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Review

Sleep, oscillations, interictal discharges, and seizures in human focal epilepsy

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ABSTRACT

Bidirectional interactions between sleep and epilepsy are known since antiquity, however only the introduction of the method of electroencephalography (EEG) in 1929 contributed to objectively investigate and further unravel these obvious clinical relationships. Despite the increasing evidence over the last century, certain aspects of epilepsy and sleep interactions are still incompletely or not well understood. This article discusses the influence of sleep on adult focal epilepsy as assessed objectively via EEG, and highlights new developments of the last decade regarding sleep microstructure and new markers of the epileptogenic zone such as high-frequency oscillations > 80 Hz. It further describes evidence obtained from invasive intracranial EEG, as this is a unique method to assess directly cortical activity of superficial and deep structures of the human brain. Important achievements of the last decade were to unravel how epileptic activity is modulated by sleep, underlining the role of sleep slow waves to enhance epileptic activity, to demonstrate that seizure types are differently affected by sleep, and to show that sleep may be useful to better identify the epileptogenic zone for epilepsy surgery in drug-resistant epilepsy.

1. Introduction

The introduction of electroencephalography (EEG) into clinical practice in 1929 represented the major milestone to study epilepsy and its relationships with sleep (Berger, 1929; Loomis et al., 1937). Gibbs and Gibbs (1947) were the first to show that the quantity of interictal epileptiform discharges (IEDs) increased with sleep, even if waking EEGs were normal. Penfield and Jasper (1954) extended this knowledge by reporting a significant increase in IEDs in the acute electrocorticography of the temporal lobe, when certain patients became drowsy or fell asleep, whereas they observed a complete arrest of IEDs in awake patients. Despite the increasing evidence over the last decades, certain aspects of epilepsy and sleep interactions are still incompletely or not well understood. This article will provide an overview of the most important inter-relationships between sleep and adult focal epilepsy as assessed objectively via EEG, highlight new developments of the last decade regarding sleep microstructure and new markers of the epileptogenic zone such as high-frequency oscillations (HFOs). It will pay particular attention to evidence obtained from invasive intracranial EEG (iEEG), as iEEG presents a unique possibility to assess directly cortical activity of superficial and deep-seated brain structures. After reading this article, readers will be able to understand these interactions, in particular they will appreciate the modulation of epileptic activity by sleep in human focal epilepsy, understand that certain types of focal seizures are closely linked to sleep, and gain insights into how sleep could be used to better identify the epileptogenic zone for epilepsy surgery in drug-resistant focal epilepsy.

2. Overview of sleep and sleep-specific oscillations

2.1. Traditional view of sleep and new aspects on role of local generation of sleep

Sleep is traditionally considered a global phenomenon that affects the whole brain uniformly and simultaneously (Fuller et al., 2011). More recent research provides increasing evidence suggesting that sleep is indeed locally modulated, and that sleep is only global, when a large and widespread number of cortical regions are synchronously involved (for a review see Siclari and Tononi, 2017).

The most convincing evidence for a local modulation of the central control of sleep in humans is based on iEEG recordings obtained from patients with drug-resistant focal epilepsy during presurgical epilepsy evaluation (Magnin et al., 2004, 2010; Bódizs et al., 2005; Nir et al., 2011; Nobili et al., 2011; Sarasso et al., 2014; Frauscher et al., 2015a; De Carli et al., 2016; Piantoni et al., 2017; von Ellenrieder et al., 2019 in review). Major advances of iEEG studies were to show that the

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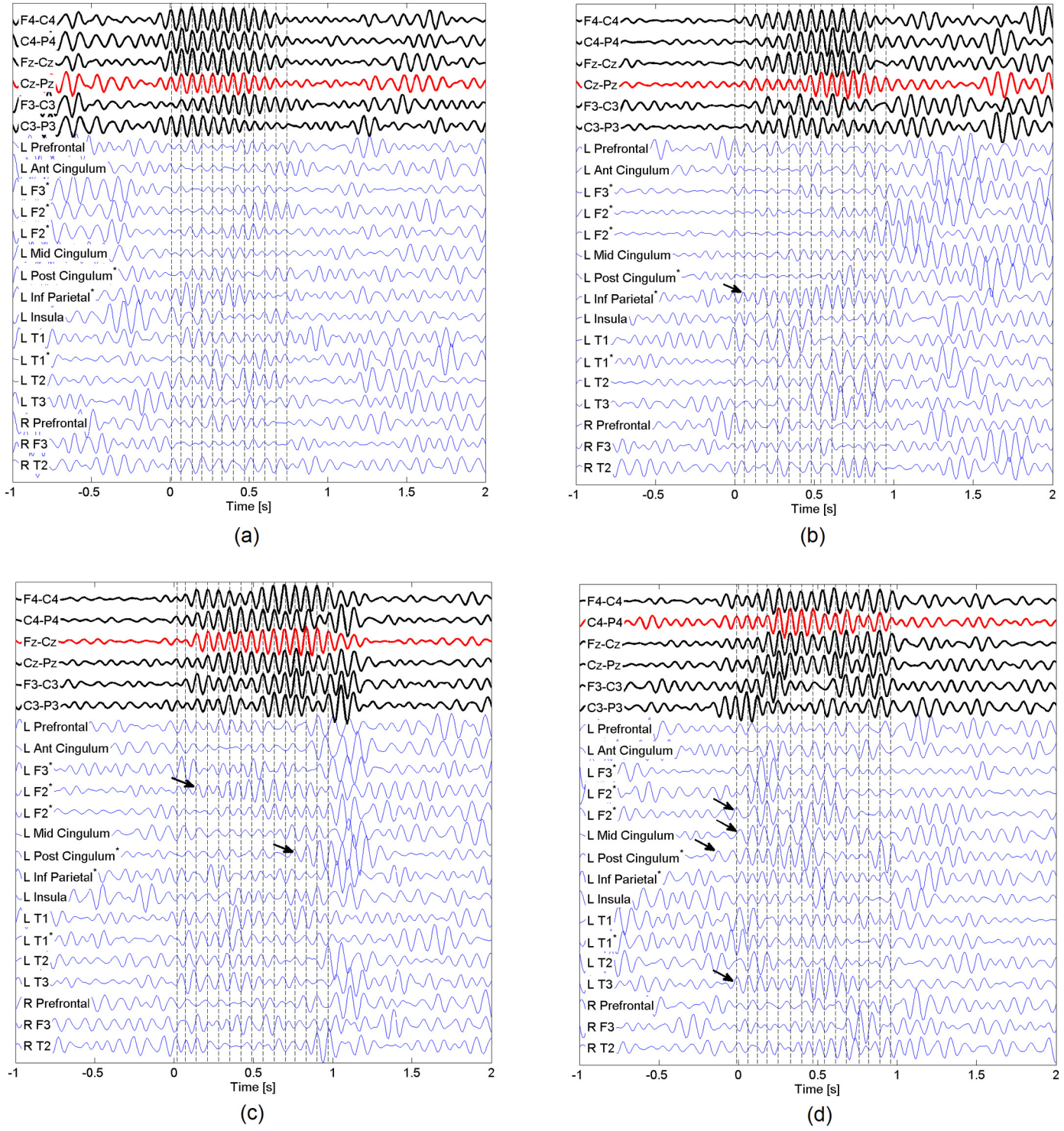

Fig. 1. Examples from simultaneous scalp EEG spindles and intracranial spindle activity. Only the sigma band component (10–16 Hz) is shown. Four examples from spindles of the same subject are shown. The scalp channel with the red trace is the channel in which the spindle was marked. Time zero is the marked spindle onset. Other scalp channels are in black, and intracranial channels are in blue. The brain regions from which the channels are recorded are indicated on the left, a star indicates that the channel showed significant increase in sigma band energy compared to the control intervals in the average of 50 scalp spindles. Arrows indicate intracranial sigma activity that fulfills the criteria to be considered a spindle. The examples demonstrate that even though in some channels there was a frequent increase of sigma band energy at the same time as in the scalp spindles, the involved channels and underlying synchrony are not consistent.
Source: Frauscher et al. NeuroImage (2015a) published open access using a Creative Commons Attribution CC-BY licence. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

transition from wakefulness to sleep does not occur simultaneously (Bódizs et al., 2005; Magnin et al., 2010; Sarasso et al., 2014), and that even during consolidated N3 sleep, certain brain regions exhibit wake-like activity (Magnin et al., 2010; Nobili et al., 2011; De Carli et al., 2016). Our group showed that the intracranial involvement during scalp spindles showed no consistent pattern, and exhibited unexpectedly low synchrony across brain regions (see Fig. 1), contributing to the concept of sleep as a local phenomenon (Frauscher et al., 2015a).

2.2. Sleep-specific oscillations

The most important sleep-specific oscillations are sleep spindles, sleep slow oscillations < 1 Hz and delta wave activity between 1-3 Hz. Sleep spindles are distinct EEG events, which are the hallmark of NREM sleep stage N2. They are characterized by waxing and waning oscillations with a frequency between 10 and 16 Hz and duration between 0.5 and 2 s (Loomis et al., 1935; Gibbs and Gibbs, 1950; Jankel and Niedermeyer, 1985). Sleep spindles are attributed an important role for memory consolidation, cortical development, and sleep stability (Khazipov et al., 2004; Dang-Vu et al., 2010; Fogel and Smith, 2011). Sleep slow oscillations are characterized by a rhythmic alternation between activated (up, when pyramidal cortical neurons are depolarized) and deactivated (down, when pyramidal cortical neurons are hyperpolarized) states. They were shown to orchestrate physiological brain rhythms, by linking beta, gamma and ripple bands to the slow wave "up" state (Haider and McCormick, 2009; Crunelli and Hughes, 2010; Timofeev and Chauvette, 2017). Similar to sleep spindles, they play an important role for memory consolidation during sleep (see review article of Rasch and Born, 2013). K-complexes are the hallmark of N2 sleep. They are functionally attributed a role in information processing; their role regarding arousal or sleep stabilization is less clear, and remains still a subject of controversy (for a review see Colrain, 2005).

3. Focal interictal EEG markers and modulation by sleep

Following the first observations in the fifties and sixties (Gibbs and Gibbs, 1947; Penfield and Jasper, 1954), the current literature suggests a strong modulatory influence of sleep on focal interictal epilepsy biomarkers. In this review, we will discuss IEDs as a traditional epilepsy EEG biomarker as well as high-frequency oscillations > 80 Hz (HFOs) as a promising new biomarker for the epileptogenic zone (see review of Thomschewsky et al., 2019) in patients with focal epilepsy.

3.1. IEDs as traditional marker of epilepsy

IEDs are very brief epileptic events lasting < 200 ms occurring without clinical symptoms outside the context of seizures (interictal period). They are the traditional biomarker of epilepsy. A meta-analysis including a total of 42 conventional scalp and intracranial studies which comprised a net of 1458 patients showed that relative to REM sleep, the focal IED rate was 1.11 times higher in wakefulness, 1.75 times higher in stage N1 sleep, 1.69 times higher in stage N2 sleep, and 2.46 times higher in stage N3 sleep (Ng and Pavlova, 2013). These data imply that discharge rates are highest in NREM sleep (particularly stage N3) and comparable between wakefulness and REM sleep with the latter having a slightly lower IED rate. Importantly, not only the rate of IEDs increases, but also the electrical field becomes more widespread during NREM sleep and more locally constrained during REM sleep (Sammaritano et al., 1991). This latter aspect is probably best explained by increased EEG synchronization during NREM sleep due to sleep slow oscillations, and increased EEG desynchronization during REM sleep due to cholinergic modulation (Shouse et al., 2000; Frauscher et al., 2016).

3.2. HFOs as promising new marker of the epileptogenic zone

HFOs are a promising comparatively new marker of the epileptogenic zone. HFOs are defined as isolated events with at least four consecutive oscillations exceeding 80 Hz standing clearly out of the surrounding background. Depending on the frequency, most authors distinguish between ripples (80-250 Hz) and fast ripples > 250 Hz (Frauscher et al., 2017). HFOs are not only pathologic in nature, but occur also under physiological conditions, and their rates are reported to vary depending on the localization (von Ellenrieder et al., 2016). A recent multicenter study is the first to provide region-specific normative values for physiologic HFOs in a common stereotactic space (Frauscher et al., 2018). In order to develop normative values of intracranial EEG activity, the authors carefully selected iEEG channels showing normal physiologic EEG activity defined as i) absence of interictal activity during the recording period, ii) exclusion of a significant slow wave anomaly, and iii) being outside of lesional tissue as assessed with MRI. Physiologic ripples were shown to be particularly frequent in eloquent cortical areas, with highest rates in the occipital cortex, medial and basal temporal region, transverse temporal gyrus and planum temporale, pre- and postcentral gyri, and medial parietal lobe. In contrast, physiologic fast ripples are practically inexistent, which makes them a better candidate for defining the epileptogenic zone, when present. Physiological HFOs were attributed a role for sleep-dependent offline processing of cortical networks, memory consolidation, and task processing (see review of Thomschewsky et al., 2019). Vaz et al. (2019) for instance provide evidence in epilepsy patients undergoing iEEG that ripples coupled between the mesiotemporal lobe and association cortex may constitute a neural mechanism for actively retrieving memory representations in the human brain.

Similarly to the distribution of IEDs, HFO rates are highest and most extended during NREM sleep, and lowest and most restricted during REM sleep and wakefulness (Staba et al., 2004; Clemens et al., 2007; Bagshaw et al., 2009; Dümpelmann et al., 2015; Sakuraba et al., 2016; von Ellenrieder et al., 2017; Al-Bakri et al., 2018). Importantly, rates of HFOs were consistently across the different studies -independently of the sleep stage- higher inside than outside the seizure-onset zone. Table 1 provides an overview of the existing literature on HFOs and sleep.

3.3. Sleep microstructure and IEDs/HFOs

Recent research tried to answer the important question of why epileptic activity is enhanced during NREM sleep and suppressed during REM sleep. Our group investigated whether the sleep-related activation of focal IEDs and HFOs is uniformly distributed across NREM sleep or whether it is facilitated by sleep slow oscillations < 1 Hz (Frauscher et al., 2015b). Sleep slow oscillations were shown to orchestrate different cortical rhythms in the physiological condition (Haider and McCormick, 2009; Crunelli and Hughes, 2010; Timofeev and Chauvette, 2017).

We found that 79% of IEDs and 65% of ripples occurred during high-amplitude widespread slow waves compared to 21% of IEDs and 35% of ripples that occurred during an equal number of non-slow wave control segments (Frauscher et al., 2015b). We further demonstrated a positive correlation between rate of epileptic activity and amplitude of the sleep slow wave, with highest rates of IEDs and ripples during the top 5 % of highest amplitude slow waves. This finding extended the current literature showing that the expression of IEDs during sleep is related to the cyclic alternating pattern (CAP) and more specifically pattern A1 which consists of a synchronous EEG pattern such as present in recurrent slow wave activation periods (for a review CAP and epilepsy see Halász, 2013).

Surprisingly and in contrast to our primary hypothesis based on experimental research showing that physiological and pathological ripples occur during the "up" state of the slow wave (Bragin et al., 1999; Grenier et al., 2001, 2003), we found that IEDs and ripples occur during the "down" state and more precisely in the transition periods.

As synchronization in the CNS is achieved primarily through inhibitory mechanisms (Farrant and Kaila, 2007; Mann and Paulsen, 2007; Engel, 2012), dysfacilitation during the hyperpolarizing 'down' state could predispose to neuronal hypersynchronization resulting in IEDs. This hypothesis is supported by different experimental studies pointing to the paradoxical role played by $GABA_A$ receptor-mediated inhibitory mechanisms in synchronizing neuronal networks and generating epileptic activity (for a review, see Avoli and de Curtis, 2011).

Table 1
Overview of the different studies investigating HFOs in the context of sleep.

Authors	N	Method	Main finding
Staba et al., 2004	25	Modulation of HFOs by sleep	HFO rates are highest in NREM sleep, and lowest in REM sleep. Ripples decline more drastically compared to fast ripples during REM sleep.
Clemens et al., 2007	7	Coupling of slow waves, spindles and ripples	Ripple activity increases before spindle peaks and distinctly decreases after the peak.
Bagshaw et al., 2009	9	Modulation of HFOs by sleep	HFOs have their maximal rate in the same sleep stages as IEDs. The duration of HFOs is relatively stable across the sleep–wake cycle.
Dümpelmann et al., 2015	15	Modulation of HFOs by sleep	HFOs in all brain regions except the frontal lobe were modulated by sleep.
Frauscher et al., 2015b	8	Coupling with slow waves	Different coupling of physiological and pathological HFOs in relation to slow waves.
Frauscher et al., 2016	12	Coupling with rapid eye movements	Different coupling of physiological and pathological HFOs in relation to rapid eye movements during REM sleep.
Nonoda et al., 2016	13	Coupling with different frequencies of slow waves	Epileptic HFOs are coupled with slow waves of 3-4 Hz more tightly compared to physiological HFOs, which are coupled to slow waves of 0.5-1 Hz.
Sakuraba et al., 2016	13	HFO suppression during REM inside / outside the EZ	The suppressive influence of REM sleep on HFOs is less prominent inside than outside of the EZ.
Von Ellenrieder et al., 2016	45	Coupling with slow waves	Interaction with slow waves during sleep improves discrimination of physiologic and pathologic HFOs.
Bruder et al., 2017	19	Coupling with sleep spindles	There was a significant ripple amplitude peak - spindle trough – coupling. The amplitude was higher in epileptic ripples compared to spindle ripples.
Song et al., 2017	23	Phase-event amplitude coupling of slow waves and HFOs	Phase-event amplitude coupling between ripples and sleep oscillations may be useful to distinguish pathologic and physiologic events in frontal and parietal SOZ.
Von Ellenrieder et al., 2017	17	Sleep-homeostatic properties of HFOs	There were different sleep homeostatic properties of physiological and pathological HFOs.
Al-Bakri et al., 2018	5	Modulation of HFOs by sleep	HFO rates increase with sleep depth (S4 > S3 > S2 > S1)
Gliske et al., 2018	121	Analysis of HFO rates over long periods of time and multiple days	HFO patterns change even two weeks after implantation
Iimura et al., 2018	24	Coupling of slow waves and HFOs	High values of rates and modulation index correspond to severity of epileptogenicity. Epileptic spasm children achieving seizure freedom following surgery exhibited strong coupling between slow waves and FRs.
Mooij et al., 2018	19	Coupling of scalp-EEG recorded physiological ripples with sleep-specific EEG transients	Scalp-EEG recorded physiological ripples co-occur with sleep-specific transients
Motoi et al., 2018	123	Coupling of slow waves and HFOs	The modulation index provided useful information for the prediction of postoperative seizure outcome.

Legend. EZ, epileptogenic zone; FR, fast ripples; HFO, high-frequency oscillations; SOZ, seizure-onset zone

This suggests that it is rather synchronization than hyperexcitability, which is the underlying factor for enhancing epileptic activity during sleep.

More importantly, we were able to show a distinct coupling of physiological and pathological HFOs to slow waves. This is illustrated in Fig. 2. A follow-up study in a large sample of 45 patients with drug-resistant focal epilepsy confirmed these results, and showed that the phase of the slow waves improves the separation between channels recording from normal and epileptic brain regions (von Ellenrieder et al., 2016).

Similar results were found in the meantime through different approaches such as analysis of the modulation index or phase amplitude coupling between high and low frequency oscillations (Nonoda et al., 2016; Song et al., 2017; Iimura et al., 2018; Motoi et al., 2018). Amiri et al. (2016) also found that phase-amplitude coupling between high (gamma, ripple) and low (theta or lower) frequencies was highest in stage N3 and lowest in REM sleep, and was higher in the seizure onset zone than in other regions. The reason for the discrepant findings between previous work (Bragin et al., 1999; Grenier et al., 2001; Grenier et al., 2003) and those of our group and others (Frauscher et al., 2015b; von Ellenrieder et al., 2016; Song et al., 2017) is unclear. One reason might relate to how the state of the slow waves was defined. Whereas Bragin et al. (1999) and Grenier et al. (2001) used micro-electrode recordings, our group and others used macro-electrode recordings requiring indirect identification of the state of the slow wave by considering that physiologic activity in the gamma and ripple bands decreases during the down state (Grenier et al., 2001; Mukovski et al., 2007). Another reason may be that ripples recorded with microelectrodes do not fully correspond to ripples recorded with macroelectrodes. Combining macro- and micro-electrode recordings in patients with epilepsy will help to answer this question.

In analogy to these results, we suggested that it is desynchronization which suppresses epileptic activity during sleep. The state of maximal EEG desynchronization is phasic REM sleep (REM sleep with rapid eye movements). In order to investigate our hypothesis we compared EEG segments from phasic REM sleep to EEG segments from tonic REM sleep (REM sleep without rapid eye movements). We found that both IEDs and ripples are most suppressed during phasic REM sleep (Frauscher et al., 2016). Campana et al. (2017) showed similar results, with lowest IED rates during phasic as compared to tonic REM sleep. In addition, there was a reduced level of synchronization during phasic REM sleep both on a large (global) and small (local) spatial scale.

The significance of hippocampal sleep spindles and their relation to epileptic activity was discussed for many years. Hippocampal spindles have been considered a physiological phenomenon, an evoked response to afferent epileptic discharges, or even the expression of an epileptic manifestation (Montplaisir et al., 1981; Malow et al., 1999). We investigated the presence and rate of hippocampal spindles in focal drug-resistant epilepsy patients undergoing combined scalp-iEEG (Frauscher et al., 2015c). Our data showed that hippocampal spindles represent a physiological phenomenon, with an expression that is diminished in epilepsy affecting the temporal lobe. Hippocampal spiking lowered the rate of hippocampal spindles. One possible explanation can be found in a hypothesis of Pierre Gloor, who proposed that spike-wave discharges of generalized absence seizures are generated by the same thalamo-cortical circuits as physiological spindles but occur in the presence of hyperexcitable and hyperresponsive cortical neurons (Gloor, 1978; Kostopoulos, 2000).

3.4. Circadian/multidien rhythm and IEDs/HFOs

Whereas the evidence on the distribution of IEDs stems mostly from one night or few nights of recordings, recently available data from an FDA-approved closed-loop implantable brain stimulator for detecting and treating seizures (NeuroPace) has afforded an unprecedented opportunity to monitor human brain activity with intracranial recordings continuously over very long recording periods of up to years (Anderson et al., 2015; Spencer et al., 2016; Baud et al., 2018). Spencer et al.

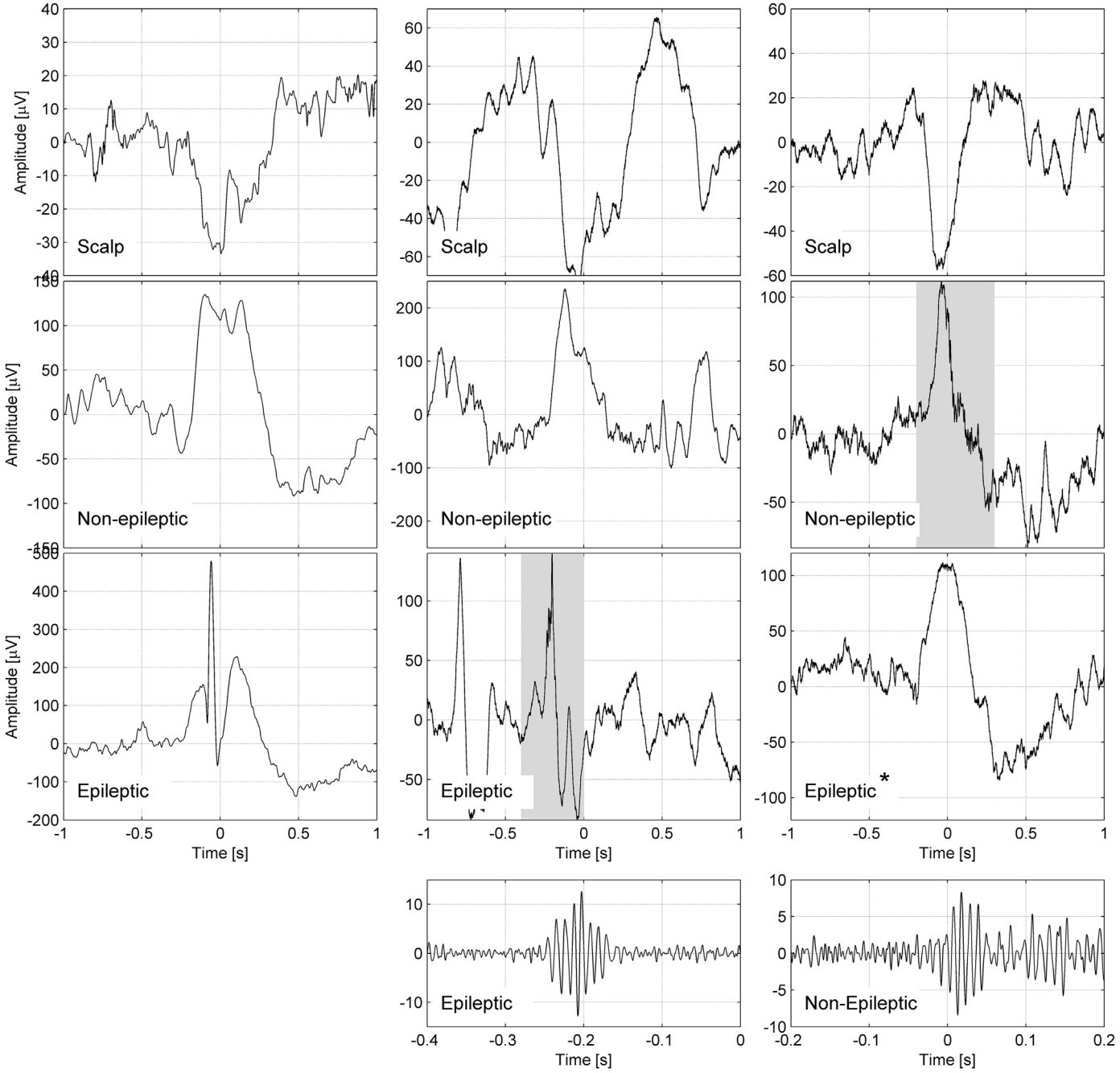

Fig. 2. Representative examples for the coupling of epileptic spikes and HFOs across the slow wave cycle. Example of a slow wave and an epileptic spike (*left*), a slow wave and an HFO in a channel with epileptic activity (*middle*) and an HFO in a channel with normal EEG activity (*right*). The *top row* shows the slow wave in a scalp channel, the *second row* shows the same time period for an intracerebral channel with normal EEG activity (presumably from healthy brain tissue), and the *third row* an intracerebral channel with epileptic EEG activity. The *bottom row* shows the HFO signal with a different time and amplitude scale, corresponding to the shaded periods in the intracerebral channels. All the channels are in the left frontal region [anterior cingulate gyrus (LCA1–2), orbitofrontal area (LOF1–2, LOF2–3), second frontal gyrus (LCA7–8), third frontal gyrus (LOF9–10)], each example corresponds to a different patient. The scalp slow wave on the right panel is of shorter duration than the scalp slow waves on the left or middle panel. Note that the spike and the HFO in the intracerebral channel with epileptic activity (*middle*) occur prior to the peak of the scalp negative half-wave, whereas the HFO in the channel with normal EEG activity (*right*) occurs after the peak of the scalp negative half-wave. *In this example a normal sleep slow wave and no epileptic spike is seen in a channel called 'epileptic' because it has spikes at other times.
Source: Frauscher et al. (2015b) published open access using a Creative Commons Attribution CC-BY licence.

(2016) analyzed data from 134 drug-resistant focal epilepsy patients over an 84-day period. The authors found that IED detections showed a robust circadian pattern in all subjects with uniform peaks during normal sleep hours, regardless of the location of the seizure-onset zone. Baud et al. (2018), who analyzed iEEG data from 37 subjects with recording durations of up to 10 years revealed that, in addition to well-known circadian rhythms, IEDs fluctuate with slower multidien rhythms (rhythms with a time period of several days) of typically 20-30 days that vary across subjects but are relatively stable within subjects over many years (see Fig. 3). Regarding HFOs, Gliske et al. (2018) showed variability in rates and location of HFOs during prolonged iEEG recordings.

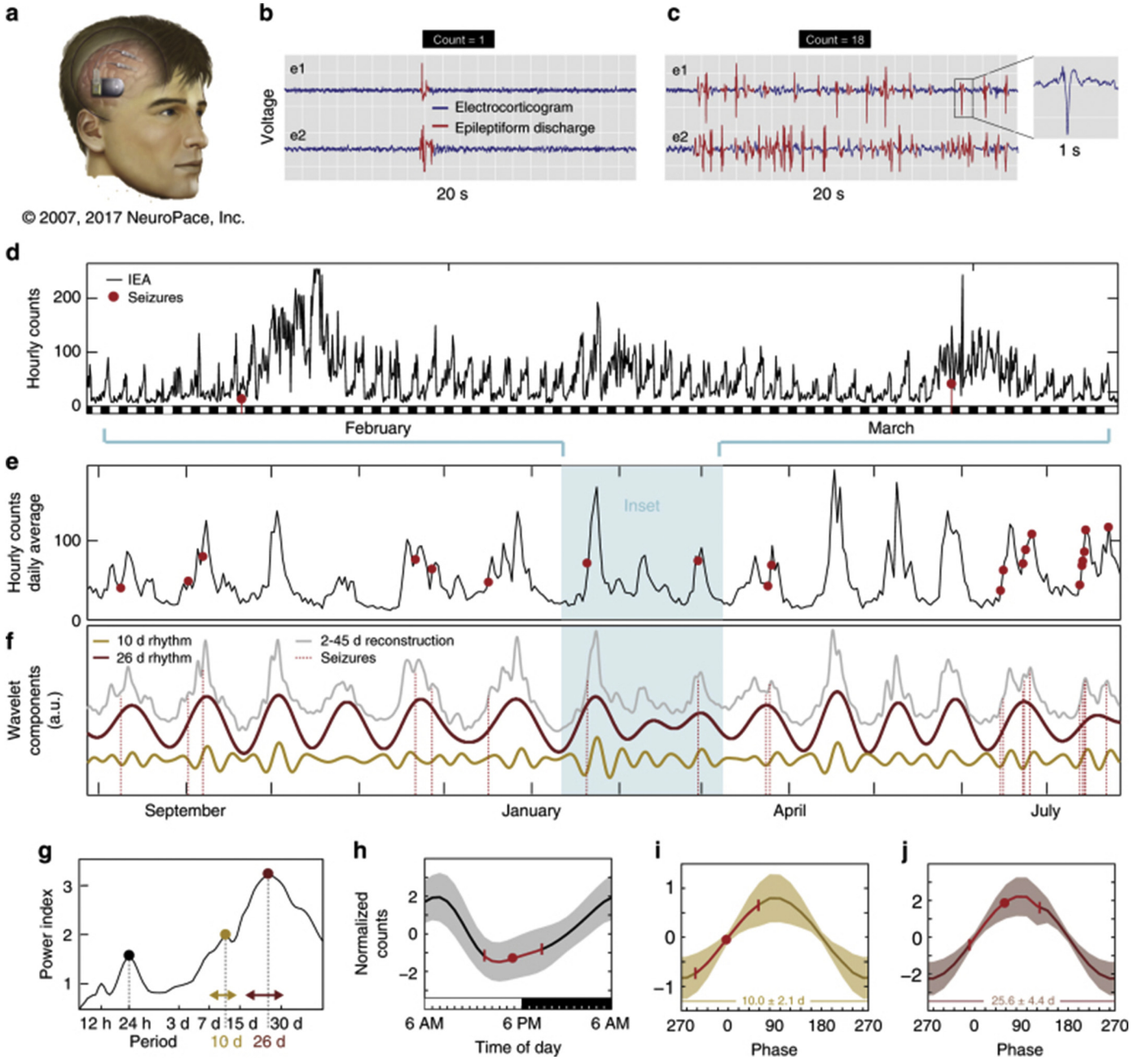

Fig. 3. Representative subject demonstrating circadian and multidien rhythms in IEA, as well as preferential timing of seizures. (a) RNS System comprising cranially implanted neurostimulator connected to intracranial leads (image used with permission from NeuroPace, Inc.). (b) EEG showing a single-epileptiform discharge (spike) in channels corresponding to left (e1) and right (e2) hippocampal leads. (c) EEG recorded 1 week later at the same time of day showing higher count of epileptiform discharges, i.e., higher IEA. Inset magnifies one typical element to show waveform morphology. Hourly (d, cyan inset) and daily (e) fluctuation in IEA in one subject over 2 and 12 months, respectively. Red dots indicate times of seizure occurrence. (f) Wavelet decomposition revealing two component multidien rhythms with periodicities of 10 and 26 days. Combining all multidien wavelet coefficients reconstructs the daily IEA time-series (gray curve, 2–45 d, Pearson correlation $r = 0.93$, $p = 0$). (g) Corresponding periodogram showing ultradian (12 h), circadian (24 h), and multidien (10 and 26 d) peaks in periodicity. Period length displayed on the *x*-axis, and power index (square root of spectrogram power) on the *y*-axis. Horizontal double-arrows show span of corresponding wavelet coefficients included for (**f**) (peak period ± 33%). (h) Average normalized amplitude of the circadian rhythm as a function of time of the day showing phase preference of seizures near the trough at 5 PM ($n = 74$ seizures, mean ± SD in red, $p = 10^{-4}$, Omnibus test, see Methods section). Black and white rectangles (d, h) represent night (6PM–6AM) and day (6AM–6PM), respectively. (i, j) Average normalized amplitude of the 10 d and 26 d IEA rhythms as a function of their underlying phase (*x*-axis, full 360 degrees phase; *y*-axes have different scales). Seizures demonstrate phase preference for the up-slope of both rhythms (10 and 26 days, $n = 66$ seizures, mean ± SD in red, $p = 0.0002$ and $p = 0.002$, respectively, Omnibus test).
Source: Baud et al. (2018) published open access using a Creative Commons Attribution licence.

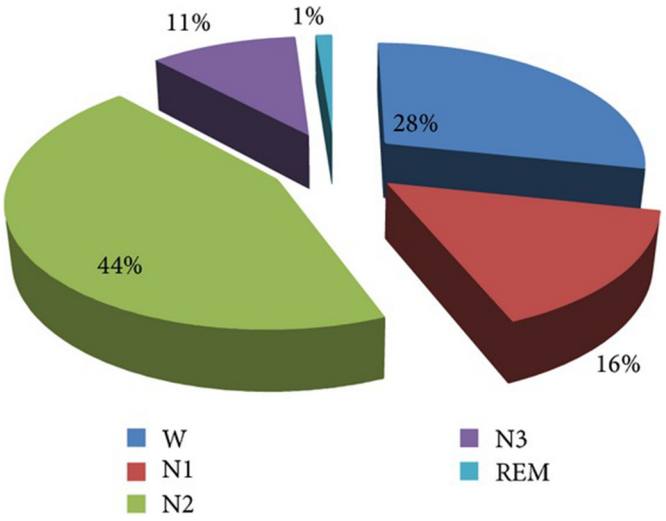

Fig. 4. shows the distribution of the 1990 focal seizures in wakefulness and specific sleep stages.
Source: Ng and Pavlova (2013) published open access using a Creative Commons Attribution licence.

4. Modulation of focal seizures in adults by sleep

In this part of the review, we will focus on modulation of focal seizures by sleep and circadian rhythm in general.

4.1. Focal seizures and distribution across sleep and wake cycle

The tendency for specific periods of the day to be more susceptible for seizure occurrence is known for a long time (Gowers 1881). Within the last 3 decades, there have been multiple studies identifying specific vulnerable time periods in both adults and children (Quigg et al., 1998; Durazzo et al., 2008; Hofstra et al., 2011; Loddenkemper et al., 2011; Pavlova et al., 2012; Gurkas et al., 2016). Moreover, different epileptogenic regions may differ with respect to their vulnerable period (Quigg and Straume, 2000). Most of the data in this area come from patients recorded in epilepsy monitoring units, but there are also few studies using ambulatory home EEG recordings or are obtained from the NeuroPace trial.

Studies showed that depending on the lobe of origin, focal seizures occur preferentially at different times of the day (Herman et al., 2001; Mirzoev et al., 2012; Durazzo et al., 2008; Karafin et al., 2010; Nzwalo et al., 2016; Spencer et al., 2016): Frontal lobe seizures occur mostly out of sleep, with an early morning peak; mesiotemporal seizures were shown to have two diurnal peaks, morning and late afternoon (including when evaluated in a non-circadian environment), while occipital seizures peak in the early evening and rarely occur during sleep. Peaks of parietal seizures were less clear and varied across different studies.

Analysing a total of 1990 seizures from 9 studies showed that focal seizures occurred most frequently in NREM sleep, at an intermediate frequency in wakefulness, and with lowest frequency in REM sleep (Ng and Pavlova, 2013). This is illustrated in Fig. 4. Note is made that some of the evaluated studies consisted of nocturnal sleep recordings only, which may have underestimated the percentages of seizures occurring during wakefulness.

Interestingly, nocturnal seizures are associated with more severe and longer hypoxemia events, and more frequently followed by postictal generalized EEG suppression, both factors implicated in sudden unexpected death in epilepsy (Latreille et al., 2017).

Epileptic seizures are not only modulated by the sleep wake rhythm, but also the circadian rhythm. A link between phase shifts of melatonin secretion and epilepsy, as well as a decreased expression of genes involved in circadian regulation such as CLOCK or BMAL1 have been shown in the epileptic focus (for a detailed review on the circadian rhythm and epilepsy, see Khan et al., 2018). Moreover, the diurnal occurrence of epileptic seizures was shown to have similarities to the circadian rhythm of cortisol (van Campen et al., 2015). In this context, it is interesting to mention, that analyzing data from NeuroPace demonstrated that seizures occur preferentially during the rising phase of multidien IED rhythms (Baud et al., 2018).

5. Contribution of sleep to localize the epileptogenic zone

Knowledge in sleep electrophysiology is important for clinical neurophysiology. This has become even more important in the context of prolonged video-EEG monitoring, as necessary for presurgical epilepsy evaluation. The notion that epileptic activity in temporal lobe epilepsy is more focally confined during REM sleep as compared to NREM sleep where it becomes more frequent with an extended field can be valuable for better localizing the epileptic focus (Sammaritano et al., 1991; von Ellenrieder et al., 2017). Moreover, IEDs present in REM sleep might be particularly localizing, as they may occur only in brain regions with high epileptogenicity, where inhibitory influences of desynchronization are overridden by the pathological malfunction of this tissue. Sleep has further become very important regarding analysis of HFOs. As HFOs are extremely short events with a significantly lower signal-to-noise ratio than IEDs, recordings with few or no artifacts are needed (Zijlmans et al., 2017). This is in particular the case when recording of HFOs are performed on the scalp. Coupling to sleep-specific transients might further contribute to increase specificity of HFOs for delineating of the epileptogenic zone, as it might help to separate physiological from pathological HFOs (Frauscher et al., 2015c; Frauscher et al., 2016; von Ellenrieder et al., 2016; Nonoda et al., 2016; Bruder et al., 2017; Song et al., 2017; Iimura et al., 2018; Motoi et al., 2018). One paper showed that that the suppressive influence of REM sleep on HFOs is less prominent inside than outside of the epileptogenic zone (Sakuraba et al., 2016). The less suppressive effect of REM sleep inside the epileptogenic zone may hence provide a specific marker of epileptogenicity, which awaits further investigation.

6. Outlook and future directions

In summary, this article reviewed the influence of sleep on human focal epilepsy from a neurophysiology point of view. Although substantial progress has been made in the last decades, many aspects await further clarification or are still only incompletely understood. Identified areas for future research comprise the integration of sleep in the presurgical investigation of drug-resistant focal epilepsy. Currently, the state of vigilance is still frequently not acknowledged, when evaluating new biomarkers for the epileptogenic zone. This, however, could lead in fact to optimized results for identification of the epileptogenic zone, given the above discussed properties of REM sleep with a less suppressive effect on epileptic activity inside than outside the epileptogenic zone (Frauscher et al., 2016; Sakuraba et al., 2016). Another interesting research area is to clarify the pathways by which focal seizures are coupled to different phases of the circadian rhythm and sleep-wake cycle. This may not only inform on new treatment options, but also prompt to consider chronotherapy in the treatment of epilepsy.

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