Sleep and Epilepsy are Bedfellows

Péter Halász*
National Institute of Clinical Neuroscience, Budapest

Abstract
Recent sleep research provides us new data solving several hidden aspects of epilepsies. Intent of this short note is to call attention to the newly revealed interrelationships of epilepsy and NREM sleep.

The main underlying engine behind activation of epilepsy in sleep is that NREM sleep put into motion the burst-firing mode of the cortico-thalamic system and develops extended and extremely synchronized slow oscillation and spindling over wide fields of the cortex offering large scope for epileptic synchronization.

Sleep research revealed that the same slow wave and spindle activity which gates interictal and ictal epileptic manifestations is the substrate of sleep homeostasis and is responsible for renewing the daily potenciated synapses to make them again possible to learn. Epilepsy is a derailment of plasticity; enlarging synchronised neuronal excitation in neo- and archi-cortical plasticity prone brain structures interfering with sleep plasticity functions.

Therefore the marriage of sleep and epilepsy is a deadly clasp; a vitious circle like cascade develops: NREM sleep slow wave and spindling gates epilepsy and the epileptic activation interferes with sleep plastic functions may cause chronic enduring cognitive impairment. This kind of pathomechanism is detected with different degree of severity in several epileptic syndromes constituting around more than half of the epileptic population. In the clinical practice only dignostic sleep studies are able to detect this insidious process in our patients.

INTRODUCTION
IEDs are gated by sleep slow waves associated with homeostatic dynamics, except idiopathic focal childhood epilepsies associated with spindles

Both clinical observational and EEG data provide long ago abundant evidences about the intimate connection between NREM sleep and epilepsy [1]. In certain part of epilepsies seizures appears particularly around sleep (either during sleep-wake transitions or in slow wave sleep (SWS)) and the highly increased appearance of interictal epileptiform discharges (IEDs) in NREM sleep is even more conspicuous in almost all forms of epilepsy.

Interrelations of sleep and epilepsy
The recognition of a new micro-cyclicity within NREM in the mid-eighties entitled cyclic alternating pattern (CAP) opened the way for a more fine graded analysis of the distribution of IEDs across sleep cyclicity. The study of timing IEDs beyond their distribution according to the sleep stages, have clearly shown that CAP serves as gates for them [1,2]. CAP reflects the input related selective responsivity of the brain during sleep. It is composed by compensatory slow wave bouts (CAP A1 phase), when homeostatic pressure is high and an arousal like pattern (CAP A2-3 phases) when the homeostatic pressure is low. The gating function of CAP is associated with the slow wave response in all epilepsies except in the idiopathic hyperexcitability syndromes (Rolandic epilepsy and Panayitopoulos syndrome) where IEDs are associated with sleep spindles [3].

IEDs are timing on the descending slope of slow oscillation's up-states
Recent studies went deeper in understanding the connection of IEDs and sleep EEG graphoelements, especially the slow waves. An even more precise coupling between the functional state of the neuronal membranes of cortical pyramidal cells and IEDs have shown. We know from the early nineties after the research of Steriade and co-workers that slow wave oscillation in NREM consists of an up and down fluctuation [4]. The down-states represent drastic decrease in neuronal activities characterized by hyperpolarisation, while during the upstates a rich, near to wake state level oscillation activity is riding on the depolarisation from spindles to ripples. Frauscher et al., [5] have found that the timing of IEDs is on the descending slope of up-states of slow oscillation, just at the transition toward the down-states.

NREM sleep enlarge the epileptic network
NREM sleep not just increase the occurrence of IEDs compared
to wakefulness, but increase the field of the spikes and increase their appearance on the contralateral side and lastly increases the synchrony between bilateral events. We can say that NREM sleep enlarges the epileptic network or more precisely shows us in the wake state hidden parts of the interictal network. In NREM sleep we can detect the whole spectrum of generalisational tendencies and bilateral involvement in interictal epileptic activity. In REM sleep on the contrary epileptic manifestations – if at all – are strictly localized. We can say NREM sleep reveals the whole face of epilepsy exploring the dark side detectable only during „moonlight” (sleep).

**Burst-firing mode of the cortico-thalamic system during NREM sleep fuels the activation of IEDs**

The main underlying engine behind this activation is that sleep puts into motion the burst-firing mode of the cortico-thalamic system and develops extended and extremely synchronized slow oscillation and spindling over wide fields of the cortex offering large scope for epileptic synchronization [6].

**Epilepsy being a derailment of plastic changes interferes with the plastic functions of slow wave sleep**

More and more arguments show that epilepsy is an intrinsic disorder of plastic changes, an exaggeration of the long term potentiation like synaptic processes, a derailment of the process by which learning and memory come about. Therefore is epilepsy so ubiquitous hosted by the archicortex (hippocampus) and neocortex which especially take part in plastic changes in the brain. It is possible, that epilepsy is the price we pay for the abilities of learning.

That is the point where epilepsy and (NREM) sleep congregate as bedfellows (has a common bed). The most interesting result of the contemporary sleep research is the recognition that the cyclic decline of sleep slow wave oscillation during NREM sleep from evening to morning refresses the daytime potentiated synapses and regenerate their learning capacity for the next day (synaptic homeostasis theory of sleep [7]).

**Epileptic sleep activation interferes with plastic sleep function resulting cognitive impairment**

As it was mentioned important part of epilepsies became activated by NREM sleep. Among these epileptic syndromes several is associated with cognitive impairment rising up the possibilities of a casual link between the sleep activation and the cognitive decline.

We have increasing evidences for at least three kind of pathomechanisms by which the epileptic activation may cause severe cognitive consequences.

The first is coming from observations about cognitive decline associated with an immense interictal sleep activation in the form of continuous electrical status epilepticus in NREM sleep (ESES). This condition is age dependent, but because shows very low responsiveness to the traditional antiepileptic drugs, usually leaves after the cessation of discharges severe mental impairment. The cognitive disorder is proportional to the localisation and extension of the discharges. Two kinds of etiology seems to be outlined. Smaller part of the cases with ESES are children with atypical Rolandic epilepsy and Panayiotopoulos syndrome and the larger part have initially more or less severe frequently polyeval continuation structural brain damage [8], among them with conspicuously high number of children having early thalamic haemorrhage. According to some studies in children with ESES and mental impairment an important deficit has been found in the physiological dampening process of slow oscillation, ensuring the regeneration of synapses during sleep [9].

The finding seems to confirm the hypothesis of CA Tassinari, who was the first to assume that the cause of the cognitive decline is the interference of epileptic discharges with the plastic functions of sleep (the possibilities to learning) of the affected children [10]. If it is true not the interictal epileptic activity per se is guilty for the mental symptoms, but the interference with sleep; the lack of downscaling in slow wave oscillations.

The second type cognitive impairment caused by epileptic interference with sleep plastic functions is what we see in Medial Temporal Lobe Epilepsy (MTLE) where intensive medio-temporal origin interictal spiking interferes with memory consolidation interrupting the physiological hippocampo-frontal dialogue. The work of Buzsáki and co-workers provided both experimental and human clinical evidences for this kind of pathomechanism [11,12].

A third line is coming from the recognition and studies of the so called, Epileptic Encephalopathies” (EEs). Epileptic encephalopathies constitute a contradictory, however widely used category in epilepsy, recognised by the International League against Epilepsy (ILAE). EEs are epilepsy-related mental global malfunctioning conditions of the brain. Its main criterion is that the associated cognitive symptoms are caused by epilepsy itself. In other words, the effect of those factors causing the epilepsy as well as the adverse impact of the actual antiepileptic drugs in contributing to the global cognitive dysfunction, need to be excluded.

There is a conceptual difference between EEs and encephalopathies with epilepsy. In the latter group there is a common cause e.g. tuberous sclerosis, underlying both epilepsy and the mental symptoms, while for example in Electrical Status Electrics in Sleep (ESES) belonging to EEs, it is likely that the sleep-related interictal discharges themselves are related to the cognitive deterioration.

The EE syndromes start typically in infancy or in early childhood. They are characterized by an active EEG with abundant interictal signs not related to a single focus; occurring dominantly in, or activated during SWS. The specific combination of symptoms constituting different EEs might be due to a common pathomechanism originating from different etiologic factors. Some of the syndromes may have a genetic background; not been clarified in most of them. Typically, there is a progression to the full-blown picture; which may become stagnant and resistant to treatment after.

The pathomechanism of cognitive impairment is supposed to be the the interference of the abundant interictal and ictal discharges with the widespread cortico-thalamic network...
which has leading role in fueling the functions of the associative neocortex. (See in [13] for Lennox-Gastaut syndrome) Here the epileptic disorder is usually very early and assumed to take over the organisation of physiological network. To understand the two steps in the evolution of EEs recently it was proposed [14] to add the adjective “developmental” and name those encephalopathies, in which a developmental component in addition to an epileptic component exists, as “developmental epileptic encephalopathies”.

Besides the epileptic macro-discharges an abundance of pathological high frequency ripples is also characteristics and seems to have a forecasting significance [15,16] of EEs. The presence of pathological high frequency oscillation is largely increased in NREM sleep [17]. Due to the technical developments, these pathological ripple discharges are more and more detectable not only by intracranial electrodes, but also by the scalp leads.

Clinical sleep studies should be the litmus paper to unmask the hidden dark side of epilepsy

In this short note I tried to demonstrate the important role of sleep in the development of enduring progressive epileptic disorders and in a considerable amount of them leading to cognitive impairment. The research of interrelationship of sleep and epilepsy recently opened new vistas, having important heuristic significance. From the practical side we should emphasize the importance to incorporate sleep studies into the evaluation of epileptic patients and have a more insight to the dark side of epilepsy, hidden in sleep, and clinical sleep studies should be the litmus paper to unmask them.

SUMMARY

Sleep slow waves provide a common interface between epilepsy and NREM sleep. Sleep slow waves (and spindles) are products of the NREM sleep working mode of the corticothalamic system which fuels the activation of epileptic manifestations (seizures and interictal events as spikes and pathological HFO) in sleep. The same slow waves and spindles contribute in sleep plastic functions (memory and learning). Epileptic manifestations when activated during sleep interfere with the plastic functions of sleep (synaptic homeostasis and memory consolidation) and probably being one of the most important causative factors of cognitive impairment in most of the severe childhood epilepsies and of medial temporal lobe epilepsy. The relationship with NREM sleep provides a common pathomechanism of a devastating vicious circle for these epilepsies.

REFERENCES