# The medial temporal lobe epilepsy is a bilateral disease – novel aspects

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**SUMMARY**

**Introduction.** Medial temporal lobe epilepsy (MTLE) is the most frequent form of epilepsy in adulthood. It is classified as local/regional epilepsy. However, there is increasing evidence of the involvement of both temporal lobes and this provides abundant arguments to question this view, and consider MTLE as one of the typical bilateral system epilepsies.

**Aim.** To provide a contemporary review of medial temporal lobe epilepsy, discussing the bilateral aspects, with reference to epilepsy surgery.

**Methods.** A literature review and a resume of the author's own experiences with MTLE patients.

**Results.** Recent electrophysiological and neuroimaging data provide convincing data supporting that MTLE is a bilateral disease. The uni-and bilateral features form a continuum and the participation rate of the two temporal lobes determine course and surgical perspective of the individual patient.

**Conclusions.** The contradictory data of invasive presurgical evaluations of MTLE patients suggest that there need to identify further indicatory markers of bilaterality and thus change the presurgical evaluation from the non-invasive towards the invasive ways. The mechanisms of the interrelationship between the two temporal lobes in MTLE warrants further research.

**Key words: medial temporal lobe epilepsy (MTLE) • bilateral network • secondary epilepsy • bilaterality and surgical outcome**

## INTRODUCTION

Medial temporal lobe epilepsy (MTLE) is the most frequent form of epilepsy in adulthood. During the last 60–70 years epileptology has collected substantial data about the clinical, electroencephalographic and neuroimaging symptoms of MTLE, together with the natural course and treatability of its phenotypical variations. The tempolar lobe, which containing the hippocampal structure, is an important part of the limbic system; which is one of the ancient bases of our emotional and visceral brain being in close connection with the memory system.

Both the anatomical and the pathogenetic substrate of MTLE is the hippocampus, the most epilepsy prone structure of the brain due to its plastic (learning and memory related) functions. The pathogenetic process of MTLE follows a "two steps" model. Typically an early hippocampal impairment is the first step. This "initial precipitatory injury" (IPI) is mostly complicated with febrile convulsion(s) or status epilepticus (presumably on the basis of some kind of a genetic predisposition). The impairment remains unnoticed while the hippocampus undergoes important epileptogenic synaptic transformations during a time – span of several years (a ripening process). The synaptic reorganisation of the hippocampus (usually the head of hippocampi) leads to cell loss and a consequent gliotic atrophy in the CA1-CA3 sector of the pyramidal layers, called "hippocampal sclerosis" (HS) (figure 1).

This long latency process separates the causative event from the first epileptic seizure (latency period), and appears before or during adolescence.

The original hippocampal damage and the conse-

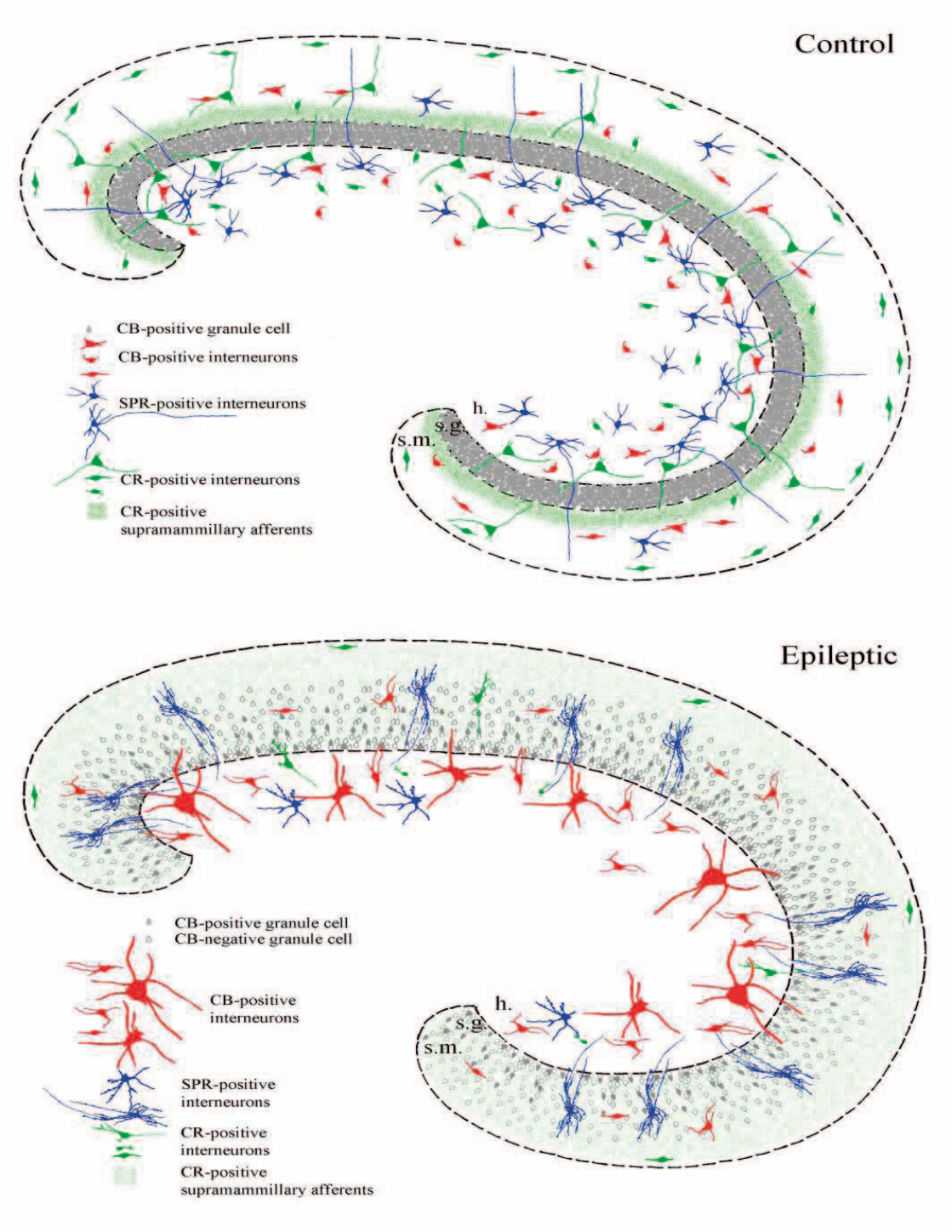


**Figure 1.** Schematic showing the hippocampal synaptic reorganisation, compared with the normal situation, based on finding of resected specimens from surgically treated MTLE patients (Maglóczky and Freund, 2005). The transformation of cellular elements are highlighted.

MTLE – medial temporal lobe epilepsy.

quent epileptic synaptic transformation was described in the early fifties by use of histological specimens (Sano and Malamud, 1953) and later by studying the surgically resected hippocampal tissues (Maglóczky and Freund, 2005).

The same sequence of events develops due to other pathogenetic lesions, as most frequently, near hippocampal slowly progressing tumours, cavernomas, or dysgenetic lesions, which may all behave as independent epileptogenic agents inducing HS "duouble lesion". The ILAE has recently proposed a classification of HS types (Blümcke et al., 2013).

HS may be the result of other remote focal/regional epileptic disorders related even to extra-temporal sources from certain cortical (for example low parietal) territories with strong functional connection to the hippocampal structure (Halász, 2010a).

Due to the multiple functions of the temporal lobes the semiology of MTLE seizures is very rich and variable. The seizures are often preceded by fully conscious heralding symptoms the so called "auras".

Hypomotor seizures (without gross motor involvement) with "arrests" are typical. Due to the propagation of the seizures either towards the basal ganglia (dystonic features), or to the frontal convexity some contralateral motor involvement may occur. The bulk of events are the so called "automatisms" being the most intriguing phenomena of the seizure repertoire. An altered state of consciousness is associated to dominant hemisphere seizures, but it is not always seen in the non-dominant ones. Emotional symptoms, generally negative ones, like fear are features of the non-dominant temporal lobe. In dominant hemisphere ictal and postictal aphasia, reflecting the propagation of the seizure activity towards the neighboring speech network is also a frequent significant seizure event.

**MTLE is classified as focal/regional epilepsy, but there is increasing evidence that both temporal lobes are involved, and the relationship with the hippocampal-limbic memory system (see Halász, 2016b) provides abundant arguments to change this view, and consider MTLE as one of the typical bilateral system epilepsies.**

## AIM

In the present review, I will focus on two features of MTLE: A) System epileptic features with bilateral representations, B) Experiences and lessons provided by invasive presurgical evaluations.

The interrelationship between MTLE and the declarative memory system is discussed in the second part of this review.

## METHODS

A literature review and a resume of the author's own experiences with MTLE patients.

## REVIEW AND DISCUSSION

### Bilateral phenomena and interaction between the two temporal lobes in MTLE

The exploration of different aspects in MTLE has developed exponentially in the last two decades. The increasing interest in neuroimaging and neuropsychology in line with new electrophysiological signal – analytical approaches have provided a rich data set about the bilateral presence of alterations. At the same time the practical importance of unilaterality or bilaterality has increased consequent to the development of surgical treatments. The interest in the bilateral organisation of MTLE is also fueled by the network-theory of epileptic disorders with special emphasis on the limbic system. Several experts have long suggested, that MTLE is a bilateral disease (Sano and Malamud, 1953; Margerison and Corsellis, 1966; Spencer, 2002).

Several studies reported that MTLE patients with bilateral alterations had poorer treatment outcomes and also with worse surgical outcomes compared to patients with unilateral symptoms (Eberhardt et al., 2000; Janszky et al., 2003).

#### *Neuroimaging data*

The first classical MRI-studies verified the bilateral structural involvement in MTLE (Berkovic et al., 1991; Jack, 1994; Fish and Spencer, 1995; Ho et al., 1996; Quigg et al., 1997; Araujo et al., 2006; Keller and Roberts, 2008) and more sophisticated methods including different kind of morphometries have subsequently provided additional further evidence (Mackay et al., 2000; Eberhardt et al., 2000; Seidenberg et al., 2005; Chernov et al., 2009). MRI morphometry (Labate et al., 2010; Bonilha et al., 2012), and hippocampal T2 relaxometry (Okujava et al., 2004; Suemitsu, 2014) have provided additional evidence. Bilateral white matter alterations were revealed by diffusion tensor imaging (DTI) (Mackay et al., 2000; Concha, 2005; Seidenberg et al., 2005; Yu et al., 2008; Gross, 2011; Haneef, 2014). MRI-spectroscopy also explored bilateral changes (Ende, 1997; Ber-

nasconi et al., 1999; Eberhardt et al., 2000; Someya et al., 2000; Zubler et al., 2003; Chernov et al., 2009). Bilateral hypometabolism was also shown by FDG-PET studies in 20–50% of patients (Koepp, 1997; Chassoux, 2004; Joo et al., 2004; Kim, 2006).

*Electrophysiological data*

The most frequent bilateral findings have been shown in MTLE with electrophysiological methods. The bilateral independent nature of interictal epileptiform discharges is commonly accepted, particularly in non rapid eye movements (NREM) sleep (Gibbs and Gibbs, 1941; Lieb et al., 1986; Clemens and Majoros, 1987; Sammaritano et al., 1991; Williamson, 1993; Clemens et al., 2003; Mallow, 2005). The data for presurgical invasive electrophysiologal explorations have shown that scalp EEGs can poorly reflect the space and time dynamics of the seizure – inducing networks and in particular the bilateral relationships remain hidden (Aghakhani et al., 2014).

*Neuropsychology has also revealed bilateral functional deficits*

Bilateral memory dysfunctions have been shown even in patients with unilateral lesions and seizure onset (Dupont et al., 2002). Patients with bilateral lesions exhibited worse cognitive functions in neuropsychological studies.

*Electro-clinical seizure semiology*

The occurrence of bilateral independent electro-clinical seizures in a part of MTLE patients is a common clinical experience that has been proven by the invasive bitemporal presurgical evaluations. The semiological analysis of seizures recorded by long term video-EEG monitoring was expected be an appropriate method to study laterality relations in seizures. However, in reality the seizure symptoms cannot always be accurately separated even in those cases where the seizure propagation is reflected by the transmission of the ictal EEG activity to the contralateral side.

*How do bilateral phenomena fit into the pathomechanism of MTLE?*

Although the difference between uni-, and bilateral MTLE seems straight-forward, no clear-cut definition has been worked out. Unilateral seizures starting always on the same side are widely considered "unilateral MTLE", however, this concept does not consider the additional aspects such as interictal electrographic symptoms, neuroimaging findings, neuropsychological results etc. It is not determined either, how many contralateral seizures are allowed in "unilateral epilepsy", where is the cutting point for calling it bilateral MTLE. The results of invasive studies have taught us that a scalp recording is often insufficient in localizing the onset of the seizures. Another lesson of invasive studies is that there is an important discharge-traffic between the two medio-temporal regions both ictally and interictally. These hidden aspects beyond the overt clinical seizure laterality data, highlight the possibility that several factors shape the underlying laterality constellation.

An explanation for the bilateral phenomena may be that the original epileptogenic lesion had originally affected both temporal lobes. This assumption may be justified in postencephalitic or posttraumatic epilepsies, however, it is not generally valid; there are many clearly unilateral epileptogenic lesions presenting with bilateral functional changes (e.g. taking the simplest: MTLE caused by temporal tumours).

Morrell (1985) has demonstrated that both mirror spike-focus and contralateral seizures may be caused by unilateral slowly progressing brain tumours. The existence of the secondary temporal epileptogenesis may well be supported in animal models, however, its validity in human MTLE is not that clear, leastwise regarding seizure-genesis.

## The influence to the contralateral side, and the co-operation of the temporal lobes in MTLE

There are several data about the relationship between the temporal lobes within the framework of physiological functioning, e.g. memory functions. The most likely scenario is that the propagation of epileptic excitation to the contralateral side increases the coupling of the two temporal lobes developing hyper-connectivity between them. However there is growing evidences showing that although the coupling between the two temporal lobes is abnormally high, it is indeed reduced just before the spikes. This brief decoupling might be consistent with a deficit in the mutual inter-hemispheric hippocampal inhibition; predisposing to spike generation (Faizo et al., 2014).

A similar aspect was recognised in the work of Chkhenkeli et al. (2007) dealing with a chronic and extremely severe patient population, where the activity of one of the temporal lobes exerted an important

influence to the contralateral one. Two thirds of their patients have shown bilateral interictal/ictal epileptic activity. They have demonstrated examples a) how the seizure activity in one of the temporal lobes can suppress the interictal discharges in the contralateral lobe; b) how the termination of the seizure in one lobe activates a seizure in the contralateral lobe; c) the dormant interictal or ictal activity in the contralateral lobe were activated by the surgical resection of the seizure onset region on the other side. These examples revealed that bi-directional cross-temporal links may exert excitatory, inhibitory or liberator influences, and understanding them may support therapeutical interventions.

The existence of mutually suppressive interactions between symmetric temporal lobe structures have also been observed in several experimental studies (Meglio et al., 1976; Duchowny et al., 1981; Fernandes de Lima et al., 1990).

The importance of inter-temporal interactions have been confirmed also by recent connectivity studies (Bettus et al., 2009; Pittau et al., 2012). Frings et al. (2009) investigating the interhemispheric hippocampal connectivity with fMRI assessed the time course of hippocampal activity during spatial memory tasks in 14 patients with unilateral HS and unilateral MTLE by measuring the interhemispheric hippocampal coupling. The interhemispheric connectivity exhibited negative correlation with age at onset of epilepsy. They concluded that the change in interhemispheric interplay might reflect the loss of coupling across the time course of the epileptic process in MTLE.

Morgan et al. (2011) investigated the mutual interaction of the two hippocampi, with high resolution fMRI, using Granger causality. They have shown that the inter-hemispheric hippocampal connectivity and the Granger causality change time-dependently in MTLE. The connectivity diminishes first, then in 10 years it grows linearly correlating with the yearly progression of the epilepsy process. Based on Granger causality data, the long-term increase of interhemispheric hippocampal connectivity is related to the effect of the contralateral hippocampus exerted on the ipsilateral one.

Presently we do not have a comprehensive concept about the way the epileptic excitation of one of temporal lobes is transmitted to the contralateral side. If we assume that the originally unilateral epileptic affection, producing the same unilateral seizures (with or without interictal bilateral spiking) is able to induce seizures on the contralateral side realising the so called "secondary epileptogenesis", this process should have been traced and followed by a certain time span. From this point of view the terms of contra lateral spiking and contra lateral propagation of seizures, as well as the participation of the contra lateral temporal structures, might be key points of the contralateral induction of the epileptic process.

### The theory of the interictal mirror focus and secondary epileptogenesis

The studies of Frank Morrell (1985) have pioneering significance in this field. In his first series of 68 patients having temporal, frontal or parietal histologically verified benign cerebral tumours bilateral (homotopic contralateral) independent spikes were present in 38% of the patients. After resection of the tumour the contralateral spiking gradually disappeared, while in 8 patients the contralateral spikes remained (the clinical course of these patients is unfortunately unknown). In his second series of 123 left temporal epileptic non-lesional patients operated in the Montreal Neurological Institute from 1960 to 1980, 42 (38%) had been identified as having contra lateral spikes. The duration of the epilepsy correlated positively with the frequency of contra-lateral spiking. In his third series consisting of 57 patients with frontal tumours 38% had contra-lateral epileptiform discharges. The duration of the epilepsy has also correlated positively with the frequency of spikes. In patients over the age 25 years, the frequency of contralateral discharges was lower.

Based on the features of the discharge transfer between the two hemispheres Morrell (1985) assumed three stadiums in the evolution of "secondary epileptogenesis" (now we would prefer to call it as "interictal mirror focus"): 1) Dependent stadium: The seizures originate from the side of the primary focus: after the resection of the primary focus the dependent focus disappears, 2) Intermediate stadium: bilateral interictal spiking, after the resection of the primary focus the contralateral discharges waste through a continuous "running down", Independent stadium: The contralateral discharges do not disappear after the resection of the primary focus.

Morrell had also shown that the genesis of mirror spike-focus is related to the axonal transport from the original to the secondary focus: since the interruption of axonal transport by the application of cycloheximide, a blocker of protein synthesis, prevented the development of the mirror-focus. The same was not replicable

with the simple interruption of the electrical impulses using lidocaine (Wilder and Morrell, 1967).

Summing up, Morrell's works proved that similarly to the kindling phenomenon the interictal discharges may be transferred to the contralateral side and they are able to induce similar homotopic secondary spiking both in animal experiments and humans. This process leads to the independency of the contralateral spiking. Thus, Morrell has proven that during learning process, epilepsy leads to the development of secondary interictal discharges in a connected contralateral region becoming later independent from the primary focus.

### Is there secondary epileptogenesis in humans?

The applicability of the results and conclusions of Morrell to MTLE is limited. His material did not model MTLE, since he had investigated the transmission to the contra lateral hemisphere via the corpus callosum instead of the interhippocampal connections considered now to be the main routes for the transmission of MTLE seizures. Additionally, he had primarily studied the transfer of interictal discharges and the fate of the seizures was little investigated.

The interictal independent spiking in humans is compatible with the unilateral seizure onset, however, the presence of bilateral spiking worsens the surgical outcome (Schulz et al., 2000). The studies with intracranial EEGs have demonstrated that complex partial seizures generally propagate to the contralatera1 hemisphere (Lieb et al., 1986; Spencer et al., 1992). Wieser and Siegel (1991) observed a better prognosis in patients without (or with rare) propagation of the ictal EEG pattern to the contralateral temporal lobe. In addition, in cases whereby the propagation of the EEG seizure pattern to the contralateral side occurred, the outcome was worse if the propagation time was <10 s (Lieb et al., 1986). In another invasive study of MTLE, Spencer and Spencer (1996) used bilateral temporal, frontal, parietal, and occipital depth or subdural electrodes to define the site of the EEG seizure onset and the site of EEG seizure termination. They found a significantly greater proportion of seizure-free patients when the termination and the onset location of the EEG seizure pattern coincided. Holmes et al. (1997) have observed in patients with bitemporal scalp IEDs and poorly localized ictal scalp EEG onsets that 100% lateralization of intracranially recorded ictal onsets was associated with a good outcome. Sperling and O'Connor (1990) reported that patients with isolated auras and subclinical seizures, who had a lateralized depth EEG seizure pattern, had a better outcome than patients without isolated auras and subclinical seizures. To study ictal scalp EEG propagation patterns as indicators of bitemporal epileptogenicity was considered an important indicator by Steinhoff et al. (1995). In patients with bitemporal interictal epileptiform discharge interictal epileptic discharges (IEDs) was found in significantly more patients with asynchrony and switch of lateralization than in patients with unitemporal IEDs (Hennessy et al., 2001).

To confirm the secondary contralateral epileptogenesis due to induction by an earlier unilateral epilepsy seems to be exceptionally difficult. The confirmation would be acceptable only with long term follow up video-monitoring documentation, hitherto very rarely undertaken (Lüders, 2001; Halász et al., 2007). Presumably this constellation is realized after long time. Secondary epileptogenesis shows similarities with the kindling phenomenon (one of the basic mechanisms of epileptogenesis) and both seem to decline across the phylogenesis (Tsuru, 1981).

### The transmission pathways of spikes and seizures to the contralateral side

It is an essential and unresolved question how and through what pathways can the epileptic excitation propagate to the contralateral side? The most frequent bilateral interictal electrophysiological symptom is the independent bilateral spiking; detected from the mesiotemporal structures, mainly from the hippocampus itself. The bilateral activation of spiking affected 60% of patients during NREM sleep (Williamson et al., 1993; Ergene et al., 2000). The spiking is usually not bilaterally synchronous, therefore the secondary nature of the bilateral spike activity is not obvious. The spike's side-dominance have evidenced that it is usually congruent with the side of seizure onset and the side of the epileptogenic lesion. The Morrell experiments evidenced that secondary contralatal spiking became independent later. The bilateral presence of spike discharges is not necessarily connected to, but may be influenced by structural alterations. The occurrence of bilateral seizures is much more seldom and we do not know how much, if at all, spikes have a precipitator role in the development of contralateral seizures, or vice versa. The evolution of contralateral seizures seems to be rather influenced by repeated seizure propagation to the contralateral temporal lobe (Janszky et al., 2001).

The first deep electrode studies on spontaneous MTLE seizure-propagation in humans were performed by Spencer et al. (1992). They found that out of the 11 patients' 55 seizures starting in one of the temporal lobes, 4 evolved synchronously in the hippocampus and the neocortex, and 51 (!) just in one hippocampus. They detected three types of seizure-spread: 1) from the hippocampus to the homolateral neocortex (32 seizures); 2) to the contralateral hippocampus first (13 seizures); 3) concurrently to the contralateral hippocampus and the homolateral neocortex (10 seizures). The involvement of the contralateral neocortex occurred just through the contralateral hippocampus. These data suggest the existence of a human short direct interconnection: a hippocampal commissure. Other clinical observations on the interhippocampal seizure propagation (Lieb et al., 1986; Erőss et al., 2009; Rosenzweig et al., 2011), also clearly suggest the existence of a short direct interconnection not involving the cortical mantle.

We obtained similar experiences during 14 MTLE patients' foramen ovale investigations (unpublished data) recording 33 seizures starting in one of the foramen ovale electrodes. The shortest seizure-travelling time could be measured between the two foramen ovale electrodes in 11 patients. The spread of seizures from the contralateral foramen ovale electrodes to the scalp leads was quicker than to the homolateral scalp leads in half of the patients. Direct spread to the contralateral scalp occurred in just 3 patients. Whenever a contralateral foramen ovale propagation occurred, a simultaneous homolateral scalp-spread could be seen as well. The average propagation-time was 6.1 sec from a foramen ovale lead to the contralateral one; 8.9 sec from a foramen ovale electrode to one of the homolateral scalp electrodes and 8.3 sec from a foramen ovale electrode to the contralateral scalp.

A workup of our material was performed by Erőss et al. (2009) investigating interhemispheric propagation of mesial temporal lobe epilepsy seizures in patients undergoing long-term video-EEG monitoring with combined scalp and foramen ovale electrodes. They found two propagation types. The majority (80%) of 65 seizures belonged to type1 first propagating to the contralateral foramen ovale electrode, against type 2 first propagating to the contralateral scalp electrodes. The inter-foramen ovale electrode propagation time was significantly shorter for type 1compared to type 2 seizures. More patients with type 1 seizure propagation significantly more often had mesiotemporal structural alterations evident on MRI, and became more often seizure-free after surgery compared to patients with type 2 seizure propagation, in whom surgery could not even be indicated because of independent bilateral ictal seizure-onset. The predominance of type 1 with shorter propagation times provides further support to the existence of a direct and dominant interhemispheric pathway without the involvement of the ipsilateral temporal cortex in mesial temporal lobe epilepsy.

The studies of Gloor et al. (1993) on the anatomical background of seizure propagation have highlighted the involvement of the posterior hippocampal commissure in human MTLE, while the anterior hippocampal commissure was shown to be rudimental or absent.A callosal route may practically be excluded regarding the earliest seizure-spread to the medial structures; typically seen long before the involvement of the neocortex. The role of the anterior commissure had appeared more than improbable, too; given its lack shown by Gloor et al. (1993) and by others revealing the absence of an inter-amygdalar connection in primates (Demeter et al., 1985). However, recent tensor imaging studies have shown the existence of this travelling-route again (Miro et al., 2015). The possibility of a frontobasal track has not been explored since only a few studies have used simultaneous frontobasal and temporal electrodes (Lieb et al., 1991). The inter-hippocampal propagation route was verified recently by Lacuey et al. (2014) in MTLE patients. By electrical stimulation of the fornix they could detect cerebro-cerebral evoked potentials in both hippocampal deep electrodes without the involvement of the contralateral temporal neocortex or amygdala. This study confirms the existence of connections between bilateral mesial temporal structures in some patients explaining seizure propagation between homotopic mesial temporal structures without the involvement of the neocortex.

It seems unequivocal that the bilateral functional involvement in MTLE may result in bitemporal functional changes. It is possible that the contralateral structures are not just passive objects of seizure-spread; rather, they may have an active role. It is clear that the two temporal lobes, especially the hippocampi and the amygdalae work together also in normal conditions sharing the limbic functions.

According to the experiences gained during the presurgical workup of MTLE patients, there are abundant data on the bitemporal seizure dynamics: a) Seizures travel from one to the contra lateral side with variable

latency within half minutes); b) Rarely, one side initiates the ictal state propagating immediately to the other side where the full-blown seizure develops. In the case the seizure onset side is just a trigger and the executing temporal lobe is the contralateral one (flip-flop mechanism). In this variant the symptomatogenic contralateral side is obviously not just a passive recipient but the epileptic excitability should be present hidden there.

Further analysing foramen ovale electrode recordings, our research group has revealed peculiar dynamics after the contralateral seizure-propagation (Hajnal et al., 2014) (figure 2). We observed sudden changes in the activity: the frequency increased and the amplitude decreased, like a new start of a seizure, either in the ipsi-or the contra-lateral side. Sometimes, in accordance with these changes, the contralateral activity attenuated as being inhibited. In other seizures the contralaterally propagated seizure presented unexpected changes e.g. electromorphological features with unexpected frequency-gain and amplitude decrease. These changes might have reflected the mutual influence of the temporal lobes to each other.

Sometimes the epileptiform activity, including seizure-onset, may manifest on the opposite side compared to the presumed epileptogenic lesion e.g. tumour or trauma. Mintzer et al. (2004) have presented several cases where the ictal changes on the scalp could be observed on the contra lateral side compared to deep electrode findings verifying the seizure onset on the side of the severe hippocampal lesion.

### The course of MTLE

Many researchers doubt if MTLE is a progressive condition, while others consider it an evidence. Several experimental data support the progressive nature of MTLE (Pitkanen and Sutula, 2002; Sutula, 2004): the kindling model (Stafstrom and Sutula, 2005), the important synaptic reorganisation shown in human surgical specimens (Figure 62) (Maglóczky and Freund, 2005) and data on high frequency oscillation (HFO) in experimental hippocampal sclerosis (Staba et al., 2007). Also some MRI and MR-spectroscopic studies have provided data on the progressive nature of MTLE. Bernasconi et al. (2002, 2005) and Lee et al. (1998) have shown a correlation between the duration of epilepsy and the seizure-related temporo-cortical atrophy. The interictal neurophysiological features were shown to change progressively just in a few studies, but the presence of a progressive cognitive decline is unequivocal (Jokeit and Ebner, 2002; Helmstaedter, 2002; Hermann et al., 2002; Oyegbile et al., 2004; Nolan et al., 2004). At the same time, no correlation could be found between the duration of epilepsy and the degree of hippocampal/amygdalar atrophy on one hand and between seizure frequency, seizure-duration and seizure number versus MR-spectroscopic changes (NAA/Cr) on the other (Li et al., 2000; Burneo et al., 2004). Furthermore, the proportion of bilateral epileptic manifestations does not increased with epilepsy duration (Janszky et al., 2003).

The contradictory results of the long-term retrospective studies may mainly be attributed to the inherent methodological difficulties. There are only few prospective studies (Brielmann et al., 2002; Fuerst et al., 2003). These longitudinal volumetric studies revealed the progressive volume-loss of the hippocampus across the years.

The causative factors of the further progressive changes and its relation to the nature of the ongoing epileptic process needs more long-term research.

### MTLE as system epilepsy

The emerging view of epileptic networks (van Diessen et al., 2013) seems to provide a new framework for conceptualising idiopathic epileptic disorders without lesional origin, or even to those lesional epilepsies which tend to involve extended bilateral cerebral circuits. As Wolf (2006) summarized: "Both localisation-related" and "generalized" idiopathic epilepsies are about to be understood as related variants of system disorders of the brain, with an ictogenesis making pathological use of existing functional anatomic networks". We can add to this statement that not only "ictogenesis" but probably interictal discharges may have a role in the epileptic transformation of certain physiologic systems.

Since epilepsy is known to be the pathological facilitation of normal physiological functions, it has for a long time been suspected that different physiological working systems of the brain provide templates for epileptic disorders resulting in specific features. The idea of the so called "system epilepsies" has been recently increasingly emphasized during discussions of the new epilepsy classification (Wolf, 2006; Halász and Kelemen, 2009) and network epilepsies (Halász, 2010b,c; Stefan and da Silva, 2013).

Epileptic discharges and seizures can be activated by triggering a function which the epilepsy is connected with, as seen in sensory reflex epilepsies (the visual stimulation activates the epileptically facilitated occip-

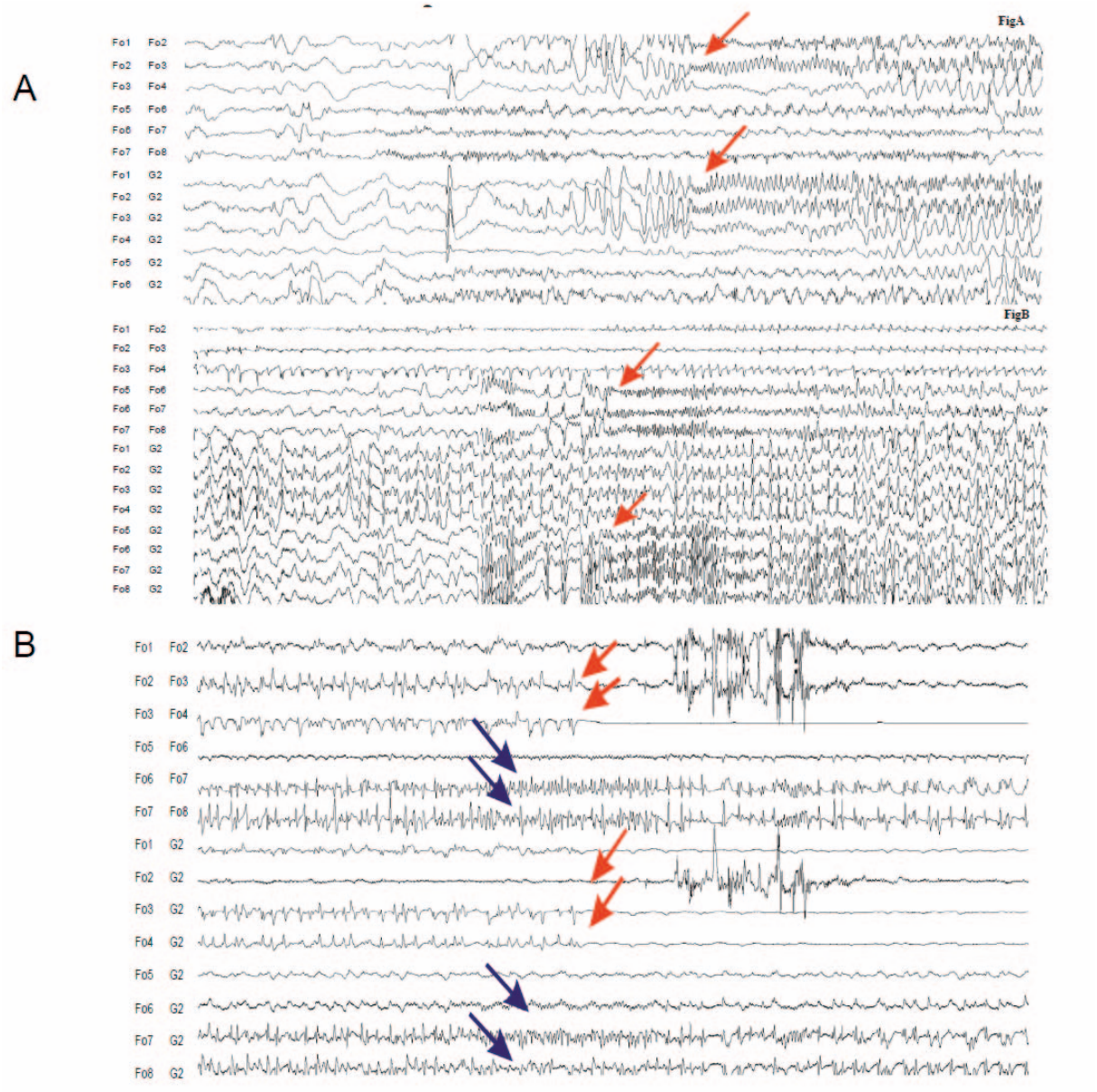


**Figure 2.** Changes during seizure activity in the FO electrodes of MTLE patients (A). Two different seizures bellow each other. Sudden increase and amplitude decrease within the ictal activity (red arrows) (B) During some of such changes (blue arrows) the activity in the contralateral leads became inhibited (red arrows).

FO – foramen ovale, MTLE – medial temporal lobe epilepsy

ital cortex). In recent years we have learnt more about the elicitibility of seizures by several types of sensory stimulation or by mental and physical activities either in the so called generalized epilepsies (Goossens et al., 1990) or in epilepsies related to dysgenetic cortical malformations (Palmini et al., 2005).

System epilepsies display a relationship between the physiological function of the affected system and the features of the epilepsy. The system-epilepsy concept can be valid not only for the so called idiopathic epilepsies, but also epileptogenic lesions may increase the propensity of a system to respond with epileptic manifestations as if being "hijacked" by the epileptogenic process (Benhakker and Huguenard, 2009).

In certain system-epilepsies the normal functions of the system may suffer interference by the epileptic man-

ifestations. In MTLE the hippocampo-limbic spiking during NREM sleep interferes with the memory consolidation through modifying the sharp wave ripple activity during sleep, leading to memory disturbances (this aspect will be treated in more details in the second part of the paper).

MTLE is the epilepsy of the limbic system, activating emotional visceral and especially memory functions. Bertram et al. (1998) hypothesized that the process of seizure initiation affects broad circuit interactions involving multiple independent limbic structures, and that the midline thalamus may act as a physiological synchronizer. We have seen that during SWS the epileptic discharges are extensively activated over both hemispheres in which the connectivity of the hippocampal formations interconnected by a hippocampal commissure and involving the fornical system as well. The sleep related activation, extending the discharges both in time and space, makes the system more sensitive and penetrable for further epileptic discharges.

If the amygdala and the anterior limbic structures are involved, emotional symptoms develop both in the ictal states (seizures originating from the non-dominant amygdala manifesting fear symptoms) and interictally (conditioned fear reactions also from the non-dominant side). With the help of stereotactically implanted deep electrodes, we will be able to better learn the subcortical three-dimensional connections and the impulse traffic of the system providing us with data about the impact of interictal discharges in anxiety and in visceral symptoms.

The limbic system has strong to- and-from connections with the temporal and frontal structures based both on classical anatomical studies and recent connectivity data (Reep et al., 1984). The inter-connectivity between the temporal and frontal areas helps to understand better the working memory disturbances in MTLE. We have highlighted above that also the fornix participates in the co-operation of the two temporal lobes by transmitting the pathological epileptic discharge stream (Jang and Kwon, 2014).

The physiological and pathological role of the insula has also been explored by the deep electrodes during presurgical evaluations (Isnard and Maugueire, 2005). The insula is an ancient secondary sensory field with significance in pain and visceral processing and in other autonomic regulations. It is in close interconnection with the amygdala and other mesiotemporal structures. Some of the MTLE symptoms have insular origin and the pathological hyper-excitability fuels several to-and from connection with the insula.

### Lessons learned from tempolar lobe surgery

At the beginning of temporal lobe surgery the overwhelming majority of MTLE patients were operated based on a non invasive presurgical evaluation. Patient outcomes seemed to be much better compared with pharmacotherapy (Engel et al., 2012), however, the rate of success long-term never exceeded 70–80% of the operated patients, and the rate of patients who remained seizure free without antiepileptic drugs remained much less (Télez-Zelentano et al., 2005) than expected. The success rate was generally achieved by partial lobectomies, with variable extension, performed in patients with unilateral seizure onset on the scalp video EEG (exhibiting congruent seizure semiology) with or without a neuroimaging lesion. With non-lesional patients, success rates were lower. The methodology of presurgical evaluation has become more and more sophisticated both in capturing of seizures and interictal activity (including HFO); and in different neuroimaging and EEG-neuroimaging fusion techniques as well. The invasive experiences helped to explore the relationship among the denominator players in MTLE; while more and more contradictory data came to light, rendering harder the selection of suitable surgical candidates.

Aghakhani et al. (2014) undertook a comprehensive publication search, systematically reviewed the literature on MTLE patients who had presurgical evaluations. They explored the congruency of MRI findings with seizure laterality on intracranial EEG, and seizure outcome of patients. One of the important results of this analysis was that 73% of patients supposed to have bilateral temporal lobe epilepsy based on scalp EEG findings proved to be unilateral after invasive EEG exploration, even after the exclusion of studies reporting on 90–100% unilateral rate in TLE in their sample. The 58% of these patients had Engel I and 9% had Engel II outcomes after unilateral surgery. Another conclusion was that a bitemporal or ambiguous seizure onset is a weak predictor of bilateral temporal lobe epilepsy. Although the unilateral patients had better outcomes compared to the bilateral patients, the degree of lateralisation in those with bilateral seizure onset had a limited role in selecting the side of surgery. Overall, the seizure laterality seemed not to be the most relevant aspect of the successful selection of seizure side.

The interesting results of this thoughtful analysis

suggest for uni- versus bi-laterality, that bilateral seizures proved by invasive exploration and the proportion of the laterality are not necessarily the leading and exclusive aspect of surgical side selections. These data support the important role of several other aspects, beyond purely the seizures laterality, need to be taken into consideration in the choice of the side of surgery

We conclude that the side of seizure onset is just one of the aspects needed to determine surgical outcome. For gaining quantitative markers of bilaterality, additional parameters and constellations, not directly connected to the seizures laterality, need to be searched for. Such markers could include a more scrutinized evaluation of interictal discharges with their HFO content, the spike independent HFO data, the dynamics in the invasive electrodes during seizures, the laterality data of seizure termination, the lesional background and the data of long term progression.

We can construct a new approach on the bilateral existence of MTLE assuming a continuum of the two sides' role. At one end of the continuum we see the fully unilateral cases having the best surgical prognosis; and the independent bitemporal seizure-onset cases with surgical failures on the other. In the intermediate zone, the structures of both temporal lobes participate; presenting variable amount of bilateral symptoms.

We propose to search for new indicators of bilateral participation instead of trying to separate roles of the two temporal lobes. This new approach is beyond the surgical option, but is also beneficial for surgery. It needs to take into consideration more factors, and make things more complex, but holds out to create a more coherent image about MTLE as a bilateral system epilepsy. It means to shift our scope from the simple standard lobectomies toward a more invasive approach and the use stereotaxic techniques which allow a better visualization of the spatial aspects of the epileptic networks.

## CONCLUSIONS

- MTLE is a bilateral disease. The uni-and bilateral features form a continuum and the degree of participation of the two temporal lobes determine the course and treatability of individual patients.
- During presurgical evaluation of MTLE patients, the bilateral participation of not purely the seizure related ones but the interictal features need more attention compared to the present practice. More patients with seemingly bilateral MTLE may benefit from unilateral surgery. With regards to improving the diagnostic accuracy, further indicators of bilaterality should be identified and presurgical evaluation needs to shift from the non-invasive to that of invasive.

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## CONFLICT OF INTEREST

The author has no conflict of interest to declare.

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