

Review

Derailment of Sleep Homeostatic Plasticity Affects the Most Plastic Brain Systems and Carries the Risk of Epilepsy

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Abstract

Although a critical link between non-rapid eye movement (NREM) sleep and epilepsy has long been suspected, the interconnecting mechanisms have remained obscure. However, recent advances in sleep research have provided some clues. Sleep homeostatic plasticity is now recognized as an engine of the synaptic economy and a feature of the brain's ability to adapt to changing demands. This allows epilepsy to be understood as a cost of brain plasticity. On the one hand, plasticity is a force for development, but on the other it opens the possibility of epileptic derailment. Here, we provide a summary of the phenomena that link sleep and epilepsy. The concept of “system epilepsy”, or epilepsy as a network disease, is introduced as a general approach to understanding the major epilepsy syndromes, i.e., epilepsies building upon functional brain networks. We discuss how epileptogenesis results in certain major epilepsies following the derailment of NREM sleep homeostatic plasticity. Post-traumatic epilepsy is presented as a general model for this kind of epileptogenesis.

Keywords: sleep homeostatic plasticity; epileptic derailment of functional brain networks; system epilepsy

1. Introduction to the Basic Phenomena Connecting Sleep and Epilepsy

1.1 Sleep Homeostasis

The concept of sleep homeostasis emerged from studies on sleep regulation by Borbély [1]. This on-demand model connected sleep regulation with activity from the preceding day, thereby confirming an exponential relationship between the duration of wakefulness and the power of sleep slow waves (0.75–4.0 Hz) in the subsequent sleep period. In other words, the longer the previous waking time, the greater the sleep slow wave power. The term “duration of wakefulness” includes daytime activities, i.e., synaptic use. This model is supported by studies showing that sleep deprivation exponentially increased slow wave power in the subsequent sleep period [2,3].

This model involved the notion of “use-dependent” regulation [4], which is best seen in the realms of slow oscillation (SO) on the descending slopes of the first sleep cycles- and prevailing in the frontal lobes and the left hemisphere. This SO sweeps posteriorly from the frontal to the occipital lobes [5].

Studies in anesthetized animals revealed an additional cortical SO (≤ 1 Hz) characterized by peculiar “ups and downs” on electroencephalography (EEG) and reflecting the synchronized membrane polarization changes of pyramidal cells and interneurons [6–8]. The up-state (depolarization) envelops several faster rhythms- sleep spindles and ripples- and rich synaptic traffic near the waking level. The hyperpolarized (down) state does not contain any unit or

synaptic activity and is a “black hole”, also termed “disfacilitation” [9]. Similar up and down states of SO were also found in naturally sleeping animals [10]. This rhythmicity is assumed to have an essential role in sleep plasticity functions.

There is abundant evidence for the importance of slow wave activity. However, what is the function of slow waves that are strongly protected by homeostatic forces?

Tononi and Cirelli [11,12] have elaborated upon their popular “synaptic homeostatic hypothesis”, which postulates that synaptic facilitation builds up (upregulates) throughout the day and is then downregulated during sleep. An alternative concept is that cortical synapses are depressed (downregulated) by waking activities and upregulated by sleep SO via silent (down) states [13].

Another level of non-rapid eye movement (NREM) sleep oscillation is an EEG micro-cyclicity termed the cyclic alternating pattern (CAP) [14]. The CAP has recently been linked to brain structures [15].

Activity within the frame of CAP reflects an ongoing spontaneous cortical activity during NREM sleep. This is characterized by periodic EEG activity (CAP and non-CAP periods) that recurs with a frequency of up to one minute. The existence of CAP reflects the sleeping brain's flexible adaptation to external and internal conditions. CAP patterns are consistent with micro-arousals manifesting as two types, depending on and indicative of the actual balance between sleep-promoting and arousal forces. A well-known arousal pattern (A3 in CAP terms) emerges at low



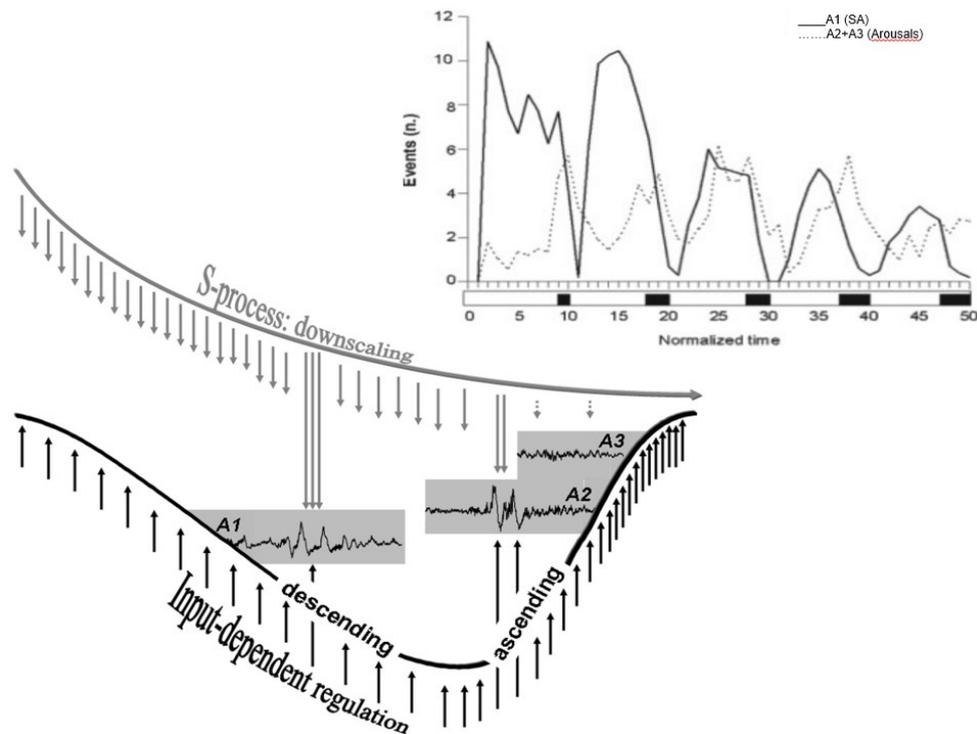


Fig. 1. Schematic representation of the distribution of different cyclic alternating pattern (CAP) responses for the descending (D) and ascending (A) slopes of sleep cyclicity. On the D slope, a phasic auditory input evokes phasic slow wave responses (CAP A1 phases, upward arrows) that provide instant homeostatic “delta injections”. On the A slope, the response is similar to the known electroencephalography (EEG) + autonomic arousal response (A2 and A3 phases). The upper insert shows the distribution of CAP phases during a typical night’s sleep. Black bars on the horizontal line represent rapid eye movement (REM) sleep phases. (A1 = slow wave EEG response. CAP A2–3 response = traditional arousal) Note the exponential decay of A1 responses that follow the decrease in homeostatic pressure, in contrast to A2 and A3.

homeostatic pressure and is characterized by the attenuation of EEG activity with fast rhythms, muscle and autonomic changes. When the homeostatic pressure is high, such as in the deepening periods (descending slopes) of the first NREM sleep cycle, a paradoxical (anti-arousal) slow wave response (CAP A1) occurs [16] (Fig. 1).

Reactive CAP A1 slow waves provide immediate homeostatic protection [17]. The continuous slow waves of deep slow wave sleep show a prolonged and delayed homeostatic response to synaptic up-scaling (exhaustion) depending on previous use. In contrast, the phasic slow wave reactions of CAP A1 occur instantly as slow wave “injections”. Both types reimburse slow waves’ amount and prevail over the frontal lobes.

1.2 Homeostatic Plasticity and Epilepsy

Plasticity is the general capability of the brain’s neural elements, from synapses to networks, to modify (up- or down-regulate) their response in reaction to previous activity in the form of long-term potentiation (LTP) or depression (LTD). LTP is defined as a persistent increase in signal transmission between two neurons by synapses, as observed by recent patterns of activity [18], whereas LTD is the opposite. In other words, as defined by Steriade [9], an “activity-

dependent alteration in the strength of connections among neurons, through which information is stored”.

Plasticity and epilepsy are closely related but differ in their effects on the brain. Plasticity is a building force, whereas epilepsy is a disfigured and exaggerated caricature that distorts the affected functions.

It appears that an intrinsic aim of cortical networks is to achieve a slow wave “state”. Interestingly, isolated slabs and even cortical cell cultures follow this rule, thus hinting at homeostatic regulation [19,20].

Cortical deafferentation has been shown to lead to a compensating (homeostatic) upregulation of neural excitability. Greater damage induces stronger upregulation that may result in epileptic excitation. Thus, while homeostatic force can neutralize a small amount of harm, greater damage needs stronger compensation. This may result in derailment of paroxysmal activity, as seen in post-traumatic epilepsy [21,22].

The isolated cortex and hippocampus “operate extremely close to the transition point between a quiescent state and an abnormally active epileptic state” [9,23,24]. Wherever plastic processes occur, an epileptic shift is close by.

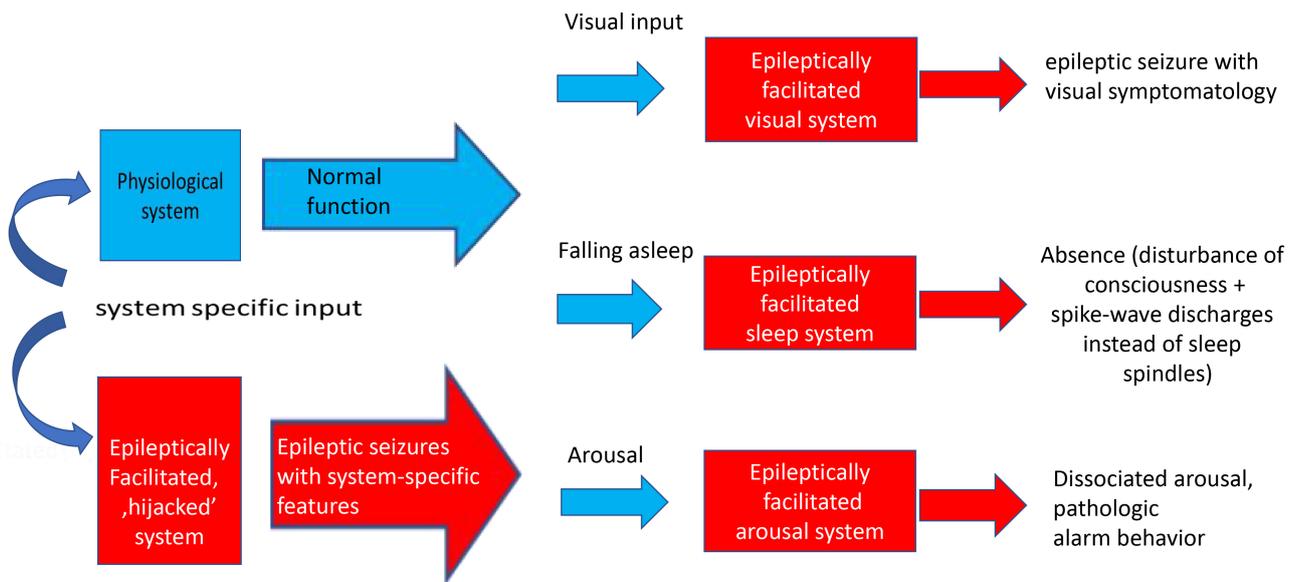


Fig. 2. Schematic illustration of the system epilepsy concept, wherein the epilepsy is built upon physiological systems that share a common process of epileptogenesis.

Goddard and Douglas [25] first proposed that the plastic process of the memory trace (engram)-formation is similar to epileptogenesis.

LTP is the elementary model of long-term plasticity and the basis of kindling, with daily electrical stimulation resulting in hyperexcitation and the development of an epileptic process leading to spontaneous seizures [26,27]. Similarly, experimental epileptic foci that bombard distant regions with spikes may establish secondary spike foci that subsequently become independent. Such secondary cortical spots “learn to be epileptic” due to the plastic and potentially progressive runs induced by recurrent interictal epileptiform discharges (IEDs) [28,29].

1.3 System Epilepsy

The concept of system epilepsy considers epilepsy to be a network disease. This concept may overcome the untenable dichotomy between “focal” and “generalized” epilepsies (Fig. 2). and reveal that epileptogenesis has a common molecular and electrophysiological mechanism that originates from the derailment of normal brain functioning in systems that are most liable to plasticity [30–35]. According to this concept, the differences between epilepsies lie only in the localization and specificity of the affected systems. Concerning seizure-triggers, besides accepted reflex epilepsies we incorporated seizures initiated by the activation of the affected physiological brain system (like falling asleep, or arousal).

2. Sleep-Related System Epilepsies are the Result of Sleep Homeostatic Derailment

Non-rapid eye movement (NREM) sleep is initiated by a switch to the burst-firing working mode of the thalamocortical system.

While the thalamus faithfully transmits stimuli to the cortex during waking, during NREM sleep a powerful γ -Aminobutyric acid ergic (GABAergic) inhibitory machine released from the ascending reticular inhibition stops this transmission, leading to the burst-firing working mode of the thalamocortical network. Self-sustaining inhibitory cycles during NREM sleep produce sleep spindling and slow (0.75–4.0 Hz) oscillation [9].

The sleep EEG envelope is regulated by the use-dependent homeostasis reflecting sleep need, providing brain-wide synaptic refreshment and responding to local needs. Thus, homeostatic power may promote an epileptic transformation.

According to the system epilepsy concept, epilepsies build on certain brain systems. IEDs, including spikes and ripples, as well as seizures, move together and accumulate during slow wave sleep [9,36].

Thus, epilepsy is deeply interwoven with sleep, and even sleep constituents transform into interictal epilepsy patterns. Epilepsy, therefore, deserves to be called the most important sleep disorder.

2.1 Medial Temporal Lobe Epilepsy as Epilepsy of the Declarative Memory System

Medial temporal lobe epilepsy (MTLE) may be considered system epilepsy since it affects the bilateral episodic memory system with the hippocampi and manifests abundant interictal and ictal memory disturbances. NREM sleep is essential in the memory process, and the unstable hippocampal memory engrams are replayed and transmitted to the frontal lobe during NREM sleep [37–39].

Any injury to certain hippocampal sectors (a first hit) may induce a 7–7.5 year-long “rewiring” process in synap-

tic structure and connectivity [40]. The discharges from a damaged hippocampus to produce nonsense information, rather than useful memory fragments, may obstruct the hippocampo-frontal memory correspondence [41,42]. Memory consolidation is accomplished by the interplay of sleep slow waves, sharp-wave ripples, hippocampal spindles, and ripples [36]. Slow waves orchestrate this teamwork by placing it under homeostatic regulation [43–46].

An essential step in epileptic transformation leading to MTLE is the metamorphosis of hippocampal sharp-wave-ripples to an epileptic pattern, epileptic spikes, and pathological high frequency oscillations (HFOs) [36]. The mechanism underpinning this transformation was described recently [47].

During the process of epileptic transformation, the number of evolving hippocampal spikes correlates inversely with the number of spindles [42], with the decrease in spindles also contributing to the memory disturbances of MTLE patients.

The role of the homeostatic process is supported by the circadian and night-time distribution of evolving interictal spikes. These prevail during high homeostatic pressure periods such as the first part of night sleep and the evening-afternoon time of day, as compared to the morning hours [48].

Both the interictal and ictal symptoms of MTLE are interwoven with memory disturbances [49,50]. The insidiously evolving interictal memory impairment remained undetected for a long time because it can only be shown by neuropsychological follow-up studies. In ictal symptomatology, pure amnesic seizures, *déjà-* and *jamais vu*, as well as psychic or intellectual auras (dreamy states) are consistent with memory disturbances.

Disturbances of consciousness by focal onset temporal lobe seizures may also be thought of as memory-knockouts that evolve because of hippocampal involvement, i.e., a hippocampal “knockout” by seizure, as revealed by deep electrodes. Patients lose contact but not their muscle tone. They do not fall, but cannot understand speech during the seizure. This symptomatology can be understood as an acute memory loss, or a transient loss of the capacity to recognize things, language, or people.

The memories evoked by stimulation of the exposed temporal cortex of epileptic patients [51] also support the association between epilepsy and the memory system.

2.2 Absence Epilepsy is the Epilepsy of the Corticothalamic “Falling Asleep” Process

The corticothalamic network hosts the function of falling asleep. Absence epilepsy (AE) is linked to this network and is thus considered to be a corticothalamic system epilepsy [52].

This notion is based on studies reporting that spike wave discharges (SWD) emerge from the same circuit that normally produces sleep spindles [53]. Using ablation ex-

periments, Steriade *et al.* [54] showed that “SWD originate in the neocortex and are disseminated through mono-, oligo- and multi-synaptic intracortical circuits, and exhibit generalized features”.

Experiments by Meeren *et al.* [55,56] confirmed the focal onset of seizures deemed “primary generalized”. In addition, several clinical and EEG reports have highlighted the focal features of apparently generalized SWD. However, caution is needed when using the term “focal” in the original sense (as in traditional focal epilepsies) because absences build up (enrolled) step-by-step, mostly from a fronto-cortical network in each seizure, in contrast to the permanent epileptogenic zones of focal epilepsies [57]. It is important to note that a genetic background allowing epileptic transformation in those critical periods has been shown both in animals [58] and humans.

The regulation of sleep spindling and other sleep rhythms appears to be controlled by the thalamic reticular nucleus [59] via mutual interaction between its GABAergic neurons, thereby regulating the level of output inhibition exerted on thalamic relay cells [60]. Based on studies with animal models, SWD of absence seizures also appear to originate in the thalamus by a mechanism like spindle generation [61] and which is based on reduced GABAergic inhibition [62].

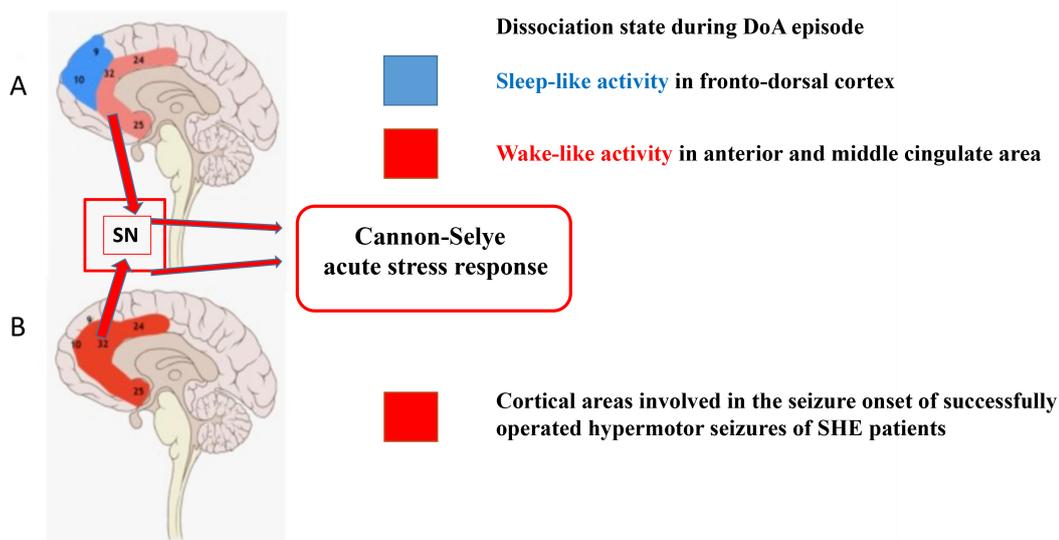
Absences are linked to transitional periods between wakefulness and N2 sleep, and are referred to as “critical” vigilance levels. Whereas absences seemingly occur in wakefulness, they actually emerge during falls of vigilance. This vigilance level-dependence explains their distribution throughout the 24-h sleep/wake cycle [63].

When arousals in sleep induce absences, EEG microstructural analysis can reveal the actual link with reactive sleep-like (slow wave) anti-arousal responses because there is a strong positive correlation between CAP A1 and SWD. Additionally, SWD is prevalent in the first sleep cycles and declines later with the decay of the delta power from evening to morning [64]. Regarding the deepening slopes of sleep dominated by subtype A1, the CAP-related activation of SWD increases three-fold compared to ascending slopes containing more A2 and A3 events [65].

Further supporting the nature of “falling asleep epilepsy”, more SWD occurs during fluctuations toward NREM sleep than toward wakefulness or REM sleep [66].

The vigilance-level dependence of absences is also supported by neuroimaging showing increased connectivity in the anterior thalamic structures during the falling asleep period of genetic juvenile myoclonic epilepsy patients [67].

The slow wave-dependence of SWD links absences to homeostatic regulation and supports the notion of a corticothalamic, falling-asleep system epilepsy underpinned by a genetic predisposition, thus making AE another network disease.



Note the anatomical overlap in figure A and B at the level of middle-anterior cingulate cortex, key part of both circuits

Fig. 3. The overlap of state dissociation in DOA and SHE patients. (A) Dissociation state during DOA episodes (findings of SPECT, EEG, and Loretta studies). Blue: fronto-dorsal sleeping part; Red: anterior cingulate activated part. (B) The localisation of the onset zones of sleep related hypermotor seizures, successfully operated on. Note the overlap between A and B activated zones. The red arrows represents the role of salience network (SN) and Cannon-Selye acute stress response (in frame). DOA, disorders of arousal; SHE, sleep-related hypermotor epilepsies; SPECT, single-photon emission computed tomography.

2.3 Sleep-Related Hypermotor Epilepsy, the System Epilepsy of the Arousal System, and an Epileptic Counterpart of Disorders of Arousal

2.3.1 Disorders of Arousal (Arousal Parasomnias)

Disorders of arousal (DOA) episodes are consistent with dissociated arousals from NREM sleep, representing partial sleeping and partial awake states, and confirmed by brain imaging, Loretta, and Single-photon emission computed tomography (SPECT) studies [68–70]. While frequent in childhood, they also occur in adulthood where they manifest as more violent forms compared to the childhood variants [71,72]. DOA episodes form a spectrum from disoriented arousals to sleep walking (somnambulism), sleep eating, sleep sex, to sleep terror. The latter manifests as panic-like alarm-behavior with high heart and respiratory rates, emotional alarm symptoms, and disorientation.

Such episodes typically appear at the turning points of the first sleep cycles between the through and the ascending slope, linking with micro-arousals within sleep and resulting in a pathological state dissociation [73,74]. Sleep deprivation is the most important trigger for DOA episodes.

2.3.2 The Epileptic Counterpart: Sleep-Related Hypermotor Epilepsy

The concept and nomenclature of nocturnal dystonia have changed from sleep-dependent movement disorder to epilepsy [75,76].

While the etiology of most sleep-related hypermotor epilepsies (SHE) is unknown, a small group termed autosomal dominant nocturnal frontal lobe epilepsy is characterized by gene mutations. The best known is mutation of the nicotinic acetylcholine receptor gene, which hypersensitizes the cortex and allows exaggerated and pathological frontal arousals [77].

Both DOA events and SHE seizures link to sleep micro-arousals. Moreover, both also emerge during periods of high homeostatic pressure such as in sleep after sleep deprivation, as well as the descending slopes of sleep in the first part of the night. The frequency of seizures decreases across the night sleep, thereby paralleling the homeostatic decay. Therefore, a homeostatic effect also occurs in SHE and DOA.

The symptomatology of SHE and DOA indicates their close relationship. Based on video-EEG studies [78], their symptoms showed only severity/quantitative differences, making them typically indistinguishable based on semiology.

The strong link between DOA/SHE and arousal is supported by the finding that three-quarters of DOA events and half of SHE events are preceded by arousal. Regarding their order of severity (DOA milder, non-epileptic; SHE more severe, epileptic), several SHE seizures occur per night, in contrast to just one or two DOA events. Moreover, one-third of DOA episodes were triggered by a stimulus, whereas <10% of SHE seizures “required” a trigger.

The symptomatic similarity of DOA and SHE and the family/genetic links suggest a shared mechanism [79–82].

The localization of brain-activation in the two groups provides further evidence of their shared relationship. In DOA the anterior cingulate cortex is “awake”, the fronto-dorsal cortex is “sleeping”, and similar regions (the anterior cingulum, the prefrontal cortex and the anterior insula) host the seizure onset zones of successfully operated SHE patients [83–87] (Fig. 3).

Of note, this region overlaps with the cingulo-frontal region of the salience network (SN) [88] with direct links to the Cannon-Selye-type stress reaction [89]. The salience network can mobilize fight-flight reactions and is remarkably similar to the most severe phenotypes (sleep terrors and hypermotor seizures) of the two syndrome spectrums.

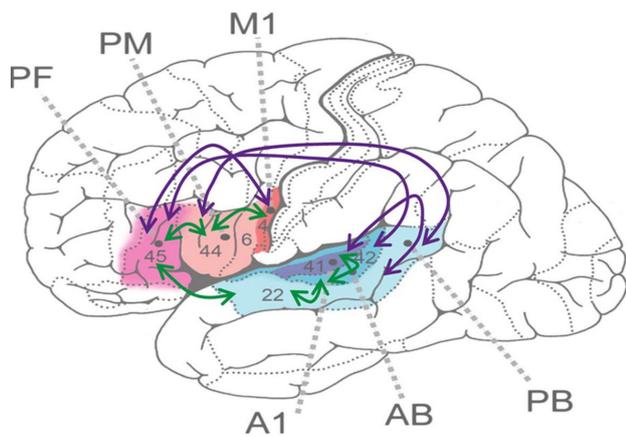


Fig. 4. The human perisylvian language network. M1, primary motor area of speech expression (flesh-colored); PM, premotor area; PF, prefrontal area working memory (pink); A1, AB, PB, auditory areas. The purple arrows represent interconnections among areas that exist only in humans. Reproduced with permission from Schomers MR, Neurocomputational Consequences of Evolutionary Connectivity Changes in Perisylvian Language Cortex, 2017 [90].

The symptomatology of SHE seizures is consistent with a dissociated state reflected by EEG, autonomic, emotional alarm and motor arousals without awareness of a partially sleeping brain and disoriented mind.

It is striking that two similar conditions exist which are both strongly associated with the arousal system’s hyperfunction and manifest NREM sleep dissociation during periods of high homeostatic pressure. Although there have been efforts to find features with differential diagnostic values, the heuristic similarity of these two conditions must be emphasized [81,82].

A cholinergic origin has been demonstrated only in the epileptic group. However, the many similarities as well as family and individual overlaps between the two conditions support a common origin of arousal.

2.4 The Spectrum of Self-Limited Focal Childhood Epilepsies, a System Epilepsy of the Perisylvian Human Communication Network

The anatomical regions around the Sylvian fissure are termed the perisylvian network (PN). The PN covers the lower lateral surface of the frontal lobe from the prefrontal areas including the Broca area, through the opercular structures and the parieto-temporal areas with the Wernicke field, the first and second temporal gyri, and partially the occipital cortex. The abundance and complexity of the involved regions occupying an important central part of the cortex reflect the high phylogenetic advance of human communication. This network organizes writing, reading, speaking, and calculation with the auxiliary machinery of hearing, sound production, articulating, and even vision [90] (Fig. 4, Ref. [90]).

The spectrum of self-limited focal epilepsies (SeLFE) comprises the most frequent childhood epilepsies that can be considered system epilepsies, i.e., network diseases of the PN. The focus here is only on the part of the spectrum where the spectral cohesion is clear.

In this paper involved conditions include: (1) non-epileptic pattern-carriers of centrotemporal spikes (CTS), involving mainly the relatives of SeLFE children; (2) typical SeLFE with centrotemporal spikes (SeLECTS; Rolandic epilepsy) and presenting with rare focal sensory-motor seizures and CTS during NREM sleep; (3) atypical SeLECTS characterized by more seizures and frequent CTS over both hemispheres, as well as early onset, more prominent cognitive deficits, and occasional opercular status epilepticus in sleep; (4) developmental epileptic encephalopathies developmental/epileptic encephalopathy with spike wave activation in sleep (DEE-SWAS) where spikes and slow waves cover widespread regions of both hemispheres more or less continuously in slow wave sleep, as well as electrical status epilepticus in sleep (ESES) and Landau-Kleffner syndrome, with a regional ESES-like EEG pattern.

Recent neuropsychological research has revealed mild cognitive deficits even in “benign” SeLECTS children, mainly affecting their language functions. The language deficit is more important in atypical forms and culminates at the encephalopathic end of the spectrum. CTS-activity that accumulates in NREM sleep appears to increase from asymptomatic CTS carrier relatives, through SeLECTS and atypical SeLECTS children, to DEE-SWAS patients (Fig. 5, Ref. [91]). The degree of CTS-activity parallels that of HFO (ripples), considered to be the best markers of epileptogenicity [92]. Thus, no ripples associate with CTS in non-epileptic CTS carriers, and HFO activity parallels the severity of epilepsies in the spectrum. The mechanism of metamorphosis from sparse or frequent spiking to the ESES EEG pattern is still unclear. In ESES, a bilateral tsunami of spikes floods both hemispheres and tends to be continuous during NREM sleep. IEDs are rare during waking, and

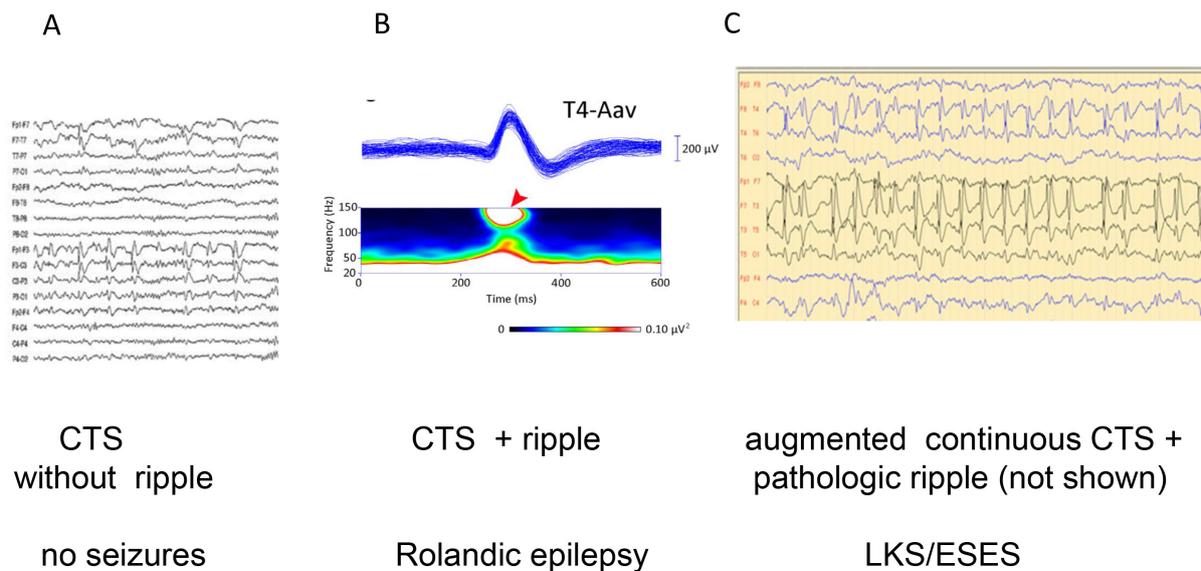


Fig. 5. Three forms (A, B, C) of the centrotemporal spikes (CTS) across the self-limited focal childhood epilepsy spectrum. Left (A), CTS without epileptic seizures; middle (B), self-limited childhood focal epilepsy with centrotemporal spikes (SeLECTS) with ripples superimposed on CTS (spectrogram: top, averaged spikes; middle, spectral frequencies superimposed on spikes (red arrow)). Right (C), the electrical status epilepticus in sleep (ESES) discharge pattern assumed to be consistent with augmented CTS with pathological ripples (not shown). Reproduced with permission from Kobayashi K, *Epilepsy with electrical status epilepticus during slow sleep and secondary bilateral synchrony*. 1994 [91]. LKS, Landau-Kleffner syndrome.

REM sleep is free of discharges. Anti-seizure medication does not always work, and a permanent mental handicap may occur if the ESES duration exceeds 18 months [93].

Although it is assumed that the electrical pattern of electrical status epilepticus in sleep/Landau-Kleffner syndrome is consistent with exaggerated CTS discharges, this requires further study. A large body of literature supports the notion of a focal origin and secondary bilateral synchronization behind the bilateral manifestations [94–98].

Bölsterli *et al.* [99–101] reported a deficit of sleep slow wave downscaling in ESES patients. This finding suggests that a sleep homeostatic disorder underpins the cognitive loss related to the extraordinary increase in epileptic EEG manifestations. The remaining PN epilepsies are also shown to link with sleep homeostasis, even bi-directionally.

The concept of system-epilepsy links epilepsies to a derailment of physiological brain functions, i.e., seizures manifest the disfigured features of the hosting brain-systems. This concept also appears to be valid for SeLFE. Such epilepsies can be considered network diseases of the PN, where the high-level plasticity required for communication is sensitive to epileptic derailment.

3. A Closer Look at the Paroxysmal Derailment of Homeostatic Plasticity

Stimulation of the thalamus or cortex with spindle-like frequencies in experimental settings can evoke augmenting (an increase of amplitudes) or recruiting (runs of repeated

potentials) responses [102]. The parameters of the evoked potentials resemble spindles, thus allowing them to be considered as potential spindle-models. Like spindling, augmenting responses generate plastic changes in thalamic and cortical neurons that outlast the stimulation. They reach their highest amplitudes during slow wave sleep and are disrupted by arousal. These experimental data indicate the thalamocortical system can perform short-, mid- and long-term synaptic changes, which may eventually lead to the generation of self-sustained paroxysmal discharges [103,104].

Sleep SO in the thalamocortical system induces long-term neuronal facilitation. In the waking period following NREM sleep, evoked somatosensory synaptic and local field potentials are higher than during previous waking [105].

These results suggest that LTP occurs during slow-wave sleep, with the latter providing the conditions for homeostatic plasticity as well as potential epileptic derailment.

Post-Traumatic Epilepsy as a Model for Epileptic Transformation

Post-traumatic epilepsies are well-known complications of brain injuries. Acute symptomatic seizures often evolve shortly after the trauma, and chronic epilepsy may develop later. Between 20–60% of epilepsies originate from traumatic injuries [106], while 86% of early acute symptomatic seizures are followed by epilepsy within two years [107].

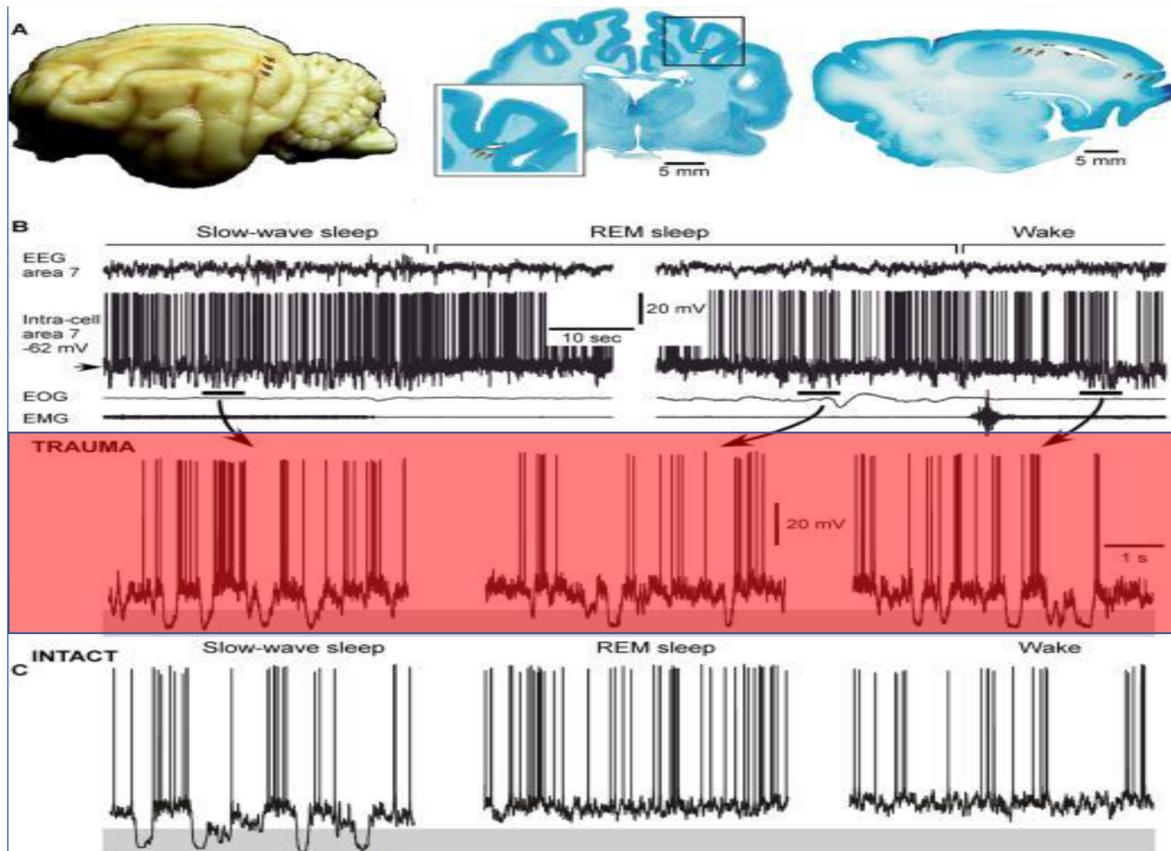


Fig. 6. The cortical undercut model of penetrating wound epileptogenesis. (A) Cat brain depicting localization of the undercut (arrows). Left: global view; middle: frontal section; right: middle and sagittal sections. (B) Intracellular and field potential recordings during different states of vigilance. The epochs indicated by horizontal bars are expanded below. Note the presence of large amplitude hyperpolarizing potentials (indicated by the shadowed area) during NREM and REM sleep, as well as in the waking state. (C) Intracellular neuronal recording in the intact cortex (Reproduced with permission from Timofeev I, Posttraumatic epilepsy: the roles of synaptic plasticity. 2010 [22]). NREM, non-rapid eye movement; REM, rapid eye movement.

The homeostatic origin of trauma-induced epileptogenesis has been revealed by cortical undercut models. The partial deafferentation of the cortex caused by the trauma results in the inability to maintain neuronal activity, as reflected by the prolongation of silent (down) states during slow-wave sleep, as well as in waking and REM sleep. This requires a homeostatic recovery with the potential for epileptic derailment [22,108].

The cortical undercut is an accepted model for penetrating wound epileptogenesis and works well in rats, mice, and cats. It reproduces the paroxysmal pattern seen in brain injuries, with acute symptomatic seizures first being triggered by the trauma, followed by a latent period, and then spontaneous and unprovoked seizures evolving later [109].

This theory proposes that an increase in overall network-silence would increase excitability. Indeed, the duration of silent states was shown to correlate with the instantaneous firing rates [110], with the intrinsic and synaptic excitability increasing within and around the undercut cortex (Fig. 6, Ref. [22]).

4. Highlights and Conclusions

NREM sleep homeostatic regulation provides a strong protection and repair mechanism that enables brain plasticity and allows change and development.

Exaggerated homeostatic plasticity in NREM sleep enables the epileptic transformation of physiologic networks to epileptic systems. Up-and-down states of sleep SO may play a key role in this process.

Pathological HFO mark epileptogenesis and epileptic progression in certain brain systems.

MTLE, AE, SHE, and SeLFE are hosted by brain systems with high plasticity, thus making them network diseases linked to sleep homeostatic plasticity.

Abbreviations

CAP, Cyclic alternating pattern; CTS, centrotemporal spike; DEE-SWAS, Developmental/Epileptic Encephalopathy with Spike Wave Activation in Sleep; DOA, Disorders of arousal; EEG, electroencephalography; ESES, electrical status epilepsy in sleep; HFO, High frequency

oscillation (ripple); IED, interictal epileptiform discharge; LDP, long-term depression; LTP, long-term potentiation; MTLE, medial-temporal lobe epilepsy; PN, Perisylvian human communication network; RE, Rolandic epilepsy; SeLECTS, self-limited childhood focal epilepsy with centrotemporal spikes; REM sleep, rapid eye movement sleep; NREM sleep, non-rapid eye movement sleep; SeLFE, self-limited focal epilepsies; SHE, Sleep-related hypermotor epilepsy; SO, Slow oscillation; SPW-R, sharp wave – ripple; SWD, spike-wave discharge; TRN, the reticular nucleus of the thalamus; AE, absence epilepsy.

Author Contributions

PH had the idea. PH, IT, AS participated in its elaboration. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest. Peter Halász is serving as one of the Guest editors of this journal. We declare that Peter Halász had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Gernot Riedel.

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