

# The relationship of medial temporal lobe epilepsy with the declarative memory system

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## SUMMARY

**Introduction.** Medial temporal lobe of epilepsy (MTLE) is considered as local/regional epilepsy. However, as was discussed in Part I of this review (Halász, 2016a) there is more evidence regarding the involvement of both temporal lobes so as to consider MTLE as one of the typical bilateral system epilepsies.

**Aim.** To provide contemporary review of MTLE in relation to the declarative memory system and the newly recognized hippocampo-frontal memory consolidation during slow wave sleep.

**Methods.** A review of the available literature on experimental and clinical data and also the authors own studies in MTLE patients.

**Review, discussion and results.** New experimental and clinical neurophysiological data have shown that MTLE is closely linked to the hippocampal memory system. It is likely that hippocampal spiking is the epileptic variations of the normal sharp wave ripple events mediating the encoding and consolidation of memory engrams by a hippocampo-frontal dialogue during slow wave sleep.

**Conclusions.** The source of memory impairment in MTLE patients is not merely the cell loss and synaptic transformation of the hippocampal structure, but the every night interference with memory consolidation due to interictal spiking.

**Key words:** Medial temporal lobe epilepsy • memory consolidation • hippocampal memory • slow wave sleep sharp wave ripple • sleep spiking effect

## INTRODUCTION

Medial temporal lobe of epilepsy (MTLE) is considered a local/regional form of epilepsy. However, as was discussed (Halász, 2016a) there is increasing evidence of the involvement of both temporal lobes, and the relationship with the hippocampal-limbic memory system provides abundant evidence to change this view, and consider MTLE as one of the typical bilateral system epilepsies.

## AIM

Providing a contemporary review of the MTLE in relation with the declarative memory system and the newly recognized hippocampo-frontal memory consolidation during slow wave sleep based on relevant literature review and the authors own studies.

Following items will be discussed:

- a) the nature of memory disturbances in the interictal and ictal states of MTLE patients;
- b) the memory process and role of sharp-wave ripple events in encoding and consolidation;
- c) how does the hippocampo-neocortical memory process change in MTLE;
- d) some therapeutic consideration.

## METHODS

Updated (2016) review of the available literature on experimental and clinical data including the author's own studies concerning MTLE and memory consolidation, electrophysiological and sleep studies.

## REVIEW, DISCUSSION AND RESULTS

### The nature of memory disturbances in the interictal and ictal states of MTLE patients

The most prominent cognitive consequence of MTLE is the side-specific memory-deficit. In the dominant side of MTLE, both declarative verbal memory consolidation and the newly learned material's recall are deficient (Ozkara et al., 2004; Castro et al., 2013; Witt et al., 2014). In MTLE of the non-dominant hemisphere, there is a visuospatial memory deficit, which is less clear; possibly due to the insufficient visuospatial test-battery. The presence of an atypical hemispheric speech-dominance makes the classification of the memory-loss more difficult (Helmstaedter et al., 1999). The extent of the loss of memory correlates with several factors: hippocampal damage (Baxendale et al., 1998; Sawrie et al., 2001) the degree of bilateral involvement, the severity of epilepsy, the number of generalized clonic-tonic seizures (GTCs), the patient's age at the time of the initial hippocampal damage as well as the mental reserve-capacity.

The side specific memory disturbance in MTLE is primarily caused by the early hippocampal injury (see first part of this review). Secondly, the structural changes leading to the epileptic transformation render the hippocampus – or at least a certain part of it (Sano and Malamud, 1953; Margerison and Corsellis, 1966) working as a discharging lesion producing spiking and seizures. The effect of slow wave sleep (SWS) spiking on cognitive performance has not been hitherto enough explored.

The traditional treatment of MTLE as noted in textbooks have not emphasized either its essential impact on memory, or the nightly activation of interictal epileptic discharges (IEDs) during non-REM (NREM) sleep. The hiding of these features can be partly explained by the richness of the ictal and interictal symptoms dominating the electro-clinical picture. Another reason could be the delayed development of standard neuropsychological testing, and what is even more important, it's almost exclusive use during presurgical evaluations. A third reason might be the hidden localisation of the structures harbouring the pathological impulse traffic involved in memory disturbances; scalp EEG can hardly detect these structures' activity, coming to light only by the use of intracranial and intracerebral electrodes.

One should possibly put a greater emphasis on the

interpretation of MTLE symptoms in relation to the memory system. The déjà vu and jamais vu auras are obviously consistent with episodic memory symptoms. Jackson's dreamy states (see below) may be interpreted as pathological memory-symptoms; and the oro-visceral, emotional and autonomic automatisms might also be associated with the memory system. It is possible that the peculiar impairment of consciousness in MTLE patients is more related to the memory system than we have expected. The contact disturbances during the automotor seizures with no loss of body tone and with preserved orientation reaction might be caused by the interference with memory recall resulting in basic difficulties of the recognition of the environment and interrupting self identity. Hughlings Jackson, the first big master of epileptology recognized the "psychic aura" or "intellectual aura" phenomenon also called "dreamy state" in MTLE. It is characterized by a funny double existence: a past experience emerging spontaneously like a hallucination e.g. some scenes that had occurred in the past; is vividly perceived by the patient, parallel with the actual reality. Jackson localised his dreamy state to the uncus hippocampi with anatomical accuracy; proven by the post-mortem analysis of the temporal lobe of his famous patient Z; followed by him for long before the patient died (Jackson found a small cystic lesion at the uncus hippocampi) (Jackson, 1958). Penfield, who introduced epilepsy surgery as a standard treatment option in Montreal, could elicit this kind of memory delusions by stimulating during surgery the exposed cortex of epileptic patients with an electrical current (Penfield and Jasper, 1954). Later, Bancaud and co-workers performing stereotactic surgery in epilepsy had shown that for such epileptic memory delusions the involvement of an extended neuronal network (amygdala, hippocampus, and temporal cortex) is necessary, far beyond the uncus hippocampal area identified by Jackson or Penfield (Bancaud et al., 1994).

Those surgical trials resecting bi-temporal structures to treat MTLE patients with bilateral epileptic symptoms ended with severe memory impairments. The tragic consequences of these surgical interventions in the early fifties provided lessons for the whole international epileptology and neuropsychology community about the important role of temporo-medial structures essentially the hippocampus, in memory functions (Scoville and Milner, 1957).

Another aspect of the relationship of MTLE with the memory system is associated to the physiological

mechanism by which memory engrams are created in the hippocampus and are later consolidated for long term in the frontal cortex.

Fell et al. (2001) studying epileptic patients with hippocampal deep electrodes in the Bonn Epilepsy Centre, have first shown transitory gamma synchronisation during successful learning of declarative memory tasks in the rhinal cortex and the hippocampus. Later, increasing evidence has revealed that gamma synchronisation is not only present in local medio-temporal structures connected to memory functions, but during cognitive tasks in general (Llinás and Ribary, 1993; Cantero et al., 2004). Cantero et al. found that the gamma coherence is elevated during wakefulness compared to slow wave sleep or REM sleep. They assumed that the decrease of cognitive function in slow wave sleep is underlain by a decrease of gamma coupling; causing the difficulties to remember our dreams among others (Fell et al., 2003). The degree of the loss of dreams is proportional with the time elapsed with NREM sleep between the time of dreaming and wakening.

### **The memory process and role of sharp-wave ripple (SPW-rs) events in encoding and consolidation**

The memory process contains three steps: encoding, consolidation and recall. Increasing evidence has shown in the last twenty years, that the engrams first develop in transitory and vulnerable forms in the hippocampus (Buzsáki, 2015). They gain a more stable form later during the consolidation process where they contact with the other engrams already stored in the frontal cortical stores. This consolidation-process happens during slow wave sleep without awareness. This timing is highly appropriate because the immediate processing, transmission and storage of a substantial amount of data during wakefulness would overload the same restricted capacity; while the reduced input and the lack of conscious elaboration during sleep, release more capacity for memory consolidation.

The analyses of the effect of sleep on learning have shown an increase both in declarative and procedural tasks; if the experimental learning was followed within 16 hours by slow wave sleep. The learned material followed by sleep became more resistant against interference and forgetting (Stickgold and Walker, 2013; Buzsáki, 2015; Feld and Diekelmann, 2015).

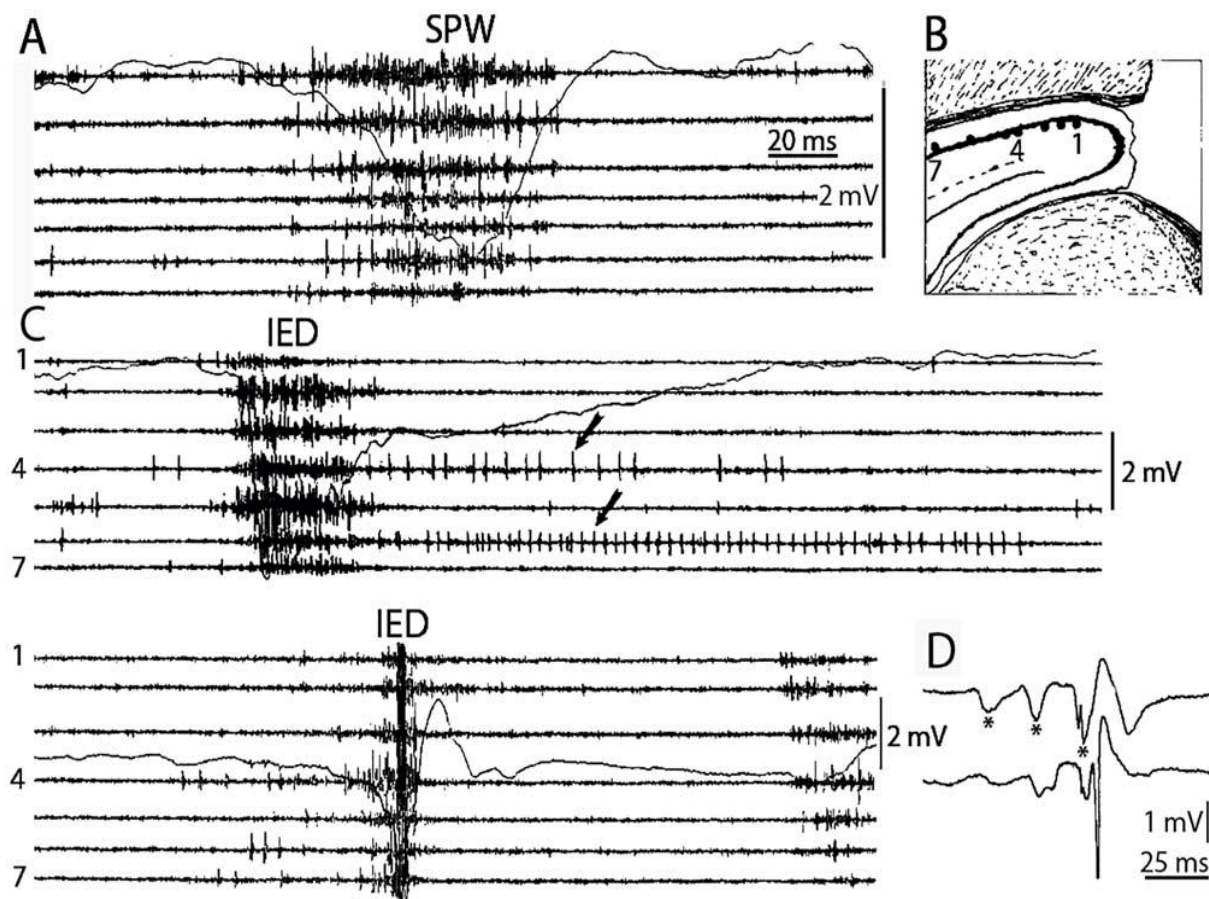
The second step of the memory process, the consolidation, was explored at the turn of the century by Chrobak and Buzsáki, 1996, 1998; Born et al., 2006;

Born, 2010; Buzsáki, 2015. It was first assumed and later confirmed (Wilson and Naughton, 1994) that repetition was a peculiar mechanism for reactivation. The engrams encoded in the hippocampus during the awake state, were reactivated (repeatedly) in a more condensed and rapid form guided by the slow oscillation in the same hippocampus. Subsequently, they were transmitted in a consolidated form to the extra-hippocampal frontal neocortex, and were connected to the earlier stored memories. This scenario has been confirmed for the explicit (declarative) memories. Later it was shown that in the processing of procedural memory, the basal ganglia have a similar role; like the hippocampus for declarative memories.

There are also chemical effects, strongly influencing the memory process. The acetyl-cholinergic transmitter system has a strong impact in the hippocampal structure. Cholinergic agonists facilitate encoding and inhibit consolidation during slow wave sleep (Hasselmo, 2006).

Special attention has been paid, recently, to a hippocampal electrophysiological event, which has important role in memory processing both in experimental animals and in humans: it is the sharp-wave ripple (SPW-rs) phenomenon. SPW-rs is a robust, far reaching population episode, the most synchronized event of the mammalian brain (Buzsáki, 2015), which elevates the excitability of the hippocampus and connected structures (Buzsáki, 1986; Chrobak and Buzsáki, 1996; Csicsvári et al., 1999). It emerges during slow wave sleep or during consummatory behaviour in the waking state when the hippocampal inhibitory influence decreases. It is blocked by the active waking state (theta activity). SPW-rs is the inner event of the hippocampus, which can also be detected in isolated hippocampal slices as well. The “ripple” is a high frequency (200 Hz in animals, 150 Hz in humans) event, originating in the CA1 region of the hippocampal pyramidal layer; in close connection with the sharp wave originating in CA3 (figure 1) (Buzsáki, 1986). The sharp wave is a 40–150 ms duration, maximum 2.5 mV amplitude depolarization-event, involving the hippocampal pyramidal cells. Almost 50% of the hippocampal neurons (50–150 000 neurons) participate in this event. The ripple is a fast oscillatory response to the sharp wave, which is a local event between the CA3 pyramidal cells and the perisomatic inhibitory neurons (Schlinghoff et al., 2014; Gulyás and Freund, 2015).

The SPW-rs complex which is an extensive hyper-



**Figure 1.** Hippocampal field potentials and laminar unit discharges in intact rats (A), and in hippocampus disconnected from its subcortical connections (B). The similarity of the physiological sharp-wave ripple (SPW) events (A), and interictal epileptic spikes (IED) in C and D. Frequency of ripples are greater and the duration of field potentials is longer (D) (Buzsáki, 1986).

synchronous episode, is able to elicit an LTP (long term potentiation) effect changing the synaptic weights between hippocampal neurones.

LTP was discovered by Bliss and Lomo (1966) in the hippocampus of the rabbit. He stimulated the perforant pathway of the hippocampus, registered the response in the dentate gyrus excitatory postsynaptic potential (EPSP). When he used repetitive stimulation the next stimulus evoked longer and higher EPSP, and this feature of responsivity was maintained permanently. Earlier, in 1894, Ramón y Cajal already assumed that the basis of the memory should be the plasticity of the communication ability of the cells. Donald Hebb developed this idea further. He hypothesized that the pre-synaptic cell during the repetitive stimulation induce some kind of growth process and metabolic changes in the postsynaptic neuron. The physical and biologic basis of the phenomenon is still not entirely under-

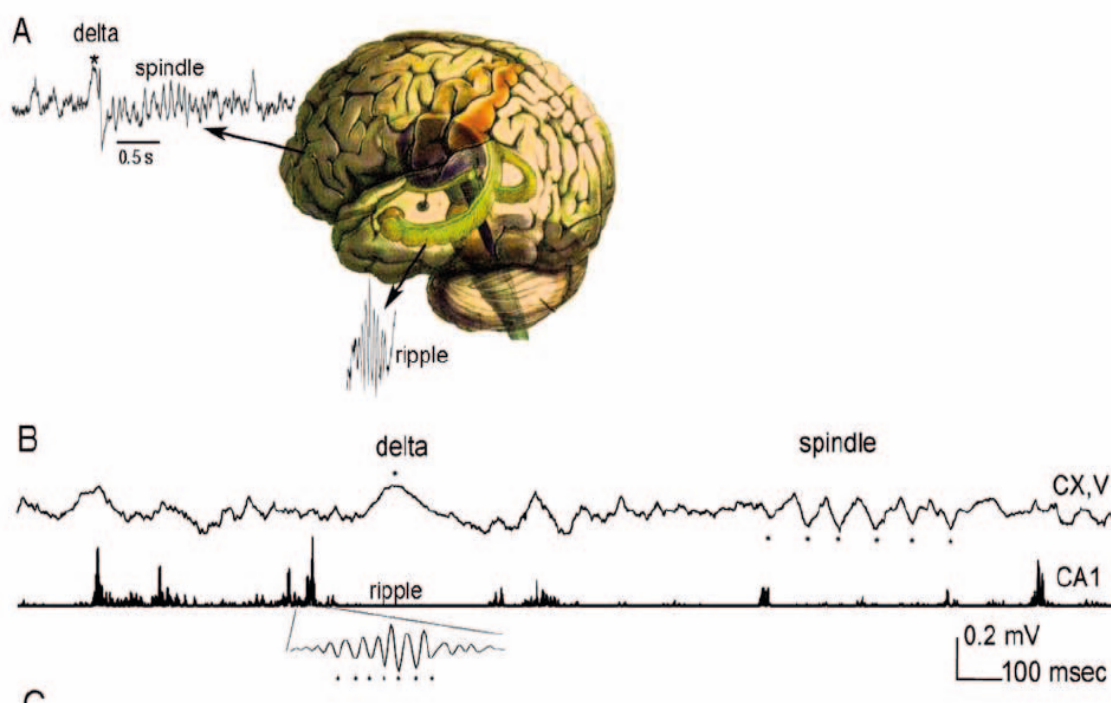
stood. Anyhow, LTP is associated with the increase of the number and amount of synaptic transmitters of postsynaptic receptors, which strengthens the connection between the two cells.

The LTP phenomenon is considered to be the basic model of plasticity and learning.

During the second step reactivation process during SWS the single memory engrams lose their context-dependent individual features and are consolidated in averaged, common schema-like extracts (gist) in the frontal neocortex. We call "abstraction" when the engrams lose their context-dependency during consolidation. This neurophysiological process is presumed to involve overlapping fields during the iterative reactivations, and strengthens abstract meanings through the increase of synaptic weights, according to the Hebbian rules.

The two-step model of memory processing has been supported by several researchers (see in Buzsáki's sum-





**Figure 2.** Hippocampo-frontal coupling of cortical deltas (0.5–4.0 Hz), sleep spindles and hippocampal sharp-wave ripples. Hippocampal sharp-wave ripples induce prefrontal slow waves and spindles during memory tasks (reproduced from Buzsáki, 2015).

mary in 2015). Additional convincing evidence has been provided by the abolishment (resection) of the SPW-rs; after which consolidation did not occur (Girardeau et al., 2009). Those observations showing that the cellular spike sequences in slow wave sleep were identical with their sequence during the wake SPW-rs, but compressed and faster; this was helpful in the comprehension of the consolidation mechanism (Nádasdy, 2000; Foster and Wilson, 2006; Ji and Wilson, 2007). There is still no proof of this mechanism in humans. The increase of SPW-rs after learning seems to be supporting (O'Neill et al., 2008; Cheng and Frank, 2008).

The two-step model has been a great progress because it has finally provided a substrate for memory processing within the temporal lobe and has proposed a clear neurophysiological mechanism for memory-encoding and consolidation, involving hippocampal and neocortical structures. At the same time it has explained the clinical experience of memory disturbances in temporal lobe epilepsy.

Besides the hippocampo-cortical dialogue the memory process is supported by thalamo-cortical oscillations. It is well known that sleep spindles are enveloped by the up-state of the slow oscillations (< 1 Hz) and they

are coupled with ripples during learning (Clemens et al., 2011). The coupling and fine tuning of these three oscillations render the cortex receptive for plastic changes and they orchestrate the hippocampo-cortical dialogue as well (Born et al., 2006; Born, 2010; Mölle and Born, 2011). The role of sleep spindling is shown by the increase of both spindle density and the length of stage 2 SWS related to visuospatial or verbal learning (Siapas and Wilson, 1998; Fogel and Smith, 2006; Staresina et al., 2015) (figure 2).

Gais et al. (2002) have shown the increase of frontal spindle-density during the first 90 minutes of sleep after intensive declarative tasks. Schabus et al. (2004) compared those subjects who had increased spindle activity after learning with those who did not. The increase of spindle activity positively correlated with an increased performance after sleep. These results support the role of spindling in the consolidation of declarative memory.

Ample data evidence the role of spindling also in the protection of memory engrams during the consolidation process (Born, 2010; Diekelmann and Born, 2010; Payne and Kensinger, 2011; Lewis and Durant, 2011). The studies confirming the role of “space cells” in the

spatial memory of rats by showing the reactivation of the hippocampal engrams during slow wave sleep in higher speed compared to the encoding (Wilson and Naughton, 1994; Skaggs and Naughton, 1996; O'Neill et al., 2010).

Several important details of the hippocampo-neocortical dialogue wait for further clarification (Buzsáki, 1996, 1998; Diekelmann and Born, 2010). Originally the “dialogue” was thought to be unidirectional but now the bidirectional information flow seems to be more likely.

### **How does the hippocampo-neocortical memory process change in MTLE?**

We could see that the most important contributor of the hippocampal memory process is the SPW-rs. This complex is an intensive synchronous excitatory event at the edge of the shift toward epileptic excitation possibly explaining why the hippocampus is the most epilepsy-prone structure of the brain. The sharp wave-ripple pair is the physiological counterpart of the pathological (epileptic) geminate: the spike-pathological ripple. The high frequency ripple activity above 250 Hz is held to be the present essential marker of epilepsy (Buzsáki, 2015). The epileptic spike differs from SPW-rs only in its smaller duration and higher voltage. While in rat the duration of SPW-rs is 30–150 milliseconds and its amplitude does not exceed 2 mV; in humans the spike amplitude is higher and the duration is shorter while the associated ripples show higher synchrony and higher amplitude (figure 1). This parallelism between the physiological and pathological variants clearly shows how close is the shift towards epilepsy. This example alights that the expression “hijacking” by epilepsy is somewhat misleading. This phrasing reflects the idea of something completely different from the physiological activity called “epilepsy”, which “hijack” a physiological system. In reality, as shown above, epilepsy is rather a derailment from physiological functioning towards a highly intensive synchronous excitation. Therefore, an epileptic derailment may anytime occur whenever and wherever important plastic changes occur.

Earlier in the literature the negative cognitive effect of interictal discharges have been vividly discussed. These studies had, however, serious limitations because they mainly targeted waking activity and they did not deal with MTLE patients. The intensive sleep activation of interictal discharges have been rarely investigated in MTLE patients (Clemens et al., 2003).

Recently, Shatskikh et al. (2006), by the stimulation of the ventral commissure, have elicited large popula-

tion spikes in the CA1 region of hippocampal pyramidal neurones and registered the analogue spikes with the spontaneous ones of the CA1 region. The stimulated animals showed serious cognitive deficits both in spatial and verbal memory tasks suggesting that the interictal spiking may be related to the memory loss of temporal lobe epilepsy patients.

Frauscher et al. (2015) have studied the hippocampal sleep spindling in humans by implanted deep electrodes. The hippocampal spindling proportionally decreased with the amount of spiking. They assumed that the physiological spindling activity has been transformed to spikes in MTLE in analogy with the bilateral spike-wave activity which is assumed to be the pathological counterpart of spindling in idiopathic generalized epilepsy.

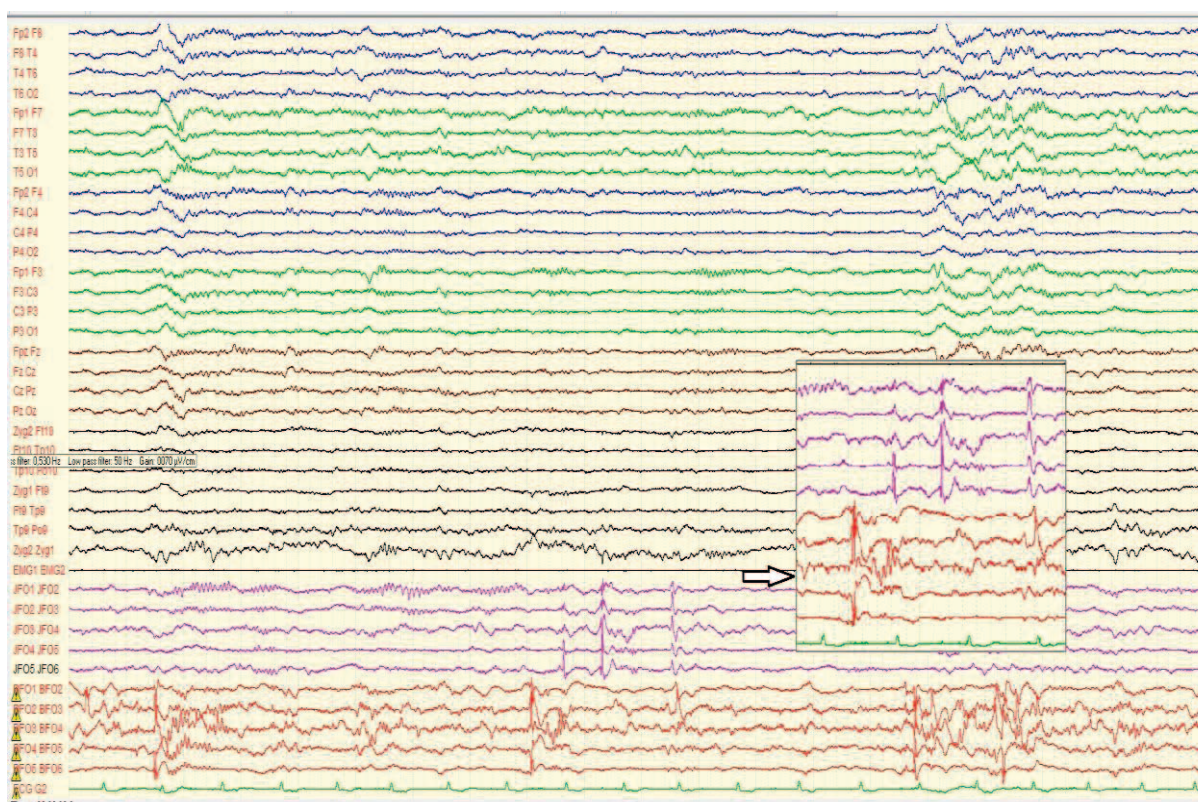
Recently Gelineas et al. (2016) provided elegant experimental evidence for the SPW-Rs transformation into IEDs in a rat kindling model. They have shown that during the course of temporo-frontal memory consolidation the epileptic IEDs interferes as “dummies” with the consolidation process.

These experimental data suggest that the second and more important cause of memory disturbances in MTLE is related to a malfunction-continuous spiking-contributing to the effect of the static, chronically present hippocampal sclerosis, further ruining memory (figure 3).

The practical lesson of the above is that the real evaluation of the MTLE patient's condition is impossible without sleep studies. From the theoretical point of view, we need to keep in mind the importance of slow wave sleep in the development, activity and prognosis of MTLE.

### **Some therapeutical considerations**

Based on the assumed impact of interictal spiking during slow wave sleep on the insidiously developing memory deficit of our patients, we need to find new therapeutic approaches. The antiepileptic drugs presently used have no effect against interictal spiking, although regarding the new drugs and all kinds of IEDs, this has not been systematically investigated. A possible new line of treatment could be to restore the harm on slow waves or supplementing slow waves to support sleep plastic functions (Bellei et al., 2014). Some trials for boosting slow wave sleep have been started to increase cognitive functioning, but we are just at the beginning of a long way to get achievements in this field.



**Figure 3.** Complex interrelationship between the left and right medio-temporal region's interictal epileptic activity. Scalp and foramen ovale (FO) record in a MTLE patient with bilateral spiking. There is more slow components in the right temporal scalp leads (blue), but spikes are not present. At the same time the FO leads show independent spike discharges over both sides. The FO leads contain six electrode points recorded in a bipolar way. They occupy the last 10 channels of the record: five over the right (purple) and five over the left (red) side. Sleep spindles are seen on the left side, but the right side contains slow swings and few physiological elements. In the insert the bilateral independent discharges are enlarged. Seizures were started from the right FO leads (not showed). The insert shows the bilateral independent presence of spikes in the bilateral FO electrodes over the medio-temporal structures.

## CONCLUSIONS

- MTLE is the epileptic disorder of the hippocampofrontal memory system, which is interwoven with, sleep slow oscillation.
- It is likely that more MTLE symptoms are related to memory disturbances than we have expected.
- The most important consequence of the hippocampal participation in MTLE is that the interictal spiking penetrates into the physiological hippocampofrontal memory system, interfering with memory consolidation during slow wave sleep.
- New therapeutic strategies are needed for targeting the interictal events and the disturbance of sleep plastic functions; beyond the present practice, dealing with only the seizures.

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## CONFLICT OF INTEREST DISCLOSURE

The author has no conflict of interest to declare.

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