Review article

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Interictal epileptiform discharges in sleep and the role of the thalamus in Encephalopathy related to Status Epilepticus during slow Sleep

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ABSTRACT – EEG activation of interictal epileptiform discharges (IEDs) during NREM sleep is a well-described phenomenon that occurs in the majority of epileptic syndromes. In drug-resistant focal epilepsy, IED activation seems to be related to slow wave activity (SWA), especially during arousal fluctuations, namely phase A of the cyclic alternating pattern (CAP). Conversely, in childhood focal epileptic syndromes, including Encephalopathy related to Status Epilepticus during slow Sleep (ESES), IED activation seems primarily modulated by sleep-inducing and maintaining mechanisms as reflected by the dynamics of spindle frequency activity (SFA) rather than SWA. In this article, we will review the effect of sleep on IEDs with a particular attention on the activation and modulation of IEDs in ESES. Finally, we will discuss the role of the thalamus and cortico-thalamic circuitry in this syndrome.

Key words: continuous spike-and-wave discharges during sleep, EEG, encephalopathy related to status epilepticus during slow sleep, sleep, thalamocortical system

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Sleep consists of repetitive cycles where NREM and REM sleep alternate with a periodicity of about 90-100 minutes. Each state requires distinctive regulatory mechanisms and exerts a different modulatory effect on physiologic and epileptic activity (Amzica, 2002; Brown *et al*., 2012). In this article, we will review the effect of sleep on interictal epileptic discharges (IEDs) with a particular attention on the activation

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and modulation of IEDs in the syndrome of Encephalopathy related to Status Epilepticus during slow Sleep (ESES). Finally, we will discuss the role of the thalamus and the cortico-thalamic circuitry in this syndrome.

Activation of IEDs during sleep

Scalp EEG studies have shown that NREM sleep increases the number of IEDs and favours seizure occurrence both in focal and generalized epilepsies while REM sleep does not (Ferrillo *et al*., 2000; Herman *et al*., 2001; Campana *et al*., 2017). NREM sleep can also facilitate the spread of IEDs, both ipsilaterally and contralaterally from the primary focus in focal epilepsy (Malow *et al*., 1998; Sammaritano *et al*., 1991), especially during arousal fluctuations, namely phase A of the cyclic alternating pattern (CAP) (Halász *et al*., 2004; Parrino *et al*., 2006). Conversely, this phenomenon is not observed in REM sleep, where a reduced spatial and temporal summation of electrical signals is observed, thereby limiting the propagation and scalp EEG expression of the IEDs (Sammaritano *et al*., 1991; Frauscher *et al*., 2016; Campana *et al*., 2017).

The mechanisms by which NREM sleep activates IEDs have been extensively studied since the original publication by Gibbs and Gibbs on the usefulness of sleep to record IEDs (Gibbs and Gibbs, 1947). Experimental data have demonstrated that the same physiological thalamocortical and cortical oscillations operating during NREM sleep and leading to the appearance of the typical physiological graphoelements (e.g. spindles and K complexes) also favour the occurrence of IEDs. In particular, the presence, during NREM sleep, of a continuous alternation between neuronal depolarization (up-state or activated state) and hyperpolarization (down-state or silent state) at the cellular level creates a state of instability that enables the epileptogenic cortical substrate to produce IEDs (Steriade *et al*., 1993; Amzica, 2002). Intra-cerebral sleep EEG recordings in epileptic patients have confirmed these findings showing that IEDs are modulated by cortical sleep slow waves being significantly more frequent during the transition from up to down state (Frauscher *et al*., 2015). Moreover, the presence of infraslow oscillations, as observed by both quantified and visual EEG analysis, seem to further increase the occurrence and the spread of IEDs by creating an additional instability operating at a macroscopic level (Vanhatalo *et al*., 2004; Halász *et al*., 2013; Gibbs *et al*., 2015; Zubler *et al*., 2017). Accordingly, Ujma *et al*. showed that IEDs recorded with subdural electrodes were maximally associated with phase A1 of the CAP (Ujma *et al*., 2015). Finally, these observations have been confirmed by Stereo-EEG studies, showing that the lowest level of IED production is observed during the plateau of delta activity, corresponding to a stable and spatially homogeneous production of delta activity in different brain regions (Gibbs *et al*., 2016; Zubler *et al*., 2017).

Activation and modulation of IEDs during sleep in ESES

ESES provides perhaps the most spectacular example of EEG activation of IEDs during sleep. The peculiar characteristic of this epileptic syndrome is state dependency. In wakefulness, the EEG is usually abnormal, showing paroxysmal foci in the fronto-temporal or centro-temporal regions or isolated bursts of diffuse spike-wave activity. During NREM sleep, an EEG pattern of nearly continuous, pseudo-rhythmic bursts of diffuse IEDs arises. This pattern typically stops upon entering REM sleep where IEDs become fragmented, less continuous and more localized (Tassinari *et al*., 2012). The shape and field potentials of IEDs in ESES show similarities with the IEDs of other childhood focal epilepsy syndromes such as benign epilepsy with centro-temporal spikes (BECTS), Panayiotopoulos syndrome (PS), atypical BECTS and Landau-Kleffner syndrome (LKS). Although IEDs are often bilateral, in ESES, as in these other syndromes, a leading hemisphere usually drives the IEDs with different degree of secondary bilaterality during sleep (Halász *et al*., 2005). Because of clinical and EEG similarities between ESES and these syndromes, it is therefore argued that ESES is at the far end of this continuum of syndromes. Indeed, BECTS, PS, atypical BECTS, LKS and ESES share a similar perisylvian location of IEDs, an important increase in IEDs during sleep, a deterioration of language and executive functions of various intensities as well as common genetic mutations (De Negri, 1997; Doose *et al*., 2001; Hahn *et al*., 2001; Halász *et al*., 2005; Panayiotopoulos *et al*., 2008; Lemke *et al*., 2013; Lesca *et al*., 2013; Turner *et al*., 2015). Sleep-related IED activation in ESES is henceforth thought to represent an extreme exaggeration of what is seen in BECTS during sleep, both in space and synchronicity (De Negri, 1997; Halasz *et al*., 2014).

Earlier EEG studies based on visual sleep stage scoring in patients with BECTS had identified slow wave sleep has a potent activator of IEDs (Beaumanoir *et al*., 1974; Dalla Bernardina *et al*., 1982; Clemens and Majoros, 1987), with the descending slope of the cycles having the greatest activating properties (Clemens and Majoros, 1987). By using spectral EEG analysis methods to compare IED dynamics on EEG plotted with temporal series of SWA, the main indicator of sleep depth, or spindle frequency activity (SFA), it was shown

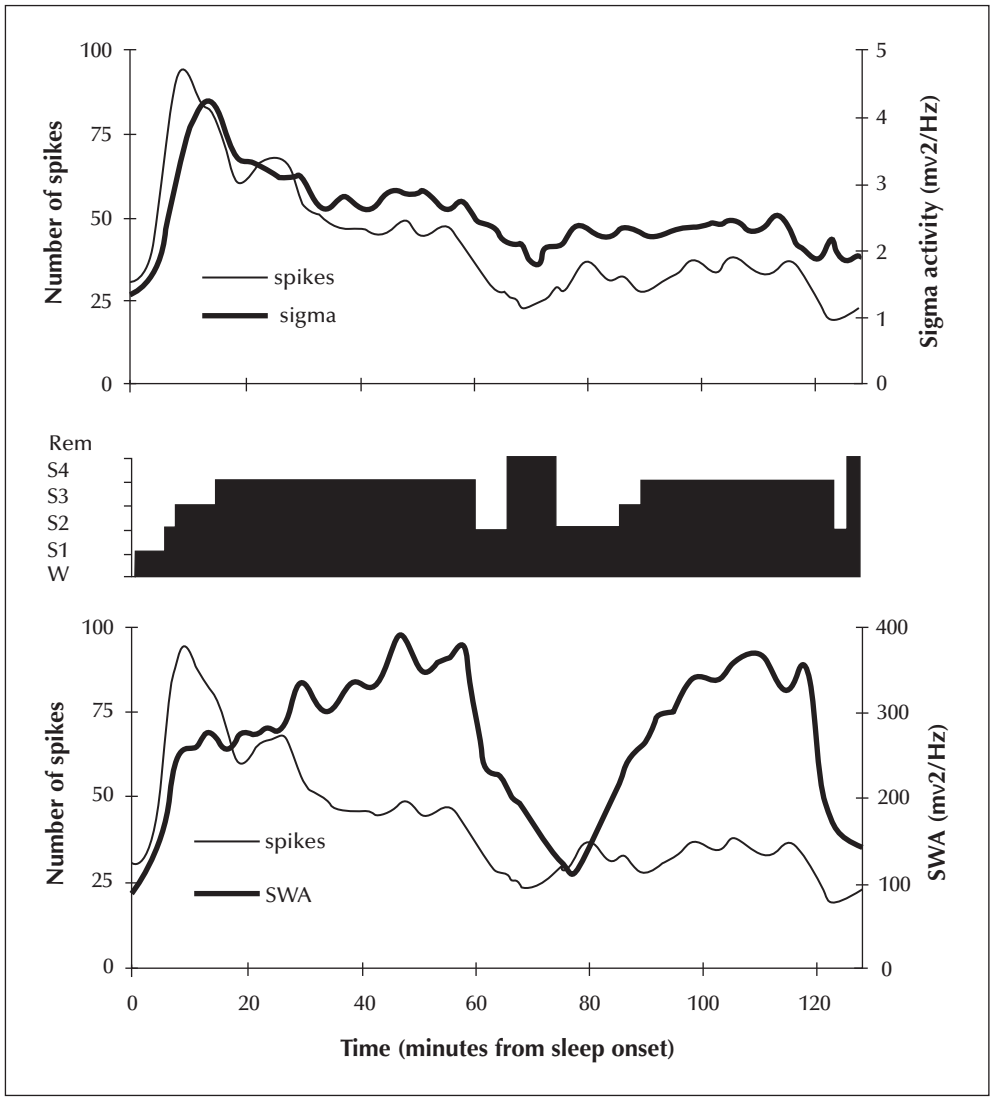

Figure 1. Temporal series of spikes per minute plotted together with spindle frequency activity (sigma activity; upper graph) and slow-wave activity (SWA; lower graph) in a patient affected by Landau-Kleffner Syndrome. Hypnogram is shown in the center. Notice the better temporal relation between spikes per minute and spindle frequency activity with respect to SWA. Modified with permission from Nobili *et al*., 2000.

that a higher correlation between IED distribution and SFA with respect to SWA exists in BECTS, PS, LKS and ESES (Nobili *et al*., 1999, 2000, 2001; Beelke *et al*., 2000) (*figure 1*). This finding differs from what is observed in adults with focal epilepsy, where IEDs are known to be strongly modulated by arousal fluctuations (CAP) (Terzano *et al*., 1991). Indeed, Terzano *et al*. have shown that IEDs in BECTS were not modulated by the CAP (Terzano *et al*., 1991). Moreover, when limiting the analysis to the part of the first NREM sleep cycle where SWA and SFA show a diverging behaviour (SWA increases and SFA decreases), Ferrillo *et al*. (2000) showed that correlation coefficients between SFA and IEDs in childhood focal epilepsy syndromes were highly positive while correlations between SWA and IEDs were always negative, implying the existence of mutually exclusive sleep-related IEDs facilitating mechanisms.

In ESES, the tremendous amount of IEDs hinders the application of spectral EEG analysis. However, the cyclic organization of sleep in ESES is grossly preserved showing a standard ultradian rhythm with approximately 80% of total sleep time spent in NREM sleep versus 20% in REM sleep (*figure 2; upper panel*). This has permitted Nobili *et al*. to compare the physiological evolution of SWA and SFA EEG power in control subjects to the time series of IEDs in children with ESES (Nobili *et al*., 2001). Since SWA distribution is characterized by an exponential decay from the first to the last NREM sleep cycle during the night, one could

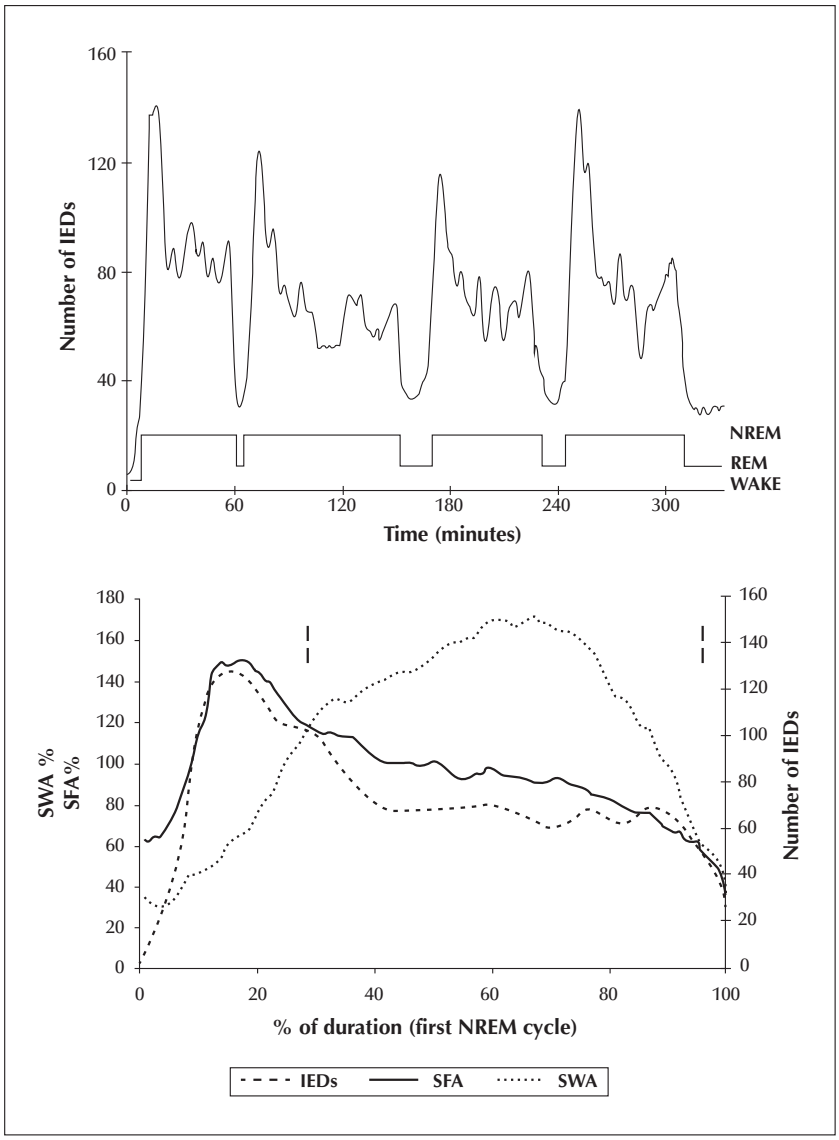

Figure 2. Upper panel - temporal distribution of spikes during the whole night in a single representative subject with ESES. Notice the rather stable values of IEDs over the consecutive cycle. The hypnogram is shown under the IED profile. Lower panel - Model of normalized SWA and SFA time course in the first NREM sleep cycle in ESES. The distribution of IEDs per minute in a single subject shows a strong correlation with SFA and an inverse time course with respect to SWA, especially between the two dotted vertical lines where SFA and SWA have diverging behavior. ESES, Encephalopathy related to Status Epilepticus during slow Sleep; IEDs, interictal epileptiform discharges; SFA, spindle frequency activity; SWA, slow wave activity. Modified with permission from (Nobili *et al*., 2001).

hypothesize that a similar decay in IED production should occur throughout the night. However, as shown in *figure 2* (*upper panel*), the mean IED count did not change throughout the consecutive NREM cycles. Correlation analysis showed that the temporal distribution of IEDs was also positively correlated with SFA (*figure 2; lower panel*). This finding suggests that the IED activation throughout the night in ESES seems to be more sensitive to the sleep-promoting and -maintaining mechanisms than to the homeostatic process related to sleep depth.

Data on IED frequency extracted from the aforementioned studies are summarized in *table 1*. Values of IED frequency during NREM sleep show a constant increase from "benign" focal epilepsy syndromes to ESES. Of note, this progression also mirrors the clinical continuum of language and executive function deterioration observed in some of these children. Indeed, a peculiar aspect of these epileptic syndromes is their exclusive occurrence during a specific developmental period, from 2-14 years, an age when cortical synaptogenesis, abundant axonal sprouting and

Table 1. Spike index comparison during NREM and REM sleep in different syndromes of focal childhood epilepsy.

	No. subjects	Age	NREM spike index	REM spike index
BECTS	9	7.4 (2.5)	23.5 (9.8)	6.3 (4.4)
PS	5	5.8 (2.1)	32.8 (12.3)	16.1 (8.6)
LKS	3	4.3 (0.5)	40.6 (5.6)	21.6 (3.8)
ESES	5	5.6 (1.1)	69.6 (10.1)	34.2 (4.7)

Spike index: number of spikes/minute; parenthesis: standard deviation; BECTS: benign epilepsy with centrotemporal spikes; PS: Panayiotopoulos syndrome; LKS: Landau-Kleffner; ESES: electrical status epilepticus during sleep.
Data extracted from Beelke *et al*., 2000; Nobili *et al*., 2001, 2000, 1999.

elemental functional network are being established (De Negri, 1997; Panayiotopoulos *et al*., 2008; Kurth *et al*., 2010). The abundance of IEDs during NREM sleep has lead to the hypothesis that excessive IEDs interfere with SWA production and/or modulation thus impeding the recuperating, downscaling and learning properties of slow wave sleep (see Rubboli *et al*., p. S62-S70). It is also interesting to note, as evidenced in *table 1*, that an increase in IEDs is observed not only during NREM sleep but also during REM sleep, especially in LKS and ESES where the spike index remains very high during this state. In the future, further assessment of these phenomena might improve our understanding of the neuro-developmental deficits in ESES and more precisely the impact of IED frequency in different sleep states.

ESES: does the thalamus play a role?

The nature of IEDs in ESES during NREM sleep seems to be strongly linked to the cortico-thalamic circuitry. Patry *et al*. speculated that a "particularly active synchronizing system… could account for the extreme activation of the spike and wave discharges" (Patry *et al*., 1971). Although it is unlikely that the IEDs initiate in the thalamocortical circuit as once thought, this system is certainly implicated in its activation, apparently promoting and/or maintaining their occurrence, especially in the context of an immature hyperexcitable brain. Indeed, the observed correlation between IEDs and SFA in ESES seems to suggest that the same thalamocortical oscillations responsible for spindle occurrence create a neurophysiological substrate that favours the activation and spread of IEDs in an hyperexcitable immature cortex. Therefore, although the cortex is the minimum substrate necessary for the production of IEDs, connectivity of thalamic structures seems to have a role in their synchronization and spread (Steriade and Contreras, 1995). Once the oscillation has been set in motion, the cortex and thalamus is hypothesized to form a unified oscillatory network in which both structures drive each other (Meeren *et al*., 2005). Using positron emission tomography with [18F]-fluorodeoxyglucose (FDG-PET) to study functional changes in cortical and thalamic metabolism, most studies found no significant or asymmetric metabolic changes in thalamic nuclei, therefore downplaying the role of the thalamus in ESES (Maquet *et al*., 1995; De Tiège *et al*., 2013, 2008). However, recent data suggest that reduced thalamic volume and hypo- or hypermetabolism can be observed in ESES, highlighting the complexity of studying this dynamic process (Agarwal *et al*., 2015; Sánchez Fernández *et al*., 2017).

The decrease or absence of metabolic changes in the thalamus does not, however, equate to thalamic silence. Using functional MRI (fMRI) analysis in a child with atypical BECTS and linguistic difficulties, Mirandola *et al*. highlighted the involvement of a wide cortico-subcortical network that involved the thalamus during sleep IEDs (Mirandola *et al*., 2013). Such a thalamic involvement was absent during wake IEDs, in line with the role of spindle-generating mechanisms, favouring the activation and propagation of IEDs during sleep through secondary bilateral synchrony (Morrell *et al*., 1995; Nobili *et al*., 1999, 2001). A thalamic involvement during sleep-related IEDs has also been shown in some children with ESES (Siniatchkin *et al*., 2010).

Another intriguing association between ESES and the thalamus concerns early thalamic lesions which have been suggested to play a role in generating ESES by damaging the thalamocortical circuit (Monteiro *et al*., 2001; Leal *et al*., 2018). Cohorts of children with early acquired thalamic injury have shown that approximately a third of these children go on to develop ESES (Veggiotti *et al*., 1998; Monteiro *et al*., 2001; Guzzetta *et al*., 2005; Sánchez Fernández *et al*., 2012). However, most reports

linking thalamic injuries to sleep EEG activation and ESES concern children with extensive brain damage that also included cortical and white matter injuries. In the presence of such injuries, children should nevertheless be monitored closely for paroxysmal activity during sleep and cognitive deterioration (Kelemen *et al*., 2006).

Taken together, the available data support a role for the thalamus in the pathophysiology of ESES and other childhood focal epilepsies, not at the forefront of IED production, but as a necessary facilitator of sleep-related IEDs. This emphasizes the concept of the "cortico-thalamo-cortical loop", which seems to require cortical dysfunction as well as thalamic overexcitation to produce the EEG pattern of ESES (Sánchez Fernández *et al*., 2013). A change in the regulatory loop, induced by cortical alterations (structural or not), could result in a loss of feed-forward inhibition to thalamocortical neurons and favours a robust oscillatory cortico-thalamo-cortical network (Beenhakker and Huguenard, 2009; Paz *et al*., 2010). On the other hand, the presence of a cortical deafferentation from thalamic inputs could also alter this loop and create a state of cortical hyperexcitability. The reason why only a percentage of children develop ESES remains unanswered. One hypothesis could be the severity or specificity of cortico-thalamic circuitry damage and/or rearrangements (Halász *et al*., 2005; Kelemen *et al*., 2006; Sánchez Fernández *et al*., 2013). Again, the presence of certain region-specific genetic predispositions such as mutations in the *GRIN2A* gene, might precipitate the appearance of this syndrome (Lemke *et al*., 2013; Lesca *et al*., 2013; Turner *et al*., 2015).

Conclusion

Activation of IEDs during NREM sleep is a well-described phenomenon that occurs in the majority of epileptic syndromes. In adults with drug-resistant focal epilepsy, IED activation seems to be related to SWA and arousal fluctuations, especially with phase A1 of the CAP (Ferrillo *et al*., 2000; Parrino *et al*., 2006; Ujma *et al*., 2015). In most childhood focal epileptic syndromes, including ESES, IED activation during sleep seems primarily associated with SFA rather than SWA (Ferrillo *et al*., 2000b; Nobili *et al*., 2001). In ESES, however, such an activation is extremely pronounced. The reason for this is still unclear although evidence suggests the necessary interplay between the cortex and the thalamus. Indeed, the role of the thalamus, as part of the "cortico-thalamo-cortical loop", seems essential but not at the forefront of the pathophysiology. Linking the anatomo-electro-clinical findings and the genetic profile with sleep disturbances and cognitive impairment might be key in future studies to elucidate and perhaps halt this harmful developmental process. □

Disclosures.
None of the authors have any conflict of interest to declare.

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