UNIVERSITY OF PAVIA
PhD in "Psicologia, Neuroscienze e Statistica Medica"
Doctorate cycle: XXXII
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PROGNOSTIC FACTORS OF POSTOPERATIVE SEIZURE OUTCOME IN PATIENTS WITH TEMPORAL LOBE EPILEPSY AND NORMAL MAGNETIC RESONANCE IMAGING

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Academic year 2018/2019

1. INTRODUCTION

1.1 ANATOMY OF THE TEMPORAL LOBE

Approximately 17% of the volume of the human cerebral cortex, 16% in the right and 17% in the left hemisphere, forms the surfaces of the temporal lobes [Mai et al, 2008].

Like the other lobes of the cerebral hemisphere, the temporal lobe is delineated by cortical landmarks.

On the lateral surface, the lateral sulcus or sylvian fissure marks the separation of the temporal lobe from the frontal and parietal lobes. The temporal lobe caudally joins the parietal and occipital lobes, without any clearly defined boundary, except the inconspicuous temporo-occipital incisure (Figure 1).

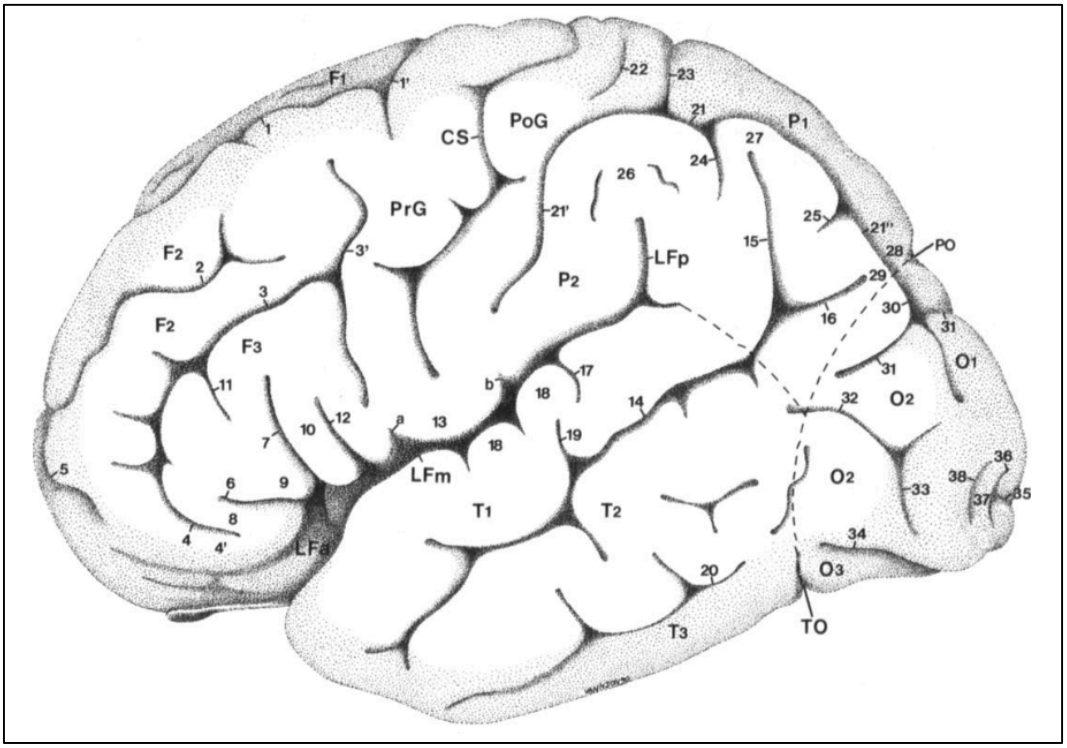

Figure 1 Lateral aspect of the left hemisphere. The dotted lines show the theoretical boundaries between the different lobes. Fissures or sulci separating the lobes: *LFa* lateral fissure, anterior segment; *LFm* lateral fissure, middle segment; *LFp* lateral fissure, posterior segment; *CS* central sulcus; *PO* parieto-occipital fissure; *TO* temporo-occipital incisure. Temporal lobe: *T1* superior temporal gyrus; *T2* middle temporal gyrus; *T3* inferior temporal gyrus; *14* superior temporal sulcus, *17* transverse temporal sulcus; *18* transverse temporal gyri; *19* sulcus acousticus; *20* inferior temporal sulcus [Duvernoy, 1999].

Two, superior and inferior, temporal sulci divide the lateral surface of the temporal lobe into three, superior, middle, and inferior, temporal gyri.

The superior temporal gyrus (T1) runs parallel to the lateral fissure. Its anterior end is a part of the temporal pole. The upper margin of the superior temporal gyrus forms the temporal operculum. It continues into the lateral fissure by a large cortical area, sometimes called the superior surface of the temporal lobe. This surface can only be observed when the superior overlying margin of the lateral fissure has been removed. From front to back the superior surface of the temporal lobe is divided into three parts: the planum polare, the transverse temporal gyri, and the planum temporale. The planum polare, with an uneven aspect, is separated from the insula by the inferior circular sulcus. The transverse temporal gyri (or Heschl's gyri) are sometimes reduced to only one gyrus. But most commonly there are one anterior transverse temporal gyrus and one posterior transverse temporal gyrus, separated by an intermediate transverse temporal sulcus. They originate from the retro-insular area of the lateral fossa. They then follow an oblique oral course and reach laterally the outward aspect of the superior temporal gyrus, where they often assume the shape of one or two lobules partially grooved by the sulcus acousticus branching from the superior temporal sulcus. Those transverse temporal gyri are caudally separated from the planum temporale by the transverse temporal sulcus which can usually be described on the lateral surface of the superior temporal gyrus. The planum temporale varies eminently in size. It may be short if the ascending posterior segment of the lateral fissure stems out close to the transverse gyri, or conversely quite spacious if the said segment is caudally stretched out, or even nonexistent.

The middle temporal gyrus (T2) reaches to the temporal pole orally and the occipital lobe caudally, without any clear-cut boundary.

The inferior temporal gyrus (T3) is not very visible on the lateral surface, but more so on the inferior temporal surface. This gyrus is caudally separated from the occipital lobe by the temporo-occipital incisure.

The temporal pole is formed by the combination of the superior, middle, and inferior temporal gyri, which overlap the inferior surface of the temporal lobe.

The inferior surface of the temporal lobe displays three gyri: the inferior temporal, fusiform, and parahippocampal gyri (Figure 2).

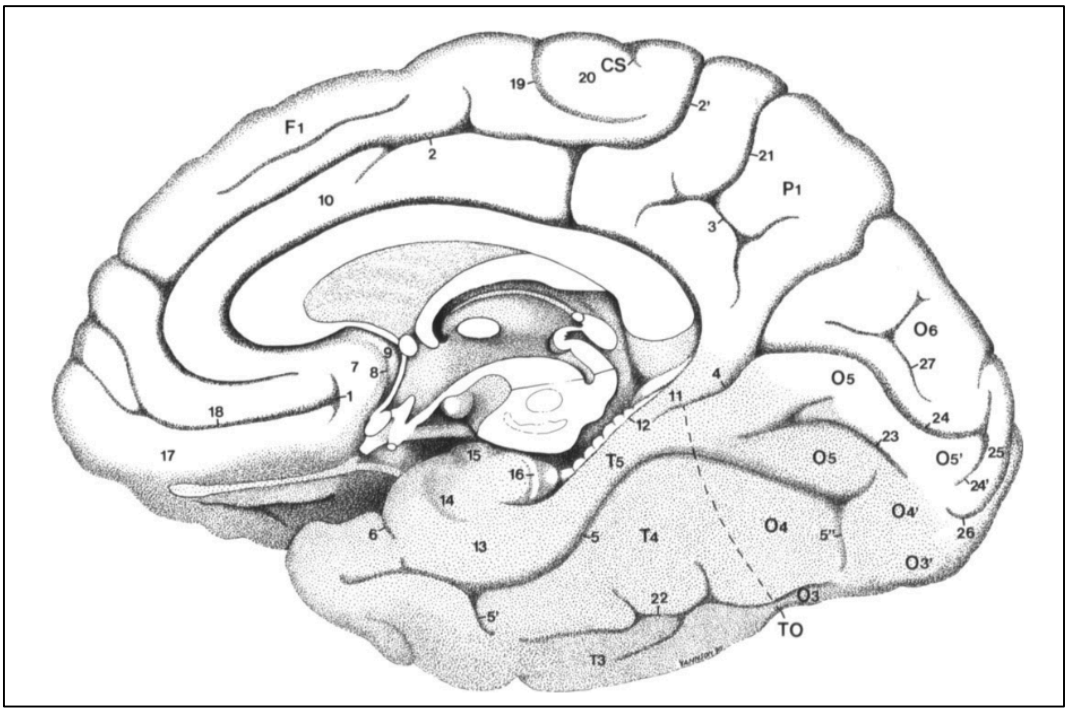

Figure 2 Inferomedial aspect of the right hemisphere. *5* collateral sulcus; *T5* parahippocampal gyrus; *12* gyrus dentatus; *13* piriform lobe; *14* gyrus ambiens; *15* semilunar gyrus; *16* band of Giacomini; *T3* inferior temporal gyrus; *22* lateral occipitotemporal sulcus; *T4* fusiform gyrus; *TO* temporo-occipital incisure [Duvernoy, 1999].

The inferior temporal gyrus (T3). Its boundaries are the inferior temporal sulcus on the lateral surface of the hemisphere and the lateral occipito-temporal sulcus on the inferior surface. It thus constitutes the inferior margin of the temporal lobe and stretches backward to the temporo-occipital incisure.

The fusiform gyrus (T4). Its boundaries are clearly defined. We find: the lateral occipito-temporal sulcus laterally, the collateral or medial occipitotemporal sulcus medially, and the anterior and posterior transverse collateral sulci rostrally and caudally. The fusiform gyrus does not extend to the temporal pole.

The parahippocampal gyrus (T5) and the lingual gyrus (itself part of the occipital lobe) together form the medial occipitotemporal gyrus. The parahippocampal gyrus is separated from the fusiform gyrus by the collateral sulcus. It can be divided into two segments. The posterior segment is narrow; its flat superior surface - or subiculum - is separated from the hippocampus by the hippocampal sulcus. The anterior segment is more voluminous; it is called the piriform lobe, comprising the anterior part of the uncus and the entorhinal area. The uncus curves posteriorly to rest on the parahippocampal gyrus itself, separated from the latter by the uncal sulcus. The uncus is functionally divided into two parts: one anterior and one posterior. The entorhinal area is the lower part of the piriform lobe and encroaches (especially in man) upon the posterior segment of the parahippocampal gyrus.

In the mesial part of the temporal lobe is located the hippocampus (Figure 3).

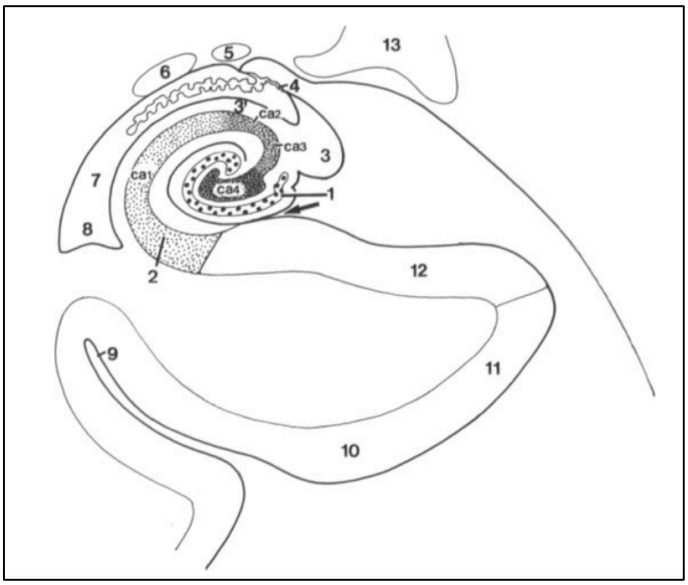

Figure 3 *ca1, ca2, ca3, ca4* fields of cornu ammonis; *4* tela choroidea of temporal horn*; 5* stria terminalis; *6* tail of caudate nucleus; *7* temporal horn of lateral ventricle; *8* collateral eminence; *9* collateral sulcus; *10* parahippocampal gyrus; *11* entorhinal area; 12 subiculum; 13 lateral geniculate body [Duvernoy, 1999].

The hippocampus is bilaminar: one lamina rolled up inside the other: the cornu ammonis and the gyrus dentatus. According to different aspects of the pyramidal neurons forming the cornu ammonis, this layer may be subdivided

into four fields: CA1, CA2, CA3, and CA4 which may have specific functions and pathology. The cornu ammonis and the gyrus dentatus are separated from the parahippocampal gyrus by a narrow hippocampal sulcus. The hippocampus is mainly intraventricular and accordingly externally inconspicuous. It is divided into body, head, and tail. The hippocampal body (or middle part) is hidden by the fimbria which stems from the crus fornicis. Sometimes the dentes of the gyrus dentatus are superficially visible and compose the margo denticulatus. The hippocampal head (or anterior part): its intraventricular part is composed of "digitationes hippocampi"; its extraventricular part is visible on the uncal surface and comprises the gyrus uncinatus, the band of Giacomini, and the uncal apex. The hippocampal tail (or posterior part) is also partially visible on the surface: one part is the continuation of the gyrus dentatus as fasciola cinerea, and the other part is the continuation of the cornu ammonis as gyrus fasciolaris. Some protrusions of the hippocampus, called the gyri of Andreas Retzius, are sometimes visible in the subsplenial area [Duvernoy, 1999].

The amygdala is a group of several nuclei located in the medial part of the temporal pole, anterior to and partly overlapping the hippocampal head. The nuclei are organized in three groups: corticomedial nuclei in the anterior part of the uncus, basolateral nuclei comprising the infero-lateral two-thirds of the amygdala, and a central group, which receives afferent fibers from the other two groups of nuclei (Figure 4).

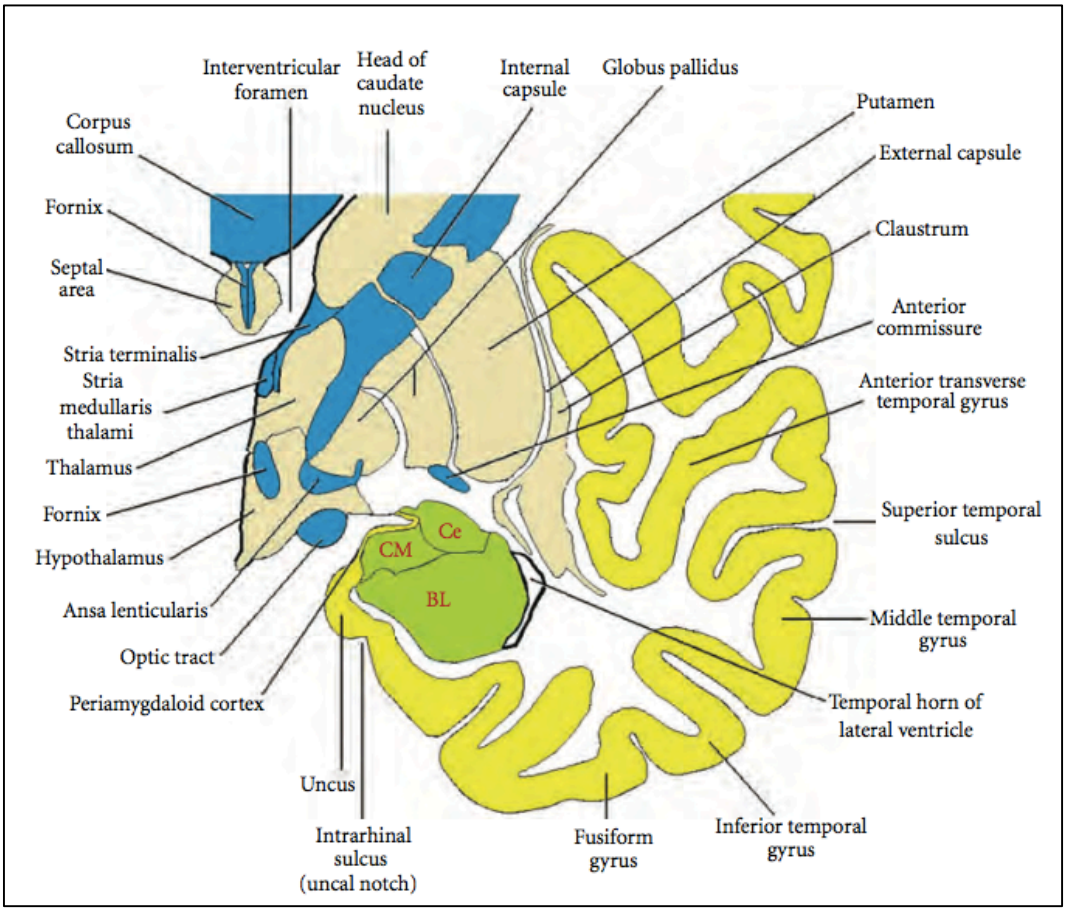

Figure 4 Drawing of a coronal section through the temporal lobe and adjacent structures, at a level anterior to the hippocampal head. The amygdala is coloured green, with the positions of its three nuclear groups indicated: corticomedial (CM), basolateral (BL), and central (Ce). Selected bodies of white matter are coloured blue [Kiernan, 2012].

1.2 EPILEPSY: DEFINITION AND GENERAL CONCEPTS

In 2005 the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) defined conceptually epilepsy and epileptic seizures [Fisher et al, 2005]. According with that definition, an epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain and epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.

A practical clinical definition of epilepsy was then proposed in 2014 [Fisher et al, 2014]. Epilepsy is a disease of the brain defined by any of the following conditions:

1. At least two unprovoked (or reflex) seizures occurring >24 h apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epileptic syndrome. An electroclinical syndrome, however, is a complex of clinical features, signs, and symptoms that together define a distinctive, recognizable clinical disorder. These often become the focus of treatment trials as well as of genetic, neuropsychological, and neuroimaging investigations [Berg et al, 2010].

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

Usually the ictal semeiology reflects the cortical area involved by the discharge, its origin and diffusion. An epileptic discharge can activate or inhibit the cerebral cortex and widespread according to different propagation pathways, so that an epileptic seizure can show very different clinical pictures, varying from patient to patient. According to other hypotheses, subcortical

motor centers such as the basal ganglia and brainstem [Tassinari et al, 2005] could also be involved in the genesis of critical semiology.

The last classification of epilepsies was made in 2017 (Figure 5).

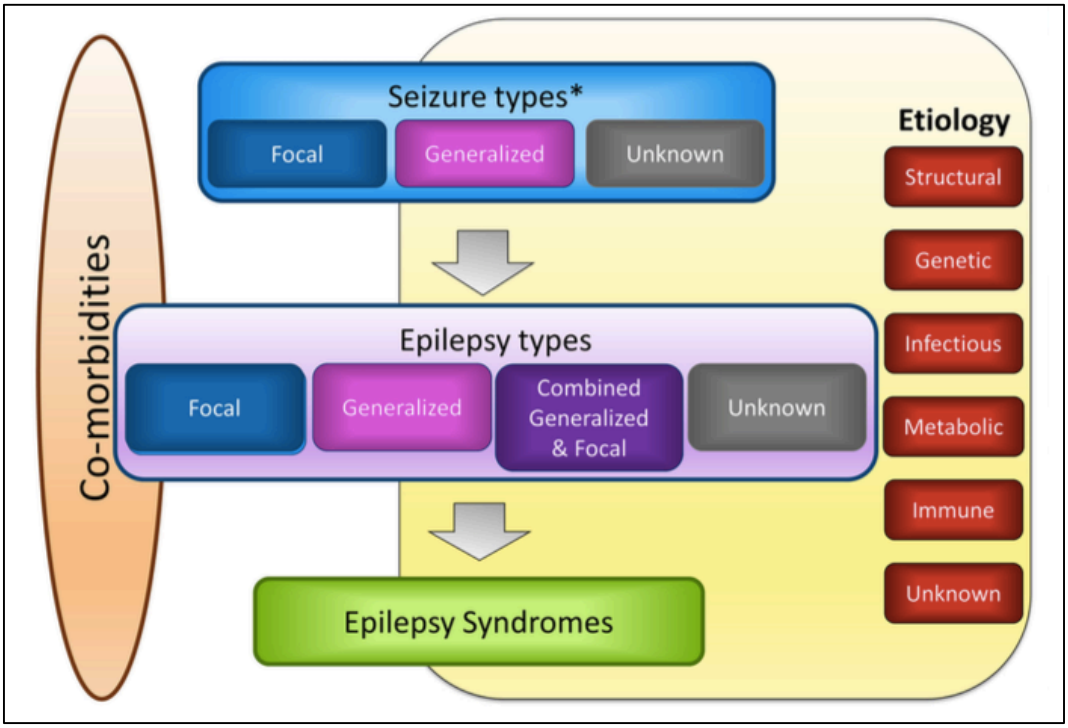

Figure 5 Framework for Classification of the Epilepsies [Scheffer et al, 2017].

Seizures are classified into focal onset, generalized onset and unknown onset. Seizures are considered focal when the semiology suggests a seizure onset localized in a specific site of the brain, generalized when both the hemispheres are early involved.

The epilepsy type can be focal, generalized, combined generalized and focal or unknown. For a diagnosis of Generalized Epilepsy, the patient would typically show generalized spike-wave activity on EEG. Individuals with generalized epilepsies may have a range of seizure types including absence, myoclonic, atonic, tonic and tonic-clonic seizures. The diagnosis of generalized epilepsy is made on clinical grounds, supported by the finding of typical interictal EEG discharges. Focal epilepsies include unifocal and multifocal disorders as well as seizures involving one hemisphere. A range of seizure types can be seen including focal aware seizures, focal impaired awareness seizures, focal motor

seizures, focal non-motor seizures, and focal to bilateral tonic-clonic seizures. The interictal EEG typically shows focal epileptiform discharges but the diagnosis is made on clinical grounds, supported by EEG findings.

Patients that experience both generalized and focal seizures have combined generalized and focal epilepsy.

An epilepsy syndrome refers to a cluster of features incorporating seizure types, EEG and imaging features that tend to occur together. It often has age-dependent features such as age of onset and remission (where applicable), seizure triggers, diurnal variation and sometimes prognosis. It may also have distinctive co-morbidities such as intellectual and psychiatric dysfunction, together with specific findings on EEG and imaging studies. It may have associated etiological, prognostic and treatment implications. There are many well recognized syndromes, such as childhood absence epilepsy, West and Dravet syndromes.

From the moment that the patient presents with their first epileptic seizure, the clinician should be aiming to determine the etiology of the patient's epilepsy. A range of etiological groups has been recognized with emphasis on those that have implications for treatment. Often the first investigation carried out involves neuroimaging, ideally MRI where available. This enables the clinician to decide if there is a structural etiology for the patient's epilepsy. The five additional etiological groups are genetic, infectious, metabolic and immune, as well as an unknown group. The structural etiology is critical for epilepsy surgery.

The incidence of epilepsy (number of new cases in a given period of time) varies considerably with age. Epidemiological studies have demonstrated a bimodal distribution of incidence with peaks in childhood and after 60 years. The median incidence was estimated at 47.4 per 100,000 persons / year [Kotsopoulos et al, 2002]. Sex differences occur only for particular epilepsies. The estimated prevalence is around 700 per 100,000 people in developed

countries, with higher rates in developing countries [Hirtz et al, 2007; Ngugi et al, 2010]. The concomitant prevalence of active epilepsy is around 0.5% in the world population (about 50 million people in the world) [Leonardi and Ustun, 2002]. The 5-10% of the population will have at least one epileptic seizure during their lifetime, and 30% of these people will develop a chronic illness [Benbadis and Luders, 1996].

1.3 EPILEPSY SURGERY

Epilepsy surgery is a therapeutic option to be considered in focal disabling or drug resistant focal epilepsies, provided that the benefit/risk ratio for surgery is a priori acceptable. Drug resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [Kwan et al, 2010].

Once the history of disabling medically refractory focal seizures is clearly established, the principal requirement for resective epilepsy surgery is the identification and accurate localization of the epileptogenic zone, the removal (disconnection, irradiation, or coagulation) of which will determine seizure freedom without a new unacceptable handicap.

Resective surgery is exclusively considered when seizures are focal, i.e., when they arise from a limited portion of one hemisphere, and when they represent unequivocally the electroclinical expression of a nonidiopathic focal epilepsy syndrome. The minimum required for answering to these issues includes a good description of seizure semiology, interictal EEG data (particular attention must be paid to the constant or variable location of interictal spikes, the possibility that their topography has evolved with time, and their unilateral, bilateral or multifocal origin), and a good MRI scan. A neuropsychological evaluation must be done to determine the patient's baseline cognitive function and to help estimate the risk to those functions if a surgical resection were to be done. In some cases with structural etiology, these data proved sufficient enough to decide whether surgery can be performed, even without additional EEG/video monitoring. This should concern those patients with history of drug-resistant seizures associated with a well-limited brain lesion (e.g., dysembryoplastic neuroepithelial tumor, cavernoma, etc.), providing that a good concordance exists between the localization of the lesion, the clinical semiology of the seizures as reported by the patient and/or his/her family, and the the interictal scalp-EEG abnormalities interictal scalp-EEG abnormalities.

In any case, when there exists a doubt, these patients should be referred to a specialized center for long-term video-EEG monitoring. The vide-monitoring allows the localization of interictal epileptiform discharges (the irritative zone) and, above all, localizing the seizure onset zone and documenting the seizure type(s).

Selected candidates for epilepsy surgery may also undergo fluorodeoxy glucose positron emission tomographic scans (FDG-PET) to look for a localized hypometabolism concordant with electro-clinical data and functional MRI (fMRI) to localize some functional areas of the brain and their relationship to a suspected epileptogenic zone.

Invasive recordings may be needed when noninvasive data remain insufficiently concordant, discordant, or inconclusive, and when they suggest an early involvement of highly eloquent areas [Lüders, 2008]. Some centers use subdural grid and/or strip evaluations, some others use depth electrode evaluations.

Stereoelectroencephalography (SEEG) refers to the methodology of stereotactically-guided depth electrode recordings, which was originally developed by Bancaud and Talairach in France. SEEG recordings allow to study the spatiotemporal dynamics of seizure discharges with respect to their clinical features, and with a high degree of anatomical precision. Ictal anatomo-electro-clinical correlations based on SEEG recordings are utilized in identifying the cortical area(s) primarily involved in the generation of spontaneous ictal discharges, and provide a guide to tailored cortical resection. The placement of depth electrodes should include the region of presumed ictal onset zone according with non-invasive data, the areas of apparent spread of the ictal discharge, the possible lesion demonstrated by MRI and the functionally critical structured presumably closed or embedded in the epileptogenic zone. In Figure 6 is reported an example of SEEG implantation.

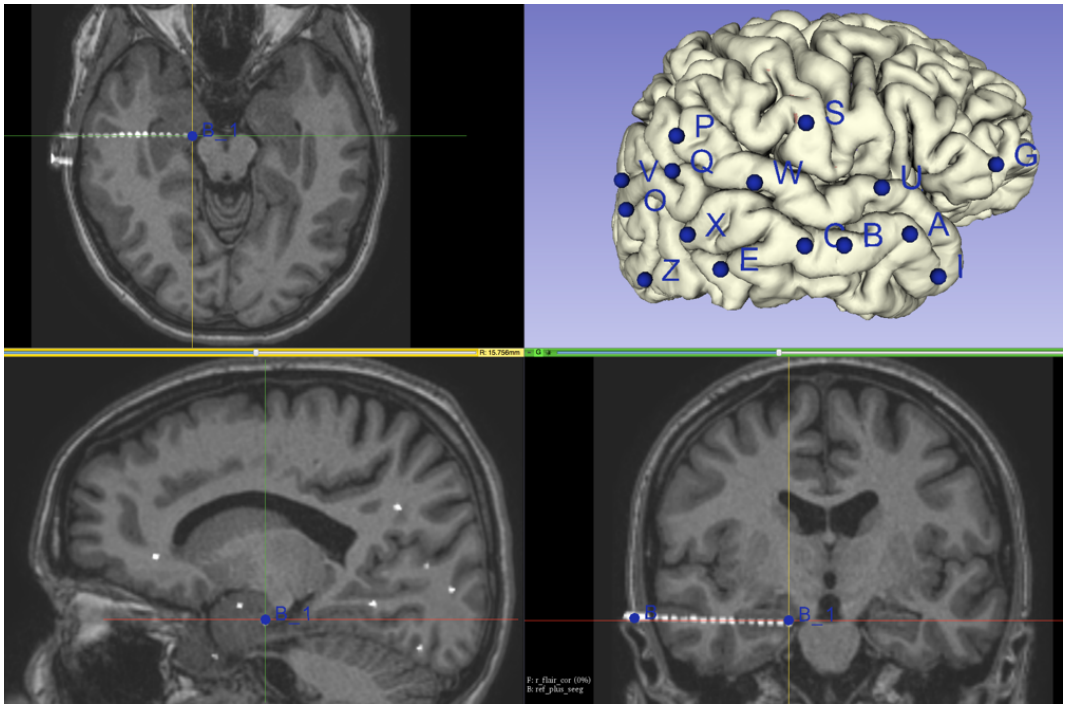

Figura 6 SEEG implantation involving the right temporal, occipital and parietal lobes. Electrodes A, B, C and I are localized in the antero-mesial portion of the temporal lobe. The mesial contacts of B are in the parahippocampus (leads 1 and 2) and in the hippocampus (3, 4, 5, and 6).

1.4 TEMPORAL LOBE EPILEPSY

Temporal lobe epilepsy (TLE) is the most commonly reported form of refractory epilepsy and accounts for the majority of adult patients with focal seizures. Classically, mesial TLE refers to TLE implicating mainly the hippocampal formation, especially in the case of hippocampal sclerosis (HS). However, cases of TLE with HS have been described with other seizure onset zones or pathological findings affecting other mesial temporal structures (e.g. amygdala, enthorinal cortex), or the temporal pole, leading to the term of "limbic epilepsy" which refers to seizures originating from temporal limbic structures [Engel, 2001; 2006]. In contrast, neocortical TLE is the term used to describe temporal lateral or basal seizure onset zones, in the absence of any pathology of the mesial temporal structures.

In 2004, a subcommission of the International League Against Epilepsy (ILAE) [Wieser et al, 2004] established that MTLE with HS should be described as a sindromic entity, based on a sufficient cluster of signs and symptoms, with the suggestion that mesial TLE with HS is a subtype of the larger syndrome of mesial TLE.

The concept of mesial TLE has origins in the description of Ammon's horn sclerosis, of which the first historic report was published by Bouchet and Cazauvieilh in 1825. In this early report, hardening of the mesial temporal lobe was described in postmortem brains, as well as the hallmarks of sclerotic transformation characterized by neuronal loss within the hippocampus. Based on the studies of Bouchet and Cazauvieilh and his own, Sommer presented the first detailed histological description of Ammon's horn sclerosis, noting particular neuronal loss in an area known as Sommer's sector or CA1 neuronal [Sommer, 1880]. In 1956 Cavanagh and Meyer brought to light a clear link between Ammon's horn sclerosis and TLE [Cavanagh and Meyer, 1956].
In patients with drug-resistant focal epilepsy requiring surgery, hippocampal sclerosis is the most common histopathological diagnosis among adults [Blümcke et al, 2017]. The most frequent pattern of hippocampal sclerosis

involves neuronal loss in all hippocampal segments (type 1) and is associated with favorable seizure relief after surgical resection. However, atypical patterns with cell loss restricted either to the CA1 region (type 2) or CA4 (type 3), are recognized by histopathological inspection. These patients experience their first seizures at a significantly later time point and have less favorable seizure relief after surgery. There are also often alterations within the dentate gyrus and granule cell loss in the dentate gyrus is associated with cognitive dysfunction.

Concerning the natural history of mesial-TLE with HS retrospective studies have demonstrated a high incidence of "initial precipitating incidents" (febrile seizures, trauma, hypoxia intracranial infection), usually before age 5 years and a latent period between the "initial precipitating incident" and onset of habitual seizures; there can be familiar history of TLE; a silent period usually occurs between first habitual seizure and drug resistance [Wieser, 2004]. Habitual seizures usually begin between 4 and 16 years [Wieser, 2004].

In its typical presentation, mesial TLE with HS is characterized by a strong association with antecedent febrile seizures, progressive development which leads very frequently to drug-resistance, topographic distribution of interictal and ictal EEG abnormalities which tend to be focused around the anterior and basal temporal lobe regions, and neuropsychological and functional neuroimaging data which also point to mesial temporal lobe structures [Rosenow et al, 2002]. This entity is likely to produce automotor seizures, with a relative absence of tonic-clonic generalized seizures and status epilepticus. Initial loss of contact without aura is uncommon and rather suggests a mesiolateral onset of seizures [Maillard et al, 2004]. Seizures often initiate with epigastric sensation [French et al, 1993], but emotional (e.g. fear) or other psychic (e.g. déjà-vècu) auras and autonomic symptoms (flushing, palor, mydriasis, tachycardia, etc.) are also common. Some patients can have olfactory sensations [King and Ajmone-Marsan, 1977], but the question of a possible orbito-frontal involvement must be raised. Auras may occur in isolation, or progress towards a motionless stare, oroalimentary automatisms

(e.g. lip smacking, chewing), less frequent verbal automatisms, and progressive clouding of consciousness. Hand automatisms are frequent and tend to be predominantly ipsilateral to the sclerotic hippocampus, due to contralateral dystonic posturing [Kotagal et al, 1989]. At this stage, loss of consciousness is common, but the patient may remain responsive, even in conjunction with automatisms [Ebner et al, 1995]. When present, clearly intelligible ictal or immediate postictal speech is suggestive of non-dominant hemisphere involvement [Gabr et al, 1989]. Seizures typically last for one to two minutes. There is transient postictal disorientation and, with onset in the language-dominant hemisphere, there may also be some degree of postictal aphasia. Postictal nosewiping, typically performed with the hand ipsilateral to the seizure onset zone, is recognized as a frequent symptom [Leutamezer et al, 1998]. Other critical phenomena have been described as ictal vomiting suggesting seizure onset in the right hemisphere [Kramer et al, 1988], the urinary urgency which is associated with seizure onset in the non-dominant hemisphere [Baumgartner et al, 2000]. Ictal spitting also suggests seizure onset in the non-dominant temporal lobe [Voss et al, 1999] as well as post-ictal cough [Wennberg, 2001]. Patients are most frequently amnesic of the ictal phase, however the aura is usually remembered.

This classic ictal clinical presentation, when complete, is suggestive of mesial temporal lobe seizure onset, but there are no definitive features which distinguish patients with HS from those with other mesiotemporal lesions or without any detectable MRI abnormalities. Yet, even typical ictal symptomatology may be due to the spread of ictal discharges from other temporal and even extratemporal areas. Conversely, although seizures may be of mesiotemporal lobe origin, they can manifest with very atypical clinical features.

Evidence of extrahippocampal pathology in patients with mesial TLE was first published by Cavanagh and Mayer (1956). Pathological findings were then observed in various structures such as uncus, entorhinal cortex, amygdala, temporal pole and temporal neocortex [Yilmazer-Hanke et al, 2000; Spanedda

et al, 1997; Levesque, 1991]. Accordingly, MRI studies showed atrophy in the amygdala, entorhinal cortex, temporal pole, but also disclosed volume reduction of the fornix, mamillo-thalamic tract and mammillary bodies [Coste et al, 2002; Moran et al, 2001]. Likewise, functional neuroimaging (FDG-PET) may show extensive interictal hypometabolism, predominating over the epileptogenic mesial temporal structures and temporal pole, but also affecting the ipsilateral temporal neocortex and perisilvian areas [Semah et al, 1995; Chassoux et al, 2004].

In line with these pathological, morphological and metabolic change, intracerebral EEG data have shown that a hippocampal onset was reported to account for only 20-65% of seizures of patients with mesial TLE [Munari et al, 1994; Chabardès et al, 2005].

Based on intracerebral electrophysiological data, Kahane and Bartolomei proposed a classification of different subtypes of TLE in 2010: mesial, temporopolar, mesiolateral, lateral and temporal plus (Figure 7).

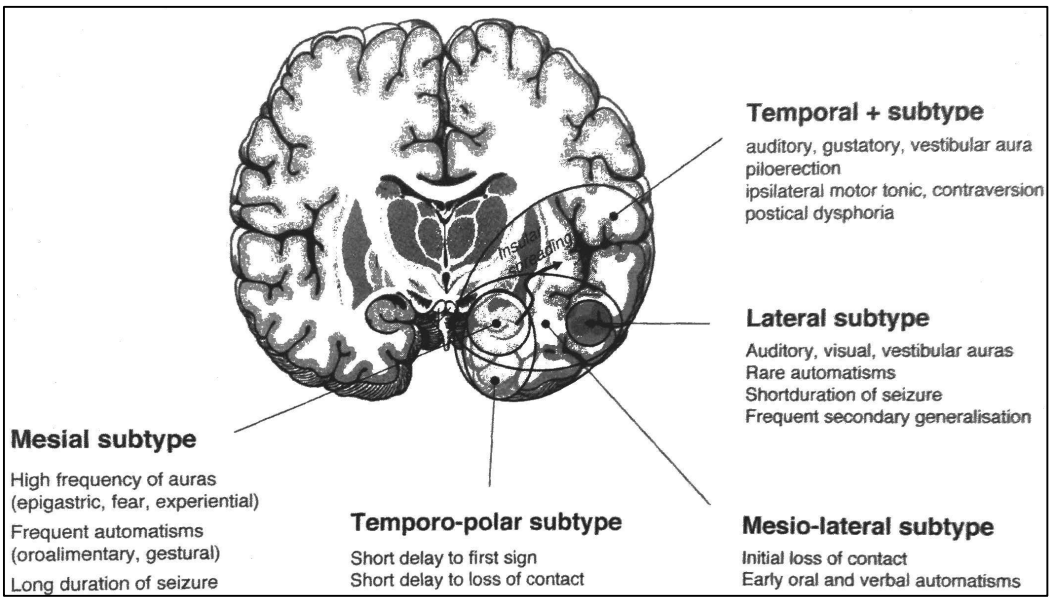

Figura 7 Classification of TLE subtypesand their main ictal clinical manifestations [modified from Kahane and Bartolomei, 2010].

Seizures of the mesial subtype may originate from the hippocampus, but also from the amygdala [Munari C et al, 1994; Spanedda F et al, 1997], the

paraippocampus gyrus [Wennberg et al, 2002] and from the entorhinal cortex [Spencer and Spencer, 1994; Bartolomei et al, 2005]. The symptoms and clinical signs do not necessarily derive from mesial temporal involvement and may reflect seizure spread over extra mesial temporal structures, such as for epigastric aura which could be related to insular propagation [Isnard et al, 2000]. Results of intracerebral stimulation suggest that fear aura could be a symptom of involvement of the amygdala [Meletti et al, 2006] and experiential phenomena of an involvement of the rhinal cortex [Bartolomei F et al, 2004]. The dreamy state seems to be due to a prevalent involvement of hippocampus, amygdala and rhinal cortex [Vignal et al, 2007]. Furthermore, patients with hippocampal onset may have predominantly epigastric auras and early oral automatisms, while those with extrahippocampal onset may have predominantly experiential auras and early motor involvement of the contralateral upper limb without oral automatisms [Gil-Nagel and Risinger, 1997]. The temporo-polar subtype shows seziures with early loss of awareness suggesting a crucial role of the temporal pole in seizure propagation [Chabardès et al, 2005].

In the mesiolateral subtype the ictal discharge simultaneously involves the mesial and lateral portion of the temporal lobe [Bartolomei et al, 1999]. This subtype has many clinical overlaps with the temporo-polar subtype with early loss of awareness and early oral and verbal automatisms [Maillard et al, 2004]. Cases of TLE with HS, where seizures originate from the temporal neocortex (lateral subtype), are anecdotal [Arzimanoglou and Kahane, 2008]. Although rare, such cases should be suspected in the presence of auditory aura, early loss of contact, short duration of seizures and frequent secondary generalization [Maillard et al, 2004]. In the temporal-plus subtype there is an early involvement of extratemporal areas such as orbitofrontal cortex, insula, frontal and parietal operculum, temporo-occipital junction [Ryvlin & Kahane, 2005]. Clinical signs associated with this type of epilepsy are gustatory hallucinations, vertigo, auditory illusions, deviations of eyes and head, piloerection, ipsilateral dystonias and postictal dysphoria [Barba et al, 2007].

Mesial TLE involves a network that is extremely important for emotion regulation and social behavior. Psychiatric disorders are frequent in epileptic patients, in particular with TLE and have often been classified as "epileptic personality disorder" [Blumer, 1999]. Some of these behavioral disorders, particularly the depressive ones, may be due to a dysfunction of neuronal network related to epileptogenic focus [Kanner et al, 2012].

Despite the great improvement of neuroradiological techniques, that allow detecting the great bulk of lesions that cause TLE, such as HS, low-grade epilepsy-associated tumors, vascular malformations, malformations of cortical development, scars, 30% of drug-resistant TLE is MRI negative [Muhlhofer et al, 2017].

The chances of being seizure-free after surgery are higher in patients with MRI-visible or histopathological-confirmed lesions than in non-lesional patients [Téllez-Zenteno et al, 2010; Krucoff et al, 2017], with the proportion of seizure-free patients in MRI-negative TLE being 51% compared with 75% in HS+ mesial TLE [Muhlhofer et al, 2017].

When MRI fails to detect a lesion, fluorine-18 fluorodeoxyglucose positron emission tomography (18F-FDG PET) may be useful to disclose a hypometabolism in the temporal lobe [Carne et al 2004; LoPinto-Khoury, 2012] that can strengthen the surgical indication. The presence of temporal lobe hypometabolism ipsilateral to the EEG side of seizure onset is associated with Engel class I postoperative outcomes in 75–80% of MRI-negative TLE [Capraz et al, 2015].

It is possible that, in some patients operated on for TLE, histopathological evaluation of surgical specimens reveals MRI-occult structural lesions. In fact, several surgical series [Capraz et al, 2015; Burkholder et al, 2014, Vale et al, 2012; Fong et al, 2011; Smith et al, 2011] of MRI-negative TLE report variable, but substantial, percentages of cases with HS or cortical malformations as histopathological findings. On the other hand, there are also MRI-negative TLE

series with prevailing unremarkable histological findings [Kogias et al, 2018; Lee et al, 2014; Ivanovic et al, 2017].

Surgical indications are clear in lesional TLE, while they are still undefined in patients with TLE and normal MRI. In these patients, the analysis of clinical history, electro- clinical data (video-electro-encephalography, VEEG) and other diagnostic non-invasive exams often fails to correctly define the epileptogenic zone (EZ), thus requiring invasive EEG. The question as to which patients are candidates to invasive EEG monitoring, and which patients can be offered surgery with only non-invasive presurgical work-up is still debated. Furthermore, it is not clear which prognostic factors are associated with postoperative seizure outcome [Muhlhofer et al, 2017].

2. AIM

In this retrospective study, we consider a single-centre cohort of patients with temporal lobe epilepsy and normal MRI who underwent temporal lobe resections. The aim of the study is to identify prognostic factors associated with favorable seizure outcome among several presurgical, surgical and postsurgical variables in order to optimize the selection of those patients that can really benefit from epilepsy surgery.

3. MATERIAL AND METHODS

3.1 PATIENTS

One thousand seven hundred and fifty-nine patients were operated on at the "C. Munari" Epilepsy Surgery Centre – Niguarda Hospital in Milan between January 1996 and June 2017 for drug-resistant focal epilepsy. Among this series we selected patients that underwent temporal lobe resections and without structural lesions at preoperative MRI. Data were collected by retrospective review of patients' clinical records and of a prospectively filled database.

3.2 PRESURGICAL EVALUATION

Demographic and anamnestic data

Clinical records were reviewed for age at seizure onset, age at surgery, epilepsy duration, family history of epilepsy, epileptologically relevant antecedents, febrile seizures (FS), comorbidities, and estimated seizure frequency.

Neuroimaging

In all patients, brain MRI studies were performed by an Achieva 1.5-T magnet (Philips Healthcare; Best, The Netherlands). During the presurgical evaluation, MRI studies were performed according to a standardized protocol including T1- and T2-weighted images with FLAIR sequences in several planes, and a volumetric T1-weighted sequence; additional sequences were acquired according to each patient's requirements for diagnostic purposes. Sequences, especially fluid-attenuated inversion recovery (FLAIR) and T1-IR, were constantly updated and set to obtain optimal visualization of lesions. Acquisition and interpretation of each study were conducted and validated by neuroradiologists expert in epileptic disorders. The MRI studies were then reviewed by epileptologists and neurosurgeons, who agreed that images did not show any structural abnormality and were, therefore, identified as normal. From 2012, a 18F-FDG PET scan was performed for most patients, to point out hypometabolic areas correlated with seizure onset on scalp EEG. Patterns of hypometabolism were defined as ispilateral temporal and ipsilateral temporal and extratemporal (modified from Yang et al 2014).

Scalp VEEG

All patients underwent VEEG long-term monitoring, with the aim to record habitual seizures. Both interictal EEG epileptiform abnormalities and ictal EEG modifications were classified as unilateral temporal, unilateral temporal-plus (temporal and extratemporal) and bilateral (independent bilateral epileptiform abnormalities or independent bilateral ictal onset). Possible contralateral diffusion was also considered, according to the definition

previously provided by others [Steinhoff et al, 1995; Schulz R et al, 2000] (Figure 8).

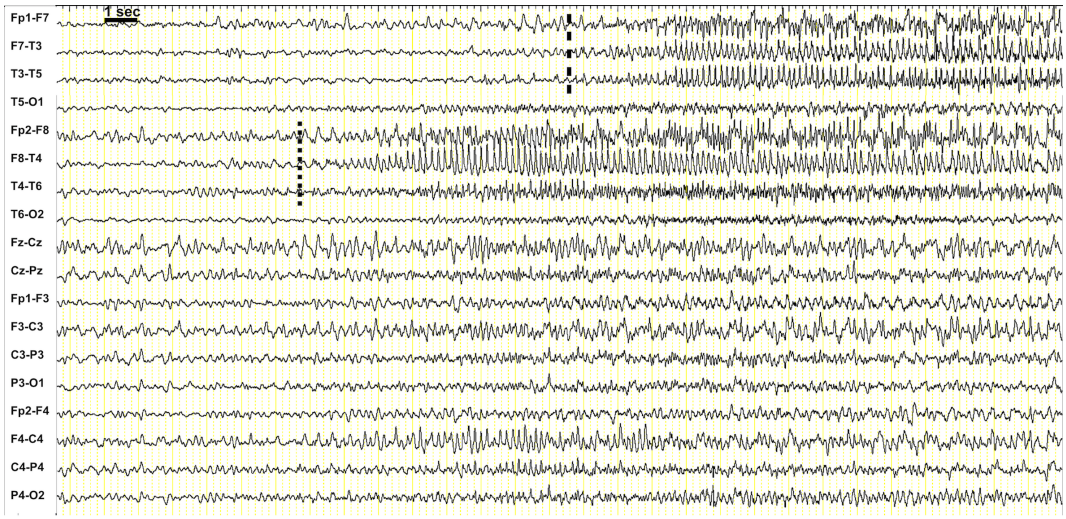

Figure 8 Ictal EEG recording of a typical example of a discharge with contralateral diffusion. Dotted line indicates the onset of a right temporal discharge. After 8 seconds, the ictal electrical activity, with a comparable frequency, is clearly visible on the left temporal derivations (dashed line).

Stereo-electro-encephalography (SEEG)

SEEG was performed when non-invasive investigations failed to correctly localize the EZ. Number and arrangement of intracerebral electrodes were tailored for each patient according to the presumed localization of the EZ [Cossu et al, 2005]. The localization of the ictal discharge as recorded at SEEG was defined as temporal or temporal and extratemporal (temporal-plus). The seizure pattern was defined as predominantly "antero-mesial" (seizure onset in hippocampus, amygdala, parahippocampal gyrus and temporal pole) or "neocortical" (seizure onset in the temporal neocortex).

Ictal clinical semiology

Both scalp VEEG and SEEG monitoring allowed collecting data on type and chronology of ictal symptoms (auras) and signs. Supplemental ictal clinical information anamnestically reported by patients or by seizure witnesses were also considered.

Neuropsychology

Neuropsychological testing included the main areas of cognitive functions and mood. The complete neuropsychological test battery with the cognitive domains explored and administered tests are available in Table 1.

Table 1. Neuropsychological test battery: cognitive domains explored and administered tests

DOMAINS	TEST
Language (production/comprehension)	Phonemic fluency Semantic fluency Naming Token test Reading - time - accuracy
Verbal memory (short-/long-term)	Digit span Working memory Paired associated words Short story recall
Visuo-spatial memory/Visuo-constructive functions	Corsi span Corsi supraspan Rey complex figure copy Rey complex figure recall Camden short recognition memory test Visual exploration Bell's test
Attention/executive functions	Attentional matrices Trail making A Trail making B
Visual perception	Benton line orientation Benton facial recognition test
Abstract reasoning	Raven's coloured progressive matrices
Mood	Beck depression inventory II (BDI-II)

The hemispheric dominance for language was defined in selected cases using intracarotid amytal test, and, more recently, by functional MRI. Further information about language localization was obtained in patients undergoing SEEG evaluation by intracerebral electrical stimulations.

3.3 SURGERY AND POSTSURGICAL EVALUATION

All patients underwent tailored resections within the anatomical limits of the temporal lobe. Patients with anatomo-elettro-clinical correlations consistent with mesial temporal lobe epilepsy underwent antero-mesial temporal lobectomy. The remaining resections were tailored according to the epileptogenic zone detected during SEEG, within the limits of the temporal lobe. All surgeries were conducted using microsurgical techniques and neuronavigation.

Surgical specimens were routinely processed for histological and immunohistochemical investigations [Blümcke et al, 2017]. Pathology was defined according to the ILAE classification of focal cortical dysplasias (FCD) [Blümcke et al, 2011] and hippocampal sclerosis (HS) [Blümcke et al, 2013].

Clinical records were reviewed also for surgery-related complications and new, unexpected postoperative neurological deficits, as well as for seizures occurring in the first 7 days after surgery (acute postoperative seizures, APOS). Six months after surgery, all patients were re-evaluated by routine EEG and brain MRI. Subsequently, clinical follow-up was performed yearly by outpatient visits. Neuropsychological testing was repeated postoperatively at different time intervals.

3.4 SEIZURE OUTCOME

Postoperative seizure outcome was assessed according to the Engel's classification [Engel et al, 1993]; patients were assigned to two outcome groups: favorable (free from disabling seizures, corresponding to Engel's class I) and unfavorable (corresponding to Engel's classes II–IV).

3.5 DATA ANALYSIS

Statistical analysis was performed to investigate which variables were associated with seizure outcome, as assessed at last available follow-up (favorable vs. unfavorable). The following variables were analyzed using a univariate logistic regression with the Wald's test (when the value of one category was equal to 0 a Fisher's test was used):

– Demographic and anamnestic data: gender, age at seizure onset, age at surgery, epilepsy duration, dominance for language, family history of epilepsy, antecedents/comorbidities, FS and estimated seizures frequency (daily [more than 30/month], weekly [5–30/ month], monthly [1–4/month], sporadic [less than 1/ month]).

– EEG findings: inter-ictal EEG, ictal EEG, contralateral diffusion of the discharge, SEEG (performed/not per- formed), SEEG ictal discharge (temporal vs. temporal-plus), SEEG seizure pattern (mesial vs. neocortical), 18F-FDG PET (performed/not performed), 18F-FDG PET site of hypometabolism (ipsilateral temporal/ ipsilateral temporal and extratemporal).

– Ictal clinical semiology: aura (present/absent), different kinds of aura (epigastric, auditory, visual, olfactory, gustative, psychic, autonomic and sensitive), verbal or gestural warning of incoming seizure, oral automatisms, lateralizing signs (dystonia, limb automatisms, head deviation and postictal language disturbance), loss of contact, secondary generalization, falls and awareness at the end of the seizures.

– Surgical and postsurgical data: side, surgery type, histology, APOS, postoperative EEG.

A multivariate logistic regression model was then built to identify variables independently associated with the odds of an unfavorable outcome, after exclusion of reciprocally correlated variables and considering only the ones reaching significance at the univariate analysis. Statistical significance was assumed at $P < 0.05$. Statistical analysis was performed using the statistical software STATA (version 5.1, StataCorp, College Station, Texas, USA).

4. RESULTS

Forty-eight patients fulfilled the selection criteria and were included in the analysis (Figure 9): they represent the 5.5% of the total number of patients that underwent temporal lobe resections in our Institution in the considered period. The amount of patients with MRI-negative TLE in the period considered is stable over time.

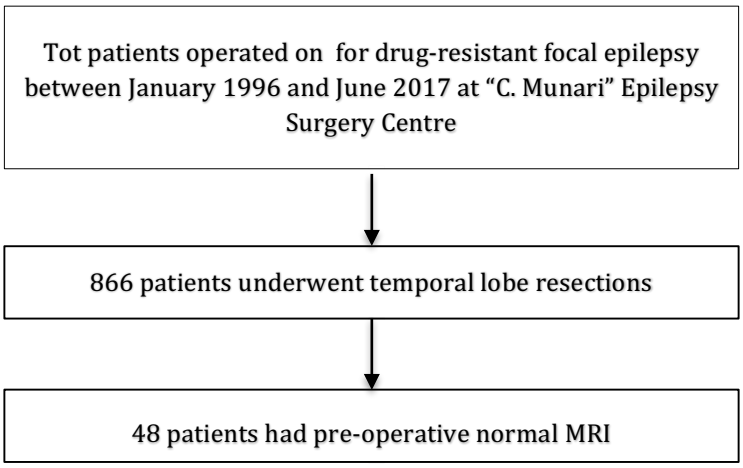

Figure 9 Flow-chart of the selected population.

4.1 DEMOGRAPHIC AND ANAMNESTIC DATA

There were 19 (39.6%) females and 29 (60.4%) males. The mean age at seizure onset was 15.2 years (SD ±9), the mean age at surgery was 31.7 years (SD ±9) and the mean duration of epilepsy was 16.5 years (SD ±8.4). Ten (20.8%) patients had a family history of epilepsy. The following epileptologically relevant antecedents were reported: 1 threatened abortion, 2 dystocic deliveries, 3 perinatal troubles, 3 infections of central nervous system, 1 radiosurgery for artero-venous malformation. Eight patients (16.7%) experienced FS (6 simple and 2 complex) in infancy.

Three patients had comorbidities: celiac disease, systemic lupus erythematosus, thyroiditis in 1 patient each.

Seizure frequency was daily in 8 (16.7%) patients, weekly in 18 (37.5%) patients, monthly in 18 (37.5%) patients and sporadic in 4 (8.3%) patients.

4.2 NEUROIMAGING

According to the selection criteria, none of the patients presented structural lesions at brain MRI.

Seventeen (35.4%) patients underwent ^{18}F-FDG PET. At the visual analysis, all these patients had a definite, hypometabolic area in the presumably epileptogenic temporal lobe as indicated by the electro-clinical data. In 11 cases hypometabolism involved also extratemporal areas (opercular-insular in 5 cases, frontal cortex in 4 cases, parieto-occipital in 2 cases). Ten out of these 11 patients were evaluated by SEEG monitoring before surgery.

4.3 SCALP VEEG AND SEEG FINDINGS

Seizures were recorded in 46 (96%) patients during scalp VEEG monitoring and in all the 26 (100%) patients that underwent SEEG. Details about scalp VEEG and SEEG findings are summarized in Table 2.

Table 2. Interictal and ictal VEEG and SEEG findings	
VEEG [a]	**N [c] (%)**
Interictal epileptiform abnormalities	
unilateral temporal	14/48 (29.2%)
unilateral temporal-plus	21/48 (43.7%)
bilateral	13/48 (27.1%)
Ictal onset discharge	
unilateral temporal	23/46 (50.0%)
unilateral temporal-plus	23/46 (50.0%)
bilateral	0/46 (0.0%)
Contralateral discharge diffusion	18/46 (39.1%)
SEEG [b]	**N [c] (%)**
Ictal discharge	
temporal	11/26 (42.3%)
temporal-plus	15/26 (57.7%)
Seizures pattern	
mesial	14/26 (53.8%)
neocortical	12/26 (46.2%)
[a] video-electroencephalography; [b] stereo-electroencephalography; [c] number of cases.	

After non-invasive evaluation, 22 patients whose data co-localized to one temporal lobe proceeded directly to surgery. In these cases, electroclinical data (corroborated in 4 cases by metabolic findings) were consistent with the involvement of mesial temporal structures in seizure onset. In the remaining 26 patients, with partially inconclusive non-invasive data suggesting a neocortical and/or extratemporal involvement, surgery was guided by a SEEG investigation.

4.4 ICTAL CLINICAL SEMIOLOGY

Details about ictal clinical signs and symptoms of the 48 patients are summarized in Table 3.

Table 3. Ictal clinical semiology	
Symptoms/signs	**N [a] (%)**
Aura	
psychic	25 (52.1%)
epigastric	21 (43.8%)
autonomic	18 (37.5%)
auditory	11 (22.9%)
visual	9 (18.8%)
somato-sensory	7 (14.6%)
gustative	4 (8.3%)
olfactory	3 (6.3%)
Warning	
verbal	17 (35.4%)
gestural	8 (16.7%)
Dystonia*	
contralateral	17 (35.4%)
ipsilateral	2 (4.2%)
bilateral	4 (8.3%)
Head deviation*	
ipsilateral	15 (31.3%)
contralateral	4 (8.3%)
Oro-alimentary automatisms	36 (75.0%)
Gestural automatisms*	
ipsilateral	19 (39.6%)

contralateral	1 (2.1%)
bilateral	10 (20.8%)
Loss of contact	44 (91.7%)
Secondary generalization	18 (37.5%)
Falls	8 (16.7%)
Postictal speech impairment	25 (52.1%)
Awareness	36 (75.0%)
[a] number of cases; *lateralizing signs are referred to the side of surgery	

No aura was reported by 8 (16.7%) patients. Among the other 40 (83.3%) patients, 30 reported more than 1 type of aura.

4.5 SURGERY AND POSTSURGICAL EVALUATION

Although all resections were tailored according to each patient's specific requirements, as revealed by preoperative evaluation, three main patterns of resection could be ex post recognized: antero-mesial temporal lobectomy (34 patients, 70.8%); complete temporal lobectomy (10 patients, 20.8%); lateral cortectomy (4 patients, 8.3%). Twenty-one (43.7%) patients were operated on in the dominant hemisphere for language; in these cases the posterior portion of the first temporal gyrus was spared irrespective of the type of resection.

Histology revealed type I FCD in 11 cases, type II FCD in 1 case and HS in 2 cases (1 type I and 1 type III). Histological evaluation was unremarkable (no lesion or unspecific gliosis) in 34 (71%) cases.

Mild surgical complications occurred in four patients, 1 with wound dehiscence and 3 with intracranial bleeding at the surgical site, none of which required surgical treatment. One patient suffering a postoperative bleeding developed mild permanent speech impairment.

Eight (16.7%) patients presented APOS. The postoperative EEG showed epileptiform abnormalities with variable localizations in 29 (60.4%) patients.

4.6 NEUROPSYCHOLOGICAL DATA

Hemispheric dominance for language was left-sided in 44 patients and right-sided in 4.

Preoperative and last available postoperative results of neuropsychological evaluations have been analysed.

A preoperative evaluation was available in 41 patients. Eleven of them had a completely normal neuropsychological profile; 9 of them received an antero-mesial temporal lobectomy and 2 a complete temporal lobectomy. Only 8 of these 11 patients were re-tested postoperatively: 3 were completely normal, 1 showed a decline in episodic memory and 4, all operated on in the dominant hemisphere with an antero-mesial temporal lobectomy, exhibited a reduction in language and verbal memory skills (details about cognitive decline in these 5 patients and percentages of score reduction are available in Table 4.

Table 4. Percentage score reduction between pre- and postoperative neuropsychological evaluation in the five patients with normal preoperative scores and postoperative decline. Score reduction was recorded only for the reported tests.

Case N.	Test	Percent postoperative score reduction
18	Phonemic fluency Short story recall	-15 -38
29	Short story recall	-29
37	Phonemic fluency Semantic fluency Short story recall	-34 -30 -67
42	Semantic fluency Short story recall	-38 -45
46	Phonemic fluency Semantic fluency Short story recall	-63 -43 -77

Abnormal neuropsychological scores were recorded in 30 patients at preoperative test. A postoperative evaluation was available in 25 of these 30 cases: 6 patients (5 with an antero-mesial temporal lobectomy, 1 with a lateral cortectomy) had completely normalized scores and in 19 patients the pathological profile did not change significantly. As a whole, the percentages of patients with a pathological score at the preoperative and, respectively, at

the last available postoperative evaluation did not significantly differ in any of the considered domains.

4.7 SEIZURE OUTCOME

The mean postoperative follow-up was 82 months (SD ±74; range 12-252); a total of 28 (58.3%) patients were in Engel's class I (17 patients Ia, 1 patient Ib, 7 patients Ic and 3 patients Id), 5 (10.4%) patients were in class II, 5 (10.4%) patients were in class III and 10 (20.8%) patients were in class IV. Patients in Engel's class I were 28/48 (58.3%), 26/44 (59.1%) and 14/26 (53.8%) 1, 2 and 5 years after surgery, respectively.

At the end of follow-up antiepileptic drugs were withdrawn in 5 (10.4%) patients and tapered in 14 (29.2%) patients in Engel's class I.

Details on the association of the different variables with seizure outcome at univariate analysis are reported in Tables 5 to 8.

Table 5. Results of univariate statistical analysis of demographic and anamnestic features vs. seizure outcome

Variable	Type	Categories	Engel's class I	Engel's classes II-IV	P-value
Gender	binomial	male	18 (62.1%)	11 (37.9%)	0.517
		female	10 (52.6%)	9 (47.4%)	
Dominance for language	binomial	left	27 (61.4%)	17 (38.6%)	0.192
		right	1 (25.0%)	3 (75.0%)	
Familiarity	binomial	no	22 (57.9%)	16 (42.1%)	0.904
		yes	6 (60.0%)	4 (40.0%)	
Antecedents/Comorbidities	binomial	no	21 (60.0%)	14 (40.0%)	0.701
		yes	7 (53.8%)	6 (46.2%)	
Febrile seizures	binomial	no	21 (52.5%)	19 (47.5%)	0.098
		yes	7 (87.5%)	1 (12.5%)	
Seizure frequency	multinomial	daily*	3 (37.5%)	5 (62.5%)	
		weekly	11 (61.1%)	7 (38.9%)	0,401
		monthly	12 (66.7%)	6 (33.3%)	0,218
		sporadic	2 (50.0%)	2 (50.0%)	1

*Reference category

Table 6. Results of univariate statistical analysis of VEEG [a], SEEG [b] and ^{18}F-FDG PET[c] findings vs. seizure outcome

Variable	Type	Categories	Engel's class I	Engel's classes II-IV	P-value
Interictal EEG	binomial	unilateral temporal	13 (92.9%)	1 (7.1%)	**0.010**
		other	15 (44.1%)	19 (55.9%)	
Ictal EEG	binomial	unilateral temporal	17 (73.9%)	6 (26.1%)	**0.017**
		other	10 (43.5%)	13 (56.5%)	
Contralateral discharge diffusion	binomial	no	23 (82.1%)	5 (17.9%)	**<0.001**
		yes	4 (22.2%)	14 (77.8%)	
SEEG[b]	binomial	no	13 (59.1%)	9 (40.9%)	0.922
		yes	15 (57.7%)	11 (42.3%)	
SEEG[b] ictal discharge	binomial	temporal	5 (45.5%)	6 (54.5%)	0.284
		temporal-plus	10 (66.7%)	5 (33.3%)	
SEEG[b] seizure pattern	binomial	mesial	10 (71.4%)	4 (28.6%)	0.233
		neocortical	5 (41.7%)	7 (58.3%)	
^{18}F-FDG PET [c]	binomial	no	14 (45.2%)	17 (54.8%)	**0.016**
		yes	14 (82.4%)	3 (17.6%)	
^{18}F-FDG PET [c]	binomial	temporal	6 (100.0%)	0 (0.0%)	0,515
		temporal and extratemporal	8 (72,7%)	3 (27,3%)	

[a] video-electroencephalography; [b] stereo-electroencephalography; [c] Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography

Table 7. Results of univariate statistical analysis of ictal clinical semiology vs. seizure outcome

Variable	Type	Categories	Engel's class I	Engel's classes II-IV	P-value
Aura	binomial	no	3 (37.5%)	5 (62.5%)	0,250
		yes	25 (62.5%)	15 (37.5%)	
Psychic aura	binomial	no	11 (47.8%)	12 (52.2%)	0.160
		yes	17 (68.0%)	8 (32.0%)	
Epigastric aura	binomial	no	14 (51.9%)	13 (48.1%)	0.304
		yes	14 (66.7%)	7 (33.3%)	
Autonomic aura	binomial	no	17 (56.7%)	13 (43.3%)	0.762
		yes	11 (61.1%)	7 (38.9%)	
Auditory aura*	binomial	no	25 (67.6%)	12 (32.4%)	**0.025**
		yes	3 (27.3%)	8 (72.7%)	
Visual aura	binomial	no	22 (56.4%)	17 (43.6%)	0.575
		yes	6 (66.7%)	3 (33.3%)	
Somato-sensory aura	binomial	no	25 (61.0%)	16 (39.0%)	0.375
		yes	3 (42.9%)	4 (57.1%)	
Gustative aura	binomial	no	25 (56.8%)	19 (43.2%)	0.490
		yes	3 (75.0%)	1 (25.0%)	
Olfactory aura	binomial	no	25 (55.6%)	20 (44.4%)	0.255
		yes	3 (100.0%)	0 (0.0%)	
Warning	binomial	no	14 (60.9%)	9 (39.1%)	0.733
		yes	14 (56.0%)	11 (44.0%)	
Dystonia	binomial	contralateral	8 (47.1%)	9 (52.9%)	0.244
		other	20 (64.5%)	11 (35.5%)	
Head deviation	binomial	ipsilateral	6 (40.0%)	9 (60.0%)	0.088
		other	22 (66.7%)	11 (33.3%)	

Oro-alimentary automatisms	binomial	no	6 (50.0%)	6 (50.0%)	0.501
		yes	22 (61.1%)	14 (38.9%)	
Gestural automatisms	binomial	ipsilateral	13 (68.4%)	6 (31.6%)	0.254
		other	15 (51.7%)	14 (48.3%)	
Loss of contact	binomial	no	4 (100.0%)	0 (0.0%)	0.130
		yes	24 (54.5%)	20 (45.5%)	
Secondary generalization	binomial	no	20 (66.7%)	10 (33.3%)	0.135
		yes	8 (44.4%)	10 (55.6%)	
Falls	binomial	no	27 (67.5%)	13 (32.5%)	**0.017**
		yes	1 (12.5%)	7 (87.5%)	
Post-ictal speech impairment	binomial	no	18 (78.3%)	5 (21.7%)	**0.009**
		yes	10 (40.0%)	15 (60.0%)	
Awareness	binomial	no	5 (41.7%)	7 (58.3%)	0.183
		yes	23 (63.9%)	13 (36.1%)	

[a] not significant; * Auditory hallucinations in 8 cases, auditory illusions in 3 cases

Table 8. Results of univariate statistical analysis of surgical and postsurgical variables vs. seizure outcome

Variable	Type	Categories	Engel's class I	Engel's classes II-IV	P-value
Side	binomial	dominant	9 (42.9%)	12 57.1%)	0.059
		non-dominant	19 (70.4%)	8 (29.6%)	
Surgery type	multinomial	antero-mesial temporal lobectomy*	19 (55.9%)	15 (44.1%)	
		complete temporal lobectomy	7 (70.0%)	3 (30.0%)	0.489
		neocortectomy	2 (50.0%)	2 (50.0%)	1
Hystology	multinomial	Uninformative*	19 (55.9%)	15 (44.1%)	
		Type I FCD	6 (54.5%)	5 (45.5%)	1
		Type II FCD	1 (100.0%)	0 (0.0%)	1
		HS	2 (100.0%)	0 (0.0%)	0.5
APOS [a]	binomial	no	26 (65.0%)	14 (35.0%)	0.051
		yes	2 (25.0%)	6 (75.0%)	
Postoperative EEG: epileptiform abnormalities	binomial	no	16 (84.2%)	3 (15.8%)	**0.006**
		yes	12 (41.4%)	17 (58.6%)	

[a] acute postoperative seizures; * Reference category.

An unfavourable seizure outcome was significantly associated with auditory aura, falls, postictal speech impairment, bilateral or extra-temporal interictal EEG abnormalities, contralateral diffusion of the discharge and presence of epileptiform abnormalities at postoperative EEG. Patients who underwent ^{18}F-FDG PET had a significantly more favourable outcome. Age at seizure onset, age at surgery and duration of epilepsy were not significantly associated with seizure outcome.

A multivariate logistic regression model showed that auditory aura, contralateral diffusion of the ictal discharge at VEEG evaluation and use of ^{18}F-FDG PET were independently associated with seizure outcome (Table 9).

Table 9. Multivariate logistic regression analysis for the risk of seizure-recurrence

	OR [a]	**95% OR [a] CI [b]**	**P-value**
Auditory aura	0.031	0.002 – 0.453	**0.011**
Contralateral discharge diffusion	0.027	0.003 - 0.214	**0.001**
Use of ^{18}F-FDG PET	9.43	1.189 – 74.693	**0.034**

[a] Odds Ratio; [b] Confidence Interval.

5. DISCUSSION

This retrospective study provided evidence that, if carefully selected, patients with MRI-negative TLE may be good candidates to resective surgery, although the seizure outcome is less favourable than in patients with lesional TLE [Muhlhofer et al, 2017]. At last available follow-up, 58.3% of our patients were in Engel's class I. A slight decrease of class I outcome to 53.8% was recorded 5 years postoperatively. Auditory aura and contralateral diffusion of the discharge at scalp VEEG were found to be independent predictors of an unfavourable outcome in this cohort; use of ^{18}F-FDG PET was independently associated to postoperative seizure freedom.

The frequency of auditory auras in TLE is low, ranging from 5 to 7% in largest series [Dupont et al, 2015; Ferrari-Marinho et al, 2012; Asadi-Pooya et al, 2016; Asadi Pooya et al 2017; Radhakrishnan et al, 2018]. The rate of patients with auditory auras in our cohort is 22%, a figure which might reflect a specific feature of MRI-negative TLE [Radhakrishnan et al, 2018]. Several studies have investigated the predictive value of single ictal symptoms and signs, including auditory auras, on seizure outcome after temporal lobe epilepsy surgery [Dupont et al, 2015; Radhakrishnan et al, 2018; Wang et al, 2013; Ataoglu et al, 2015; Dupont et al, 2015; No et al, 2017]. While Dupont et al., in 305 surgical cases, found no association between any type of aura and seizure outcome, a number of studies reported auditory auras as predictors of seizure recurrence after TLE surgery. Asadi-Pooya et al. found a significantly worse postoperative outcome in patients with auditory aura compared with those without. They concluded that these cases should be considered for a different approach when performing epilepsy surgery, including SEEG evaluation to study possibly involved networks [Asadi-Pooyaa et al, 2017]. Radhakrishnan et al., in a series of 344 patients who received anterior temporal lobectomy, reported that the presence of auditory and of vertiginous auras were significantly associated with an unfavourable seizure outcome. Their conclusion was that "auditory and vertiginous auras are red flags which need attention before ATL". Barba et al., while evaluating failures of TLE surgery, identified at single-symptoms analysis that a number of semeiological features, including auditory illusions,

were more frequently associated with temporal-plus epilepsies, which showed a significantly worse outcome at surgery. In the same paper, cluster analysis identified a cluster including only auditory hallucinations and illusions as markers of temporal-plus epilepsy [Barba et al, 2007].

We may postulate different reasons to explain the association between auditory auras and unfavourable seizure outcome after surgery. First, assuming that auditory auras are localizing symptoms consistent with the involvement of the superior temporal gyrus, in particular of its intermediate portion for illusions and of the Heschl's gyrus for hallucinations, resection in this area may have been insufficient for fear to damage the Wernicke's area in patients operated on in the dominant hemisphere. Nevertheless, this may be the case in only 4 of our 11 patients with auditory auras. Second, patients with ictal auditory illusions and hallucinations may have an extensive epileptogenic zone out-passing the limits of the temporal lobe ("temporal plus" epilepsy), a factor which, for this reason, may be associated with an unfavourable outcome if resection is limited to the temporal lobe [Barba et al, 2007; Barba et al, 2016]. As a matter of fact, there is evidence, provided by neurophysiological testing during invasive EEG investigations, that acoustic phenomena may be elicited by electrical stimulations of extratemporal areas, including the frontal operculum [Thompson et al, 2015] and of the insular cortex [Pugnaghi et al, 2011; Mazzola et al, 2017]. Another study on frequency analysis and functional MRI supported the possible role of the insula in acoustic processing [Zhang et al, 2019]. The hypothesis of an extratemporal origin of some auditory auras is also suggested by the reporting of opercular [Thompson et al, 2015] and insulo-opercular [Freri et al, 2017] epilepsies associated to auditory auras, as well as the presence of 7% of patients with extratemporal epilepsy in a series of patients with auditory auras [Asadi-Pooya et al, 2017]. This does not necessarily imply the existence of extratemporal acoustic areas, considering that, given the wide connectivity of the primary acoustic cortex [Cui et al, 2017], this may be activated by an ictal discharge with an extratemporal origin. A well localized and lateralized ictal and interictal EEG is correlated with a favourable postoperative outcome in MRI-negative TLE [Capraz et al, 2015;

Ivanovic et al, 2017; Tatum et al, 2008]. Our analysis corroborates this data and, in addition, shows that contralateral diffusion of the discharge is an independent prognostic factor for seizure recurrence. The role of the contralateral propagation of the ictal discharge at scalp EEG as a prognostic factor of postoperative seizure outcome in TLE is somewhat controversial. In some studies, this variable is scotomized [Tatum et al, 2008; Pataraia et al, 1998], in others no significant association, or only a trend towards association with poorer outcome, were found [Malter et al, 2016; Monnerat et al, 2013]. Conversely, Schulz et al. reported a negative significant association between contralateral propagation and postoperative seizure outcome, postulating that this may be an index of bilateral epileptogenicity [Schulz et al, 2000]. Another study on HS-related TLE found that the risk of long-term unfavourable postoperative outcome was higher in patients with contralateral diffusion of the ictal scalp EEG discharge [Lee et al, 2006]. Sirin et al. provided further evidence of the negative predictive value of contralateral diffusion on postoperative outcome by analysing a cohort of HS patients; they concluded that this finding increases the risk of false lateralization [Sirin et al, 2013]. Seizure recurrence after surgery in patients with contralateral involvement of the ictal discharge is possibly due to an epileptogenic network involving also the contralateral temporal lobe, even if a postsurgical VEEG monitoring would be necessary to support this hypothesis. The interpretation of electro-clinical correlations is essential and often challenging in MRI-negative TLE. Therefore, long-term VEEG evaluation is a crucial step in the presurgical work-up, as it provides key information about factors with prognostic relevance since the early phases of the selection procedure.

Use of ^{18}F-FDG PET has been suggested in MRI-negative patients, including those with TLE. In these patients, the presence of a hypometabolism co-localizing with the electro-clinical findings may allow proceeding to surgery without further investigations [Capraz et al, 2015]. The small number of patients of our cohort submitted to ^{18}F-FDG PET prevented a reliable analysis of the impact of ^{18}F-FDG PET findings on seizure outcome. Nevertheless, it was clear that use of ^{18}F-FDG PET represented an independent predictor of a

favourable seizure outcome. We postulate that ^{18}F-FDG PET strongly contributed to corroborate the surgical indication in patients with consistent electro-clinical findings, and to optimize the strategy of SEEG explorations in case of partial incoherence of non-invasive information. Notably, all but one of the patients with a temporal and extratemporal hypometabolism were evaluated by SEEG monitoring, indicating that metabolic findings were relevant to guide the presurgical work-up in this cohort of patients. Unfortunately, we could not investigate the metabolic pattern of patients with a contralateral diffusion of the ictal EEG discharge, because 14 out of 18 patients with this EEG pattern were evaluated before the introduction of PET scan in our hospital. We cannot therefore exclude the presence of bilateral hypometabolism in similar cases, with lower chances of postoperative seizure freedom.

Patients with seizure recurrence had more frequent secondary generalizations compared to seizure-free cases (44.4% and 66.7% of Engel's class I, respectively), although this difference did not reach statistical significance ($p=0.135$). As a matter of fact, secondary generalization has been associated to a worse seizure outcome after TLE surgery in most series [McIntosh et al, 2004; Jeha et al, 2006; Bone et al, 2012]. We may postulate that in our analysis statistical significance was not reached for the small size of our sample. Alternatively, a possible explanation is that in our data collection we did not include secondary generalizations which occurred at seizure onset. Of note, some studies reported a significantly higher proportion of secondary generalization in patients with HS-related TLE [No et al, 2017; Bone et al, 2012], which are recognized as those with the best seizure outcome among TLE surgically treated.

The question of the selection criteria for surgery and, specifically, the need for invasive investigations in MRI-negative TLE is still open. Patients with clinical symptoms consistent with antero-mesial TLE, well localized and lateralized ictal and interictal EEG abnormalities and no diffusion of the discharge are probably good candidates for surgery. On the other hand, our

data suggest that, in patients with symptoms evocative of a neocortical seizure onset (auditory aura), or with contralateral diffusion of the discharge, surgery should be considered with caution. In similar cases, SEEG is likely to represent a useful tool to correctly identify the EZ, but the criteria for indications to this evaluation are still undefined. According to the results provided by other studies, the use of SEEG investigations with appropriately placed extra-temporal electrodes may be helpful in patients whose past history or electroclinical data suggest the possibility of temporal-plus and neocortical (especially in the dominant hemisphere) epilepsies [Asadi-Pooya et al, 2017; Chassoux et al, 2018].

Analysis of the neuropsychological profile and outcome after surgery was not the main goal of this study. Indeed, the relatively small size of our cohort and the considerable number of the neuropsychological tests performed prevented a reliable stratification of data for statistical analysis. Furthermore, the available data were incomplete and not systematically collected. Nevertheless, in our sample there is no evidence of gross cognitive deficits at the postsurgical clinical follow up. This finding corroborates recent evidence in large samples of patients submitted to surgery for TLE [Salvato et al, 2016]. It should be underlined, however, that in our patients with intact cognitive profiles, a postoperative decline may be observed, especially in those operated on in the dominant hemisphere. On the other hand, in patients with preoperative neuropsychological impairments, no additional deterioration was recorded postoperatively, with a subset of patients experiencing normalization of their cognitive functions.

A substantial subset of our patients (34/48, 71%) had unremarkable histological findings. The reported rate of negative or unspecific histological findings in surgical specimens of MRI-negative TLE patients is highly variable, ranging from 28% to 85% across series [Capraz et al, 2015; Burkholder et al, 2014; Vale et al, 2012; Fong et al, 2011; Smith et al, 2011; Lee et al, 2014; Suresh et al, 2015; Kuba et al, 2011; Luther et al, 2011; Bell et al, 2009]. Discrepancies may be due to a number of factors, including methods used for

specimen processing, criteria for definition of non-lesional MRI, evolution of MRI techniques allowing detection of subtle lesions with high-field magnets. As a matter of fact, despite the improvement of neuroradiological techniques and expertise over time in our Centre, the amount of patients with MRI-negative TLE isn't decreased over time. Although our cohort was imaged by a 1.5T magnet, the rate of histologically negative cases is in line with a case series of 3T MRI-negative TLE [Kogias et al, 2018], confirming the reliability of our neuroradiological selection. Moreover, in 11 (23%) of our patients, a type I FCD was found at histology. This type of cortical malformation, unlike HS that should be rarely missed, may be easily undetected at MRI [Najm et al, 2018; Wang et al, 2013].

The question about the aetiology of TLE is particularly intriguing in patients presenting with negative MRI and unremarkable histology after surgery, especially in those who achieve seizure freedom after temporal lobectomy (55.9% in our cohort), in whom the etiological factor has been supposedly removed. Indeed, a 50% rate of postoperative seizure freedom in patients with no specific lesion at histology has been recently reported also in a large series of operated on patients [Blümcke et al, 2017]. Another study reported that 61.5% of patients operated on for MRI-negative TLE with unremarkable histology were seizure-free [Ivanovic et al; 2017]. Moreover, no difference in seizure outcome was recorded between cases with negative histology and those with a demonstrated pathological substrate (most of which with a diagnosis of FCD I), which one could ascribe to the small size of our sample. However, other studies have reported seizure freedom rates in histologically negative and, respectively, in FCD I cases operated on for TLE comparable to those reported in the present study [Ivanovic et al; 2017; Fauser et al, 2013].

It is possible that the identification of etiological factors in histologically negative cases may be provided by processing surgical specimens not only with the aim to detect structural abnormalities using traditional histological procedures but also searching for molecular or genetic biomarkers. According to the heterogeneity of electro-clinical findings, pointing at mesial, neocortical or "temporal-plus" patterns, we may postulate that this undetected aetiology

may underlie different types of epileptic networks within or close to the temporal lobe. The distinct nature of this non-lesional TLE is also suggested by the less favourable results obtained by surgery compared to lesional TLE. These features may legitimate the hypothesis of a genetic or metabolic aetiology, not exclusively localized in the temporal lobe and with a possible time-dependent evolution.

The retrospective, single centre nature of the present study limits its general relevance. Another limitation of the study is represented by the small size of the selected cohort, probably for the current reluctance to refer for surgery MRI-negative TLE patients (5.5% of the total number of patients that underwent temporal lobe resections in our Institution). Also, an overestimation of MRI-negative cases may have occurred owing to the use of a 1.5T magnet, which, especially in less recent years, could have missed some subtle structural abnormality. Furthermore, only few patients were imaged by ^{18}F-FDG PET, preventing a reliable assessment of the usefulness of this diagnostic tool in this clinical setting. Another limitation of the study is that any genetic analysis wasn't performed. This further information could have explained, in some cases, the unfavourable outcome.

On the other hand our study has considered a rather large constellation of factors, including anamnestic, clinical, EEG, neuropsychological, surgical, histological and outcome data of MRI-negative TLE.

The presented results may encourage further research, especially on MRI and histologically negative TLE. Improving the interpretation of ^{18}F-FDG PET findings to optimize surgical selection, establishing shared indications to invasive exams, investigating the possible aetiology of this specific disease are among the points which deserve attention.

6. CONCLUSIONS

The analysis of this cohort of operated on patients with MRI-negative TLE suggests that surgery can be an effective treatment option, provided that an accurate presurgical work-up is performed.

A substantial subset of cases required a SEEG investigation for the identification of the EZ.

Surgery should be considered with caution in patients with auditory aura and contralateral diffusion of the discharge, because they are more likely to experience an unfavourable outcome.

The use of ^{18}F-FDG PET may contribute to a favourable seizure outcome.

MRI-negative TLE is probably a distinct disorder, with often undefined aetiology deserving further investigation.

REFERENCES

Arzimanoglou A, Kahane P (2008). The ictal onset zone: general principles, pitfalls and caveats. In: Lüders HO (ed). Textbook of Epilepsy Surgery. London: Informa Healthcare; pp. 597-602.

Asadi-Pooya AA, Wyeth D, Nei M et al (2017) Postsurgical outcome in patients with auditory auras and drug-resistant epilepsy. Epilepsy & Behavior 66: 49–52.

Asadi-Pooya AA, Nei M, Sharan A et al (2016) Auras in patients with temporal lobe epilepsy and mesial temporal sclerosis. J Neurol Sci 364: 24-26.

Ataoğlu EE, Yıldırım I, Bilir E (2015) An evaluation of lateralizing signs in patients with temporal lobe epilepsy. Epilepsy Behav 47: 115-119.

Barba C, Barbati G, Minotti L et al (2007) Ictal clinical and scalp-EEG findings differentiating temporal lobe epilepsies from temporal 'plus' epilepsies. Brain 130: 1957-1967.

Barba C, Rheims S, Minotti L et al (2016) Temporal plus epilepsy is a major determinant of temporal lobe surgery failures. Brain 139: 444–451.

Bartolomei F, Barbeau E, Gavaret M et al (2004) Cortical stimulation study of the role of rhinal cortex in déjà vù and reminiscence of memories. Neurology 63; 858-864.

Bartolomei F, Khalil M, Wendling F et al (2005) Entorhinal cortex involvement in human mesial temporal lobe epilepsy: an electrophisiologic and volumetric study. Epilepsia 46: 677-687.

Bartolomei F, Wendling F, Vignal JP et al (1999) Seizures of temporal lobe epilepsy: identification of subtypes by coherence analysis using stereo-electro-encephalography. Clin Neurophysiol 110: 1741-54.

Baumgartner C, Groppel G, Leutmezer F et al (2000) Ictal urinary urge indicates seizure onset in the nondominant temporal lobe. Neurology 55: 432-434.

Bell M, Rao S, So E et al (2009) Epilepsy surgery outcomes in temporal lobe epilepsy with a normal MRI. Epilepsia 50: 2053–2060.

Benbadis SR, Luders HO (1996) Epileptic syndromes: an underutilized concept. Epilepsia 37: 1029-1034.

Berg AT, Berkovic SF, Brodie MJ et al (2010). Revised terminology and concepts for

organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 51: 676–685.

Blümcke I, Aronica E, Miyata H et al (2016) International recommendation for a comprehensive neuropathologic workup of epilepsy surgery brain tissue: A consensus Task Force report from the ILAE Commission on Diagnostic Methods. Epilepsia 57: 348–358.

Blümcke I, Spreafico R, Haaker G et al (2017) Histopathological Findings in Brain Tissue Obtained during Epilepsy Surgery. N Engl J Med 377: 1648-1656.

Blümcke I, Thom M, Aronica E et al (2011) The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. Epilepsia 52: 158–174.

Blümcke I, Thom M, Aronica E et al (2013) International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: a Task Force report from the ILAE Commission on Diagnostic Methods. Epilepsia 54: 1315-1329.

Blumer D (1999). Evidence supporting the temporal lobe epilepsy personality syndrome. Neurology 53: S9-12.

Bone B, Fogarasi A, Schulz R et al (2012) Secondarily generalized seizures in temporal lobe epilepsy. Epilepsia, 53(5): 817–824.

Bouchet C, Cazauvieilh JB (1825) De l'épilepsie considérée dans ses rapports avec l'aliénation mentale. Arch Gen Med 9: 510-42.

Burkholder D, Sulc V, Hoffman E et al (2014) Interictal scalp electroencephalography and intraoperative electrocorticography in magnetic resonance imaging-negative temporal lobe epilepsy surgery. JAMA Neurol 71: 702-709.

Capraz IY, Kurt G, Akdemir O et al (2015) Surgical outcome in patients with MRI-negative, PET-positive temporal lobe epilepsy. Seizure 29: 63–68.

Carne RP, Brien TJO, Kilpatrick CJ et al (2004) MRI-negative PET-positive temporal lobe epilepsy: a distinct surgically remediable syndrome. Brain 127: 2276–2285.

Cavanagh JB, Meyer A (1956) Aetiological aspects of Ammon's horn sclerosis associated with temporal lobe epilepsy. Br Med J 2: 1403-1407.

Chabardès S, Kahane P, Minotti L et al (2005) The temporopolar cortex plays a pivotal role in temporal lobe seizures. Brain 128: 1818-1831.

Chassoux F, Navarro V, Catenoix H et al (2018) Planning and management of SEEG (2017) Neurophysiol Clin 48(1): 25-37.

Chassoux F, Semah F, Bouilleret V et al (2004) Metabolic changes and electro-clinical patterns in mesio-temporal lobe epilepsy: a correlative study. Brain 127(Pt 1): 164-174.

Cossu M, Cardinale F, Colombo N et al (2005) Stereoelectroencephalography in the presurgical evaluation of children with drug-resistant focal epilepsy. J Neurosurg 103: 333–343.

Coste S, Ryvlin P, Hermier M et al (2002) Temporopolar changes in temporal lobe epilepsy: a quantitative MRI-based study. Neurology 59(6): 855-861.

Cui Z, Wang Q, Gao Y et al (2017) Dynamic Correlations between Intrinsic Connectivity and Extrinsic Connectivity of the Auditory Cortex in Humans. Front Hum Neurosci 11: 407.

Dupont S, Samson Y, Nguyen-Michel VH et al (2015) Are auras a reliable clinical indicator in medial temporal lobe epilepsy with hippocampal sclerosis? Eur J Neurol 22(9): 1310-1316.

Dupont S, Samson Y, Nguyen-Michel VH et al (2015) Lateralizing value of semiology in medial temporal lobe epilepsy. Acta Neurol Scand 132(6): 401-409.

Duvernoys HM (1999) The human brain surface, blood supply, and three-dimensional sectional anatomy. New York: Springer Wien New York.

Ebner A, Dinner DS, Noachtar S et al (1995) Automatisms with preserved responsiveness: a lateralizing sign in psychomotor seizures. Neurology 45: 61-64.

Engel J Jr, Van Ness PC, Rasmussen TB et al (1993) Outcome with respect to epileptic seizures. In: Engel J Jr, editor. Surgical treatment of the epilepsies NY: Raven Press 609–621.

Engel J Jr (2001) A Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy: Report of the ILAE Task Force on Classification and Terminology. Epilepsia 42(6): 796–803.

Engel J Jr (2006) Report of the ILAE Classification Core Group. Epilepsia 47(9): 1558–1568.

Engel J Jr, McDermott MP, Wiebe S et al (2012) Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA 307: 922–930.

Engel J Jr, Wiebe S, French J et al (2003) Quality Standards Subcommittee of the American Academy of Neurology; American Epilepsy Society; American Association of Neurological Surgeons. Practice parameter: temporal lobe and localized neocortical resections for epilepsy:

report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. Neurology 60: 538–547.

Fauser S, Essang C, Altenmuller DM et al (2013) Is there evidence for clinical differences related to the new classification of temporal lobe cortical dysplasia? Epilepsia, 54(5):909–917.

Ferrari-Marinho T, Caboclo LOSF, Marinho MM et al (2012) Auras in temporal lobe epilepsy with hippocampal sclerosis: Relation to seizure focus laterality and post surgical outcome. Epilepsy Behav 24: 120–125.

Fisher RS, Van Emde Boas W, Blume W et al (2005) Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 46: 470–472.

Fisher RS, Acevedo C, Arzimanoglou A et al (2014) ILAE official report: a practical clinical definition of epilepsy. Epilepsia 55(4); 475–82.

Fong J, Jehi L, Najm I et al (2011) Seizure outcome and its predictors after temporal lobe epilepsy surgery in patients with normal MRI. Epilepsia 52: 1393–1401.

Freri E, Matricardi S , Gozzo F et al (2017) Perisylvian, including insular, childhood epilepsy: presurgical workup and surgical outcome. Epilepsia 58(8): 1360-1369.

Gabr M, Lüders H, Dinner D et al (1989). Speech manifestations in lateralization of temporal lobe seizure. Ann Neurol 25: 82-87.

Gil-Nagel A, Risinger MW (1997) Ictal semiology in hippocampal versus extrahippocampal temporal lobe epilepsy. Brain 120: 183-92.

Hirtz D, Thurman DJ, Gwinn-Hardy K et al (2007) How common are the “common” neurologic disorders? Neurology 68: 326–337.

Isnard J, Guénot M, Ostrowsky K et al (2000) The role of the insular cortex in temporal lobe epilepsy. Ann Neurol 48: 614-623.

Ivanovic J, Larsson PG, Østby Y et al (2017) Seizure outcomes of temporal lobe epilepsy surgery in patients with normal MRI and without specific histopathology. Acta Neurochir 159: 757-766.

Jeha LE, Najm IM, Bingaman WE et al (2006) Predictors of outcome after temporal lobectomy for the treatment of intractable epilepsy. Neurology 66(12): 1938-1940.

Kahane P, Bartolomei F (2010) Temporal lobe epilepsy and hippocampal sclerosis: lessons from depth EEG recordings. Epilepsia 51 (Suppl 1): 59-62.

Kanner AM, Schachter SC, Barry JJ et al (2012) Depression and epilepsy: Epidemiologic and neurobiologic perspectives that may explain their high comorbid occurrence. Epilepsy & Behavior 24: 156–168.

Kiernan JA (2012). Anatomy of the Temporal Lobe. Epilepsy Res Treat 2012: 176157.

King DW, Ajmone-Marsan C (1977) Clinical features and ictal patterns in epileptic patients with EEG temporal lobe foci. Ann Neurol 2: 138-147.

Kogias E, Altenmüller DM, Klingler JH et al (2018) Histopathology of 3 Tesla MRI-negative temporal lobe epilepsies. J Clin Neurosci 47: 273-277.

Kotagal P, Lüders H, Morris HH et al (1989) Dystonic posturing in complex partial seizures of temporal lobe onset: a new lateralizing sign. Neurology 1989; 39; 196-201.

Kotsopoulos IAW, Van Merode T, Kessels FGH et al (2002) Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. Epilepsia 43: 1402–1409.

Kramer RE, Lüders H, Goldstick LP et al (1988) Ictus emeticus: an electroclinical analysis. Neurology 38: 1048-52.

Krucoff MO, Chan AY, Harward SC et al (2017) Rates and predictors of success and failure in repeat epilepsy surgery: A meta-analysis and systematic review. Epilepsia 58: 2133–2142.

Kuba R, Tyrlikova I, Chrastina J et al (2011) "MRI-negative PET-positive" temporal lobe epilepsy: Invasive EEG findings, histopathology, and postoperative outcomes. Epilepsy Behav 22: 537– 541.

Kwan P, Arzimanoglou A, Berg AT et al (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 51: 1069-77.

Lee R, Hoogsc M, Burkholder D et al (2014) Outcome of intracranial electroencephalography monitoring and surgery in magnetic resonance imaging-negative temporal lobe epilepsy.

Lee SA, Yim SB, Lim YM et al (2006) Factors predicting seizure outcome of anterior temporal lobectomy for patients with mesial temporal sclerosis. Seizure 15(6): 397-404.

Leonardi M, Ustun T (2002). The global burden of epilepsy. Epilepsia 43 (Suppl 6): 21–25.

Levesque MF, Nakasato N, Vinters H et al (1991) Surgical treatment of limbic epilepsy associated with extrahippocampal lesions: the problem of dual pathology. J Neurosurg 75: 364-370.

LoPinto-Khoury C, Sperling M, Skidmore C et al (2012) Surgical outcome in PET-positive, MRI-negative patients with temporal lobe epilepsy. Epilepsia 53: 342-348.

Lüders HO (2008). Textbook of Epilepsy Surgery. CRC Press.

Luther N, Rubens E, Sethi N et al (2011) The value of intraoperative electrocorticography in surgical decision making for temporal lobe epilepsy with normal MRI. Epilepsia 52: 941–948.

Mai JG, Paxinos G, Voss T (2008). Atlas of the Human Brain, Elsevier, Amsterdam, The Netherlands, 3rd edition.

Maillard L, Vignal JP, Gavaret M et al (2004) Semiologic and Electrophysiologic Correlations in Temporal Lobe Seizure Subtypes. Epilepsia 45(12): 1590-1599.

Malter MP, Bahrenberg C, Niehusmann P et al (2016) Features of scalp EEG in unilateral mesial temporal lobe epilepsy due to hippocampal sclerosis: Determining factors and predictive value for epilepsy surgery. Clin Neurophysiol 127(2): 1081-1087.

Mazzola L, Mauguière F, Isnard J (2017) Electrical Stimulations of the Human Insula: Their Contribution to the Ictal Semiology of Insular Seizures. J Clin Neurophysiol 34(4): 307-314.

McIntosh AM, Kalnins RM, Mitchell LA et al (2004) Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. Brain 127: 2018–2030.

Meletti S, Tassi L, Kahane P et al (2006) Emotions induced by intracerebral electrical stimulation of the temporal lobe. Epilepsia 47 (Suppl 5): 47-51.

Monnerat BZ, Velasco TR, Assirati JA Jr et al (2013) On the prognostic value of ictal EEG patterns in temporal lobe epilepsy surgery: A cohort study. Seizure 22(4): 287-291.

Moran NF, Lemieux L, Kitchen ND et al (2001) Extrahippocampal temporal lobe atrophy in temporal lobe epilepsy and mesial temporal sclerosis. Brain 124; 167-175.

Muhlhofer W, Tan YL, Mueller SG et al (2017) MRI-negative temporal lobe epilepsy—What do we know? Epilepsia 58: 727–742.

Munari C, Tassi L, Mai R et al (1994) Analysis of clinical symptomatology during stereo-EEG recorded mesiotemporal seizures. IN: Wolf P (ed). Epileptic Seizures and Syndromes. London:

John Libbey, pp 335-357.

Najm IM, Sarnat HB, Blümcke I (2018) Review: The international consensus classification of Focal Cortical Dysplasia – a critical update 2018. Neuropathol Appl Neurobiol 44: 18–31.

Ngugi AK, Bottomley C, Kleinschmidt I et al (2010) Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia 51: 883–890.

No YJ, Zavanone C, Bielle F et al (2017) Medial temporal lobe epilepsy associated with hippocampal sclerosis is a distinctive syndrome. J Neurol. 264(5): 875-881.

Pataraia E, Lurger S, Serles W et al (1998) Ictal scalp EEG in unilateral mesial temporal lobe epilepsy. Epilepsia 39: 608-14.

Pugnaghi M, Meletti S, Castana L et al (2011) Features of somatosensory manifestations induced by intracranial electrical stimulations of the human insula. Clin Neurophysiol 122(10): 2049-2058.

Radhakrishnan A, Menon RN, Chandran A et al (2018) Do auras predict seizure outcome after temporal lobe epilepsy surgery? Epilepsy Res 147:109-114.

Rosenow F, Ryvlin P, Lüders H et al (2011) The mesial temporal lobe epilepsies, JLE eds.

Ryvlin P, Kahane P (2005) The hidden causes of surgery-resistant temporal lobe epilepsy: extratemporal or temporal plus? Curr Opin Neurol 18: 125-127.

Salvato G, Scarpa P, Francione S et al (2016) Declarative long-term memory and the mesial temporal lobe: Insights from a 5-year postsurgery follow-up study on refractory temporal lobe epilepsy. Epilepsy Behav 64: 102-109.

Scheffer IE, Berkovic S, Capovilla G et al (2017) ILAE Classification of the Epilepsies Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 58(4): 512–521.

Schulz R, Lüders HO, Hoppe M et al (2000) Interictal EEG and Ictal Scalp EEG Propagation Are Highly Predictive of Surgical Outcome in Mesial Temporal Lobe Epilepsy. Epilepsia 41(5): 564-570.

Semah F, Baulac M, Haboun D et al (1995) Is interictal temporal hypometabolism related to mesial temporal sclerosis? A positron emission tomography/magnetic resonance imaging confrontation. Epilepsia 36: 447-456.

Sirin NG, Gurses C, Bebek N et al (2013) A Quadruple Examination of Ictal EEG Patterns in

Mesial Temporal Lobe Epilepsy With Hippocampal Sclerosis: Onset, Propagation, Later Significant Pattern, and Termination. J Clin Neurophysiol 30: 329–338.

Smith A, Sani S, Kanner A et al (2011) Medically intractable temporal lobe epilepsy in patients with normal MRI: Surgical outcome in twenty-one consecutive patients. Seizure 20: 475–479.

Sommer W (1880) Erkrankung des Ammonshorns als aetiologisches Moment der Epilepsie. Arch Psychiat Nervenrk 10: 631-75.

Spanedda F, Cendes F, Gotman J (1997) Relations between EEG seizure morphology, interhemispheric spread, and mesial temporal atrophy in bitemporal epilepsy. Epilepsia 38: 1300-1314.

Spencer SS, Spencer DD (1994) Entorhinal-hippocampal interactions in medial temporal lobe epilepsy. Epilepsia 35: 721-727.

Steinhoff BJ, So NK, Lim S et al (1995) Ictal scalp EEG in temporal lobe epilepsy with unitemporal versus bitemporal interictal epileptiform discharges. Neurology 45(5): 889-896.

Suresh S, Sweet J, Fastenau P et al (2015) Temporal lobe epilepsy in patients with nonlesional MRI and normal memory: an SEEG study. J Neurosurg 123: 1368–1374.

Tassinari CA, Rubboli G, Gardella E et al (2005) Central pattern generators for a common semiology in fronto-limbic seizures and in parasomnias. A neuroethologic approach. Neurol Sci 26 Suppl 3: s225-232.

Tatum IV, Benbadis S, Hussain A et al (2008) Ictal EEG remains the prominent predictor of seizure-free outcome after temporal lobectomy in epileptic patients with normal brain MRI. Seizure 17: 631—636.

Téllez-Zenteno JF, Hernández-Ronquillo L (2012) A review of the epidemiology of temporal lobe epilepsy. Epilepsy Res Treat 2012: 630853.

Téllez-Zenteno JF, Hernández-Ronquillo L, Moien-Afshari F et al (2010) Surgical outcomes in lesional and non-lesional epilepsy: A systematic review and meta-analysis. Epilepsy Res 89: 310-318.

Thompson SA, Alexopoulos A, Bingaman W et al (2015) Auditory aura in frontal opercular epilepsy: sounds from afar. Epileptic Disord 17(2): 150-155.

Vale FL, Effio E, Arredondo N et al (2012) Efficacy of temporal lobe surgery for epilepsy in patients with negative MRI for mesial temporal lobe sclerosis. J Clin Neurosci 19:101–106.

Vignal JP, Maillard L, McGonigal A et al (2007) The dreamy state: hallucinations of autobiographic memory evoked by temporal lobe stimulations and seizures. Brain 130: 88-99.

Voss NF, Davies KG, Boop FA et al (1999) Spitting automatism in complex partial seizures: nondominant temporal localizing sign? Epilepsia 40: 114-116.

Wang ZI, Alexopoulos A, Jones S et al (2013) The pathology of magnetic-resonance-imaging-negative epilepsy. Mod Pathol 26: 1051–1058.

Wang F, Liu X, Pan S et al (2013) Electroclinical characteristics of posterior lateral temporal epilepsy. Epilepsy Behav 26(1): 126-131.

Wennberg R (2001) Postictal coughing and noserubbing coexist in temporal lobe epilepsy. Neurology 56: 133-4.

Wennberg R, Arruda F, Quesney LF et al (2002) Preeminence of extrahippocampal structures in the generation of mesial temporal seizures evidence from human depth electrode recordings. Epilepsia 43: 716-26.

Wiebe S, Blume WT, Girvin JP et al (2001) Effectiveness Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 345: 311–318.

Wieser HG (2004) ILAE Commission on Neurosurgery of Epilepsy. ILAE Commission Report. Mesial temporal lobe epilepsy with hippocampal sclerosis. Epilepsia 45: 695-714.

Yang PF, Pei JS, Zhang HJ (2014) Long-term epilepsy surgery outcomes in patients with PET-positive, MRI-negative temporal lobe epilepsy. Epilepsy & Behavior 41: 91–97.

Yilmazer-Hanke DM, Wolf HK, Schramm J et al (2000) Subregional pathology of the amygdala complex and entorhinal region in surgical specimens from patients with pharmacoresistant temporal lobe epilepsy. J Neuropathol Exp Neurol 59: 907-920.

Zhang Y, Zhou W, Wang S et al (2019) The Roles of Subdivisions of Human Insula in Emotion Perception and Auditory Processing. Cereb Cortex 29(2): 517-528.