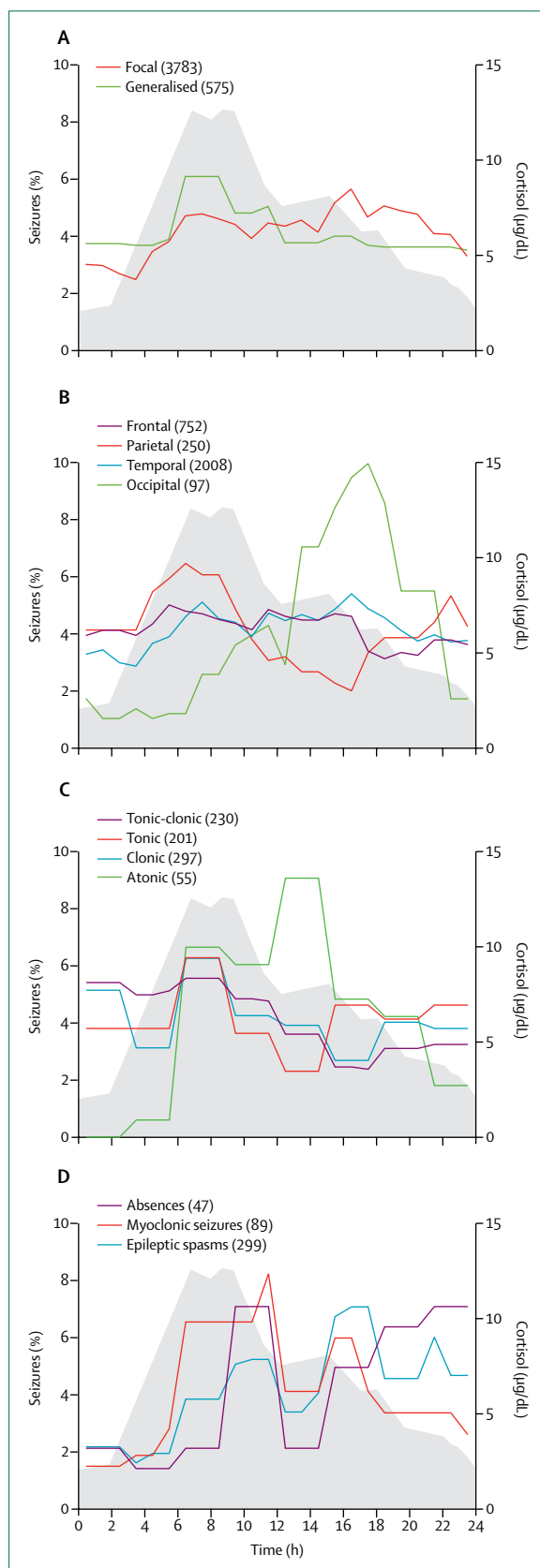
Figure 1: Periodograms and peaks of interictal epileptiform discharge rhythms
(A) Average periodograms across patients with focal epilepsy (n=37), showing ultradian, circadian, and multidien peaks. For better visualisation, grouping of data with similar patterns of occurrence of interictal epileptiform discharge rhythms (unsupervised clustering) across all patients revealed three patterns: an approximately weekly-to-biweekly rhythm (peaks at 7·5 days and 15 days, n=9), an approximately tri-weekly rhythm (peak at 20 days, n=12), and an approximately monthly rhythm (peak at 26 days, n=16). Shading indicates ±1 SD. (B) The number of patients with a peak in the periodogram at a given period. Distributions are similar in male (n=22) and female (n=15) patients with focal epilepsy. Reproduced from Baud and colleagues[1] by permission of Springer Nature.

diurnal, nocturnal, or diffuse.[21,22] The development of long-term video-EEG monitoring techniques allows objective quantification of seizure distribution over 24 h and sleep–wake cycles over several days. Advances in recording, detection, and storage of epileptiform activity using the US Food and Drug Administration (FDA)-approved closed-loop implanted neurostimulator system has allowed monitoring of neuronal activity over even longer periods of time (from months to years), thus shedding new light on the relationship between interictal epileptiform discharges (IEDs), seizures, and circadian rhythms.[1,23,24] Specifically, IEDs peaked during normal sleep hours independent of the topographic location of the electrodes, thus confirming the activating properties of sleep on IEDs regardless of location of the ictal-seizure onset zone.[24] As opposed to IEDs, seizures occurred with different circadian pattern that varied according to seizure onset zone, confirming results from studies done over shorter periods of time (up to 2 weeks).[25–28] Therefore, although IED activation is principally favoured by sleep, the transition from the interictal to the ictal state seems to be modulated by circadian and ultradian factors, with the effects being related to the location of the epileptic network or epilepsy type.[24] In addition to the activation of IEDs during nocturnal sleep, data indicate that a multidien rhythm of IED becomes evident when IEDs are measured over periods of months and years.[1] For example, a study of 37 patients with drug-resistant focal epilepsy reported multidien periodicities of IED activation with variable epilepsy period lengths across patients (commonly 20–30 days in duration), but also reported stable epilepsy periods in individual patients for up to 10 years of recordings (figure 1).[1] This pattern was similar for men and women, suggesting that this multidien periodicity is not driven by catamenial factors (eg, the menstrual cycle and related hormonal changes).

The diurnal pattern of seizure occurrence is also influenced by the type of epilepsy (generalised or focal) and the site of seizure onset (frontal or temporal; figure 2).[17,29,30] Age and seizure type (eg, tonic, myoclonic, clonic, or hypermotor) also have a role in the diurnal seizure pattern.[17,28,29,31] Studies in children and young adults (aged 1–20 years) have suggested that generalised seizures mainly occur in wakefulness and daytime.[27,28,30] In children with focal epilepsy, frontal lobe seizures occur predominantly during sleep, whereas temporal lobe seizures happen mostly during wakefulness,[27] even after partial sleep deprivation and reduction of antiepileptic drugs. In children and adult patients with mesial temporal lobe epilepsy, the majority of studies showed a bimodal distribution of seizures, with a primary peak in the late afternoon and a secondary peak in the morning.[25,38,32] Few data are available regarding the circadian distribution of the less common occipital and parietal lobe seizures, although occipital seizures seem to occur preferentially during daytime, in wakefulness, with peaks in the morning and afternoon hours; no definite pattern has been noted for parietal lobe seizures.[27,28] The influence of the seizure-onset zone on the time of seizure occurrence was also highlighted in a woman aged 57 years with focal seizures arising from two independent epileptic foci, one limbic and the other non-limbic, which showed different out-of-phase seizure patterns for each seizure-onset zone.[33]

Of note, these studies do not allow evaluation of whether the reported preferred time of occurrence of seizures is modulated by behavioural states per se (ie, wakefulness vs sleep and non-REM sleep vs REM sleep) or via their circadian modulation, or because of environmental conditions (eg, light–dark cycles). Indeed, showing that seizures in humans occur in a circadian pattern is challenging, and would necessitate specific

Figure 2: **Distribution of seizure occurrence and cortisol concentrations over 24 h**
Circadian seizure distribution for number of focal and generalised seizures over a 24-h period is displayed on top of a standard curve of plasma cortisol concentration (grey) to enable visual comparison. (A) Seizures with focal onset versus generalised seizure onset. (B) Focal seizures per lobe of origin. (C, D) Distribution of the different generalised seizure types and epileptic spasms are displayed in two separate graphs to enable clear visualisation of each seizure type. The numbers in brackets represent the number of each seizure type. Data are from a systematic review of 15 published studies that included 3783 focal seizures and 575 primary generalised seizures. Reproduced from van Campen and colleagues[37] by permission of Elsevier.

protocols (eg, consistent routine protocols and consistent light–dark cycles), which are very difficult for patients with epilepsy to adopt because of the demanding nature of these protocols. Moreover, seizures themselves might also modify body temperature and hormone secretion, thus reducing the accuracy of the circadian rhythm evaluation.

Evidence suggests that sleep and wakefulness, and not day and night, are the most robust predictors of seizures.[27,34] The influence of sleep and wakefulness is especially evident in frontal lobe epilepsy, in which seizures occur more frequently or exclusively during sleep, both during the day and night.[35] Sleep, particularly non-REM sleep (but not REM), could favour seizure occurrence, especially in genetic or lesional forms of epilepsy (such as sleep-related hypermotor epilepsy) independently from the location of the ictal-seizure onset zone.[35] However, the particular pattern of distribution of mesial temporal lobe seizures does seem to suggest a close relationship with the circadian rhythm, independent of vigilance state. Topographical EEG analyses have shown that the sleep-dependent decline of the slope of slow waves (the most accurate marker of synaptic strength) during non-REM sleep is most prominent in frontal areas, whereas the circadian modulation of the slope of slow waves is more prominent in central and occipital areas.[36] Further studies are needed to establish whether these topographical differences in the slope of slow waves can contribute to the variable influence or preponderance of seizures during sleep in different seizure-onset zones.

A predominant role of sleep versus the circadian rhythm on IED activation has been shown in a study[37] of five patients with generalised epilepsy adopting a rigorous circadian protocol, in which all behaviours, including sleep and wakefulness, were evenly scheduled across the circadian cycle, and in which environmental influences (eg, temperature and light) were maintained at a constant. In this study of five patients, three patients had sufficient IEDs to assess variability. All these three patients showed predominance of IEDs during non-REM sleep rather than wakefulness (independent of circadian influences) although some individual circadian effects on IED frequency were reported.

Robust evidence supporting a circadian modulation of seizures is derived from animal models, in which

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 the time of day resembled the distribution reported in patients with mesial temporal lobe epilepsy.[26] Similar distributions of seizures relative to time of day in nocturnal and diurnal species suggest the role of an endogenous circadian modulation in seizure distribution.[26] A mouse model of pilocarpine-induced mesial temporal lobe epilepsy adds further evidence for spontaneous seizure clusters occurring in a circadian manner at the transition between sleep and wakefulness.[38] Together, results from human and animal studies indicate that both sleep–wake behavioural components and circadian influences modulate IED activation and seizure threshold, with effects being dependent on the seizure-onset zone. Further rigorous protocols are needed to better disentangle the relative weight of vigilance states and circadian rhythms on seizure susceptibility.

Chronotype

Chronotype might be an important factor in the timing of the administration of antiepileptic drugs. A
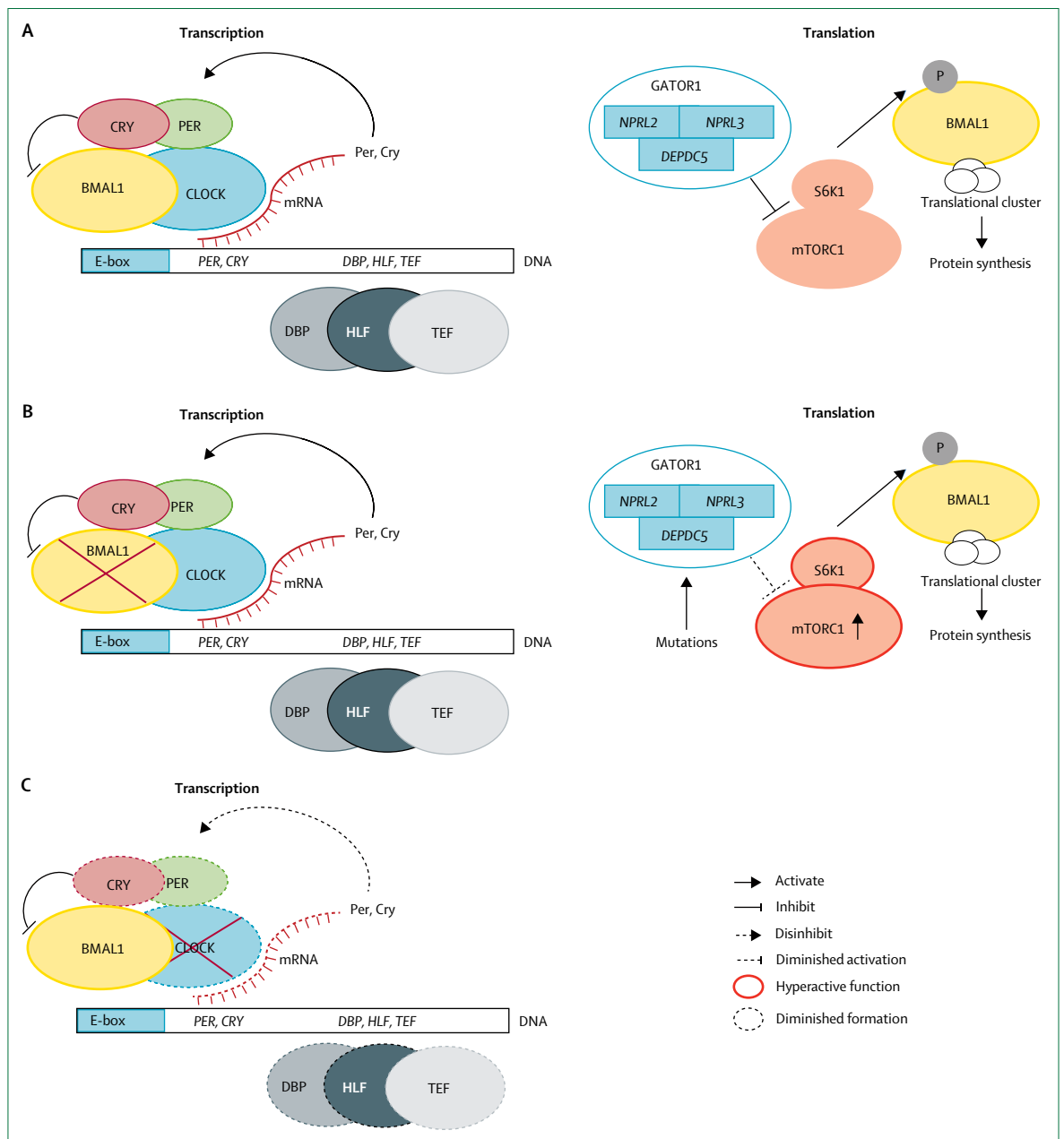
questionnaire-based study of 208 patients with epilepsy found that patients who were so-called morning types took their morning antiepileptic drugs 100 min earlier than so-called evening types on free days,[39] most probably reflecting their natural wake time. Taking antiepileptic drugs at different times in the week and with different times between dosages might influence serum anti-epileptic-drug concentrations over 24-h periods, with potential negative influences on seizure control.

Asking about preferred sleep and wake times is a simple way of understanding an individual's chronotype. Specific-ally asking about days off or free days is important, since intrinsic rhythm is best seen when wake and sleep times are not determined by work or school. Sleep diaries and questionnaires are further, simple methods to clarify chronotype. The Morningness–Eveningness Questionnaire (MEQ)[40] and the Munich Chronotype Questionnaire (MCQ)[41] are the most commonly used sleep question-naires. However, these questionnaires are not validated to establish chronotype in patients with epilepsy, and there-fore data derived from these questionnaires need to be interpreted with caution. Chronotype questionnaire results can be influenced by additional factors in patients with epilepsy, including seizure occurrence and medication effects, which could bias chronotype evaluation. Objective measures of chronotype include rest–activity patterns using actigraphy, dim-light mela-tonin onset, and the 24-h core body temperature minimum.[42]

Although some evidence indicates that epilepsy types are related to chronotype, data are conflicting. A questionnaire-based study of 200 patients (142 with focal epilepsy, 46 with idiopathic generalised epilepsy, and 12 with unclassified epilepsy) found that patients with epilepsy were more morning oriented, having earlier mid-sleep time and longer sleep duration on free days than

healthy controls, but did not find any difference between patients with focal epilepsy and those with idiopathic generalised epilepsy.[43] However, other studies have suggested that patients with idiopathic generalised epilepsy might have a late chronotype compared with patients with focal epilepsy. For example, a study of 87 patients with epilepsy (70 with focal epilepsy and 17 with idiopathic generalised epilepsy) that used MEQ found that patients with idiopathic generalised epilepsy were five times more likely to have a late chronotype than healthy controls, but no difference was found between patients with focal epilepsy and healthy controls.[44] In another study of 160 patients with epilepsy (127 with focal epilepsy and 33 with idiopathic generalised epilepsy), patients with idiopathic generalised epilepsy had lower MEQ scores (indicating evening preference) and later mid-sleep time on work and free days than patients with focal epilepsy.[45] However, in a study of 200 patients (100 with focal epilepsy and 100 with idiopathic generalised epilepsy) that used MCQ, earlier sleep times were reported in patients with epilepsy than in healthy controls, but no other differences to support differences in chronotype were found.[46]

Using dim-light melatonin onset and MEQ, a study of 28 patients with focal epilepsy, 20 with idiopathic generalised epilepsy, and 18 healthy controls found that mean MEQ scores were lower (indicating evening pref-erence) in patients with idiopathic generalised epilepsy than in those with focal epilepsy, but were not lower than in healthy controls.[47] Dim-light melatonin onset in patients with idiopathic generalised epilepsy occurred around 40–50 min later than in healthy controls and patients with focal epilepsy. These data support an endogenous late circadian phase for patients with idiopathic generalised epilepsy. Using the same measures in 60 patients with focal epilepsy, MEQ scores suggested that patients with

Figure 3: Overview of pathophysiological mechanisms
(A) Involvement of circadian clock genes in transcription (left) and translation (right) and (B, C) their role in human and animal epilepsy. (A) The core molecular circadian oscillator consists of the CLOCK–BMAL1 transcription factor complex that controls the transcription of its feedback genes *CRY* and *PER* and additional downstream genes, such as those in the PAR bZIP transcription factor family (*DBP*, *HLF*, and *TEF*; left). *PER* and *CRY* genes code for repressor proteins PER and CRY that negatively act on CLOCK–BMAL1. E-box is a binding site of the transcription factors (CLOCK–BMAL1) and has a major role in regulating transcriptional activity of several circadian genes, including *PER* and *CRY* (as indicated by the red line for Per and Cry mRNA; left). The right-hand panel shows the potential role of clock genes in protein translation. The GATOR1 complex, containing genes *DEPDC5*, *NPRL2*, *NPRL3*, controls mTORC1 activity.[54] The mTOR pathway is a key regulatory system of cell functions including protein and lipid synthesis, cell growth, and cell proliferation. The mTORC1 kinase S6K1 pathway activates BMAL1 by phosphorylation. Phosphorylated BMAL1 molecules cluster with translational factors to promote protein synthesis. Protein synthesis shows circadian variation dependent on BMAL1.[55] (B) The role of BMAL1 and dysregulation of the mTOR pathway in human and animal epilepsy. *BMAL1* knockout mice have reduced seizure threshold and an attenuated circadian pattern of electrically evoked seizures (left).[52] Mutations in the GATOR1 complex genes *DEPDC5*, *NPRL2*, and *NPRL3* disinhibit the function of mTORC1.[54,56] Patients with tuberous sclerosis complex and patients with epilepsy associated with GATOR1 mutations show a hyperactive mTORC1 that is well suited to increase S6K1 phosphorylation of BMAL1, which directly affects translational protein synthesis.[55] Interactions between BMAL1 and the mTOR pathway have a key role in protein translation (right).[55] (C) The role of CLOCK in human and animal epilepsy. *CLOCK* mRNA and CLOCK proteins are reduced in the epileptic tissue of patients with focal cortical dysplasia and tuberous sclerosis complex.[53] The decrease of CLOCK affects the feedback loop of the regulation of clock genes, because this decrease leads to diminished formation of the CLOCK–BMAL1 complex and a decrease in transcription of *CRY* and *PER* genes (as indicated by the dotted red line for Cry and Per mRNA), both of which are repressors of CLOCK–BMAL1 complex activity. Downstream genes also appear to be involved in CLOCK gene-associated epileptogenesis in both human and animal epilepsy.[53,57] DBP and HLF, both members of the PAR bZIP transcription factor family, are decreased in mice who do not have CLOCK in their excitatory neurons, and DBP is decreased in the epileptic tissue of patients with tuberous sclerosis complex.[53] Knockout mice for the PAR bZIP transcription factor family (DBP, HLF, and TEF) are susceptible to nocturnal seizures.[57] A conditional gene mouse model showed occurrence of nocturnal seizures only in mice that did not have CLOCK in their excitatory neurons, but not in mice that were missing CLOCK in their inhibitory interneurons.[53] Increase in epileptic activity is a direct consequence of CLOCK gene deletion and is not due to changes of the circadian rhythm during sleep–wake, given that the *CLOCK* gene in the suprachiasmatic nucleus is preserved in mice missing CLOCK in excitatory neurons.[53] CLOCK=clock circadian regulator. BMAL1=brain muscle ARNT-like 1. mTOR=mammalian target of rapamycin. P=phosphorylation. mTORC1=mammalian target of rapamycin complex 1.

focal epilepsy were more likely to be morning types than healthy controls, although no difference in mean time of dim-light melatonin onset that would support the questionnaire finding was found.[48] Although the data are conflicting, the evidence suggests that patients with idiopathic generalised epilepsy have a late chronotype compared with patients with focal epilepsy and healthy controls.

Pathophysiology

The pathophysiology of epilepsies has mainly been attributed to dysfunction of membrane excitability and excitatory and inhibitory neurotransmitter imbalance at neuronal circuitries.[49] In animal epilepsy models, expression of many neurotransmitter receptors (eg, benzodiazepine, GABA) and ion channels (eg, the voltage-dependent potassium channels) are under circadian regulation. Studies using ligand-binding assays have shown the highest circadian variability of ion channels expression and neurotransmitter activities in the cortex and the hippocampus.[50,51]

Two principal mechanisms can mediate the circadian variation of epileptic excitability in both human and animal epilepsy. First, core clock genes, such as aryl hydrocarbon receptor nuclear translocator-like (*ARNT*; referred to hereafter by the non-HUGO term brain muscle ARNT-like [*BMAL1*]) and clock circadian regulator (*CLOCK*) contribute to epileptic excitability,[52,53] either directly or via their transcription factors BMAL1–CLOCK, and influence the expression of other genes that are causally involved in epilepsy (eg, PAR bZIP transcription factor genes *DBP*, *TEF*, and *HLF*; figure 3).[52,53] A histopathological study reported that the CLOCK protein is substantially reduced in excitatory and inhibitory neurons in epileptic tissue of patients with focal cortical dysplasia and tuberous sclerosis complex.[53] In a conditional mouse model, deletion of *CLOCK* in excitatory pyramidal neurons but not in inhibitory interneurons led to reduced seizure threshold and overt seizures during sleep.[53] This loss of *CLOCK* in these mice was accompanied with reduced dendritic spine formation and altered electrophysiological properties of the neuronal microcircuits containing excitatory pyra-midal cells, ultimately leading to paroxysmal depolar-isation shift, a cellular hallmark of epilepsy.[58] Remarkably, CLOCK function in the suprachiasmatic nucleus, the circadian pacemaker, remains preserved and sleep–wake regulation is normal in these mice,[53] suggesting that epileptic excitability might be a direct consequence of loss of *CLOCK* function in the cortical neurons themselves, rather than mediated by suprachiasmatic nucleus activity. The *BMAL1* gene, which codes for the binding partner of CLOCK to form the transcription CLOCK–BMAL1 complex, is also directly involved in epilepsy (figure 3).[52] Deletion of *BMAL1* abolishes circadian variation of electrically induced generalised seizures in an animal model.[52] In addition, absent

BMAL1 reduces seizure threshold in *BMAL1* knock-out mice compared with wild-type mice, suggesting that *BMAL1* contributes to epileptic excitability.[52] Genes downstream of the CLOCK–BMAL1 complex, such as *DBP*, *TEF*, or *HLF*, are similarly linked to epilepsy since mice deficient in these three circadian transcription factors are highly susceptible to sleep-related seizures (figure 3).[57] Reduced CLOCK–BMAL1 functions might therefore contribute to epileptogenesis, leading to reduced number of downstream transcription factors including those of the PAR bZIP family.[53] The second mechanism contributing to circadian variation in epileptic activity is mediated by the circadian variations of the mammalian target of rapamycin (mTOR) pathway.[55,59] The mTOR pathway is a master regulatory system of cell functions and is under the control of the circadian timing system.[59] Abnormal mTOR signalling is associated with many neurological disorders, including epilepsy.[60] mTOR pathways that are hyperactive because of mutations in mTOR inhibitor genes *TSC1* and *TSC2* cause epilepsy in patients with tuberous sclerosis complex,[61] and mTOR inhibitors such as everolimus provide a novel mechanism-based approach to treating those patients.[62] Evidence of mutations in other regulator proteins (eg, the GATOR1 complex), which normally bind to mTOR to suppress the activity of the mTOR pathway in patients with sleep-bound seizures, indicates that disinhibition of mTOR signalling is also a mechanism underlying nocturnal frontal lobe epilepsy (now known as sleep-related hypermotor epilepsy).[35,54,56] Among these mutations, those that are in the *DEP*, *NPR2*, and *NPR3* genes (part of the GATOR1 complex) are specifically interesting since mutations in these genes are associated with structural focal epilepsy due to cortical dysplasia and band heterotopias (figure 3).[54,56]

Given the roles of the *CLOCK–BMAL1* gene complex and hyperactive mTOR pathway in epileptogenesis, new findings that show a close interaction between the mTOR system and circadian pathways are of particular interest. Key molecules of the mTOR pathway (such as pivotal translation factors 4EBP1 or S6K1) can modify the period and amplitude of the circadian master clock gene *CLOCK* by regulating protein synthesis.[55,63–65] BMAL1 is under similar mTOR control since it is activated by the mTOR S6K1 kinase via phosphorylation (figure 3).[55] A hyperactive mTOR pathway is thus prone to change the function of the circadian BMAL1–CLOCK complex and its down-stream transcription factors (including those in the PAR bZIP family), thereby promoting epilepsy. Given the role of mTOR pathways in cell growth[60] and the tight molecular interaction between TOR and circadian pathways, clock-controlling genes might contribute to structural changes associated with mTORopathies by amplifying excessive mTOR signalling. Treatments that target the interaction between circadian regulation and mTOR pathways are thus promising options for patients with structural epilepsy and sleep-bound seizures.

Prediction of seizures

Unpredictability of seizure occurrence is often highlighted as the main factor affecting quality of life in patients with epilepsy. Accurate seizure forecasting could enable administration of treatment to prevent or reduce the risk of a seizure, or at least improve patient safety by avoiding situations that might pose risks. Different individual factors, such as time of day, stress, or hormones, have been suggested to be useful in seizure prediction.[66] For example, using prolonged inpatient video-EEG recordings, an algorithm that calculates the likelihood of seizures occurring during wakefulness was created based on age, seizure type, and semiology.[29] However, such a wide time scale for periods of increased seizure propensity (ie, all waking hours each day) is unlikely to be sufficient for patients to make adjustments to their lifestyle or medication. In patients with focal epilepsy, continuous EEG recordings from 3 months to 9·9 years (median 2·3 years) with implantable electrodes show additional long-range modulations of epileptic discharges during ultradian and multidien periods,[1] with a high probability of seizure occurrence when circadian and multidien rhythms are aligned in phase, suggesting that such recordings can help predict occurrence of seizures.[67] Indeed, adding individual circadian seizure-occurrence information substantially improved the accuracy of the prediction algorithms.[2] Including multidien IED rhythms might further improve the accuracy of seizure-prediction algorithms. However, since only a small proportion of patients with epilepsy will have these intracranial electrodes, development of non-invasive methods is needed to allow more patients to benefit from this promising approach. For example, wearable devices, which record and analyse simultaneous electrocardiogram and accelerometer data, are being developed for objective seizure detection.[68] These devices can detect generalised tonic-clonic seizures, but the number of false positives is high, and no method is yet available for objective detection of more subtle seizures, such as focal seizures with loss of awareness.[68] Development of subcutaneous EEG electrodes could, however, offer a less invasive means for prolonged EEG recordings and seizure detections for a wider epilepsy population.[69]

Chronotherapy

Treatment strategies

Chronotherapy, which harnesses knowledge of optimal medication timing to strike a balance between desired effect and side-effects, is applied in several medical areas and treatment paradigms of recurrent or chronic conditions. Optimal timing and dosing of chronotherapy ideally requires a biomarker for immediate feedback of dose-response titration, such as that implemented in closed-loop diabetes pump treatments, in which insulin dosing is titrated to glucose concentrations.[70] An obvious treatment strategy in epilepsy is to treat at times of greatest occurrence of seizures based on the historically highest seizure frequency or epileptogenicity in relation to wakefulness and sleep, circadian or non-circadian rhythms, and ultradian or multidien rhythms.[71–74] Historical seizure patterns can also be used to predict seizures, allowing the administration of peak doses of medication at times of predicted seizures. Although some input loops are being evaluated, such as seizure detection by means of wearable devices or related seizure diaries,[3] a closed-loop clinical trial of chronotherapy has yet to be successfully implemented. Biomarkers, which have been largely selected on the basis of EEG analysis of cortical recordings, have successfully shown an ability to measure excitability,[67,75] opening the potential for a more direct excitability assessment in epilepsy. Treatment trials based on measures such as EEG abnormalities need to be done, because these trials would provide opportunities for diverse medication and treatment application; examples include higher medication doses at times of greatest seizure susceptibility, combinations of extended-release and faster-acting agents, continuous systemic or localised closed-loop medication pumps, circuitry and receptor modulation through stimulation, or optogenetics.[76]

Several studies have considered the possibility of using melatonin to improve seizure control; however, results have been conflicting, and a Cochrane review did not draw any conclusion about the role of melatonin in reducing seizure frequency.[77] Chronotherapy might also entail application of bright-light therapy, and a randomised controlled trial of 77 adults with medically intractable focal epilepsy showed some improvement in selected patients with hippocampal pathology, but also cautioned that light stimulation can provoke seizures in other patients.[78]

Targeted medication timings

Chronopharmacokinetics refers to the evaluation of circadian variability of absorption, metabolism, distribution, and elimination of molecules and antiepileptic medication. Distribution of drugs can be influenced by cyclic drug concentrations or variable blood flow through various body parts throughout the day.[79] Additionally, elimination of antiepileptic drugs can be linked to variable metabolism and excretion at different time points,[72] and these patterns can contribute to differential effects based on timing of application. Clock genes and chronotypes can also be related to medication interactions, and in turn, medications can alter clock gene expressions (eg, alteration of circadian clock genes by diazepam).[80] A study showed that valproic acid has the capability of disrupting oscillatory expression of circadian-rhythm transcription factors in cell cultures, and may therefore have profound effects on circadian rhythmicity itself.[81]

Valproic acid tolerance was optimal during the second half of the light-rest span in mice, which correlates with the second half of the night in humans.[82] In a study[83] of 17 children with exclusively nocturnal seizures, their

antiepileptic dose regimen was switched to a proportionately higher evening than morning dose. This change led to seizure freedom or more than 50% seizure reduction in 15 (88%) of the children. Only two (12%) of the patients experienced transient side-effects, such as somnolence and fatigue. Similarly, targeted, short-acting medications such as benzodiazepines, administered either systemically or locally (through implanted cranial systems or pumps) could further reduce side-effects related to continuous high medications.

Conclusions and future directions

An increasing amount of evidence supports that epileptic seizures occur in 24-h, circadian, and sleep–wake-related patterns, and studies have also shown multidien rhythmicity (most commonly 20–30 days) of epileptic activity and seizures.[1,24] Both the circadian timing system and homoeostatic sleep–wake history regulate sleep–wake timing, sleep structure, and cortical excitability within sleep and wakefulness,[6,84] and might have a role in seizure susceptibility. For example, the increase in seizure probability in the morning following sleep deprivation is likely to be related to a wake duration-dependent increase in cortical excitability and a circadian facilitation of excitability in morning hours.[18] The reduced likelihood of seizure activity in the second half of a normal waking day could be related to the circadian promotion of inhibition.[12] The preponderance of sleep-related seizures in patients with frontal lobe epilepsy seems to be related to the seizure-promoting effect of unstable vigilance, observed during non-REM sleep phases.[85,86] Clock genes (eg, *CLOCK* and *BMAL1*) and circadian transcription factors (eg, CLOCK–BMAL1) have been shown to influence excitability and seizure threshold.[52,53] These genes and transcription factors have been studied mostly in patients with lesional epilepsy

associated with focal cortical dysplasia and tuberous sclerosis complex.[55] These disorders could serve as useful models to further enhance our understanding of how the clock genes influence neuronal excitability and the reciprocal relationship between the genes and mTOR pathway, which in turn can modify the circadian genes.[55] Results might inform future treatment approaches, including gene therapy or optogenetics. Increased understanding of seizure timing and the relative contribution of circadian versus vigilance factors can improve sensitivity of seizure prediction algorithms,[2] to inform more specific treatment schedules of the traditional antiepileptic drugs for individual patients. The models may also enable alternative newer treatment options, including benzodiazepines or other drugs delivered through various application vehicles, such as intracranially implanted medication pumps to reduce side-effects and risks associated with seizures. Further studies of circadian clock genes in different types of epilepsy (such as juvenile myoclonic epilepsy and epilepsy with generalised tonic-clonic seizures on awakening) and seizure prediction models that are not dependent on intracranial EEG recordings are needed, to ensure these tailored strategies could be made available to a wider group of patients with epilepsy.

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