Pathophysiology of seizure onset in human focal epilepsy and its relevance to epilepsy surgery

Jimenez Jimenez, Diego Mauricio

Awarding institution:
King's College London

Pathophysiology of seizure onset in human focal epilepsy and its relevance to epilepsy surgery

By

Diego Jiménez-Jiménez

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Department of Basic and Clinical Neuroscience,

Institute of Psychiatry, Psychology & Neuroscience,

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DECLARATION

I confirm that the following thesis does not exceed the word limit prescribed in the College regulations. I further confirm that the work presented in the thesis is my own and all references are cited accordingly.

Diego Jiménez-Jiménez

ABSTRACT

Epilepsy is a major source of disability amongst all age groups. Most epilepsies are well controlled on antiepileptic drugs. However, significant proportions of patients are not controlled on medical treatment and may be successfully treated with resective surgery. Unfortunately, as many as 30% of patients remain with disabling seizures after resective surgery. In the present thesis I aim at identifying seizure onset patterns on intracranial EEG that are predictors of surgical outcome.

Methods: I have studied all patients operated after intracranial recordings implantation between 1999 and 2010 with a follow up period longer than 1 year. I identified the first, the second ictal patterns and the presence of preceding epileptiform discharges, and correlated their presence with surgical outcome. As the initial pattern was bilateral in 33% of patients, I used single pulse electrical stimulation (SPES) to identify bilateral connections that could be responsible for bilateral changes at seizure onset.

Results: Focal fast activity as first ictal pattern was associated with favourable outcome. Diffuse electrodecremental event as first ictal pattern was associated with poor outcome. A preceding focal, widespread or bilateral epileptiform discharge was not associated with neither favourable nor poor outcome. As second ictal pattern, fast activity was associated with poor outcome whereas diffuse electrodecremental event with good outcome. Delayed second ictal patterns (≥10sec) appear to be associated with good outcome in temporal lobe

epilepsy. Hippocampus and amygdala have a low incidence of contralateral connections (5.0%). Fusiform gyrus showed the highest incidence of contralateral functional connections (≤7.1%). Bi-temporal connectivity is related neither to bilateral seizure onset nor postsurgical outcome.

Conclusion: The prognostic value of ictal patterns depends where they occur during seizure evolution. Early bilateral changes at seizure onset cannot solely be explained by functional bilateral connections.

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DEDICATION

"Nada existe en el mundo tan dócil y débil como el agua. Pero para atacar lo duro y lo fuerte, no existe nada que pueda superarla. No hay nada que la pueda sustituir. Lo débil vence a lo fuerte y lo frágil vence a lo duro"

Lao Tzu (Siglo VI A.C.)

To God, everything is possible.

To my dad Vicente, despite your sudden departure, you have not stopped supporting and teaching me through my life.

To Evita, your presence, perseverance, and love have encouraged me always.

To Rodrigo, our innocent laughter remains in my soul and offers me peace.

To Diana, my endless love…

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GLOSSARY OF ABREVIATIONS

AEDs =	Anti-epileptic drugs
DEE =	Diffuse electrodecremental event
DTI =	Diffusion tensor imaging
EEG =	Electroencephalography
EPSP =	Excitatory postsynaptic potential
FA =	Fast activity
FIP =	First ictal pattern
IEDs =	Interictal epileptiform discharges
iEEG =	Itracranial Electroencephalography
ILAE =	The International League Against Epilepsy
LTL =	Lateral temporal lobe epilepsy
MEG =	Magnetoencephalography
MRI =	Magnetic resonance imaging
MTLE =	Mesial temporal lobe epilepsy
mTLE–HS	Mesial temporal lobe epilepsy with hippocampal sclerosis
PED =	Preceding epileptiform discharge
PET =	Positron emission tomography
SIOP =	Sustained ictal onset patterns
SIP =	Second ictal pattern
SPECT =	Single-photon emission computed tomography
SPES =	Single-pulse electrical stimulation
TLE =	Temporal lobe epilepsy

In loving memory of my dad Vicente

17 January 1946 – 16 January 2003

1. CHAPTER ONE

1 Introduction

Epilepsy is a frequent chronic neurological disease, which is characterized by propensity to suffer paroxysmal events called epileptic seizures. The International League Against Epilepsy (ILAE) defines an epileptic seizure as a "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (Fisher et al., 2005). Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure. Seizures have been broadly classified based on their clinical and electroencephalographic manifestations into two main groups:

- Generalized seizures that involve both cerebral hemispheres from onset, typically involving most of the cerebral cortex.
- Focal seizures, which have their origin in a restricted region of the cerebral cortex within one hemisphere (Alarcon, 2009b, Fisher et al., 2005).

Epileptic seizures can be associated with other signs and symptoms, constituting the specific epilepsy syndromes (Alarcon, 2009b). Each epilepsy syndrome has a specific age of onset, seizure types, source for seizures, aetiology and prognosis.

A syndrome may present more than one type of epileptic seizures (Alarcon, 2009b).

Approximately 65 million people around the world are diagnosed with epilepsy (Ngugi et al., 2010). The occurrence of this condition varies according to the socioeconomic background. The incidence of epilepsy in developed countries is 50/100,000 per year and the prevalence is estimated to be 7 per 1,000 (Thurman et al., 2011). By contrast, in developing countries the incidence is 122-190/100,000 and the prevalence is 6.7 – 8/1,000 (Placencia et al., 1992).

Nearly 30% of the patients diagnosed with epilepsy have poor seizure control despite the use of an appropriate antiepileptic therapy (Tellez-Zenteno et al., 2014). This scenario is described as drug-resistant epilepsy (Kwan et al., 2010), a condition which has a negative impact on patient's quality of life. Epilepsy surgery is an alternative to manage drug-resistant epilepsy which has proved to be a safe, presenting low rates of mortality and morbidity (0.1%-0.5%) (Engel et al., 2010, Health Quality, 2012).

Epilepsy surgery is an effective treatment in those patients diagnosed with drug resistant epilepsy (Engel and Pedley, 1998). When the surgical treatment is successful, it considerably improves patient's quality of life through improving behavioural, cognitive and social spheres (Dreifuss, 1987). Additionally, epilepsy surgery diminishes drug toxicity, which may have been caused by high doses of antiepileptic medication (Gumnit, 1988). Furthermore, epilepsy surgery has contributed to understanding the pathophysiology of the different epileptic

syndromes that are amenable to surgery, which has promoted development in neurophysiology and surgical techniques.

Epilepsy surgery aims at destroying and removing those regions of the brain that trigger seizures, i.e. epileptogenic zone (Luders et al., 2006). Unfortunately, as many as 30% of patients remain with disabling seizures after resective surgery (Kumar et al., 2013). Before undertaking surgery, it is crucial to ensure that the epileptogenic zone is well identified and to prevent any functional or cognitive deficits. Identifying the zone that causes seizures is a complex and multidisciplinary task, which may involve two stages, invasive and non-invasive presurgical assessment (Alarcon, 2009a).

Non-invasive methods include neuropsychological, neuroimaging and electroencephalographic scalp recordings (EEG), which initially allow the identification of the epileptogenic zone. Some patterns seen on scalp EEG recordings are predictors of good postsurgical outcome: presence of unitemporal interictal spikes, no bilateralization of seizure onset, and delayed spreading of seizure onset (Alarcon et al., 2001a).

The use of intracranial electroencephalography (iEEG) can provide recordings from deep structures of the brain, with greater amplitude and less muscle artefacts. Interictal patterns seen on iEEG are of limited value for localizing and lateralizing the epileptogenic zone. Consequently, iEEG recordings still need to rely on identification of seizure onset to identify the epileptogenic zone precisely (Alarcon, 2012, Kumar et al., 2013).

To date, the following intracranial seizure onset patterns have been described: 1) electrodecremental event, 2) high frequency activity, 3) irregular sharp waves intermixed with slow activity, 4) spike-wave activity and 5) rhythmic ictal transformation (Alarcon et al., 1995). Several seizure onset patterns previously described have been correlated with surgical outcome largely (Alarcon et al., 1995, Dolezalova et al., 2013, Holtkamp et al., 2012, Lee et al., 2000, Yuan et al., 2012, Spencer et al., 1992a, Kutsy et al., 1999). Authors found that fast activity is predictor of favourable surgical outcome and the presence of diffuse flattening was not correlated with poor surgical outcome (Alarcon et al., 1995, Yuan et al., 2012, Kutsy et al., 1999, Holtkamp et al., 2012). However, previous studies did not include temporal and extratemporal epilepsies in their series and patients sample were reduced.

At ictal onset, seizures may spread unilaterally, bilaterally, subcortically or cortically to areas, which are anatomically connected (Spencer, 2002a). It has been suggested that the areas recruited during the seizure may not be part of the epileptic network but supports and preserves the seizures (Spencer, 2002a). In view of such multifaceted seizure onset types, presurgical assessment can become complicated. Defining the seizure onset zone may be challenging and surgical outcome uncertain. Consequently, predicting surgical outcome based on seizure onset patterns is desirable.

In the current thesis, I will present three studies published in peer review journals that seek to clarify some aspects of the pathophysiology of focal seizure

onset and its relevance to epilepsy surgery. In the first publication, "Prognostic value of intracranial seizure onset patterns for surgical outcome of the treatment of epilepsy", the prognostic value with regard to seizure control of different intracranial seizure onset patterns were reported in a series of 69 consecutive patients undergoing resective surgery for the treatment of epilepsy. This is the largest study published to date, which includes temporal and extratemporal patients (Jimenez-Jimenez et al., 2015b). In the second study, "Prognostic value of the second ictal intracranial pattern for the outcome of epilepsy surgery", I analysed the prognostic value of the type, latency and extent of the second ictal pattern, in 63 patients, a unique study to date (Jiménez-Jiménez et al., 2016). In the third study, "Incidence of functional bi-temporal connections in the human brain in vivo and their relevance to epilepsy surgery", I estimated the incidence and latencies of human functional contralateral temporo-temporal connections in-vivo and whether the presence of such connections is related to presence of bilateral changes at seizure onset and postsurgical seizure control (Jimenez-Jimenez et al., 2015a).

2 History of epilepsy surgery

The origins of epilepsy surgery can be traced back to ancient times. Some evidence suggests that in Pre-Columbian America and Egypt, skull trepanning was performed with the objective of relieving evil humours and spirits (Lüders, 2008). In the 19th century, Benjamin Dudley published five post-traumatic epilepsy patients treated with trepanning. He found that after surgery, three of these patients become seizure free and two presented a significant reduction in seizure frequency (Patchell et al., 1987). Other surgeons documented the use of

the same technique with variable results, with infection being the most common complication (Meador et al., 1989). In London during the 19th century, Sir Victor Alexander Haden Horsley carried out the first brain resection to alleviate focal seizures (Vilensky, 2002). Surgery was a success and Victor Horsley completed more operations on post-traumatic epilepsy with favourable outcome (Vilensky, 2002).

In 1933, Hans Berger introduced the EEG. Years later, Altenburger and Foerster applied the EEG for the first time to use in epilepsy surgery in Germany (Lüders, 2008). In Canada, by the 1937, Wilder Penfield founded the Montreal Neurological Institute, and generated the modern concept of the epilepsy surgery, which included presurgical assessment with EEG, cortical stimulation, neuroradiology and neuropsychology (Magiorkinis et al., 2014). Using modern techniques, epilepsy surgery gradually become a routine treatment for epilepsy syndromes. In Paris Bickford and Cairns introduced depth-electrode insertions technique. Talairach established techniques for the stereotactic implantation of intracranial electrodes (Lüders, 2008, Magiorkinis et al., 2014). Falconer, at the Maudsley Hospital in London, standardized temporal en bloc excisions and started epilepsy surgery in the paediatric population (Magiorkinis et al., 2014).

Currently, epilepsy surgery is a safe technique used worldwide. It plays an important role in the management of drug resistant epilepsy. Additionally, invasive assessment and intracranial electrode implantation has an important function in epilepsy surgery for clinical and research purposes. New advances in digital EEG recording, neuroimaging and intracranial recordings, have generated

new avenues allowing the study of the brain and the pathophysiology of epilepsy.

3 Drug resistant epilepsy

Commonly, epilepsy syndromes are treated with antiepileptic drugs (AEDs), which are chosen according to the syndrome type. Treatment with AEDs is individualized in each patient. The goal of the treatment is to achieve seizure control or seizure remission by using the smallest AEDs dosage possible; therefore minimising drug related side effects (Kwan et al., 2010).

Unfortunately, neither seizure remission nor seizure control is always possible and the reasons for therapeutic failure remain unknown (Remy and Beck, 2006). The International League Against Epilepsy proposed and standardized and unified definition for this condition, which is called drug resistant epilepsy (Kwan et al., 2010). To be diagnosed as having drug resistant epilepsy, patients must have failed adequate trials of two antiepileptic drug regimens, correctly chosen, used and well tolerated, whether as single or combination therapies (Kwan et al., 2010). Drug resistant epilepsy patients have their seizures under poor control, and they are more susceptible to serious injuries, poor quality of life and sudden death (Nashef et al., 2007, Tellez-Zenteno et al., 2014).

4 Presurgical assessment

Presurgical assessment aims at identifying the brain region where seizures arise and the volume of tissue that is involved in generating them. Prior to surgery all candidates are exhaustively assessed in order to:

- 1) Ratify that the patient indeed has epileptic seizures.
- 2) Decide if the severity of epilepsy deserves surgery.
- 3) Decide the type of surgical procedure: resection of a lesion (lesionectomy), wider resection, multiple subpial transection, callosotomy, hemispherectomy, hemispherotomy, vagus nerve stimulation, and deep brain stimulation.
- 5) Classify the possible risks of surgery: particularly the function of the area that the surgeon plans to resect
- 6) Identify any contraindications for surgery.
- 7) Identify the source of the patient's seizures.

The common admission criteria for patients to enter pre-surgical assessment of epilepsy are the following:

- Consistent diagnosis of drug resistant epilepsy.
- Attacks must be incapacitating: seizures should affect patient's lifestyle, because of their frequency or nature.
- Patient should have the resources to handle the assessment: patients be must able to tolerate the procedures and also to accept surgical failure.
- Patient must not have any contraindications to neurosurgery.

Six conceptual cortical zones can been defined during presurgical assessment, 1) the symptomatogenic zone, 2) the irritative zone, 3) the seizure onset zone, 4) the epileptogenic lesion, 5) the functional deficit zone and 6) the epileptogenic zone (Rosenow and Luders, 2001, Alarcon, 2012).

4.1.1 Symptomatogenic zone

The symptomatogenic zone is defined as the cortical area which, when invaded by an ictal discharge produces symptoms. Thus, symptoms might arise from symptomatogenic zone or may be the result of spreading of electrical activity from its initial focus (Luders et al., 2006, Rosenow and Luders, 2001). It is thought that this zone is larger than the epileptogenic zone, determining the seizure symptomatology (Rosenow and Luders, 2001, Luders et al., 2006).

4.1.2 Irritative zone

The irritative zone is delineated as the cortical area that produces the characteristic interictal epileptiform discharges seen on the EEG. Invasive EEG, scalp EEG, magnetoencephalography (MEG), and functional magnetic resonance (fMRI) are used to identify the irritative zone (Luders et al., 2006, Rosenow and Luders, 2001). It has been postulated that clinical symptoms are manifested if the irritative zone is comprised within functional cortex (Rosenow and Luders, 2001).

4.1.3 Seizure onset zone

The seizure onset zone is defined as the cortical area where a seizure is initiated (Rosenow and Luders, 2001). Scalp and invasive EEG can localize this zone. Scalp EEG has low sensitivity to detect seizure onset, as the electrodes are placed at a distance from the cortex. Intracranial electrodes have excellent sensitivity but restricted to a limited region of the cortex (Luders et al., 2006). When described the seizure onset zone, it is assumed that by localizing the seizure onset would by sufficient to determine the epileptogenic zone. Unfortunately, the later statement it is not always certain. There is evidence that the epileptogenic zone can be more widespread than the seizure onset zone (Luders et al., 2006). Consequently, resection of the seizure onset zone does not necessarily result in seizure freedom. To date there is not a unified method that enables identification of the seizure onset zone.

4.1.4 Epileptogenic lesion

The epileptogenic lesion is any structural abnormality, which is detectable by neuroimaging techniques and is attributed to be the location of seizure origin. Video scalp EEG and Magnetic Resonance Imaging (MRI) are able to aid with the identification of this zone, since not every lesion identified in patients with epilepsy is epileptogenic (Luders et al., 2006). The most common abnormalities seen in epileptic patients with MRI are traumatic scars, hippocampal sclerosis, vascular tumours, and cortical development malformations (Cascino and Jack, 1996).

4.1.5 Functional deficit zone

This zone includes those areas with an abnormal performance during the interictal state which lead to disruption of normal synapse network (Luders et al., 2006). The most effective procedures used to identify this zone are a detailed physical examination with neuropsychological assessment, neuroimaging techniques such as PET and SPECT (Luders et al., 2006).

4.1.6 The epileptogenic zone

The epileptogenic zone is the minimal area of cortex whose resection is necessary and sufficient to render seizure freedom (Luders et al., 2006). The epileptogenic zone should include the seizure onset zone. Presently, there is not a single standard method to define the epileptogenic zone before surgery. Consequently, the presence of this zone must be assumed by inferring the presence of the other zones mentioned above (Luders et al., 2006).

To investigate and delineate the above cortical zones, two types of methods are used: non-invasive and invasive (Alarcon, 2012).

4.1.7 Non-invasive presurgical assessment

Non-invasive assessment includes different procedures, which are performed in stages starting with the least invasive. The methods used include clinical history, physical examination, scalp EEG, scalp video EEG, neuroimaging and neuropsychology (Alarcon, 2012, Rosenow and Luders, 2001).

4.1.7.1 Electroencephalogram (EEG)

The EEG is a clinical and research method, which allows recording of time variations in electrical activity from the brain. The EEG represents the compound electrical field generated by neuronal function. EEG recordings mainly represent postsynaptic potentials in the cerebral cortex. Usually, EEG recordings in clinical practice are largely obtained with electrodes placed on the scalp, the so called "scalp EEG". It has been postulated that the scalp EEG mainly records activity from the cortical gyri, as the cortex in gyri is closer to the scalp than cortex in sulci. In patients undergoing presurgical assessment of epilepsy, intracranial electrodes can be implanted inside the skull. Electrical activity from deep brain structures, such as basal ganglia, hippocampus, and amygdala, is hardly detectable on the scalp because electrical fields rapidly attenuate with distance (Alarcon et al., 1994). Recordings with scalp EEG can be obtained during preictal, ictal and post ictal period.

4.1.8 Ictal scalp EEG

EEG recorded during a seizure is called "ictal EEG". The ictal scalp EEG shows different patterns such as: a) flattening of the EEG, b) low amplitude fast activity (10–20Hz), c) rhythmic sharp waves or spikes, or slowing in the delta or theta ranges (Alarcon et al., 2001a, Pelliccia et al., 2013). Ictal EEG changes are less commonly seen during frontal seizures. Additionally, ictal changes can be absent during focal seizures, particularly during simple partial seizures.

Ictal patterns seen on scalp EEG can be unilateral or bilateral (Alarcon et al., 2001a). Unilateral focal patterns have a 95% lateralizing value (Alarcon et al., 2001a). Bilateral scalp EEG patterns are very common (70 %) in focal temporal lobe seizures, and consequently a bilateral seizure onset pattern on the scalp should not discourage surgery, since EEG patterns may be seen on the scalp only after bilateral propagation has occurred (Alarcon et al., 2001a). Intracranial recordings may be necessary to demonstrate a focal onset. Analysis of delayed rhythmic ictal EEG has been associated with predictive value of up to 79% for determining the side (laterality) of the seizure zone (Alarcon, 2012). Video telemetry is necessary to consistently obtain recordings during seizures, as seizures are not usually seen during standard EEG recordings.

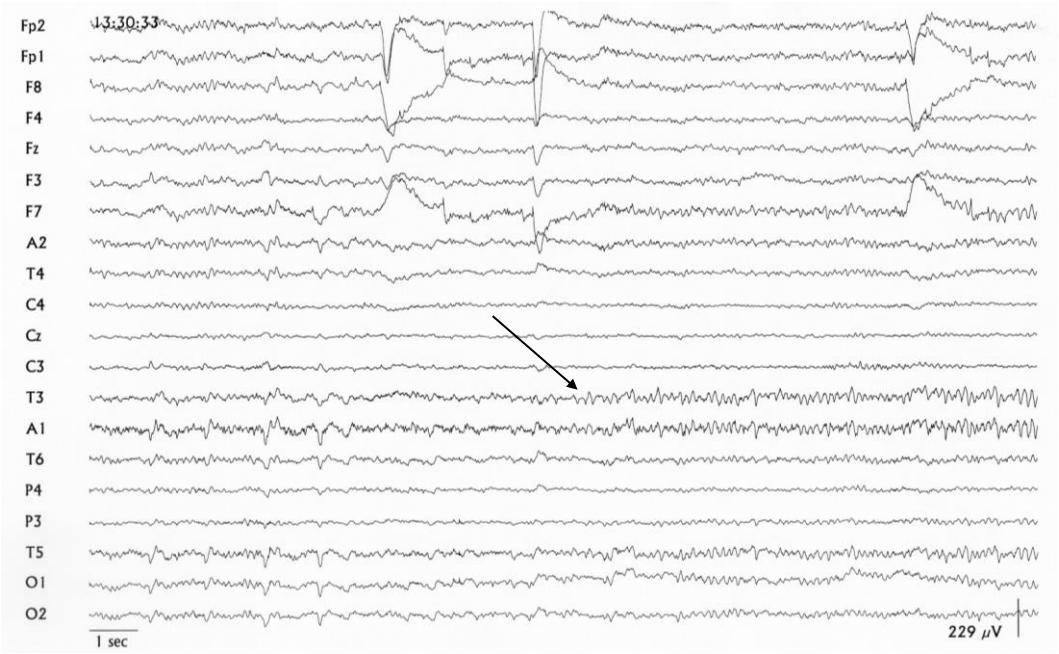

Figure 1. Focal seizure onset observed on scalp EEG recordings. Note a diffuse flattening of the EEG (electrodecremental event) followed by onset of fast activity showing largest amplitude at the left mid-temporal (A1) and Sylvian (T3) regions (arrow).

4.1.9 Neuroimaging

Neuroimaging methods have also enabled the identification of brain abnormalities and these may also assist in locating and lateralizing the epileptogenic zone. It has been suggested that MRI could detect abnormalities in around 80-90% of temporal epilepsy and 20 to 40% of extra temporal epilepsies (Duncan, 2010, Rosenow and Luders, 2001). Single-photon emission computed tomography (SPECT) and Positron Emission Tomography (PET) have began to be used routinely during recent years. PET measures brain glucose metabolism and the epileptogenic zone is seen as a hypometabolic region on the image. SPECT measures cerebral blood flow and exhibits an area of hyperperfusion within the epileptogenic zone (Cascino and Jack, 1996).

4.1.10 Invasive presurgical assessment

The invasive assessment is indicated when non-invasive procedures cannot identify accurately the site in the cortex where seizures arise from or when findings are inconsistent. As many as 25% of assessed patients will require invasive approach, which includes the use for intracranial electrodes of identifying the epileptogenic zone and carry out functional mapping (Alarcon et al., 2006, Alarcon, 2012). Once implanted, intracranial electrodes allow direct EEG recording from the potential epileptic zone.

4.1.11 Intracranial electrodes

The main types of intracranial electrodes are depth, subdural, foramen ovale and epidural electrodes (Alarcon, 2012). Intracranial EEG is the gold standard in the

evaluation of patients when non-invasive techniques are inconclusive. Intracranial EEG recordings show 3 to 5 times greater amplitude than the scalp EEG recordings. Moreover, since intracranial EEG electrodes are implanted inside the skull, recordings are free of muscle artefacts (Yuan et al., 2012, Alarcon, 2012).

The general indication for the use of intracranial electrodes is in those epilepsies where a response to resection is likely and there is ambiguous localization of the epileptogenic zone by non-invasive assessment modalities (Yuan et al., 2012, Alarcon, 2012, Rosenow and Luders, 2001). Therefore, the main purpose of the intracranial electrode implantation is to record neuronal electrical activity from brain structures that are not accessible to the surface scalp EEG. Protocols for the implantation of intracranial electrodes vary across centres (Alarcon, 2012). At King's College Hospital, intracranial electrodes are also useD to identify the epileptogenic zone by stimulating specific regions of the cortex, to identify the topography and extent of hyperexcitable areas, which might be potentially epileptogenic (Valentin et al., 2002, Flanagan et al., 2009, Valentin et al., 2005).

4.1.12 Subdural Electrodes

Subdural electrodes are assembled as strips or mats (Alarcon, 2012, Nair et al., 2008a). Electrodes are informally called "contacts". They are embedded in Silastic or Teflon (Alarcon, 2012). Strips are orientated as linear contacts, typically formed of 4 to 8 contacts. Mats are orientated as a rectangle and can contain up to 64 contacts (Lesser et al., 2010, Nair et al., 2008a, Alarcon, 2012). In both types of electrodes, each contact has a diameter of 5mm and are

separated 1cm of each one (Alarcon, 2012). Strips can be implanted via a burr hole in the skull whereas mats are placed under the dura through a craniotomy (Alarcon, 2012, Lesser et al., 2010, Nair et al., 2008a).

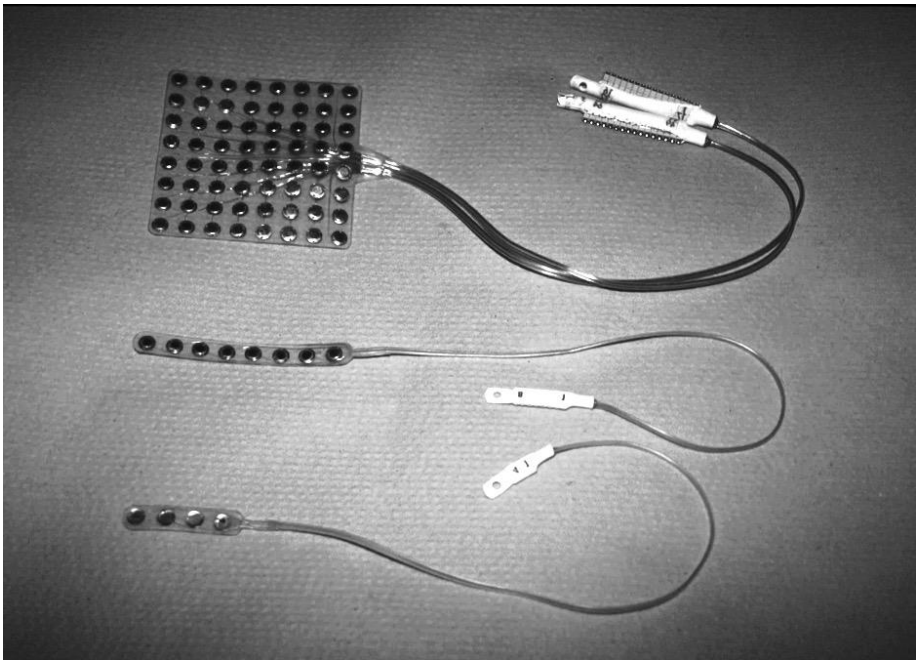

Figure 2. Subdural strips and mat (grid) electrodes.

Subdural strips are used to define the extent of the epileptogenic zone and its relationship to functional cortex prior to surgery delineation (Nair et al., 2008a). Benefits of subdural strips include ease of implantation, coverage of greater cortical areas including the parahippocampal gyrus (Nair et al., 2008a, Lesser et al., 2010, Alarcon, 2012). The most frequent complications are subdural and epidural bleeding which in a few cases can lead brain compression (Wellmer et al., 2012). Moreover, cerebrospinal fluid leakage can be induced by chronic implantation (Alarcon, 2012).

A mat is commonly used to record seizure onset, especially on the convexity of the hemispheres, and also for functional mapping (Alarcon, 2012). Postoperative MRI or X-ray can confirm its precise location (Alarcon, 2012). Risk of complications increase with the size and number of the implanted electrodes, as well as the implanted duration. The most frequent complication after implantation of these electrodes is infection, that can be reduced with the use of prophylactic antibiotics, removing the connecting cables through an incision distant from the main incision, and minimizing the duration of implantation (Yuan et al., 2012).

4.1.13 Intracerebral electrodes

The main purpose of the intracranial electrode implantation in epilepsy is to record neuronal electrical activity from brain structures that are not accessible to the surface scalp EEG. Protocols for implantation of intracranial electrodes are different in every epilepsy centre. At King's College Hospital, intracranial electrode implantation mainly involves both subdural electrodes and stereoelectroencephalography (SEEG). Once the patient recovers from electrode implantation, standard video telemetry is carried out with the intracranial electrodes to record the EEG until sufficient number of seizures occur. At King's College Hospital, intracranial electrodes are used to identify the epileptogenic zone by recording ictal and interictal activity and by stimulating the cortex with single electrical pulses in order to identify the topography and extent of hyperexcitable areas, which might be potentially epileptogenic. The latter

technique has been coined single pulse electrical stimulation (SPES) (Valentin et al., 2002, Flanagan et al., 2009, Valentin et al., 2005).

In this section, I will cover the characteristics, methodology and complications of the intracranial electrodes used for EEG recordings and data analysis in the present thesis.

4.1.14 Indications for implantation of intracranial electrodes

Intracranial electrodes are indicated in patients where resection is a likely therapeutic option but there is unclear localization of the epileptogenic zone by non-invasive assessment modalities (Yuan et al., 2012, Alarcon, 2012, Rosenow and Luders, 2001). The following two resections can be performed without studies with intracranial electrodes:

A) Lesionectomy, this procedure can be performed in those patients with a discrete cerebral non-atrophic lesion, which must be demonstrated by neuroimaging and is located in a non-functionally eloquent site. This location should be concordant with seizure semiology, with the topography of interictal discharges seen on scalp EEG, the topography of ictal onset on the scalp EEG if present, the distribution of background abnormalities in the interictal EEG, and with neuropsychological findings.

B) Temporal lobectomy, this technique could be carried out in those patients with a steady, single and temporal seizure onset on scalp EEG telemetry. This pattern should match seizure semiology, the distribution of background

abnormalities in the interictal scalp EEG, and neuroimaging and neuropsychological findings.

All patients in whom these criteria are not fulfilled can be considered for assessment with intracranial electrodes. These are patients with non-convergence of evidence from different techniques. The choice and placement of intracranial electrodes depends on the presumed site of seizure onset. As intracerebral (depth) electrodes are perceived to be more invasive that subdural recordings (Spencer, 1989), the latter are generally preferred when possible. When temporal lobe seizures are suspected, but laterality is uncertain, recordings with bilateral 8-contact subtemporal strips inserted through fronto-temporal burr holes can be carried out (Spencer, 1989). In patients with bitemporal pathology or in those where assessment with subtemporal strips is unsuccessful, recordings with bitemporal depth electrodes is recommended. When seizures are thought to arise from the frontal lobes, but laterality is uncertain, bilateral intracerebral electrodes can be used. When the seizures are thought to arise from the cerebral convexity, from peri-central regions or from the supplementary motor area, mats or strips can be used, usually implanted unilaterally.

4.1.15 Types of intracranial electrodes

The use of intracranial electrodes in epilepsy dates back to the late 30s, when Penfiled performed trephination over both temporal regions and placed electrodes on the dura for lateralizing the source of seizures in a patient with presumed bitemporal epilepsy (Almeida et al., 2005). Although, Penfield and

collaborators studied several patients with intracranial electrodes, their use did not become part of routine care until mid-1970s. In those days, electrodes were mainly designed and elaborated in the clinical institutions. Since then, several types of electrodes have been developed, and presently their elaboration and design has been taken over by industry manufactures. Following electrode implantation, video telemetry recordings are generally performed in a video-monitoring unit. After electrodes insertion, patients are allowed to recover for a period of around 24 h and then are transferred to the video-monitoring unit. Intracranial electrodes are useful for recording interictal and ictal activity and allow the study seizure onset and propagation patterns.

4.1.16 Foramen ovale electrodes

Foramen ovale electrodes are multicontact electrode bundles that can be inserted through the foramen ovale under fluoroscopic control and under general anaesthesia. The deepest contacts lay close to medial temporal structures (Fernandez Torre et al., 1999, Alarcon et al., 2001b, Kissani et al., 2001). Removal does not require general anaesthesia. Because no craniotomy or burr holes are required for their implantation, they are often considered less invasive than subdural or depth electrodes.

4.1.17 Subdural electrodes

Electrodes are placed directly on the cortical surface of the brain. These electrodes have larger resolution than scalp electrodes, have less muscle

artefacts and provide an opportunity for functional mapping and for the use of electrical stimulation to map epileptogenic tissue.

The main advantages of using subdural electrodes when compared to scalp electrodes is that subdural are closer to the source of electrical activity and there are no interposed brain coverings. Consequently, EEG signals is are recorded with higher amplitude (Alarcon et al., 1994).

Numerous materials have been used to elaborate the subdural electrodes, including platinum and silver. Subdural electrodes can be elaborated as groups of electrodes arranged in either mats (grids) or strips. A considerable number of improvements have been achieved over the past decades, such as biocompability, biostability, adequate flexibility and insolubility (Lesser et al., 2010, Nair et al., 2008b). Commonly, each electrode within a mat or strip is called a contact. Mats are arrays of contacts. Strips are single rows of contacts. At our centre, most subdural electrodes are embedded in SilasticR or TeflonR sheets. Each contact typically has 5 mm diameter and contact centres are located 1 cm away. Mats need to be introduced through a craniotomy, and can be placed under the dura over the cerebral convexity, or carefully slipped (at some risk of venous bleeding) between brain and dura. Mats are suitable for functional mapping with electrical stimulation or with evoked responses to sensory stimulation.

Strips came in single rows, typically with 4 or 8 contacts, and several can be inserted through a burr hole. If inserted through a burr hole anterior to the ear,

an 8 contact strip can be slipped under the temporal lobe and provide excellent recording from the parahippocampal gyrus. Used in this way, they can serve similar purpose to foramen ovale electrodes. General anaesthesia is required for insertion and removal. Strips can be combined with mats to cover the cerebral convexity and, if inserted parasagittally, the medial aspect of the cerebral hemispheres.

The main complications are infection and cerebral haemorrhage. Less than 2% risk of permanent neurological deficits have been reported (Kumar et al., 2013). Transitory deficits and complications are more common, present in up to 5% of patients. Transmission of Creutzfeldt-Jakob disease has been reported but can be avoided by disposing of used electrodes. Chronic implantation of mats can be associated with leakage of cerebrospinal fluid, which can be improved by keeping the head high and changing the head bandage regularly. Mat recordings appear to have a 0.85% risk of infection, which can be reduced by prophylactic antibiotics, minimising the duration of implantation and passing the cables through the scalp at a point far from the craniotomy.

4.1.18 Depth Electrodes

The stereo-encephalography (SEEG) method was created by Jean Talairach and Jean Bancaud during the 1950s in France. This technique has been mostly used in France and Italy for invasive localization in drug resistant focal epilepsy. Depth electrodes are often implanted via a stereotactic frame (therefore the term stereotactic EEG or SEEG). Electrodes penetrate into the brain and continue further to deep structures.

These electrodes are able to record from deep structures such as the hippocampus, and orbital and medial frontal cortices where subdural electrodes may provide less appropriate cover. Depth electrodes can also be used to record activity from the neocortex, but their spacial sampling frequency is lower and less regular than that of subdural mats. In our centre, these electrodes have been used to record from single unit cells, in order to study neuronal behaviour during interictal activity and SPES responses (Alarcon et al., 2012a).

Since its first development, back on the 50s, depth electrodes have evolved significantly. When first described, these electrodes were rigid, whereas current electrodes are flexible. Usually they come attached to a semi-rigid stylet giving them rigidity for avoiding errant placement. Commonly, depth electrodes are implanted through a guide cannula to further improve the accuracy of implantation. They are multicontact electrode bundles that can be stereotactically inserted through the brain under neuroimaging control. The most common material used for the contacts design is platinum, though stainless steel, nickel-chromium and gold have all been used.

When the temporal lobe is assessed, depth electrodes can be implanted either longitudinally or orthogonally. Longitudinal electrodes are implanted posteriorly to anteriorly, starting from a paramedian occipital start point and traversing the long axis of the hippocampus. When implanted orthogonally, depth electrodes are inserted perpendicularly to the cortical surface via the middle or inferior

temporal gyrus into the mesial structures. Either of these techniques can be combined with subdural strip or grid electrodes.

Currently, there are several viable techniques for implanting depth electrodes such as, framed stereotaxis, freehand passage, endoscopically assisted and frameless neuronavigation. Framed stereotaxis is the standard technique in our centre. Implantation are performed under general anaesthesia.

The main complications are infection and cerebral haemorrhage. The likelihood of complications from intracranial recordings is roughly proportional to the number of electrodes implanted. Frank meningitis or encephalitis are rare. Depth electrodes have a very low risk of infection, a 1.9% risk of haemorrhage with transitory deficits and a 0.8% risk of haemorrhage with permanent deficits (Kumar et al., 2013).

4.1.19 Interpretation of intracranial electrodes

Epileptiform discharges recorded interictally with intracranial electrodes are larger, sharper and occur more frequently than those seen on the scalp. Each patient usually exhibits several patterns of epileptiform discharges occurring independently at different sites, often including the hemisphere opposite to seizure onset. For this reason, interictal activity recorded with intracranial electrodes should be interpreted cautiously. Ictal changes can consist on flattening of the on-going EEG (electrodecremental event), low amplitude fast activity (10-30 Hz), rhythmic sharp waves or spikes, or slowing in the delta or

theta ranges. Generalised electrodecremental events (diffuse flattening of the EEG) are common at seizure onset and it has been suggested that they should not discourage surgery, since they do not seem to be associated with worse outcome (Alarcon et al., 1995). However, changes occurring diffusely at seizure onset would suggest that the seizure is generalised or, more commonly, electrodes are not placed at the site that originate seizures. Therefore, one of the objectives of this thesis is to investigate if widespread changes at seizure onset in focal epilepsy are associated in poor surgical outcome.

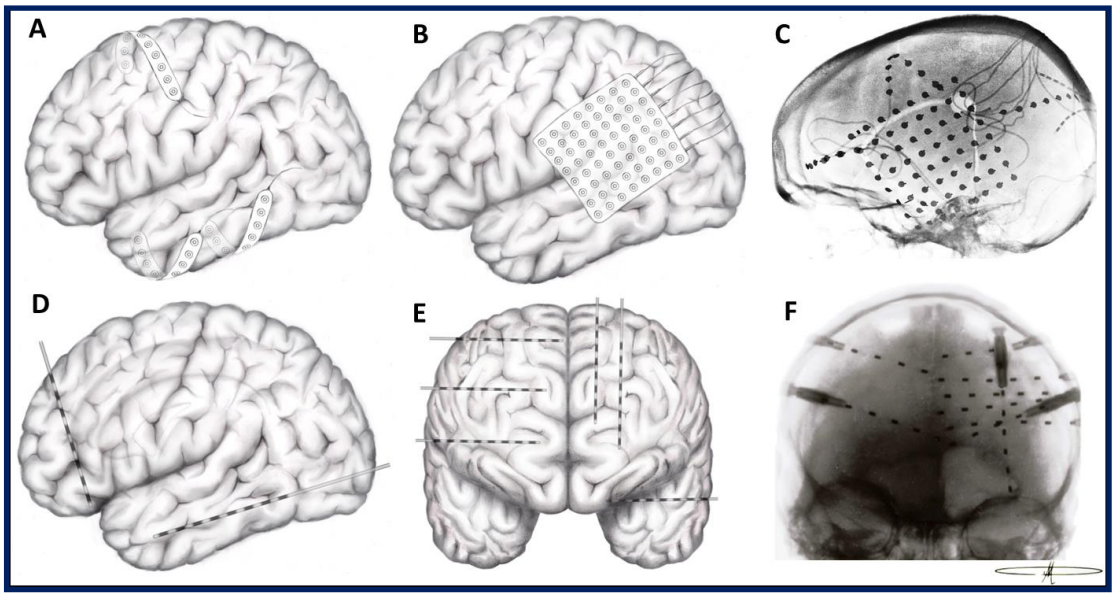

Figure 3. Different types and positions of intracranial electrodes. A) Drawing of a lateral brain view of 9-contacts subdural electrodes in subtemporal and frontal structures. B) Drawing of a lateral view of a 64-contact mat over the parieto-posterior temporal region. C) Lateral X-ray from a patient with a 64-contact mat and four 8-contact subdural electrodes. D) Drawing of a lateral view with depth electrodes over orbito-frontal, and one electrode at the hippocampus with a posterior entry. E) Drawing of an anterior posterior view with depth electrodes over frontal and temporal structures. F) Anterior posterior X-ray from a patient with frontal and orbito-frontal depth electrodes. Figure kindly provided by Dr David Martín-López, King's College London.

5 Electrical cortical stimulation during presurgical assessment

The use of intracranial electrodes provides a unique opportunity to directly measure cortical excitability with electrical stimulation, which can provide an indication of cortical epiletogenicity.

5.1.1 Cortical responses to electrical stimulation

The morphology of the evoked responses after cortical stimulation was first described in animals by Adrian back in 1936 (Adrian, 1936). He documented the presence of low amplitude superficially-generated and high amplitude deeply-generated responses originated in the body of pyramidal cells within the area of stimulation and neighbouring electrodes. These responses showed variable morphology attributed to intra-neuronal gradient shifts and slower time variations in cortical neurons. Nowadays most authors recognise the existence of at least three types of responses: N1, P1 and N2. N1 and N2 responses can be recorded simultaneously and independently after single pulse electrical stimulation (SPES). This fact was already observed by other authors (Matsumoto et al., 2007, Matsumoto et al., 2004, Enatsu et al., 2012, Matsumoto et al., 2012) who suggested a different generation mechanism for different deflections. Anodal stimulus delivered to the cortical surface directly induces depolarisation of the initial segment of the first axonal node of pyramidal neurons while cathodal stimulus indirectly activates them by activating chains of interneurons (Amassian et al., 1990). Cortical electrical stimulation is able to generate both types of responses by means of direct cortico-cortical and indirect subcortical pathways (Matsumoto et al., 2004). Direct monosynaptic-mediated responses

are masked by current injection artefact (Matsumoto et al., 2004, Enatsu et al., 2013, Keller et al., 2014), which usually lasts for 5-10 ms. Therefore, an oligosynaptic or polysynaptic mechanism mediated by small subcortical fibres and recurrent pyramidal axon collaterals has been proposed for the generation of N1 and N2 components (Keller et al., 2014, Barth et al., 1989). Simultaneously with N1 and P1 responses, multi-unit activity recordings in IV-VI cortical layers have suggested an increase in pyramidal activation and an excitatory response has been observed in single neuron studies within N1 time frames (Barth et al., 1989, Sutherling et al., 1988). Consistently with these findings, our group also evidenced the presence of bursts of high frequency firing action potentials during first 100 ms after SPES (Alarcon et al., 2012a). Conversely, the generation of N2 responses seems to be different and independent to N1 responses. N2 have shown larger distribution than N1 (Matsumoto et al., 2004). During N2 there is a decrease in multi-unit activity and a long-lasting inhibitory period with suppression of action potential firing (Barth et al., 1989). Interestingly, N2 responses show similar features to K-complexes in terms of multi-unit findings (Matsumoto et al., 2004) which is also consistent with our group findings regarding the similarity between spontaneous K-complexes and reponses to SPES after stimulation at the cingulate gyrus (Voysey et al., 2015). The observed blunted morphology of peaks in responses to SPES is thought to be related to the influence of orthodromic and antidromic excitation due to the profuse arborisation of the pre-synaptic terminals causing a variable jitter of <20ms in the pyramidal neuronal firing (Matsumoto et al., 2007, Keller et al., 2014). Variations in stimulus intensities lead to significant changes in evoked responses

amplitude (Adrian, 1936, Enatsu et al., 2012, Iwasaki et al., 2010, Stephani and Koubeissi, 2015) and morphology (Wilson et al., 1990).

5.1.2 Single Pulse Electrical Stimulation

Single pulse electrical stimulation (SPES) has become an alternative method for localizing epileptogenic cortex during interictal period (Valentin et al., 2002, Valentin et al., 2005, Flanagan et al., 2009). SPES consists in applying a brief (1 ms) electrical stimulus through electrodes during intracranial recordings. Two main types of responses to SPES have been described: 1) Early responses, which are thought to be normal cortical responses to stimulus, consisting of one or more sharp and slow transients, usually starting immediately after the stimulus. 2) Delayed responses, which are thought to be abnormal responses. Delayed responses, resemble spikes commencing more than 100 ms after the stimulus, usually seen at the areas which originate seizure onset. Delayed responses often resemble in morphology and topography the patient's spontaneous interictal discharges (Nayak et al., 2014).

An important finding is that delayed responses to SPES are mainly seen at seizure onset areas. Valentin and colleagues studied 40 consecutive operated patients with a follow-up period of at least 12 months (Valentin et al., 2005). They found that good surgical outcome was significantly better when resected areas responsible for late responses. In fact, when delayed responses to SPES were exclusively located in resected regions, 96% of the patients had a favourable outcome, and none of the 3 patients who had late responses to SPES

exclusively outside the resected region had a good outcome. Another important finding is that among the 29 patients who had delayed responses to SPES, 26 had pathological abnormalities in the areas responsible for late responses, even though 9 had normal MRI. Thus, SPES appears to be able to identify epileptogenicity in the interictal period, independently of seizure onset (Valentin et al., 2005).

SPES has offered the possibility to understand new insights into the pathophysiology of human focal epilepsies (Valentin et al., 2005, Valentin et al., 2002, Flanagan et al., 2009). Additionally, SPES has been widely used in neuroscience research studying topics such as, memory process, sleep phenomena and cortical functional connectivity (Lacruz et al., 2007, Lacruz et al., 2010a, Voysey et al., 2015).

Currently, single pulse electrical stimulation is part of routine presurgical assessment at King's College Hospital. SPES has demonstrated to be a reliable technique for identifying the epileptogenic zone, as evidenced by the close relationship between the topography of areas responsible for delayed responses location of seizure onset, surgical outcome and pathology.

6 Epilepsy syndromes suitable for surgery

Only certain syndromes are considered to be surgically treatable, by resective surgery:

a) Temporal lobe epilepsy, including mesial temporal lobe epilepsy, and any tumours and congenital malformations.

b) Extra-temporal epilepsies, that have resectable structural lesions including tumours or congenital malformations, catastrophic infantile seizures containing pathologies such as hemimegalencephaly, diffuse cortical dysplasias (Alarcon, 2009a).

6.1.1 Temporal lobe and mesial temporal lobe epilepsy syndromes

6.1.2 Anatomy of Temporal Lobe

The temporal lobes are situated below the Sylvian fissure of the cerebral hemisphere. Temporal cortex includes areas that are part of audition, olfaction, and vision. Additionally, the temporal cortex is involved in perception of both spoken and written language. The temporal lobes are divided into lateral, medial, superior and inferior surfaces (Kucukyuruk et al., 2012).

6.1.3 Medial temporal lobe structures

There are three main structures that form the medial temporal lobe. These are the hippocampal formation, amygdala and parahippocampal cortices (Van Hoesen, 1995).

The hippocampus consists of two parts: a) hippocampus proper and b) gyrus dentatus (Hayman et al., 1998). The hippocampus is an important structure involved in the formation and recall of episodic memories. It is also implicated in mesial temporal lobe epilepsy (MTLE), which shows characteristic hippocampal

atrophy. The hippocampus proper consists of cornu ammonis areas 1 to 4 (CA1 - CA4). It has 6 layers of cells, which are the stratum pyramidalae, stratum radiatum, stratum luconosum, stratum moleculare, stratum oriens and the alveus (Takano and Coulter, 2012). The alveus and stratum lacunosum contain efferent fibres whereas the rest of the 4 layers consist of pyramidal neurons, dendrites and collateral axons (Tien et al., 1992). The hippocampus formation composes the structure and consists of the dentate gyrus, subiculum, entorhinal cortex and pre and para subiculum (Wright, 1997). It is involved in memory formation, spatial navigation and attention (Hayman et al., 1998, Kiernan, 2012).

The amygdala lies anterior to the head of the hippocampus and contains several nuclei (Hayman et al., 1998, Kiernan, 2012). It is associated with mediating emotional responses, most notably fear. Electrical stimulation of the amygdala in pre surgical patients with temporal lobe epilepsy leads to a sensation of déjà vu, suggesting that the amygdala in addition to the hippocampus is involved in memory function (Lacruz et al., 2010a, Kiernan, 2012). The parahippocampal cortices lie below the medial temporal lobe structures and cover them superficially (Van Hoesen, 1995).

6.1.4 Hippocampal circuitry and properties of pathways

The hippocampus possesses a trisynaptic unilateral circuit, (Stafstrom, 2005). Signals flow through the hippocampal circuit forming a loop. The main input source is also the output target (Hayman et al., 1998). The hippocampus receives the majority of its input from layers 1 and 2 of the entorhinal cortex, and sends its output to layer 5 and the subiculum (Buzsáki, 2006). Incoming signals are

transmitted via the perforant pathway to the dendrites of the granular cells in the dentate gyrus. Perforant fibres that arise in the lateral aspect of the entorhinal cortex project to the superficial layers of the dentate gyrus (Hayman et al., 1998). Fibres arising from the medial aspect project to the deeper aspect of the dentate gyrus (Hayman et al., 1998).

The axons of the dentate gyrus form the mossy fibre pathway which relays to pyramidal neurons in the CA3 area of the hippocampus proper (Stafstrom, 2005). Other projections include the hilus of the dentate gyrus and stratum lucidum (Amaral et al., 2007). Thereon, CA3 axons synapse onto pyramidal neurons in the stratum radiatum of the CA1 region via the Schaffer collateral pathway (Amaral et al., 2007). Subsequently, output from CA1 is directed back to layer of the entorhinal cortex and subiculum (Stafstrom, 2005). Additionally CA1 and CA3 axons exit the hippocampus via the fornix and anterior commissure to the thalamus, mammilary bodies of the hypothalamus and frontal cortex to the dentate gyrus, therefore, forming another circuit (Amaral et al., 2007).

6.1.5 Properties of pathways in the hippocampus

The perforant pathway which arises in the entorhinal cortex consists of two types, lateral and medial perforant pathways depending on their site of origin within the entorhinal cortex (Johnston and Amaral, 2004). These pathways produce gluatamatergic excitatory post synaptic potentials (EPSP) (Johnston and Amaral, 2004). Furthermore, the mossy fibre pathway between the dentate gyrus and CA3 forms the largest synapses in the mammalian central nervous system (Johnston and Amaral, 2004). These too produce gluatamatergic EPSPs in

target CA1 neurons (Johnston and Amaral, 2004). The Schaffer collateral pathway consists of axons from both the ipsilateral and contralateral hippocampus, with the latter called commissural fibres (Johnston and Amaral, 2004).

Electrical stimulation increases excitation in CA1 as some CA1 axons synapse back onto CA1 neurons (Johnston and Amaral, 2004). Recurrent pathways in the hippocampus arise from recurrent excitatory connections amongst CA3 pyramidal neurons (Johnston and Amaral, 2004). Recurrent excitation leads to a positive feedback loop, which is what makes CA3 neurons inherently unstable (Johnston and Amaral, 2004). This may explain the high sensibility of the hippocampus to become epileptogenic. In addition, recurrent pathways are thought to increase overall excitability in relation to inhibition thereby resulting in excessive hypersynchronous firing as in epileptiform activity (Johnston and Amaral, 2004). Epileptiform activity can then spread to its neighbouring CA1 region (Johnston and Amaral, 2004).

6.1.6 Temporal Lobe Epilepsy: definition

Temporal Lobe Epilepsy (TLE) is a group of varied disorders sharing the same anatomical origin for seizure onset (Alarcon, 2009b). It accounts for approximately 40% of all epilepsies (de Moura et al., 2012). The ILAE divides TLE into two main categories:

1) Mesial temporal lobe epilepsy (MTLE) when the seizures arise from structures located within the deep temporal lobe structures such as the

hippocampus, amygdala and parahippocampal gyrus. MTLE with seizures arising from the hippocampus account for nearly 80% of all temporal lobe seizures (Tatum, 2011). Hippocampal sclerosis is the most common cause of MTLE (Tatum, 2011).

2) Lateral temporal lobe epilepsy (LTLE), where seizures start in the lateral neocortex.

6.1.7 Temporal Lobe Epilepsy Semiology

Seizures that originate in the temporal lobe are classified as focal and secondary generalized seizures (Fisher et al., 2005). Focal seizures are denoted by preservation of consciousness. In TLE, these types of auras occur in about 50 – 70 % of TLE patients (Tatum, 2011). Nevertheless, epigastric sensation is the most commonly mentioned aura by patients (Tatum, 2011). Secondary generalized seizures are denoted by loss of consciousness either at the onset of the seizure or through its evolution.

6.1.8 Mesial Temporal Lobe Epilepsy Characteristics

Of all temporal lobe epilepsies, MTLE is the most frequent accounting for 75% of all cases (Tatum, 2011). The most frequent pathologic substrate of mesial temporal lobe epilepsy is hippocampal sclerosis which, accounts for approximately 60 - 65% of all causes of DRE (Panayiotopoulos, 2005). MTLE with hippocampal sclerosis (mTLE - HS) has been classified as a distinct clinical syndrome, as it has its own clinical features and pathology (Marusic et al., 2007). Some sources of MTLE include viral infections, cerebrovascular disease, cortical malformations tumours, head trauma (Panayiotopoulos, 2005). The age of onset

is dependent with the aetiology however, most typically MTLE debuts during the second or third decade (Panayiotopoulos, 2005).

6.1.9 Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis Clinical Features

History of febrile seizures is frequently associated with mTLE-HS (Panayiotopoulos, 2005). During the first 5 years of life, history of hypoxia is commonly observed and cerebral infections (Spano and Mikulis, 2011). ILAE commission (2004) concluded that there might be a genetic predisposition to mTLE based on the observation that the genetic inclination to febrile seizures may cause hippocampal sclerosis thereby precipitating mTLE (Wieser and Hane, 2004).

A latency period between the acquisition of underlying pathology and debut of clinical seizures has been reported (Panayiotopoulos, 2005). Nevertheless, this is not always the case and seizures can start soon after the initial triggering events. Seizures consist of auras that typically last for several seconds (Panayiotopoulos, 2005). Auras are characteristic of mTLE-HS and occur in as many as 90% of patients (Panayiotopoulos, 2005). Epigastric sensation is the most common aura (Panayiotopoulos, 2005), followed by ictal fear, which occurs in to 80% of patients (Panayiotopoulos, 2005). Epigastric sensation is often accompanied by other auras such as déjà vu, fear or olfactory and gustatory sensations (Panayiotopoulos, 2005). These auras are then followed by generalized seizures where the patient has a fixed gaze (staring) and motor arrest (Alarcon, 2009b). This clinical feature is commonly followed by automatism such as: oro-

alimentary automatisms, restlessness, fidgeting or lip smacking. Seizures normally last for 1- 2 minutes and frequently occur in clusters of 2-3 seizures approximately once or twice a week (Panayiotopoulos, 2005). The post ictal stage includes event specific amnesia, disorientation, and dysphasia if seizure onset occurs in the dominant hemisphere (Panayiotopoulos, 2005).

6.1.10 Mesial Temporal Lobe Epilepsy – Hippocampal Sclerosis

Electroencephalographic features

Scalp EEG in combination with neuroimaging offers information about the lateralization of epileptogenic foci (Javidan, 2012). Scalp EEG is an essential test during the pre-surgery assessment (Dworetzky and Reinsberger, 2011). EEG findings can be observed during the interictal, ictal and post ictal (Wieser and Hane, 2004) Epileptiform discharges are seen over the anterior temporal region with maximal polarity over basal (F7, F8, T1 and T2) and sphenoidal electrodes. Around 70% of patients show slow wave activity in the anterior temporal regions and unilateral/bilateral interictal spike (Williamson et al., 1993). Sphenoidal spikes are often associated with seizure focus within the hippocampus (Javidan, 2012). Interictal epileptiform discharges (IEDs) increase during sleep (Alarcon et al., 2001a). When IEDs are concordant with unilateral hippocampal sclerosis, they are associated with good outcome (Dworetzky and Reinsberger, 2011). It is important to note that unilateral scalp IEDs may lead to false lateralization. Therefore ictal recordings are required (Javidan, 2012).

The ictal EEG is characterized by rhythmic activity at the temporal electrodes or focal slowing followed by 5-9 Hz activity (Pelliccia et al., 2013). Ictal EEG is compromised with delta, theta and alpha activity (Ebner and Hoppe, 1995). In a majority of cases rhythmic alpha, theta and delta activity is seen within 30 seconds of seizure onset (Javidan, 2012). Rhythmic alpha/theta activity generates a pattern that is characterized by crescendo/sinusoidal waveforms with an increase in frequency and decrease in amplitude (Wieser and Hane, 2004). As noted above, this pattern has maximal amplitude over anterior temporal regions (Wieser and Hane, 2004).

Ictal discharges may be unilateral, contralateral or bilateral (Tezer et al., 2011). Patients with unilateral interictal epileptiform discharges and approximately more than 90% discharges from the ipsilateral lobe are associated with good post surgical outcome (Tezer et al., 2011). Ictal discharges may also be noted in the contralateral temporal lobe, this is especially observed in mTLE when the underlying pathology is not hippocampal atrophy (Tezer et al., 2011). In most cases, intracranial electrodes are also used to further define seizure focus (Javidan, 2012).

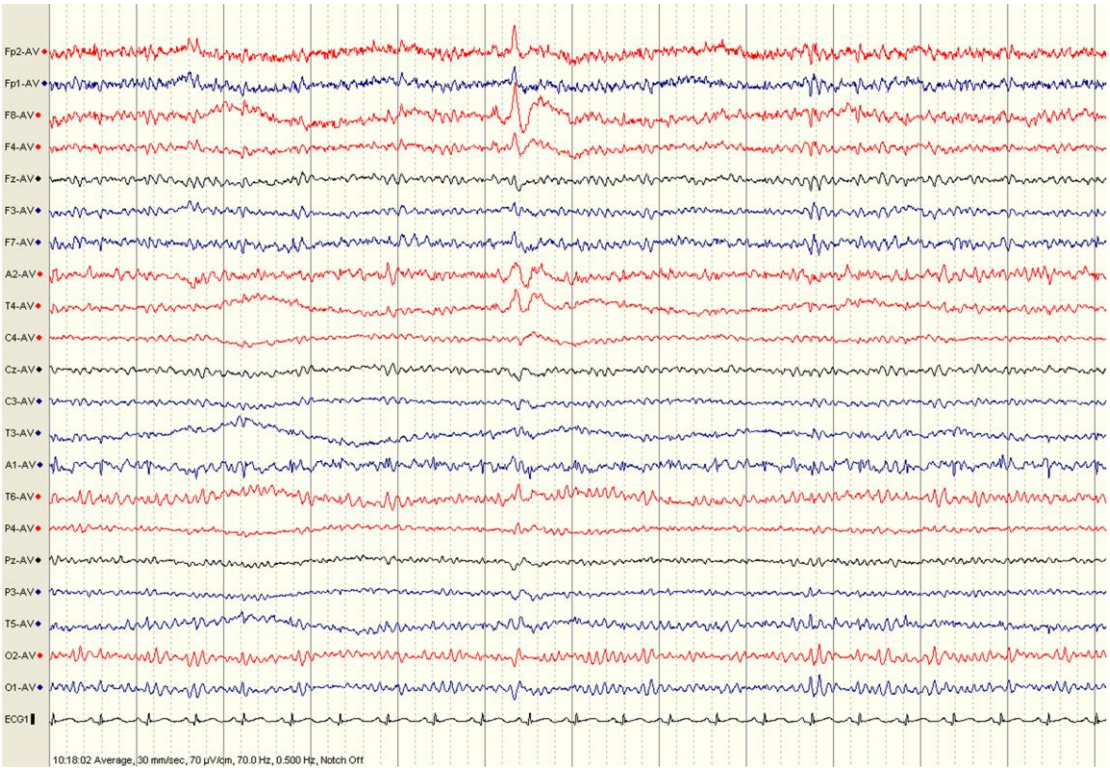

Figure 4. Scalp EEG showing right anterior temporal epileptiform discharges in a patient with mesial temporal sclerosis.

6.1.11 Extra-temporal lobe epilepsy syndromes

Roughly 20% of patients have extra-temporal epilepsy, and among this group, frontal lobe epilepsy is the most common (Zentner et al., 1996). In fact, surgical treatment in patients with extra-temporal surgery is complicated, especially if an unclear lesion is evident on structural imaging studies (Cascino, 2004). Consequently, many of these patients will require the use of additional tests, such as SPECT, PET or MEG and are potential candidates for intracranial electrode implantation (Kumar et al., 2013). It is recognised that extratemporal epilepsy has lower successful outcome rates compared to the temporal lobe epilepsy (Kutsy et al., 1999, Tellez-Zenteno and Wiebe, 2008).

6.1.12 Semiology

The semiology of extra-temporal seizures is very varied. Frontal lobe epilepsy deserves special mention because, as stated previously, it is the most common

extra-temporal focal epilepsy undergoing surgery. Thus, there are some typical clinical features within patients presenting frontal lobe epilepsy, which might help in distinguishing this epilepsy type (Alarcon, 2009b).

Patients presenting seizures from the supplementary motor cortex usually present auras, followed by unilateral tonic postures, accompanied by face muscle contractions, language disorders, sensory complex bipedal automatisms, laughter, kicking, language disorders and pelvic movements (Alarcon, 2009b). On the other hand, patients with seizures arising from the primary motor cortex present focal seizures, with tonic movements, generally followed by secondary generalization, abnormal contralateral dystonic postures, and language disturbances (Alarcon, 2009b). Seizures arising from the occipital cortex generally involve more visual components associated to simple or complex partial seizures or secondarily generalized seizures (Alarcon, 2009b). Visual symptoms are associated with occipital onset. Thus, visual components might be scotomas, hemianopsia or amaurosis, phosphenes, flashes, and sparks (Alarcon, 2009b). Other symptoms may include changes in perception, such as macropsias, micropsias, or matamorfopsia; and changes of location in the spatial plane, or image distortion (Alarcon, 2009b).

6.1.13 Presurgical assessment and surgical intervention

The identification of the cortical areas causing seizures is very important in extra-temporal lobe epilepsy because more of the epileptogenic region surrounds sensible brain tissue. Thus, more effort is needed for evaluating

potential candidates for epilepsy surgery (Cascino, 2004). In only a few patients, especially in patients who have a lesion as substrate, are surgical procedures possible without the use of intracranial (Cascino, 2004).

For surgical proposes, it is important to be aware that the electrical discharge may suddenly spreads to the temporal parietal lobes, or even to the frontal lobe, presenting signs and symptoms related to these sites, and might obscure the real seizure origin (Cascino et al., 1994).

6.1.14 Electroencephalographic features

The presence of spikes, sharp waves or focal slowing are important features in the diagnosis of extra-temporal epilepsy as these patterns where in identifying the potential ictal onset and will aid during the presurgical assessment (Mihara, 2005, Centeno et al., 2006). It is important to state that in most of patients, a routine interictal EEG does not present any change, consequently the video EEG is mandatory. Thus, it is of paramount importance to identify interictal abnormalities during video EEG and the most common extratemporal features seen are fast activity. However, in patients with frontal or parietal epilepsy in whom seizures start from basal or medial cortical areas, ictal changes may be minimal or non-specific.

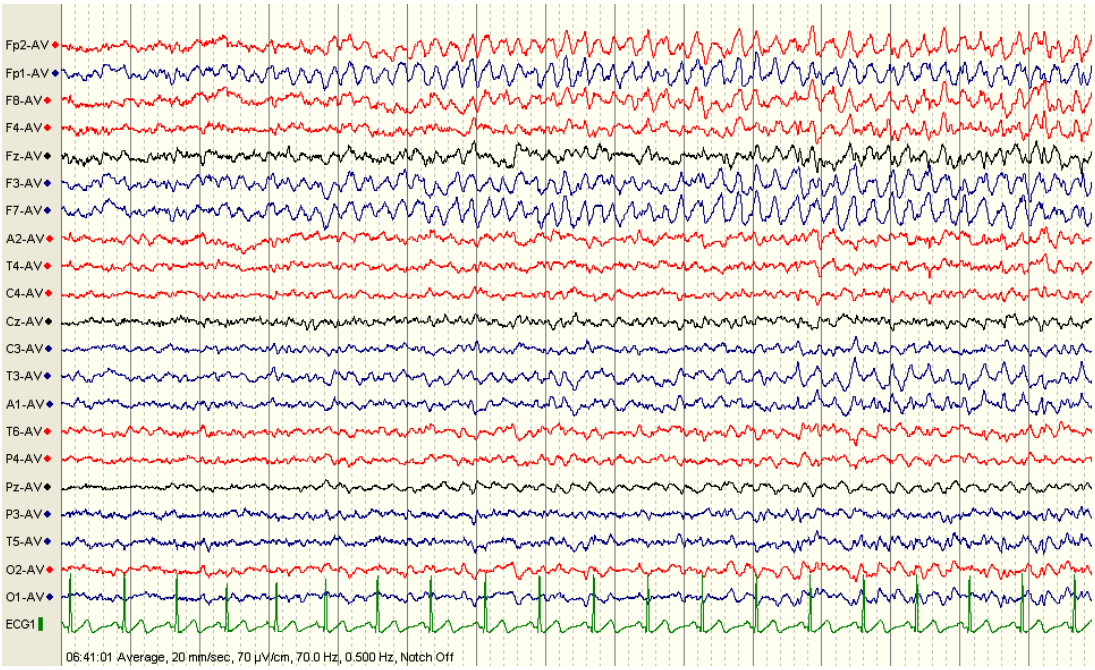

Figure 5. Frontal seizure onset seen on scalp EEG.

7 Mechanisms involved in the generation of EEG patterns seen at seizure onset

Epilepsy is characterized by a long-lasting predisposition of the cortex to generate paroxystic events called epileptic seizures. The transition from a seizure-free period (interictal) into a seizure (ictal) has been coined as ictogenesis. To understand ictogenesis, a variety of in vitro and in vivo techniques have been developed throughout the years by developing seizure-like models. Several mechanisms underlying the generation of epileptic seizures have been proposed.

Throughout the interictal period, the epileptic brain is able to generate abnormal discharges with particular morphology and distribution, which are detectable on the EEG. Such discharges are often called interictal epileptiform discharges, have short duration and have been classified into spikes, spike wave activity, or sharp waves (Noachtar et al., 1999). Clinically, interictal epileptiform discharges are widely used as a disease biomarker for epilepsy (Noachtar et al., 1999).

At a neuronal network level, an interictal spike is characterized by a sequence of fast action potentials, superimposed to a slow depolarizing potential (Uva et al., 2015). The depolarizing potential triggers a burst of action potentials lasting for 50–100ms. This is followed by a second burst of action potentials, which is presumably caused by cessation of the recurrent inhibition initiated by the first burst (Schwartzkroin and Prince, 1980, de Curtis and Avanzini, 2001). In humans, four different neuronal firing patterns have been described during interictal epileptiform discharges in patients assessed for epilepsy surgery: a) burst of high frequency firing lasting less than 100; (b) a period of suppression in firing lasting around 100–1300 ms; (c) a burst followed by suppression and (d) no-change. (Alarcon et al., 2012a, Keller et al., 2010). These findings suggest that interictal discharges involve a brief synchronised burst firing in some cells followed by longer recurrent lateral inhibition (Alarcon et al., 2012a).

The onset of focal seizures seems to be associated with longer dynamic changes than those seen in interictal discharges. Ictal changes are visually detectable on the EEG over longer periods of several seconds, much longer than those EEG

changes seen during interictal discharges. It has been reported that focal seizures are initiated by an aberrant firing rate of action potentials, affecting a large population of neurons. The increased firing rate, progressively recruits neighbouring neurons within synchronized discharges, leading to a seizure (Yaari and Beck, 2002). A focal or diffuse slow wave deflection can immediately precede ictal activity, which is followed by a variety of patterns that might be focal or widespread (Jiruska et al., 2014, Jimenez-Jimenez et al., 2015b). When recorded with intracranial electrodes, seizure onset is characterised by numerous patterns such as: high-frequency activity, (Alarcon et al., 1995, Pacia and Ebersole, 1999, Jung et al., 1999), bursts of irregular sharp and slow waves, spike-wave activity (Alarcon et al., 1995, Pacia and Ebersole, 1999), rhythmic sinusoidal activity (Alarcon et al., 1995, Pacia and Ebersole, 1999), focal or widespread flattening of the EEG (Alarcon et al., 1995, Arroyo et al., 1994).

Important issues have been raised by ictogenesis research. There is still a dispute on the role of interictal epileptiform discharges as a protective factor against seizures (de Curtis and Avanzini, 2001) or as a seizure contributor (Litt and Lehnertz, 2002). The nature of the various patterns seen at the onset of human seizures remains unclear. In the present thesis, seizure onset patterns have been investigated as prognostic factors of seizure outcome. Presently, numerous studies in humans and animals and in vitro have been carried out to improve the current understanding of the mechanisms underlying the focal ictogenesis. New concepts have been proposed, which are reviewed below.

7.1.1 In-vivo seizure onset pattern models

Numerous *in-vivo* seizure models have been developed in order to study the origin of focal ictal patterns. These studies mainly attempted to reconstruct those patterns seen in patients with mesial temporal lobe epilepsy (MTLE). To recreate electrical activity seen on EEG of MTLE in rodents, focal cortical penicillin (Matsumoto and Marsan, 1964), injection of γ-aminobutyric acid A (GABAA) receptor antagonist bicuculline methiodide (BMI) glutamate agonist kainic acid, into the coronu ammonis area 3 (CA3) area of hippocampus (Bragin et al., 2009) have been administrated by several groups. During the transition from preictal to ictal period, two main seizure onset patterns were observed: a) hypersynchronous high frequency oscillations (HFOs) in the frequency range of 80 – 600 Hz, which were seen accompanied by sharp waves and b) low voltage fast firing pattern in the beta-gamma range (Bragin et al., 2007). These patterns were followed by generalized ictal EEG discharges and clinical manifestations. A recent study was conducted in male Spregue-Dawley rats (250–300g) with electrodes implanted in the hippocampus, the entorhinal cortex, and the subiculum. Seizures were provoked by local application of 4-aminopyridine (4AP, 4–5 mg/kg ip) and picrotoxin (3–5 mg/kg ip) (Salami et al., 2015). Low-voltage fast patterns occurred at seizure onset in 82% of 4AP-induced seizures. On the other hand, in animals where seizures were induced by picrotoxin, the seizure onset pattern was always hypersynchronous. 4AP-induced seizures were more frequently associated with ripples than fast ripples, whereas picrotoxin-induced seizures were more frequently associated with fast ripples than ripples. (Salami et al., 2015).

It has been proposed that ripples reflect a summation of inhibitory postsynaptic potentials, which are generated by pyramidal cells in response to inhibitory interneuron firing. Fast ripples would represent the hypersynchronous bursting of glutamatergic cells. Therefore, these results support the hypothesis which states that the two distinct patterns at seizure onset result from different pathophysiological mechanisms (Bragin et al., 2009).

7.1.2 In-vivo seizure onset patterns models

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7.1.3 *In vitro* seizure onset patterns models

In addition to in vivo models, *in vitro* models have also been used in experimental studies of epilepsy. As in *in vivo* seizure models, ictal patterns vary depending on how seizures are induced and the region studied. Spontaneous recurrent seizures can be induced by perfusing the brain tissue with several convulsant agents such as high potassium concentrations (5mM), cobalt (He et al., 2009) low Magnesium concetrations (0.25 mM) (Derchansky et al., 2004), 4-aminopyridine (Ziburkus et al., 2006). Furthermore, GABA receptor antagonists such as penicillin, bicuculline, and picrotoxin have also been used (Uva et al.,

2009). In these models, ictal patterns in the field potential are characterized by progressive recruiting activity, where ictal discharges progressively become greater and more synchronous with time. Seizure propagation is then followed by a decremental pattern during postictal depression where the amplitude and neuronal firing rate progressively decrease (de Curtis and Gnatkovsky, 2009). It has been proposed that factors such as synaptic efficacy, intrinsic membrane properties, and neuromodulators may affect membrane currents through second messenger pathways (Dichter and Ayala, 1987).

Other authors have developed seizure models in isolated hippocampus from embryonic and neonatal rat hippocampal formation and surrounding limbic structures perfused with 4-aminopyridine (4-AP), kainate, or low Mg2+ artificial cerebrospinal fluid (ACSF) (Derchansky et al., 2004, Khalilov et al., 1997). Both seizure-like events and interictal events can be recorded with low magnesium. Interestingly, the transition from interictal epileptiform discharges to seizure like events occurred quickly and high frequency activity was present during this transition. In addition, during seizure like events, the amplitude of ictal activity increased and their frequency decreased over time. This study demonstrated that high frequency oscillations are present during the transition from interictal activity to the ictal state. This has been recently corroborated in humans, where widespread HFO were present during this transition (Perucca et al., 2013).

7.1.4 Theta rhythm

In vivo recordings carried out in awake rats, demonstrated that neuronal firing is temporally correlated with both gamma and theta activity (Bragin et al., 2005). Fast excitatory postsynaptic potentials (EPSPs) in interneurons are important for network activity during inhibition-based brain rhythms by controlling spike timing (Bragin et al., 2005). EPSPs on hippocampal interneurons have faster kinetic properties than excitatory inputs on principal neurons. This can be explained by interneurons having active dendritic conductance, a low membrane time constant, and fast EPSP kinetics mediated by the molecular composition of interneuronal AMPA receptors. Together, these factors accelerate spiking in interneurons. Additionally, perisomatic-targeting interneurons with widespread divergence of axons can synchronize hippocampal population activity by phase-locking subthreshold oscillations. Repetitive inhibitory postsynaptic potential (IPSPs) originating from a few presynaptic interneurons are effective in pacing and synchronizing spontaneous action potential in postsynaptic pyramidal neurons (Jiruska et al., 2014). Furthermore, pyramidal cells and GABAergic interneurons in CA3 are communicated. Interconnected neurons allow rapid and reliable synchronization of network activity. A small proportion of EPSPs are sufficiently strong to trigger action potentials in any postsynaptic neuron. Reciprocally connected GABAergic interneurons are important in generating gamma frequency network oscillations. It has been proposed that basket cells are synaptically interconnected and also coupled with other interneuronal classes. Therefore, the output from basket cells to their target neurons is likely to occur synchronously, which seems to be an important property in hippocampal rhythmogenesis (Jiruska et al., 2014).

7.1.5 Fast rhythms

Presurgical intracranial recordings are used to identify the epileptogenic zone in patients with epilepsy assessed for surgery. In patients as well as in animal models of mesial temporal lobe epilepsy, two predominant patterns were observed during the transition to seizures: low – voltage fast activity and high frequency oscillations (HFOs) (Bragin et al., 2005). It has been proposed that the generation of different EEG patterns depends on specific disruptions to the existing balance between excitatory and inhibitory components of the neuronal network (Bragin et al., 2009). Preictal patterns, which normally precede fast activities at seizure onset, may be mediated by either reinforcement or reduction of interictal/preictal discharges (de Curtis and Avanzini, 2001, Avoli et al., 1996). It has been hypothesized that local inhibitory networks in CA1 are responsible for the generation of ripple oscillations (Beenhakker and Huguenard, 2009). Excitation from CA3 activates CA1 inhibitory neurons. At the trough of the rhythmic local field potential, the activity of CA1 inhibitory neurons is low and increases progressively in response to the CA3 excitation. At the peak of the rhythmic local field potentials, inhibitory neuron activity is strengthened through recurrent inhibition and overpowers CA3 excitatory drive. This powerful surge of inhibition results an overall decrease in the population firing rate. The rhythmic oscillation observed in local field potential is defined by the synaptic delays and rise times associated with inhibitory events (Beenhakker and Huguenard, 2009).

Several network mechanisms have been proposed for ictogenesis, but the exact underlying mechanism remains largely unclear. Using intracranial EEG recordings, it has been proposed that hippocampal seizure onset might be the result of a development of low-voltage fast activity of 15-40 Hz, which often begins regionally and then involves extrahippocampal structures in seizure generation (Spencer et al., 1992a). The underlying neuronal mechanisms of low-voltage fast activity may involve disinhibition, in addition to enhanced excitation, resulting in hypersynchrony. A more recent study suggested that low-voltage fast activity at seizure onset is associated with reinforcement and synchronization of inhibitory networks (de Curtis and Gnatkovsky, 2009). Other authors have also observed a spatial correlation of signals during ictal low-voltage fast activity, suggesting that these discharges were mediated by a synchronization of cortical networks established by recruitment of inhibition (Bartolomei et al., 2001, Wendling et al., 2003).

Low-amplitude fast activity at seizure onset was seen in the entorhinal cortex from isolated guinea pig brain. This pattern was generated by arterial perfusion of bicuculline-methiodide (Gnatkovsky et al., 2008). This pattern was correlated with blockade of activity in the deeper layer of principal neurons. In addition, a marked increase in firing rates was seen among interneurons (Gnatkovsky et al., 2008). The authors suggested that seizure onset is mediated by inhibitory circuits by blocking neuronal firing in principal neurons, such that a transient enhancement of interneuronal network activity is responsible for excitability changes that precede seizure onset. Low-voltage fast rhythms on the EEG is

useful to identify seizure onset (Gotman et al., 1995, Fisher et al., 1992, Alarcon et al., 1995), which is during presurgical evaluation.

7.1.6 Fast ripple generation

Another interictal pattern have been observed during transition to seizure, characterized by brief runs of ultrafast activity (250–600 Hz), coined fast ripples (Jacobs et al., 2008a). Fast ripples mainly occur at seizure onset in both, animal epilepsy models (Bragin et al., 2004) and human patients (Jacobs et al., 2008b, Jirsch et al., 2006). Because fast ripples are restricted to the epileptogenic focus, they are considered as markers of eileptogenesis and also suggest that seizures are driven by the emergence of a hypersynchronous neuronal subnetwork (Bragin et al., 2005, Jirsch et al., 2006, Lasztoczi et al., 2004). According to *in vivo* studies in chronic animal models and in human temporal lobe epilepsy, it has been proposed that the underlying mechanism of the HFOs generation could be a synchronous activation of clusters of highly interconnected GABA neurons that overcome a feedback inhibition (Bragin et al., 2004, Bragin et al., 2005, Van Quyen et al., 2003).

Under pathological conditions, such as in mesial temporal lobe epilepsy, fast ripples were recorded near seizure onset, reflecting the hypersynchronous discharges of pyramidal neurons within in the epileptogenic region (Bragin et al., 1999). The CA3 region is the key structure for driving epileptogenesis and hyperexcitability in the low Mg^{2+} seizure model, leading CA1 during the preictal and ictal states. Neurons found in CA3a have more complex dendritic arbours,

probably acting as pacemaker cells by firing early and recruiting other cells into firing (Wittner and Miles, 2007). However, the exact mechanisms underlying fast ripple oscillations still remain unknown. Because many studies have shown that ripples and fast ripples appear to be coupled, (Beenhakker and Huguenard, 2009) hypothesized that these oscillations rely on similar brain states for expression. (Dzhala and Staley, 2004) and (Foffani et al., 2007) have studied the mechanisms underlying fast ripples in the CA3 region using the high K^+ bath perfusion model and the pilocarpine-treated epileptic animal model, respectively. They concluded that fast ripple generation is promoted by elevated synaptic activity, as suggested by hypersynchronous bursts among CA3 pyramidal neurons, and their oscillation frequency dependency on the precision of spike-timing.

The highly synchronized discharge of CA3 pyramidal cells has been shown to initiate sharp waves (Buzsaki and Gage, 1992, Traub et al., 2001). This has been supported by the finding that blocking adenosine receptors induces the spontaneously occurring CA3 sharp waves in hippocampal slices (Wu et al., 2002). In addition, local circuitry in the hippocampal CA3 region is capable of exhibiting spontaneous synchronous GABAergic activities in vitro (Wu et al., 2002). Spontaneous rhythmic field potentials from whole hippocampal isolates and thick slices from young and adult mice are correlated with intracellular synchronous GABAa-IPSPs in pyramidal neurons and repeated discharges in inhibitory interneurons. Thus, (Wu et al., 2002) hypothesized that a population of glutamatergic neurons arising from the hippocampal CA3 recurrent circuitry in vitro is capable of triggering discharges in a group of GABAergic inhibitory

interneurons, which in turn generate IPSP-based spontaneous rhythmic field potentials. In addition to the $GABA_A$-mediated oscillations, synergistic excitatory activity from the depolarizing GABA and glutamate NMDA receptors generates giant depolarizing potentials (GDPs) at CA3 region in postnatal day 0-10 in mice (Sipila et al., 2007).

7.1.7 Sharp wave patterns

The hippocampus is characterized by strong oscillatory network activity. Under physiological conditions, input arrives in the hippocampus via the dentate gyrus, from where information travels to CA3, then to CA1, and finally reaches the subiculum. It has been proposed that a synchronized burst of many CA3 pyramidal cells is responsible for generating the sharp wave pattern seen on the EEG (Ylinen et al., 1995). The excitation mediated by CA3 pyramidal cells is then spread to CA1 where subsequent ripple activity at around 200 Hz is developed. This oscillation is known as the sharp-wave ripple complex, which is associated with both normal and epileptic brain (Ylinen et al., 1995). Complex interconnections between GABAergic interneurons and pyramidal cells have been found to underlie the cellular basis for establishing and maintaining large scale network oscillations in the hippocampus (Buzsaki and Gage, 1992). Horizontal interneurones in CA1 and CA3 regions have been shown to burst synchronously with pyramidal cells in an acute model of epilepsy (Aradi and Maccaferri, 2004). Hippocampal interneurons may synchronize large neuronal populations via their abundant connections to pyramidal neurons and other interneurons (Buhl et al., 1994, Sik et al., 1995).

7.1.8 Electrodecremental event pattern

An electrodecremental event (EDE) is one of the most frequent patterns seen at seizure onset on intracranial EEG (Alarcon et al., 1995, Arroyo et al., 1994, Dolezalova et al., 2013, Jimenez-Jimenez et al., 2015b). This pattern is defined as a flattening of the EEG, usually diffuse or widespread. EDE may coexist or be followed by focal changes in the EEG, such as low-voltage fast activity, which subsequently increase in voltage and decreases in frequency (Alarcon et al., 1995, Arroyo et al., 1994, Ikeda et al., 1996, Dolezalova et al., 2013, Alarcon et al., 2012b)

When present at seizure onset, EDE can be focal or diffuse. A diffuse electrodecremental pattern (Alarcon et al., 1995, Fariello et al., 1979, Faulconer and Bickford, 1960) has been considered as part of a generalized onset seizure pattern, arising from brainstem (Gastaut et al., 1963). The diffuse pattern has been described as a common feature in infantile spasms (Druckman and Chao, 1955, Kellaway et al., 1979), in atonic seizures (Hooshmand et al., 1980), and in tonic seizures (Fariello et al., 1979). It has been noted that EDE is especially prevalent in tonic and atonic of the Lennox-Gastaut syndrome (Donat and Wright, 1991, Yaqub, 1993, Gastaut et al., 1963). A study conducted in 7 patients assessed with intracranial electrodes during epilepsy surgery evaluation showed that patients having diffuse EDE as seizure onset pattern tended to suffer learning difficulties, very frequent multiple type seizures, and early onset of epilepsy (Arroyo et al., 1994). More than one third of these patients had

electroclinical characteristics of the Lennox Gastuat Syndrome and almost half these patients presented a gross hemispheric lesion and hemiparesis (Arroyo, 1994). The most common structure where diffuse electrodecremental event was arising from was frontal lobe. These findings are in concordance with previous reports (Fariello et al., 1979, Gastaut et al., 1963). In focal epilepsy, when a diffuse electrodecremental event seen at seizure onset on the intracranial EEG, rhythmic high-frequency activity that subsequently decreased in frequency and increased in voltage was seen on scalp EEG(Arroyo et al., 1994). Though EDE has been extensively studied in generalized epilepsy, little research has been carried out in focal epilepsy, as such diffuse pattern would not be expected in this epilepsy type.

8 Temporal connectivity and seizures propagation in Temporal Lobe Epilepsy

Seizures in focal temporal lobe epilepsy are thought to have a localised seizure onset. Once the seizure has started, more tissue in the cortex tends to be recruited, leading to clinical and EEG changes. The term spreading has been used for many years, to describe seizure evolution into regions of the cortex, which is reflected on the EEG. The nature of seizure spreading is not well understood and has been matter of study since the EEG was used to study epilepsy. It is assumed that the brain is very well interconnected and physiological pathways are needed to process information (Spencer, 2002b). Extensive research has been performed in terms of inter-hemispheric seizure propagation, and there is still much debate regarding the different pathways used for seizure spreading. The

controversy still relies on the role of the different commissures found in the human brain: corpus callosum, hippocampal commissure and anterior commissure. In epileptic patients, some circuitry abnormalities such as, axon sprouting and pruning of dendritic branches have been showed (Sutula et al., 1989), which would suggest that epileptic patients would have modified brain networks.

In this section, findings from neuroimaging and intracranial recordings are reviewed with regard to seizure spreading.

8.1.1 Neuroimaging studies

Neuroimaging studies have been linked to medicine since X-ray invention in 1895. Since then, imaging techniques have evolved to become easier to manage and largely harmless. Positron Emission Tomography (PET) measures metabolism of substances such as glucose in the brain by binding radiotracers such as fluorodeoxyglucose (FDG). After a trace of FDG has been injected to a subject, it accumulates in different metabolic organs and tissues. FDG will determine metabolic rates of glucose in different tissues. Software is used to reconstruct where in the brain the concentration of radiotracer is increased or decreased. PET is ideal for studies aimed at evaluating metabolic changes during a task or behaviour, including seizures. It is expected that increased neuronal activity will be seen during and immediately following a seizure.

In temporal lobe epilepsy, interictal PET usually shows hypometabolism in the epileptogenic temporal lobe, or bitemporal hypometabolism with more severe hypometabolism on one side (Alarcon, 2009). The pathophysiological reason of the regional hypometabolism in epileptic patients is still unclear. However, it is known that the volume of hypometabolism is much greater than volume related to structural damage. The hypometabolic region extends beyond the epileptogenic zone.

Single-photon emission computed tomography (SPECT) measures cerebral blood flow with 99mTc-ethyl cysteinate dimer (ECD) or 99mTchexamthylpropyleneamine oxime (HMPAO). Due to its pharmacokinetics, the tracer provides a portrait of the metabolic activity in the brain at the time of injection. If injected during the seizure, the method has the potential to show the areas of seizure onset and/or propagation. It has been reported that blood flow is increased in the temporal lobe during a seizure, unlike the interictal period during which blood flow is decreased. Therefore, making both images are complementary. The regions with increased blood flow correlate well with the epileptogenic zone identified by EEG. In mesial temporal lobe epilepsy, secondarily generalized seizures, are associated with hyperperfusion in the ipsilateral temporal lobe, middle frontal and precentral gyrus, bilateral occipital lobes, and the contralateral postcentral gyrus, while hypoperfusion is observed in both frontal lobes and the contralateral cerebellum (Van Paesschen et al., 2003).

In addition to PET, functional magnetic resonance imaging (fMRI) can be used for measuring neuronal activity changes during epileptogenesis. fMRI is based on hemodynamic response, as increased neuronal activity requires more oxygen, thus altering the proportion between oxygenated and de-oxygenated haemoglobin which have different magnetic properties. The signal measured has been coined BOLD (Blood- Oxygen-Level Dependence), where changes in the ratio of paramagnetic deoxyhemoglobin and diamagnetic oxyhemoglobin are measured. A recent project employing resting state functional MRI (fMRI) in patients with MTLE revealed increased hippocampal connectivity in similar regions (Laufs et al., 2014). However, there are some technical limitations to perform this technique, which has imitated to use it widely.

DTI-based tractography allows a computer-reconstruction of WM pathways by using fraction anisotropy. Anisotropy is quantified in each voxel using an index of fractional anisotropy. Values of fractional anisotropy range from 0 (equal diffusion in all directions) to 1 (fully isotropic, where diffusion is favoured in one axis and hindered in the remaining two) (Basser and Pierpaoli, 1996). In normal tracts, water diffusion is isotropic, whereas in pathological tracts, fractional isotropy decreases substantially (Beaulieu et al., 1996).

In temporal lobe and extra-temporal resections, DTI offers valuable anatomical information, to avoid damage of functional areas. In addition, DTI may have potential capacity to increase the identification of the epileptogenic focus. In subjects with epilepsy, DTI can display acute and subacute changes in the peri- and postictal state. These changes have been reported to be essentially similar to

those seen in cerebral ischemia, with early decrease, followed by normalization of the apparent diffusion coefficient. Chronic changes are seen during the interictal state (Farina et al., 2004). DTI has also been used for tracking seizure spreading through the epileptic circuitry resulting in chronic epilepsy (Luat and Chugani, 2008).

In this section, I will review how neuroimaging has given us a better understanding of epilepsy networks in animal models and humans.

8.1.2 Animal Models

Several neuroimaging research projects have been carried out in small animals in order to have a better understanding of epileptogenesis in focal temporal lobe epilepsy. A major advantage of using small animals for neuroimaging is that studies can be controlled allowing researchers to examine the living brain in the animal before, during, and after the disease onset and disease treatment. The aim is to translate findings into humans. Results can also be compared to data collected on human patients to investigate the mechanisms of epileptogenesis.

A pilocarpine-induced seizure model in C57Bl/6 mice attempted to determine changes in metabolic activity after seizures in order to identify the areas of the brain involved in seizure spreading by using microPET R4 tomograph (Mirrione et al., 2006). FDG injection was performed while animals were awake (C57BL/6 mice, 25–30 g, n ¼ 8). Mice were then anesthetized with a ketamine / xylazine cocktail (10% xylazine, 90% ketamine) 60 min after injection of radiotracer. Before and after every scan, plasma glucose measures were obtained from each

animal. The same mice were scanned after 7 days. TLE was induced by pilocarpine injection (280 mg/kg i.p.). After 10 min, animals were given 500 Ci of 18FDG, i.p. All animals then were monitored during ^{18}FDG uptake, using video recording. A marked increase of ^{18}FDG uptake was observed in the hippocampus (33.2%) as compared to baseline scans, which was associated with duration of status epilepticus. Smaller differences were measured in thalamus (9.4%), striatum (5.5%), frontal cortex (6.1%), parietal cortex (10.4%), and cerebellum (6.5%). This study in mice, demonstrated that ^{18}FDG is sensitive to metabolic changes associated with seizure severity.

It has been proposed that drug resistant epilepsy causes inflammation and neurodegeneration. Accordingly, seizure spreading has been studied by using ^{18}FDG uptake in wild type and serine protease tissue plasminogen activator mice (tPA-/-) (Mirrione et al., 2007). In this study authors aimed at investigating patterns of ^{18}FDG uptake in different mice models (wild type and tPA-/-) and their correlation to seizure severity. Mice, aged 2-5 months, 24-34 grams were all imaged twice 7 days apart. Seizures were induced by using 100mg/kg of a 10% xylazine, 90% ketamine anaesthesia 10-min prior scan. In tPA-/- mice, there was a positive correlation between ^{18}FDG uptake and seizure activity in the hippocampus, septum, thalamus, midbrain, olfactory bulb, and cerebellum. These regional metabolic changes may represent the effect of seizure spreading whereas the hippocampus, septum, and thalamus are initially required for seizure generation (Mirrione et al., 2007).

SPECT has also been studied in kindled mesial temporal lobe seizures in non-humans primates to understand the pathways of seizure spreading. Electrical kindling is a method in which, repeated administration of electrical stimulation results in a progressive state of long term susceptibility to seizure activity. A recent study was carried out in two male rhesus monkeys (Macaca mulatta; adult monkey K: 9 kg, juvenile monkey S: 6 kg). Electrodes were chronically implanted in both monkeys in the right amygdala and white matter of frontal and occipital lobes (Cleeren et al., 2015). Daily electrical stimulation of the amygdala was performed in both monkeys, 8 weeks and 13 weeks after electrodes implantation. The amygdala was stimulated in over 340 sessions Video recordings and neuroimaging were obtained from both animals, using ictal SPECT co-registered with MRI (SISCOM). A baseline scan was taken 4-8 weeks after electrode implantation and before kindling started. Ictal SPECT was carried out using injection of 99mTc-ECD in the saphenous vein 10 seconds after the seizure was provoked. During the post ictal state, monkeys were sedated using ketamine and medetomidine. Kindled seizures were evaluated by the measurement of afterdischarge duration, clinical seizure severity ranging from I (visual searching behavior) to IV (seizure generalization), and duration of post ictal state (Cleeren et al., 2015). Over the time of kindling stimulation, afterdischarges become larger in amplitude and longer in duration in both animals. Regarding brain perfusion, in seizure stage I, the individual SISCOM images showed a distributed network of hyperperfused and hypoperfused regions throughout the cortex and in many subcortical structures. Such brain perfusion patterns remained similar in seizure stages II to IV. When investigating seizure spreading, a large hyperperfusion cluster in the contralateral hemisphere

(temporal, parietal and occipital cortices) was related to seizure severity. Extratemporal clusters were also found, showing a gradual increase in perfusion of around 50%, which was more prominent at stages III and IV. SISCOM imaging showed extensive changes in perfusion throughout the brain as seizure severity progressed during the course of amygdala kindling. One of the most surprising findings from this study was that perfusion changes were common to all seizure stages and not restricted to the stimulation location (Cleeren et al., 2015). This research showed the existence of a distributed common network involved in seizure spreading, which was different depending on seizure severity (Cleeren et al., 2015).

8.1.3 Studies in Humans

Temporal lobe epilepsy has a diversity of underlying pathologies, which has been suggested to reflect the variety of seizure onset patterns seen on the EEG (Spencer et al., 1987). In principle, focal temporal lobe epilepsy should not present widespread changes at seizure onset. If present it may confirm that the physiological network has become aberrant, allowing rapid spreading of seizures (Alarcon et al., 1995). The extension of the network appears to be reflected by the intracranial EEG (iEEG) ictal onset pattern. The presence of widespread iEEG changes in focal seizures questions the traditional view of a localised epileptogenic zone, and suggests that seizures may arise from a large or widespread network. Recent connectivity studies with neuroimaging seem to support the concept of an aberrant network found in mesial temporal sclerosis epileptic patients (Miro et al., 2015). Diffusion tensor imaging (DTI) and resting state functional MRI indicate that patients with temporal lobe epilepsy exhibit

changes in connectivity to ipsilateral and contralateral structures, and that the degree of changes is related to surgical outcome (Maccotta et al., 2013a, Bonilha et al., 2013a). Techniques, such as PET and SPECT have allowed us to better understand how seizure onset propagates to neighbourhood structures.

8.1.4 SPECT AND PET

Seizure spreading in patients diagnosed with temporal epilepsy has been a subject of debate for several years. Metabolic and blood changes have been used to solve this controversy. It has been reported that ictal SPECT has an excellent sensitivity for localizing seizure activity (Wieser and Epilepsy, 2004, Theodore, 1988). On the other hand, PET shows abnormalities in metabolism, that are bilateral in around 10 – 40 % of patients with mesial temporal lobe epilepsy (MTLE), more pronounced on the side where hippocampal sclerosis is present (Wieser and Epilepsy, 2004). A study has correlated interictal PET metabolism with ictal hyperperfusion in MTLE and hippocampal sclerosis patients (Nelissen et al., 2006). The authors studied 11 patients who had been diagnosed with MTLE and hippocampal sclerosis. In addition, 11 healthy volunteers were also studied. All patients having MTLE underwent inter-ictal and ictal SPECT. Technetium-99m-ethyl cysteinate dimer (^{99m}Tc-ECD) was used as tracer. Ictal SPECT injection was performed during complex partial seizures at a median of 27 seconds after seizure onset during video recording for clinical purposes. PET images were obtained by using FDG after injection of 150 MBq FDG. All images were flipped for aligning the seizure onset zone over the same side (Nelissen et al., 2006). Analysis was carried out with statistical parametric mapping (SPM) for comparing SPECT and PET between healthy and MTLE patients. When

comparing ictal and interictal perfusion, hyperperfusion was higher during ictal state in temporal lobe when hippocampal sclerosis was present. The areas with hyperperfusion were on the seizure onset, ipsilateral inferior frontal lobe and contralateral anterior cerebellum. Furthermore, slight degrees of hyperperfusion were seen in the ipsilateral insula and parietal lobe, and in parts of the cerebellum. Ictal hyper-perfusion was seen in all patients in the ipsilateral temporal lobe and insula. Bilateral occipital hyperperfusion was present in 90% of the patients and 50% presented ipsilateral hyperperfusion. Ictal SPECT hypoperfusion was seen in the ipsilateral frontal lobes and in a small region of the contralateral temporal lobe. PET images were asymmetrical in the temporal lobes. Interestingly, the epileptic temporal lobe was the most hypometabolic region of the brain in all patients (Nelissen et al., 2006). Frontal hypometabolism was clearer patients than in controls. This may suggest that seizure state may represent an inter-dynamic metabolic change, which may result from seizures disrupting functional pathways (Nelissen et al., 2006).

8.1.5 EEG fMRI

Tracing seizure spreading in TLE patients has been performed using EEG-fMRI, which allows to simultaneously measure hemodynamic and EEG changes. A recent study using EEG-fMRI was performed to investigate functional connectivity changes immediately prior to the appearance of interictal spikes on the EEG in patients with MTLE (Faizo et al., 2014). Fifteen patients diagnosed with MTLE and 15 healthy control subjects were assessed. For MTLE patients, all EEG-fMRI recordings were interictal. For volunteers, scans were conducted

while awake. The analysis of EEG-fMRI was conducted in 4 stages. First, identification of event-related potentials to recognize the activation of the mesial temporal lobe in the ipsilateral hippocampus. Second, time course of interictal activity within the hippocampal region. Third, functional connectivity was analysed through peak voxel to display large scale networks during spike and rest periods. Fourth, functional connectivity was correlated with seizure activity based on recordings from the last seizure (Faizo et al., 2014). Authors found that spike activation was seen in the ipsilateral hippocampus and was accompanied by increased activity in the ipsilateral parahipocampal gyrus, middle temporal gyrus, precuneus, contralateral middle temporal gyrus and insula. Activity in the ipsilateral medial frontal gyrus and the right inferior and superior frontal gyri was decreased during interictal spikes. At rest, the ipsilateral hippocampus was functionally connected with the contralateral hippocampus, the parahipocampal gyri, fusiform gyri, amygdala and cerebral cortex bilaterally. The strongest connectivity was demonstrated with the contralateral hippocampus and the parahipocampal gyrus, amygdala and cerebellar cortices bilaterally. During the pre-spike state, the ipsilateral hippocampus demonstrated connectivity to the ipsilateral parahipocampal gyrus, bilateral cerebellar cortices, ipsilateral insula, bilateral lentiform nuclei and contralateral nucleus. During the spikes the ipsilateral hippocampus showed an increased connectivity to the contralateral insula and negative correlations with both superior frontal gyri. During the pre-spike period, the connectivity of the ipsilateral hippocampus to the contralateral hippocampus, both parahipocampal gyri were significantly reduced (Faizo et al., 2014).

These findings demonstrated that reduced ipsilateral hippocampal activity and loss of bilateral hippocampal functional connectivity just prior to the manifestation of spikes on the EEG. Also, authors showed that the presence of pre-spike connectivity was related to recent seizures. This suggests that functional connectivity was influenced by the last seizure (Faizo et al., 2014). One of the most interesting findings was the loss of connectivity between both hippocampi seconds after the appearance of spikes on the EEG (Faizo et al., 2014). These results were similar to previous studies using EEG-fMRI, in which authors found reduced functional connectivity between both hippocampi in patients with unilateral MTLE compared to healthy controls (Pittau et al., 2012). These findings suggest that the brain in patients with MTLE has different behaviour during the pre-ictal and ictal periods, where hippocampal connectivity seems to be reduced.

8.1.6 DTI

Tractography is becoming part of routine clinical and research techniques in some epileptic centres. DTI is applied when assessing MTLE candidates for surgery due to its suitability for detecting white matter tracts. Recently, DTI has questioned the traditional theory with regards the functional pathways between both temporal lobes which postulates only the dorsal commissure of the hippocampus is functional in humans.

A study using DTI and statistical parametric mapping conducted in 35 MTLE patients and in 36 healthy volunteers revealed that in MTLE patients show increased median diffusivity which was observed in hippocampal,

parahippocampal region and it extended more laterally from the temporal pole to the temporo-occipital junction (Thivard et al., 2005). Additionally, decreased mean diffusivity was found contralateral to the seizure onset zone, which involved the amygdala, the temporal pole and hippocampal/parahippocampal region. Authors also found a decreased fraction of anisotropy in four different brain regions located in the hemisphere ipsilateral to the seizure onset zone. These regions included the temporal stem, laterally extending from the temporal pole to the temporo-occipital junction, the arcuate fasciculus, involving frontal and parietal regions with an extension to the parieto-occipital junction in the cingulum and the corpus callosum (Thivard et al., 2005). Surprisingly, when regression analysis was performed between mean diffusivity, fraction anisotropy, seizure onset age, duration of epilepsy and the frequency of seizures, no significant differences were found (Thivard et al., 2005). Overall, this study demonstrated that diffusion abnormalities in MTLE patients are not restricted to the seizure onset zone but more zones are involved within an epileptic network, such as the contralateral hippocampus and extratemporal structures (Thivard et al., 2005). Unfortunately, this study did not incluce intracranial EEG data, which could have traced seizure spreading to the structures studied.

The limbic system has been the subject of research with modern neuroimaging methods in patients with MTLR. The fimbria-fornix and the cingulum are limbic white matter bundles containing afferent and efferent connections fromand to the hippocampus. It is assumed that in MTLE patients, this circuitry is corrupted. Loss of neuronal cell and glisosis has been shown together with granule cell reorganization and alterations of interneuronal populations, neuropeptide fibre

networks and mossy fibre sprouting (Blumcke et al., 2013). It seems that previous histological changes may play a crucial role in altering the physiology of the limbic network. Concha et al. investigating the limbic system with DTI in 8 patients with unilateral drug resistant MTLE and 9 healthy volunteers (Concha et al., 2005). Fractional anisotropy in the fornix ipsilateral to MTS was less than the two standard deviations in 7 of 8 patients and in 5 of 8 patients on the contralateral hemisphere when compared to controls. When measuring the cingulum, the fraction of anisotropy was less than 2 standard deviations of control subjects in 4 out of 8 patients ipsilateral MTS and in 1 out of 8 patients contralateral to MTS (Concha et al., 2005). This result suggests that the limbic system is altered in patients with MTS, which may cause aberrant pathways for seizure spreading.

Recently, a study examined grey and white matter tracts in patients with TLE and bilateral hippocampus sclerosis by using DTI analysed by voxel-based morphometry focusing on commissural pathways and their role in seizure spreading (Miro et al., 2015). The study included 7 patients with drug resistant TLE who ahad bi-temporal hippocampus sclerosis, 14 patients with drug left TLE resistant epilepsy and 15 healthy control subjects. All epileptic patients underwent video EEG telemetry as part of their routine clinical care. All participants underwent whole brain structural MRI scans using a 3.0 Tesla MRI and a DTI sequence, which was carried out using diffusion tensor spin-echo planar imaging with coverage of the whole head. By voxel-wise analysis of the T1-weighted images, authors found widespread damage on the left hemisphere in all patients who had bi-temporal hippocampus disease when compared to

control subjects. A reduction in white matter pathways was also found, which was seen bilaterally in the parahipocampal gyrus, fornix, and the hippocampal commissure. Furthermore, there was a significant reduction in grey matter in the left hippocampus, thalamus and parahippocampal areas. Numerous pathways with decreased fraction of anisotropy were seen including the limbic pathways, which connects intra- and interhemispheric brain regions i.e. bilateral fornix, internal capsule, cingulum, uncinate fasciculus and the anterior commissure. An increased mean diffusion interhemispheric pathways of the body and genu of corpus callosum was seen in those patients with bi-temporal hippocampus. Additionally, limbic pathways (fornix, internal capsule and uncinate fasciculus) and extra-temporal white matter tracts close to the hippocampus, such as the inferior longitudinal fasciculus, showed an increased mean diffusion when compared to control subjects. Analysis of the limbic pathways between bi-temporal lobes and left TLE patients showed that the extent of mean diffusivity was seen only in bi-temporal patients (Miro et al., 2015). Interesting, the extent of the damage in white and grey matter was most prominent on the left hemisphere (Miro et al., 2015).

8.1.7 ELECTRICAL CORTICAL STIMULATION FOR STUDYING TEMPORAL LOBE CONNECTIVITY

In patients assessed for epilepsy surgery, intracranial electrodes are implanted to determine the location and distribution of the epileptogenic zone. In these patients, different techniques, such as Single Pulse Electrical Stimulation (SPES), has been applied for evaluating cortex connectivity and cognitive functions (Lacruz et al., 2007, Lacruz et al., 2010b).

8.1.8 Studies in animals

A model of an isolated brain of Guinea Pig has been elaborated to trace seizure spreading using imaging and electrophysiological techniques (Federico and MacVicar, 1996). Authors examined the role of GABA and glutamate receptor subtypes in controlling the spread of seizure activity across the olfactory cortex in isolated whole brain of young Hartley guinea pigs weighing 150-250 g. Animals were operated under sodium pentobarbital anesthesia (Somnotol; 30 mg/kg ip). After decapitation, the overlying skull was removed, exposing the brain. The isolated brain was then transferred to an incubation-recording chamber, which contained warm dextran free artificial cerebrospinal fluid at 12°. Extracellular and intra cellular recordings were implanted. Spontaneous field potentials produced their maximal response in the upper layer of the olfactory, peri-rhinal, and insular cortices (I-III) or in the ventral hippocampus near its temporal pole. Electrographic seizures, if evoked, were recorded at these locations. Bipolar concentric stimulating electrodes (Rhodes) were used to stimulate the lateral entorhinal cortex unilaterally. In most trails, the duration of each stimulation pulse was 0.1 ms at an intensity that evoked field potentials with the greatest magnitude. Stimulation frequency was typically 5 Hz, with stimulations lasting for 5 – 10 seconds. The brain was free of stimulation for 25 min between trials if no afterdischarges were observed, or 15 min if afterdischarges or seizure activity were observed. Brain viability was tested constantly throughout the experiment by observing the amplitude of shapes and evoked field potentials (Federico and MacVicar, 1996). Imaging trails were acquired by using an Imaging Technology 151 image processor. At least 10 digitized images were obtained after each experimental trail. Two different

images were scanned prior to electrical stimulation. Spontaneous seizures were also scanned in this study. Antagonists of $GABA_A$ receptor (bicuculline methiodide), antagonists of $GABA_B$ (CGP 35348), antagonists of NMDA recerptors (MK-801), 2-amino-5-phosphonopentanoic acid (AP5), 2-amino-7-phosphonoheptanoic acid (AP7) and K/A receptors [6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) were used to evaluate the association of these receptors during seizure induction and spreading. All drugs were applied via perfusion into the artificial cerebro spinal fluid.

After 10 trails of electrical stimulation (15V, 0.1ms 5 – 10s, 5Hz every 5 – 10 min) at the lateral entorhinal cortex of seven brains, seizure activity was provoked in all seven brains. Seizure onset was first seen in the entorhinal/hippocampus cortex, which then spread to the posteromedial cortical amygdaloid nucleous ipsilateral and then bilaterally. When bicuculline was applied to the brain (20 μM), spontaneous seizure activity was seen more diffusely throughout the cortex. Spontaneous seizures spread from the entorhinal cortex to the posteromedial cortical amygdaloid nucleus faster than those seizures evoked by electrical stimulation. Also, seizure spread was more widespread when bibiculline was present, involving the posterior perirhineal cortex and larger areas of the amygdala. At higher doses of bibiculline (100 uM), seizure spreading was even more widespread when compared to lower concentrations. In the presence of bicuculline, the amplitude of electrographic patterns at seizure onset was larger, and clinical seizures were longer when compared to those brains not exposed to bicuculline. On the contrary, when a

glutamate agonist was applied to the brain perfusion, both spontaneous and electrical induced seizures were supressed.

These results demonstrate that $GABA_A$ mediated transmission is functionally present and may play an important role within epileptic tissue in limiting the spread of seizure activity from entorhinal cortex to the posteromedial cortical amygdaloid nucleus and in creating functional pathways or preferential routes of seizure spread. $GABA_B$ mediated postsynaptic inhibition played no significant role in the induction or spread of seizure activity in this study. K/A receptors, but not NMDA receptors, are necessary for the induction and subsequent spread of seizure activity originating in the entorhinal cortex/hippocampus. Metabotropic glutamate receptors can depress the induction and subsequent spread of seizure activity in the isolated brain, suggesting that metabotropic glutamate agonists might have potential as clinical anticonvulsants.

8.1.9 Studies in humans

Seizures may spread unilaterally or bilaterally to areas that are anatomically connected (Spencer, 2002a). Reproducible patterns of seizure propagation can be correlated with known anatomical pathways and advocate for a working human hippocampal commissure (Spencer et al., 1987). The dorsal hippocampal commissure has traditionally been considered to be functional in humans (Lieb et al., 1991, Wennberg et al., 2002, Gloor et al., 1993). Within the temporal lobe, seizures can propagate as follows: 1) spreading from seizure onset zone in the hippocampus to ipsilateral neocortex 2) spreading to the contralateral hippocampus; and 3) simultaneous propagation to the contralateral

hippocampus and ipsilateral neocortex (Spencer et al., 1987, Wennberg et al., 2002). Approximately 3/4th of seizures with hippocampal seizure onset had initial spreading to the ipsilateral temporal neocortex; the remaining 1/4th showed initially contralateral spreading (Spencer et al., 1987). The most prominent seizure spreading pattern for hippocampal seizures appears to be to ipsilateral temporal neocortex or to contralateral temporal hippocampus (Gloor et al., 1993). The contralateral temporal neocortex may also be implicated, mainly after contralateral hippocampal spreading (Spencer et al., 1992b).

It has been suggested that phylogenetic involution has rendered the ventral hippocampal commissure non-functional and reduced in humans and primates (Eross et al., 2009). In contrast, in lower primates and humans there is evidence for an intact dorsal hippocampal commissure (Wilson et al., 1990, Gloor et al., 1993). The dorsal hippocampal commissure is formed by fibres typically provided by the pre-subiculum and posterior parahippocampal gyrus (Velasco et al., 2000). In monkeys, the dorsal hippocampal commissure bilaterally connects the entorhinal, parahipocampal and subicular cortices (Eross et al., 2009). This tract is also present in humans (Eross et al., 2009). This might explain why loss of CA1 neurons, which projects to the parahippocampal gyrus and presubiculum, lead to lack of propagation of hypersynchronous discharges (Velasco et al., 2000).

However, electrical stimulation of mesiotemporal structures did not demonstrate the presence of a functional hippocampal commissure (Inoue et al., 1999). Instead, data from SPES responses suggest that seizure propagation

occurs via multisynaptic pathway from the temporal neocortex to contralateral hippocampi (Wilson et al., 1990). This also explains the long interhemispheric propagation time for hippocampal onset seizures (Wilson et al., 1990, Lacruz et al., 2007). Gloor found that a small proportion of seizures propagated to ipsilateral neocortex and then to the frontal lobe, followed by contralateral hippocampus (Gloor et al., 1993). The later suggests that seizure spreading may have occurred via the anterior commissure or corpus callosum (Eross et al., 2009). Additionally, Lieb has found that there was frontal lobe involvement prior to contralateral hippocampi (Lieb et al., 1991), advocating the corpus callosum as a seizure propagation pathway (Eross et al., 2009). In contrast, Spencer found that contralateral neocortex was only implicated after contralateral hippocampus (Eross et al., 2009). The ipsilateral and contralateral frontal lobes are also implicated in temporal lobe seizure propagation (Adam et al., 1994). It has been suggested that ipsilateral temporo-frontal propagation may occur via the amygdala-cingulate or parahippocampal projections to the ipsilateral frontal lobe from where corpus callosum projections may contribute to contralateral frontal lobe ictal spreading (Lacruz et al., 2007).

Recently, in a study undertaken by Jennssen, a total of 112 temporal and extra-temporal seizures were studied using subdural grids and depth electrodes (Jenssen et al., 2011). Out of the 28 medial temporal seizures, 15 propagated to the ipsilateral temporal lobe, and only 9 spread to the contralateral medial temporal lobe and 4 to the contralateral orbital lobe (Jenssen et al., 2011). The authors also studied seizure onset patterns and their relation to seizure propagation. Ictal onset consisted of beta or faster activity in 80 seizures

(71.4%), alpha activity in 15 seizures (13.4%), theta activity in 5 seizures (4.5%) and delta activity in 12 seizures (10.7%). In addition, the ictal pattern existing at the time of propagation was beta activity (or faster) in 66 seizures (58.8%), alpha activity in 20 seizures (17.9%), theta activity in 18 seizures (16.1%) and delta activity in 8 seizures (7.1%). Thirty seizures had fast activity only at the onset and 8 only at the time of propagation. These findings suggest that the routes of propagation depend fundamentally on the area of seizure onset and its anatomical connections.

These studies provided significant understanding of seizure spreading in focal epilepsy. However, it is still uncertain if the presence of bilateral connections is related to: a) Bilateral changes seen at seizure onset; b) Postsurgical seizure control; or c) Pathways for seizure propagation.

9 Outcome from surgery

Outcome from epilepsy surgery is based on the comparison of seizure control before and after epilepsy surgery. Additionally, to reduction in seizures, neuropsychiatric and neurological deficits should be also considered. Importantly, the effects on patient's daily activities and well-being should determine the success or failure of surgery.

It is recommended that after surgery, the degree of seizure control should be evaluated regularly, initially twice a year and following once in a year. These follow ups are determined by patient's response to treatment. It is also common

that patients become seizure free after surgery; nevertheless seizures can re-emerge in the future. The following variables can be assessed in order to obtain a consistent degree in seizure control: ictal incontinence seizure, seizure frequency severity and duration, presence of an aura, which offers an opportunity to avoid injury.

Engel proposed a scale of outcome with respect to epileptic seizures. This scale quantifies the benefits of post-surgical seizure control. This scale has proven to be relatively easy to use and has a good degree of assertiveness with respect to seizure control, therefore is broadly used (Table 1). Additionally, this scale has the advantage of combining seizure control with a degree of impact on quality of life (Engel, 1993). In 2001, The ILAE proposed another postsurgical outcome scale (Wieser et al., 2001). ILAE scale measures outcome based on frequency of postoperative seizure days (Table 2). In this scale, subjective classification of seizure control or quality of life is not included (Wieser et al., 2001). Engel and ILAE classifications were compared and demonstrated good inter-rater reliability (Durnford et al., 2011).

9.1.1 Table 1 Post surgical outcome scale proposed by Engel (Engel et al., 1993).

Engel Outcome Scale (1993)		
Outcome		Definition
Group	Subgroup	
I Free of disabling seizures[a]	a	Completely seizure free since surgery
	b	Non-disabling simple partial seizures only since surgery
	c	Some disabling seizures since surgery but free of disabling seizures for two years
	d	Generalized convulsion with anti-epileptic drug withdrawal only
II Rare disabling seizures	a	Initially free of disabling seizures but rare disabling seizures now
	b	Rare disabling seizures since surgery
	c	More than rare disabling seizures after surgery but rare disabling seizures for at least two years
	d	Nocturnal seizures only
III Worthwhile improvement	a	Worthwhile seizure reduction
	b	Prolonged seizure-free intervals amounting to greater than half the follow-up period but not less than two years.
IV No worthwhile improvement	a	Significant seizure reduction
	b	No appreciable change
	c	Worse
a – excludes early post-operative seizures, ie first few weeks.		

9.1.2 Table 2. Post surgical outcome scale proposed by ILAE (Wieser et al., 2001)

ILAE outcome Scale 2001	
Outcome class	Definition
1	**Completely seizure free, no auras**
2	**Only auras, no other seizures**
3	**1 - 3 seizure days per year ± auras**
4	**4 seizure days per year to 50% reduction in baseline ± auras**
5	**more than 50% reduction to 100% increase in baseline ± auras**
6	**more than 100% increase in baseline ± auras**

2. CHAPTER TWO

1 Prognostic value of intracranial seizure onset patterns for surgical outcome of the treatment of epilepsy.

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2 Personal contributions for this publication:

- Review all clinical records for those patients who have been implanted intracranial electrodes and were operated from November 1999 to January 2010.
- Elaborate a database for entry different clinical details of the patients whom fulfilled the previous criteria.
- Review all intracranial EEG recordings of the patients 69 patients included in the study.
- Classify all the seizures (373) into the different seizure patterns included for the study.
- Perform the statistical analysis for the study.
- Select and edit different images for including into the manuscript.
- Elaborate all tables for the study.
- Write the first draft of the manuscript and submit it to respective journal.

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Prognostic value of intracranial seizure onset patterns for surgical outcome of the treatment of epilepsy

Diego Jiménez-Jiménez [a,b,c], Ramesh Nekkare [a], Lorena Flores [a], Katerina Chatzidimou [a], Istvan Bodi [d], Mrinalini Honavar [d,g], Nandini Mullatti [b], Robert D.C. Elwes [b], Richard P. Selway [e], Antonio Valentín [a,b,1], Gonzalo Alarcón [a,b,f,*,1]

[a] Department of Clinical Neuroscience, King's College London, Institute of Psychiatry, UK
[b] Department of Clinical Neurophysiology, King's College Hospital NHS Trust, London, UK
[c] Universidad San Francisco de Quito, School of Medicine, Quito, Ecuador
[d] Department of Neuropathology, King's College Hospital NHS Trust, London, UK
[e] Department of Neurosurgery, King's College Hospital NHS Trust, London, UK
[f] Departamento de Fisiología, Facultad de Medicina, Universidad Complutense, Madrid, Spain
[g] Serviço de Anatomia Patológica, Hospital Pedro Hispano, Matosinhos, Portugal

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HIGHLIGHTS

- Focal fast activity at onset was associated with favourable postsurgical outcome.
- Diffuse electrodecremental event at onset was associated with poor outcome.
- A preceding focal, widespread or bilateral epileptiform discharge was not associated with either favourable or poor outcome.

ABSTRACT

Objective: To investigate if intracranial EEG patterns at seizure onset can predict surgical outcome.
Methods: Ictal onset patterns from intracranial EEG were analysed in 373 electro-clinical seizures and subclinical seizures from 69 patients. Seizure onset patterns were classified as: (a) Diffuse electrodecremental (DEE); (b) Focal fast activity (FA); (c) Simultaneous onset of fast activity and diffuse electrodecremental event (FA-DEE); (d) Spikes; (e) Spike-wave activity; (f) Sharp waves; (g) Alpha activity; (h) Delta activity. Presence of preceding epileptiform discharge (PED) was also studied. Engel and ILAE surgical outcome scales were used.
Results: The mean follow-up period was 42.1 months (SD = 30.1). Fast activity was the most common seizure onset pattern seen (33%), followed by (FA-DEE) (20%), DEE (19%), spike-wave activity (12%), sharp-waves (6%), alpha activity (6%), delta activity (3%) and spikes (1%). Preceding epileptiform discharges were present in 75% of patients. FA was associated with favourable outcome ($p = 0.0083$) whereas DEE was associated with poor outcome ($p = 0.0025$). A widespread PED was not associated with poor outcome ($p = 0.9559$). There was no clear association between seizure onset pattern and specific pathology, except possibly between sharp/spike waves and mesial temporal sclerosis.

* Corresponding author at: Department of Clinical Neuroscience, Institute of Psychiatry, King's College London, P.O. Box 43, De Crespigny Park, London SE5 8AF, UK. Tel.: +44 207 848 5161; fax: +44 207 848 0988.
E-mail address: gonzalo.alarcon@kcl.ac.uk (G. Alarcón).
[1] Drs. A. Valentín and G. Alarcón are joint senior authors.

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Table 1
Summary of all 69 studied patients.

Patient	Telemetry duration (days)	Number of seizures	Electrodes type	SIOP	PED	Pathology	Resected lobe	Engel
1	12	2	Subdural	DEE	Widespread	MTS	Temporal	2
2	7	5	Mat and subdural	FA	Focal	MTS	Temporal	1
3	20	7	Mat and subdural	Alpha	Not present	ASTRO	Temporal	3
4	14	2	Depth	FA-DEE	Widespread	Tumour	Temporal	3
5	5	2	Depth	FA-DEE	Widespread	No changes	Temporal	1
6	20	7	Depth	DEE	Bilateral	FCD	Temporal	4
7	4	5	Subdural	Alpha	Widespread	MTS	Temporal	1
8	13	4	Depth	FA	Focal	MTS	Temporal	1
9	14	4	Depth	FA-DEE	Bilateral	Heterotopia	Temporal	2
10	8	4	Subdural	FA	Not present	Tumour	Temporal	4
11	3	3	Subdural	FA	Widespread	MTS	Temporal	1
12	11	4	Depth	Sharp-waves	Widespread	MTS	Temporal	1
13	4	6	Subdural	FA	Focal	MTS	Temporal	2
14	13	1	Subdural	FA	Not present	MTS	Temporal	2
15	6	3	Subdural	Delta	Not present	MTS	Temporal	2
16	6	3	Depth	FA	Widespread	MTS	Temporal	1
17	14	3	Mat	DEE	Widespread	EPNS	Temporal	2
18	12	9	Mat	FA	Widespread	FCD	Parietal	1
19	6	1	Mat	FA-DEE	Widespread	FCD	Frontal	4
20	8	3	Subdural	FA-DEE	Widespread	No changes	Temporal	3
21	9	3	Subdural	FA-DEE	Widespread	MTS	Temporal	3
22	5	2	Subdural	Spike-wave	Not present	MTS	Temporal	1
23	5	13	Depth	FA-DEE	Bilateral	FCD	Frontal	1
24	7	7	Depth	FA	Focal	DNET	Temporal	1
25	8	8	Mat and subdural	Spike-wave	Not present	FCD	Temporal	3
26	10	4	Subdural	Sharp waves	Widespread	No changes	Temporal	1
27	20	2	Depth	FA	Widespread	Heterotopia	Occipital	1
28	13	2	Subdural	FA	Focal	No changes	Temporal	1
29	10	4	Mat and subdural	Spike-wave	Not present	MTS	Temporal	1
30	3	3	Subdural	Spike-wave	Bilateral	DNET	Temporal	1
31	7	4	Subdural	Alpha	Widespread	MTS	Temporal	1
32	4	12	Mat	DEE	Widespread	FCD	Frontal	4
33	8	5	Subdural	Sharp waves	Not present	MTS	Temporal	3
34	7	5	Subdural	FA	Not present	MTS	Temporal	1
35	8	8	Depth and Subdural	Spike-wave	Focal	FCD	Frontal	2
36	13	4	Subdural	DEE	Widespread	No changes	Temporal	3
37	9	4	Depth	FA-DEE	Bilateral	MTS	Temporal	2
38	12	6	Depth	FA	Not present	FCD	Insula	3
39	7	5	Depth and Mat	FA	Not present	DNET	Frontal	1
40	3	10	Subdural	FA	Not present	MTS	Temporal	3
41	8	5	Subdural	DEE	Widespread	MTS	Temporal	1
42	3	14	Mat and subdural	DEE	Widespread	No changes	Temporal	3
43	7	7	Subdural	Spike-wave	Focal	MTS	Temporal	1
44	5	6	Mat and subdural	DEE	Not present	Heterotopia	Frontal	3
45	6	7	Mat and subdural	DEE	Widespread	No changes	Frontal	3
46	6	2	Mat and subdural	DEE	Widespread	ASTRO	Frontal	3
47	12	4	Subdural	FA	Not present	DNET	Temporal	1
48	16	1	Depth	FA	Not present	No changes	Temporal	1
49	9	5	Depth	Spike-wave	Bilateral	MTS	Temporal	1
50	5	4	Subdural	DEE	Bilateral	ASTRO	Frontal	4
51	5	5	Depth and Subdural	FA-DEE	Bilateral	DNET	Occipital	1
52	6	3	Mat and subdural	Sharp waves	Not present	MTS	Temporal	2
53	7	6	Subdural	FA	Widespread	No changes	Temporal	1
54	11	3	Mat and subdural	FA-DEE	Widespread	No changes	Temporal	1
55	6	13	Depth	Delta	Focal	MTS	Temporal	3
56	9	11	Subdural	Spike-wave	Widespread	MTS	Temporal	1
57	4	14	Depth and Subdural	Alpha	Widespread	FCD	Parietal	3
58	7	5	Subdural	FA	Focal	No changes	Temporal	1
59	16	5	Subdural	FA-DEE	Widespread	MTS	Temporal	1
60	3	19	Depth	FA-DEE	Bilateral	No changes	Frontal	3
61	4	5	Subdural	DEE	Widespread	DNET	Temporal	3
62	7	11	Depth and Subdural	Spikes	Bilateral	MTS	Temporal	3
63	7	8	Depth	FA	Not present	MTS	Temporal	1
64	8	3	Mat and subdural	DEE	Widespread	FCD	Frontal	3
65	5	3	Mat and subdural	FA-DEE	Widespread	MTS	Temporal	1
66	14	3	Mat and subdural	FA-DEE	Widespread	No changes	Temporal	3
67	9	4	Mat and subdural	FA	Widespread	FCD	Frontal	1
68	9	4	Subdural	FA	Bilateral	FCD	Frontal	1
69	9	4	Mat and subdural	FA	Widespread	PIC	Temporal	4

DNET = dysembryoplastic neuroepithelial tumor.
FDC = focal cortical dysplasia.
MTS = mesial temporal sclerosis.
PIC = perinatal ischemic cyst.

including various scalp, intracranial and average common references to identify the most inactive reference for review in each

remove the seizure onset zone. Intraoperative electrocorticographic recordings were used to further tailor the resection to remove

regions showing pathological slowing and epileptiform discharges (Ferrier et al., 2001). Structural lesions shown on imaging were removed unless functional mapping suggested a significant risk of functional deficits. Post-operative imaging was performed in those patients where surgery failed.

2.8. Neuropathology

Neuropathological examination of the resected specimens was carried out according to the departmental protocol outlined previously (Kumar et al., 2013).

2.9. Surgical outcome

Surgical outcome with regard to seizure control was determined at regular postoperative follow up assessments. Surgical outcome was coded according to both the ILAE and Engel surgical outcome classifications (Engel et al., 1993; Wieser et al., 2001). Surgical outcome at the longest follow-up available was used for each patient. For statistical analysis, only Engel classification was used. Grade I was considered as "good outcome" and grades II, III or IV as "poor outcome".

2.10. Statistical analysis

Univariate analysis: Two-tailed χ^2 testing with one degree of freedom and with Yate's correction was used to compare the proportion of patients with favourable outcome between the groups of patients showing each seizure onset pattern or presence/absence of PED. Existence of significant differences was assumed if $p < 0.05$. Analysis was carried out with Graphpad.
(www.graphpad.com/quickcalcs/contingency1.cfm).

2.11. Multivariate analysis

Backward stepwise multiple logistic regression analysis were undertaken using SPSS for MAC OSX version 21. Surgical outcome was the dependent variable and the following most common SIOPs were used as independent covariates: DEE, FA, FA-DEE and spike wave activity. PEDs coexisted with SIOP and therefore were not considered as independent covariates. Consequently, PEDs were not included in the model. Similarly, the location of seizure onset was not incorporated in the multivariate analysis.

3. Results

3.1. Patients

Among all 69 patients, 31 (45%) patients were female and 38 (55%) were male. The mean age at onset of epilepsy was 10.73 years (SD = 9.07). The average age at resection was 31.8 years (SD = 13.0). The mean follow-up period was 42.15 months (SD = 30.1). Table 1 summarises patients' details. Fifty-one patients (73.9%) underwent temporal lobe resections, 13 (18.8%) had frontal resections, two (2.9%) patients underwent parietal resections, two (2.9%) had occipital resections, and one patient underwent an insular resection. The most common pathology found after resection was mesial temporal sclerosis, which was present in 28 patients (40.6%), followed by focal cortical dysplasia which was present in 12 patients (17.4%), 6 patients (8.7%) revealed dysembryoplastic neuroepithelial tumor, two patients (2.9%) showed heterotopia, and non-specific changes were seen in 9 patients (13.0%).

3.2. Intracranial electrodes

Among all 69 patients, 28 patients (40.6%) had subdural strips only, 17 patients (24.6%) had depth electrodes only, 15 patients (21.7%) had a combination of subdural mat and strip electrodes, 4 patients (5.8%) had mat electrodes only, 4 patients (5.8%) had a combination of depth and subdural strip electrodes and one patient (1.4%) had depth and mat electrodes.

Regarding electrode coverage, 38 patients (55.1%) had electrodes restricted to the temporal lobes, one patient (1.4%) had electrodes restricted to the frontal lobes, 17 patients (24.6%) had electrodes in the temporal and frontal lobes, 5 patients (7.2%) had electrodes covering temporal, frontal and parietal lobes, 4 patients (5.8%) had electrodes in temporal and occipital lobes, 3 patients (4.3%) had electrodes in the temporal and parietal lobes, and one patient (1.4%) had electrodes covering the frontal and parietal lobes. Fifty patients (72.5%) had electrodes implanted bilaterally and 19 patients (27.5%) had unilateral electrodes.

3.3. Topography of resections and surgical outcome

Table 2 shows the relation between the location of resection and surgical outcome in all 69 patients. Temporal lobe resections showed the highest rate of improvement after surgery. Among the larger group of 51 temporal resections, 25 showed focal medial temporal seizure onset, 8 showed a regional onset involving medial temporal structures, and 18 showed lateral temporal onset.

3.4. Seizure onset patterns

A total of 373 seizures from the 69 patients were analysed. Representative examples of each seizure onset pattern found are shown in Figs. 1–5. The most common SIOP was FA, which was seen in 23 patients (33.3%) with a mean frequency of 25.5 Hz (SD = 21). FA-DEE was the seizure onset pattern in 14 patients (20.3%) with a mean of 16.5 Hz (SD = 24.4), DEE in 13 patients (18.9%), spike-wave activity in 8 (11.6%) patients (mean frequency = 3.5 Hz; SD = 1.07), sharp-waves in 4 (5.8%) patients (mean frequency = 4.7 Hz; SD = 0.96), alpha in 4 (5.8%) patients (mean frequency = 9.2 Hz; SD = 0.957), delta activity in two (2.9%) patients (mean frequency = 1 Hz; SD = 1.4) and runs of spikes in one (1.4%) patient at a frequency of 4 Hz.

Fifty-six patients presented a single SIOP type and 13 had different SIOPs in different seizures. Among the latter, eight patients showed all seizures arising from the same structure with different seizure onset patterns, and five patients showed seizures arising

Table 2
Percentage of patients with each outcome grade according to resection lobe for Engel and ILAE outcome classifications.

Engel class	I	II	III	IV
	%	%	%	%
Temporal resections ($n = 51$)	52.9	15.7	25.5	5.9
Frontal resections ($n = 13$)	30.8	7.7	38.5	23.1
Parietal resections ($n = 2$)	50.0	0.0	50.0	0.0
Occipital resections ($n = 2$)	100	0.0	0.0	0.0
Insular resections ($n = 1$)	0.0	0.0	100	0.0
TOTAL ($n = 69$)	49.3	13.0	29.0	8.7

ILAE class	1	2	3	4	5	6
	%	%	%	%	%	%
Temporal resections ($n = 51$)	41.2	11.8	15.7	25.5	5.9	0.0
Frontal resections ($n = 13$)	23.1	7.7	15.4	30.8	23.1	0.0
Parietal resections ($n = 2$)	50.0	0.0	0.0	50.0	0.0	0.0
Occipital resections ($n = 2$)	50.0	0.0	50.0	0.0	0.0	0.0
Insular resections ($n = 1$)	0.0	0.0	0.0	100	0.0	0.0
TOTAL ($n = 69$)	37.7	10.1	15.9	27.5	8.7	0

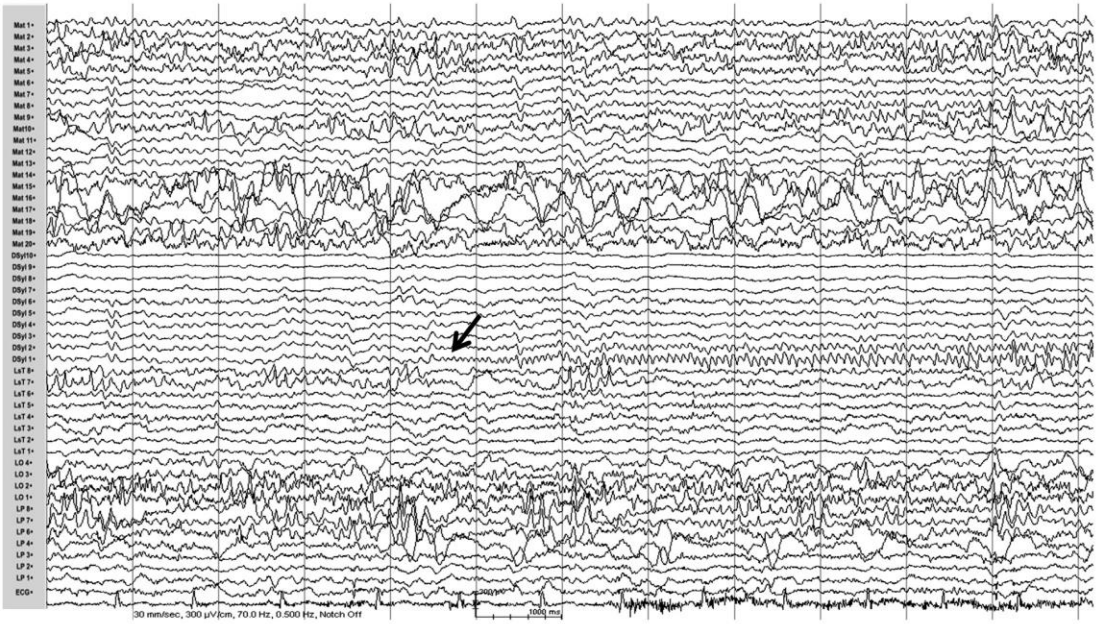

Fig. 1. Example of FA seizure onset pattern (arrow) in a patient with a 20-electrode mat over the left parietal lobe, a 10-electrode depth bundle along the left sylvian fissure, two 8-electrode subtemporal strips (parietal and subtemporal) and a 4-electrode strips over the occipital lobe, shown in common average reference. Note fast activity at 16 Hz arising at electrode 2 of the depth electrode. Mat = sylvian mat; DSyl = sylvian depth electrode; LsT = left subtemporal strip; LO = left occipital strip; LP = left parietal strip; ECG = electrocardiogram. For each strip and for the depth electrode bundle, electrode 1 is the farthest from the insertion site and 8 is the closest. For the mat, electrode 1 is at the anterior and superior corner.

independently from different structures within the same lobe. No significant differences in outcome were found between the 56 patients with a single seizure onset type and the 13 patients with more than one seizure onset type.

PEDs were present in 52 patients (75.4%), were focal in 9 patients (13.0%), widespread in 32 patients (47.0%) and bilateral in 11 patients (16.0%). When PEDs were present, they involved an average of 8 contacts (SD ± 8.43) more than the focal seizure onset patterns.

Among the 51 temporal patients, the SIOP was FA in 17 (33.3%) patients, FA-DEE in 10 (19.6%), DEE in 7 (13.7%), spike-wave activity in 7 (13.7%) patients, sharp waves in 4 (7.8%), alpha activity in 3 (5.9%), delta activity in 2 (3.9%) and rhythmic spikes in one (2%) patient. Among the 13 frontal patients, the SIOP was FA in three 3 (23.1%) patients, FA-DEE in 3 (23.1%), DEE in 6 (46.2%), and spike wave activity in one (7.7%) patient. Among the two parietal patients, the SIOPs were FA in one patient and alpha activity in another. Among the two occipital patients, FA was the SIOP in one patient and FA-DEE in another. The only insular patient showed FA as SIOP.

Among the 51 temporal patients, PEDs were present in 37 (72.5%), were focal in 8 patients (15.7%), widespread in 23 patients (45.1%) and bilateral in 6 (11.8%). Among the 18 extratemporal patients, PEDs were present in 15 (83.3%), were focal in 1 patient (5.6%), widespread in 9 patients (50%) and bilateral in 5 (27.8%).

3.5. Prognostic value of seizure onset patterns

Table 3 shows the relation between surgical outcome, SIOPs and presence of PEDs in all resections and in temporal resections. Data for extratemporal resections can be obtained by subtracting the data for temporal resections from the data for all resections. Among all patients, FA was the SIOP that showed the highest proportion of patients with Engel Grade I, accounting for 17 (73.9%) of the 23 patients, with only 6 (27.1%) presenting grades II-IV. Interestingly, when FA appeared at the same time as DEE, the proportion of Engel grade I decreased to 43%. On the other hand, we found that only 1 patient of 13 presenting DEE as the SIOP showed Engel Grade I whereas 12 (92%) showed poor outcome (grades II–IV). Among all 69 patients, 52 patients presented PED immediately before the seizure onset pattern. Interestingly, among the 11 patients with bilateral PEDs, 46% enjoyed favourable outcome.

3.6. Univariate statistical analysis

Two by two contingency tables were constructed to estimate the association between surgical outcome and different pairs of seizure onset patterns. This was carried out within the following three groups: all patients, temporal patients and extratemporal patients. The following comparisons were perfomed within each group:

(a) FA versus any other SIOP.
(b) FA versus DEE.
(c) FA or FA-DEE versus absence of FA.
(d) PED versus absence of PED.
(e) Widespread or bilateral PED versus absence of widespread or bilateral PED.
(f) PED and FA versus PED and any SIOP other than FA.
(g) FA-DEE versus DEE.
(h) DEE versus any other SIOP.
(i) FA versus FA-DEE.

The interested reader can carry out any other comparison by choosing the appropriate cells in Table 3.

Table 4 shows the 2×2 contingency tables with trends or significant associations between Engel outcome scale and seizure onset patterns in each patient group. In all 69 patients, FA showed better

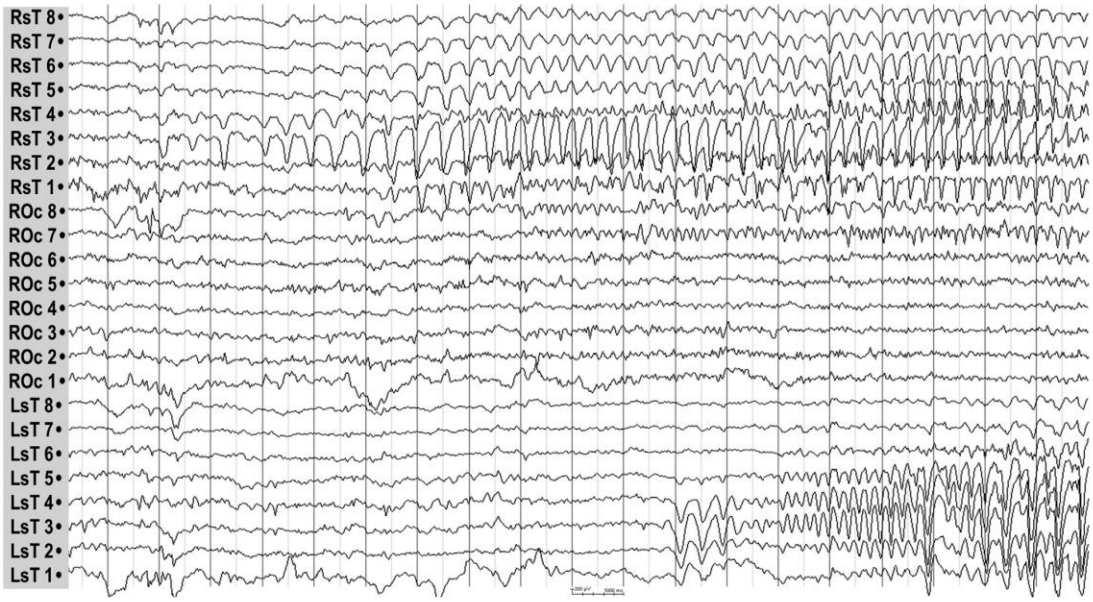

Fig. 2. Example of seizure onset pattern consisting of sharpened delta activity (arrow) in a patient with three 8-contact sudural strips (bilateral subtemporal strips and one right occipital strip), shown in common average reference. Note seizure onset with sharpened delta activity at electrodes 3–4 of the right subtemporal strip. RsT = Right subtemporal strip; ROc = Right occipital strip; LsT = Left suptemporal strip. For each strip, electrode 1 is furthest from the insertion burr hole.

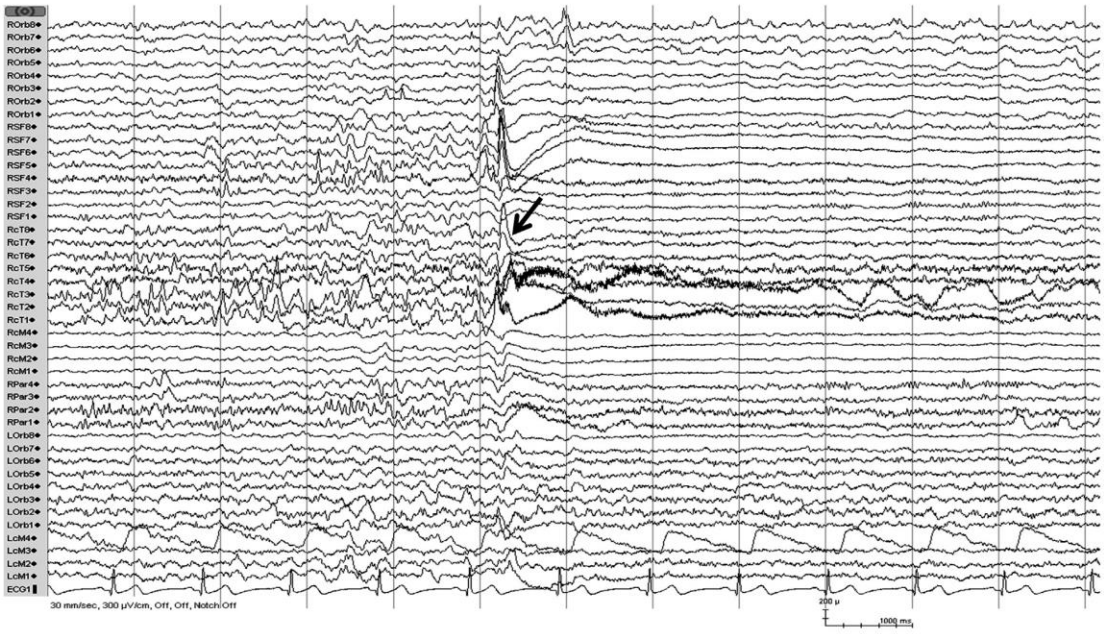

Fig. 3. Example of seizure onset pattern consisting of FA-DEE activity (arrow) in a patient with a right parietal 4-contact strip, an 8-contact strip implanted parallel to the right central fissure and reaching lateral temporal cortex, an 8-contact parasagittal strip covering the superior aspect of the right frontal and parietal lobes, two 4-contact centro-medial strips implanted bilaterally and two 8-contact anterior frontal strips implanted bilaterally reaching orbital cortices. The record is displayed with common average reference. Note fast activity restricted to electrodes 1-2 of the right centrotemporal strip starting simultaneously with a diffuse electrodecremental event involving all the electrodes of the right centro-temporal and superior frontal strips. There is PED involving largely the same contacts as the decrement. ROrb = right orbital 8-contact strip; RSF = right superior frontal/parietal 8-contact strip; RcT = right centro temporal 8-contact strip; RCM = right centro medial 4-contact strip; LOrb = left orbital 8-contact strip; LCM = left centro medial 4-contact strip. For each strip, electrodes 1 is the farthest from the insertion site and 8 is the closest.

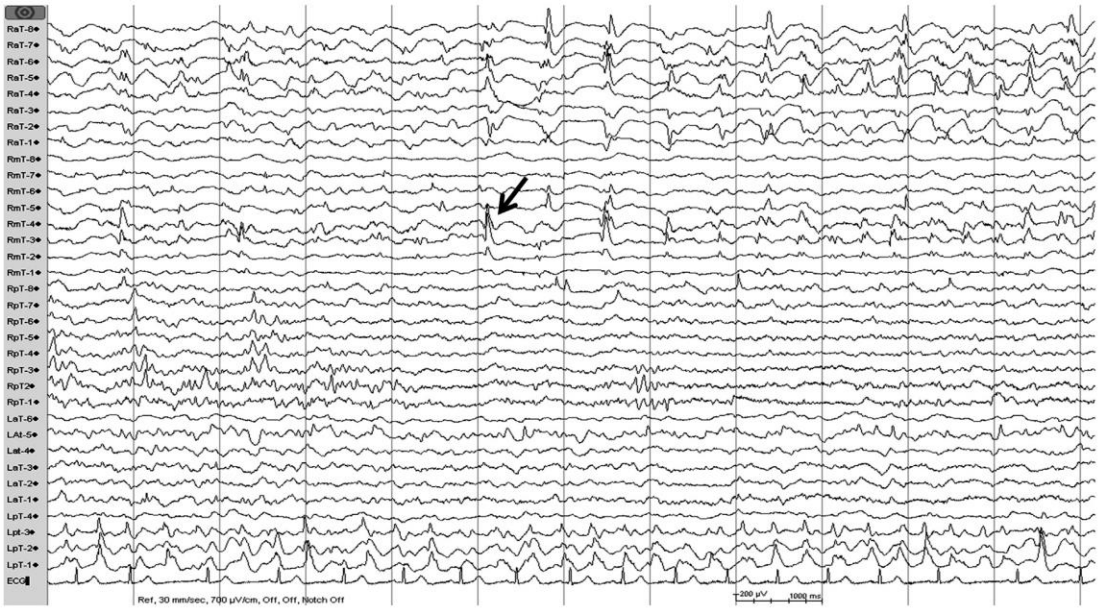

Fig. 4. Example of seizure onset pattern consisting of spike-wave activity (arrow) in a patient with bilateral subtemporal strips (anterior, mid and posterior on the right, and anterior and posterior on the left). The record is displayed with common average reference. Note seizure onset with spike-wave activity involving most electrodes of the right anterior subtempoal strip and the deepest electrodes of the right mid temporal strip. RaT = Right anterior temporal strip; RmT = Right medial temporal strip; RpT = Right posterior temporal strip; LpT = left posterior temporal strip; LaT = left anterior temporal strip. For each strip, electrode 1 is farthest from the insertion burr hole.

surgical outcome than other patterns, either when occurring on its own ($p = 0.0083$) or in association with DEE ($p = 0.039$). The better outcome associated with FA seizure onset is preserved when PEDs are present ($p = 0.0081$). In contrast, DEE appears to be a predictor of poor surgical outcome when compared with FA ($p = 0.0005$) or with any other seizure onset pattern ($p = 0.0025$).

Among temporal resections, FA onset patterns showed better surgical outcome when compared to DEE ($p < 0.0389$) (Table 3). In addition, there is a trend towards an association between DEE and poorer outcome when compared with any other seizure onset pattern ($p = 0.0721$).

Among extratemporal resections, patients with FA enjoyed better surgical outcome than those with seizures starting with other patterns ($p = 0.0263$), and specifically with DEE ($p = 0.0192$). In addition, there is a trend towards an association between DEE and poorer outcome when compared with any other seizure onset pattern ($p = 0.0601$).

3.7. Multiple logistic regression

The following covariates were used for the logistic regression model: DEE, FA, FA-DEE and spike wave activity (Model $\chi^2 = 18{,}764$, 3 df, $p = 0.00$, Goodness of fit = 29,482). Patients showing DEE were associated with a greater risk of failure to obtain Engel class I outcome compared with those not showing DEE ($b = -3{,}584$, SE = 1,323, $p = 0.007$).

3.8. Pathology

Table 5 shows the cross tabulation between seizure onset patterns and neuropathological findings for the 69 patients. Mesial temporal sclerosis and focal cortical dysplasia were the most common pathologies, accounting for 58% of patients. There was no clear association between seizure onset patterns and specific pathology, except possibly between sharp/spike waves and mesial temporal sclerosis. In the present study, FA was the most common SIOP, occurring in all pathological entities.

4. Discussion

The purpose of this study is to estimate the prognostic value of the seizure onset pattern to predict seizure control and pathology after epilepsy surgery. We found that FA was associated with favourable surgical outcome, whereas DEE was associated with poor surgical outcome. The presence or topographic extension of PEDs was not correlated with outcome. There is no clear association between pathology and seizure onset pattern.

4.1. Clinical relevance

FA was the most common SIOP in temporal and extratemporal epilepsies and its presence was associated with favourable surgical outcome. This result is in concordance to previous studies (Lieb et al., 1986; Spencer et al., 1992; Alarcon et al., 1995; Jung et al., 1999; Kutsy et al., 1999; Lee et al., 2000; Wetjen et al., 2009; Holtkamp et al., 2012; Dolezalova et al., 2013). These replicated observations support the notion that fast activity at seizure onset truly reflects in-situ generation of epileptic seizures.

In addition, more widespread patterns were also common. DEE was observed at seizure onset in 39% of patients, either in isolation (19%) or associated with fast activity (20%). DEE was associated with poor surgical outcome. Consequently, when discussing surgical outcome with patients, caution may be required if DEE is the SIOP. The prognostic significance of FA-DEE pattern appears to be in between that of FA and that of DEE.

PEDs were very common, present in 75.4% of patients, and among these, PEDs were widespread or bilateral in 63%. It would be difficult to consider PEDs as interictal activity, as they tend to

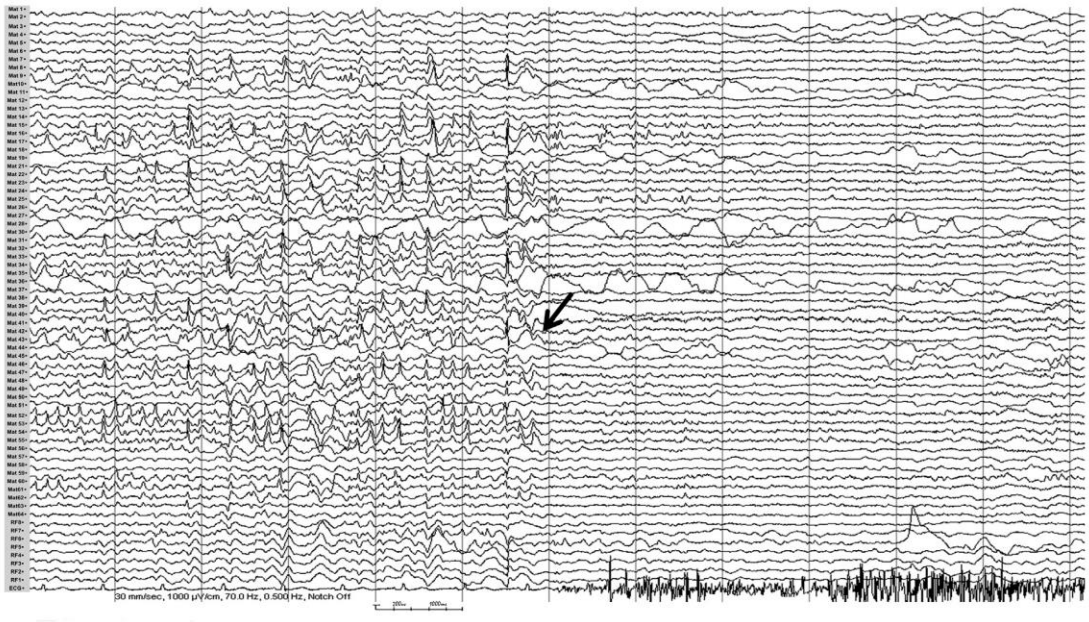

Fig. 5. Example of seizure onset pattern consisting of DEE (arrow) in a patient with a 64-electrode mat applied over the right parietal lobe and one 8-contact subdural strip implanted in the right frontal lobe. The record is displayed with common average reference. Note seizure onset starting with DEE involving all electrodes. RF = Right frontal. For each strip, electrode 1 is farthest from the insertion burr hole. For the mat, electrode 1 is at the anterior and superior corner.

Table 3
Relation between seizure onset pattern and Engel surgical outcome in temporal and extratemporal resections.

	I	II	III	IV
	%	%	%	%
All resections				
SIOP				
FA (n = 23)	73.9	8.7	8.7	8.7
FA-DEE (n = 14)	42.9	14.3	35.7	7.1
DEE (n = 13)	7.7	15.4	53.8	23.1
Spike-wave activity (n = 8)	75.0	12.5	12.5	0.0
Alpha (n = 4)	50.0	0.0	50.0	0.0
Sharp-waves (n = 4)	50.0	25.0	25.0	0.0
Delta (n = 2)	0.0	50.0	50.0	0.0
Spikes (n = 1)	0.0	0.0	100	0.0
TOTAL (n = 69)	49.3	13.0	29.0	8.7
PED				
Focal PEDs (n = 9)	66.7	22.2	11.1	0.0
Widespread PEDs (n = 32)	50.0	6.3	34.4	9.4
Bilateral PEDs (n = 11)	45.5	18.2	18.2	18.2
TOTAL (n = 52)	51.9	11.5	26.9	9.6
Temporal resections				
SIOP				
FA (n = 17)	70.6	11.8	5.9	11.8
FA-DEE (n = 10)	40.0	20.0	40.0	0.0
DEE (n = 7)	14.3	28.6	42.9	14.3
Spike-wave activity (n = 7)	85.7	0.0	14.3	0.0
Alpha (n = 3)	66.7	0.0	33.3	0.0
Sharp-waves (n = 4)	50.0	25.0	25.0	0.0
Delta (n = 2)	0.0	50.0	50.0	0.0
Spikes (n = 1)	0.0	0.0	100	0.0
TOTAL (n = 51)	52.9	15.7	25.5	5.9
PED				
Focal PEDs (n = 8)	75.0	12.5	12.5	0.0
Widespread PEDs (n = 23)	56.5	8.7	30.4	4.3
Bilateral PEDs (n = 6)	33.3	33.3	16.7	16.7
TOTAL (n = 37)	56.8	13.5	24.3	5.4

FA = fast activity.
FA-DEE = fast activity and diffuse electrodecremental event.
DEE = diffuse electrodecremental event.
PED = preceding epileptiform discharge.

Table 4
Relation between seizure onset pattern and surgical outcome. Contingency tables showing trends or significant associations.

Seizure onset patterns compared	Good	Poor	Statistic	P
All patients				
FA	17	6	χ^2 = 6.95	0.0083*
Any other SIOP	17	29		
FA	17	6	χ^2 = 12.04	0.0005*
DEE	1	12		
FA or FA-DEE	23	14	χ^2 = 4.247	0.0393*
Absence of FA	11	21		
PED and FA	12	2	χ^2 = 7.009	0.0081*
PED and any SIOP other than FA	15	23		
DEE	1	12	χ^2 = 9.126	0.0025*
Any other SIOP	33	23		
Temporal patients				
FA	12	5	χ^2 = 4.266	0.0389*
DEE	1	6		
DEE	1	6	χ^2 = 3.234	0.0721
Any other SIOP	26	18		
Extratemporal patients				
FA	5	1	χ^2 = 4.938	0.0263*
Any other SIOP	2	10		
FA	5	1	χ^2 = 5.486	0.0192*
DEE	0	6		
FA or FA-DEE	7	3	χ^2 = 6.455	0.0111*
Absence of FA	0	8		
DEE	0	6	χ^2 = 3.536	0.0601
Any other SIOP	7	5		

Good = good surgical outcome (grade I of Engel classification).
Poor = poor surgical outcome (grades II, III or IV of Engel classification).
FA = fast activity.
DEE = diffuse electrodecremental event.
FA-DEE = fast activity and simultaneous diffuse electrodecremental event.
PED = preceding epileptiform discharge.
χ^2 = two tailed Chi squared test with Yates correction (1 degree of freedom).
* Significant difference.

Table 5
Cross tabulation seizure onset pattern and pathology.

Subpopulation	Astrocytosis %	DNET %	FCD %	MTS %	No changes %	Perinatal ischemic cyst %	Tumour %
SIOP							
Alpha ($n = 4$)	25.0	0.0	25.0	50.0	0.0	0.0	0.0
Decrement ($n = 13$)	15.4	15.4	23.1	15.4	23.1	0.0	7.7
Delta ($n = 2$)	0.0	0.0	0.0	100.0	0.0	0.0	0.0
Fast ($n = 23$)	0.0	13.0	17.4	39.1	17.4	4.3	8.7
FA-DEE ($n = 14$)	0.0	7.1	14.3	28.6	35.7	0.0	14.3
Sharp-wave ($n = 4$)	0.0	0.0	0.0	75.0	25.0	0.0	0.0
Spike-wave ($n = 8$)	0.0	12.5	25.0	62.5	0.0	0.0	0.0
Spikes ($n = 1$)	0.0	0.0	0.0	100.0	0.0	0.0	0.0
TOTAL ($n = 69$)	4.3	10.1	17.4	40.6	18.8	1.4	7.2
PED							
Focal PEDs ($n = 9$)	0.0	11.1	11.1	55.6	11.1	0.0	11.1
Widespread PEDs ($n = 32$)	0.0	3.1	18.8	34.4	21.9	3.1	21.9
Bilateral PEDs ($n = 11$)	9.1	18.2	27.3	27.3	0.0	0.0	18.2
TOTAL ($n = 52$)	1.9	7.7	19.2	36.5	15.4	1.9	19.2

DNET = dysembryoplastic neuroepithelial tumor.
FDC = focal cortical dysplasia.
MTS = mesial temporal sclerosis.

be larger and more diffuse than interictal discharges, and occur immediately before each seizure, suggesting that they are involved in seizure initiation. Interestingly, their presence and topographic extension does not seem to affect surgical outcome. More specifically, the presence of a bilateral or widespread epileptiform discharge immediately preceding a seizure does not imply that the seizure is generalised, and should not necessarily preclude surgery.

With the exception of sharp/spike wave activity and mesial temporal sclerosis, there was not a clear association between seizure onset patterns and specific pathology, in concordance with previous reports in smaller series (Mathern et al., 1995; Perucca et al., 2014). This suggests that the mechanisms of epileptogenesis may be, to a degree, independent of the underlying pathology.

4.2. Statistics

An interesting finding is that DEE appears to have a prognostic value of its own, independently of FA. Apart from the comparison between FA and DEE, the most significant differences are found between DEE and any other SIOP ($p = 0.0025$, Table 3, and results from multiple logistic regression), suggesting that DEE has value of its own, independent of FA.

In contrast to DEE, our study failed to demonstrate a prognostic value for PED. There is no difference in outcome between those with PED and those without; or between those with widespread or bilateral PED and those without widespread or bilateral PED. However, there is a difference between those with PED and FA and those with PED and any SIOP other than FA, probably due to the prognostic value of FA.

4.3. Pathophysiological implications

In our study, FA, DEE and FA-DEE were the most common SIOPs. The association between favourable postsurgical outcome and FA at seizure onset suggests that FA is a reliable preoperative biomarker of the epileptogenic zone. The present clinical study is limited to the standard EEG frequency band, below 70 Hz, which was used in routine clinical recordings during the period of recruitment. The clinical use of higher frequencies up to 600 Hz and beyond is presently under evaluation (Jirsch et al., 2006; Jacobs et al., 2008; Koehling and Staley, 2011; Buzsaki and Silva, 2012).

Recordings were obtained from different brain areas and electrode types, which may have influenced the incidence of SIOPs. Indeed, DEE was more common in frontal patients (46%), which may explain the poorer outcome observed in frontal epilepsies (Kumar et al., 2013).

At the moment, the mechanisms of DEE and their relation to surgical outcome are not fully understood. It might be presumed that where the first detected SIOP is generalized, seizure onset is either diffuse or occurs at a site that has not been implanted, and that surgical outcome will consequently be poor, as suggested by our study. In principle, DEE can be explained by neuronal de-synchronisation or decrease in neuronal activity. To our knowledge, the mechanisms whereby the initiation of focal seizures can be associated with such widespread changes in neuronal activity are unknown.

The physiological significance of PEDs is also puzzling. PEDs share similar morphology to interictal epileptiform discharges, with a sharp element followed by a prominent slow wave. The slow waves of interictal epileptiform discharges are associated with a period of inhibition lasting for several hundreds of milliseconds (Keller et al., 2010, Alarcon et al., 2012a). Likewise, the prominent slow wave associated with PEDs may be dominated by neuronal inhibition. Such inhibition is activated during spontaneous epileptiform discharges, and also by electrical stimulation of most cortical regions (Alarcon et al., 2012a), suggesting a generic and broadly distributed mechanism for both. It is possible that a rebound increase in neuronal firing occurring after a period of widespread cortical inhibition might be responsible for excessive neuronal synchronisation resulting in seizures. The reasons why PEDs are widespread or bilateral in as many as 61% of patients are unclear, but may be due to the ubiquity of generic inhibitory mechanisms which are extensively found throughout the cortex and beyond (Alarcon and Cervero, 1990; Alarcon et al., 2012a).

4.4. Limitations

The main limitation of the study is the heterogeneity of the patient population and methodology used. The series includes different epilepsy and seizure types, studied with subdural and depth electrodes, with various durations of telemetry. In some conditions, the numbers are small for statistical analysis (e.g., some SIOPs, parietal and occipital resections). However, due to the large number of patients studied, in many subgroups (e.g., FA, DEE, FA-DEE, temporal and frontal resections) the number of patients is sufficient for correlation with outcome. Automatic analysis was difficult due to the enormous variety in the morphology of SIOPs, which drove the study towards more subjective visual analysis by human experts.

5. Conclusion

In the present paper, we characterise the incidence and prognostic value of focal, widespread and bilateral PEDs. FA, FA-DEE, DEE and PED are the most common SIOPs. The presence of FA as SIOP was associated with favourable surgical outcome, whereas DEE was associated with poor surgical outcome. Presence or topographic extension of PEDs was not correlated with good or poor outcome. There is no clear association between pathology and seizure onset patterns.

6. Disclosure

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3. CHAPTER THREE

1 Prognostic value of the of the second ictal intracranial pattern for the outcome of epilepsy surgery.

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2 Personal contributions for this publication:

- Review all clinical records for those patients who have been implanted intracranial electrodes and were operated from November 1999 to January 2010.
- Elaborate a database for entry different clinical details of the patients whom fulfilled the previous criteria.
- Review all intracranial EEG recordings of the patients 63 patients included in the study.
- Classify all the seizures (373) into the different second seizure patterns included for the study.
- Perform the statistical analysis for the study.
- Select and edit different images for including into the manuscript.
- Elaborate all tables for the study.
- Write the first draft of the manuscript and submit it to respective journal.

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Prognostic value of the second ictal intracranial pattern for the outcome of epilepsy surgery

Diego Jiménez-Jiménez [a,b,c,*], David Martín-López [a,b,d,e], Mojtaba A. Masood [a,b], Richard P. Selway [f], Antonio Valentín [a,b,1], Gonzalo Alarcón [a,b,e,g,1]

[a] Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK
[b] Department of Clinical Neurophysiology, King's College Hospital NHS Trust, London, UK
[c] School of Medicine, Universidad San Francisco de Quito, Quito, Ecuador
[d] West Surrey Clinical Neurophysiology, St Peter's Hospital, Chertsey, UK
[e] Departamento de Fisiología, Facultad de Medicina, Universidad Complutense, Madrid, Spain
[f] Department of Neurosurgery, King's College Hospital, NHS Trust London, UK
[g] Comprehensive Epilepsy Center Neuroscience Institute, Academic Health Systems, Hamad Medical Corporation, Doha, Qatar

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HIGHLIGHTS

- The prognostic value of ictal patterns depends on where they occur within the seizure.
- More widespread second ictal patterns are associated with poorer outcome.
- Delayed second ictal patterns ($\geqslant$10 s) appear to be associated with good outcome in temporal lobe epilepsy.

ABSTRACT

Objective: To investigate the prognostic value of the second ictal pattern (SIP) that follows the first ictal pattern (FIP) seen at seizure onset in order to predict seizure control after epilepsy surgery.
Methods: SIPs were analysed in 344 electro-clinical and subclinical seizures recorded with intracranial electrodes in 63 patients. SIPs were classified as (a) electrodecremental event (EDE); (b) fast activity (FA); (c) runs of spikes; (d) spike-wave activity; (e) sharp waves; (f) alpha activity; (g) delta activity and (h) theta activity. Engel surgical outcome scale was used.
Results: The mean follow-up period was 42.1 months (SD = 30.1). EDE was the most common SIP seen (41%), followed by FA (19%), spike-wave activity (18%), alpha activity (8%), sharp-wave activity (8%), delta activity (3%), runs of spikes (2%) and theta activity (2%). EDE as SIP was associated with favourable outcome when compared with FA ($p = 0.0044$) whereas FA was associated with poor outcome when compared with any other pattern ($p = 0.0389$). FA as SIP tends to occur after EDE (75%) whereas EDE tends to evolve from a FIP containing FA (77%). SIP extent was focal in 46% of patients, lobar in 24%, multilobar in 14% and bilateral in 16%. There is a gradual decrease in the proportion of Engel grade I with the extent of SIP. Focal and delayed (in temporal lobe epilepsy) SIPs appear to be associated with better outcome.
Conclusions: As SIP, EDE was associated with favourable surgical outcome whereas FA was associated with poor outcome, probably because outcome is dominated by FIP.
Significance: EDE as SIP should not discourage surgery. However, FA as SIP should be contemplated with caution. SIP focality and latency can have prognostic value in epilepsy surgery.

1. Introduction

Approximately 50% of patients undergoing ressective surgery for the treatment of epilepsy continue suffering from seizures after surgery (Kumar et al., 2013) despite the variety of techniques

* Corresponding author at: Department of Basic and Clinical Neuroscience, PO Box 43, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London SE5 8AF, UK. Tel.: +44 207 848 5161; fax: +44 207 848 0988.
E-mail address: diego.jimenez_jimenez@kcl.ac.uk (D. Jiménez-Jiménez).
[1] Drs A. Valentín and G. Alarcón are joint senior authors.

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available to identify the epileptogenic zone preoperatively, including interictal and ictal scalp electroencephalography (Adachi et al., 1998; Alarcon et al., 2001), neuropsychology (Akanuma et al., 2003) and neuroimaging (Koutroumanidis et al., 2004; Duncan, 2010).

Approximately 30% of patients assessed for surgery require assessment with intracranial electrodes for the identification of the epileptogenic zone (Alarcon et al., 2006; Kumar et al., 2013). Although intracranial recordings can show a wide variety of interictal abnormalities (Alarcon et al., 1994, 1995, 2012; Fernandez Torre et al., 1999a,b; Kutsy et al., 1999; Kissani et al., 2001; Flanagan et al., 2009) with various degrees of localising value (Valentin et al., 2014), ictal findings are still the gold standard in the interpretation of the intracranial recordings.

The onset of focal seizures can be associated with a variety of sustained, evolving EEG patterns which may show different prognostic values for predicting seizure freedom after surgery (Alarcon et al., 1995; Jung et al., 1999; Holtkamp et al., 2012; Dolezalova et al., 2013; Jimenez-Jimenez et al., 2015b). As the first ictal pattern (FIP), focal fast activity (FA) is associated with favourable outcome whereas diffuse EEG flattening tends to be associated with poor seizure control. In temporal lobe epilepsy, the poor seizure control associated with such diffuse FIP is not explained by the presence of bilateral functional temporal connections (Jimenez-Jimenez et al., 2015a). Ictal activity is sustained, lasting for several seconds or minutes, with ictal patterns often evolving or spreading as the seizure propagates and recruits further cortex. The patterns arising are of various nature and often complex, with FA followed by diffuse EEG flattening or vice versa, or both occurring simultaneously (Jimenez-Jimenez et al., 2015b), or FA evolving over seconds, gradually decreasing in frequency and increasing in amplitude (rhythmic ictal transformation) (Alarcon et al., 2012). In scalp recordings, unilateral delayed rhythmic activity occurring seconds after seizure onset has a 79% lateralising value, even in the absence of a focal ictal onset on the scalp EEG (Alarcon et al., 2012). The latency of seizure propagation may also influence surgical outcome. In temporal lobe epilepsy, interhemispheric propagation time shorter than 5 s was associated with poor outcome whereas propagation times longer than 50 s were associated with good seizure control (Lieb et al., 1986).

The prognostic significance of specific ictal patterns occurring after FIP in intracranial recordings is largely unknown. Our hypothesis is that the second ictal pattern (SIP) is related to the mechanisms involved in seizure spreading and affects surgical prognosis. In the present work, we investigate the prognostic value of the nature, latency and extent of SIP occurring after the FIP seen at seizure onset.

2. Methodology

2.1. Patients

The study included all 63 patients who underwent assessment with intracranial electrodes prior resective surgery for the treatment of epilepsy at King's College Hospital from November 1999 to December 2010, who had a follow up period longer than 12 months.

The study excluded the patients who: (a) had no seizures during telemetry (1 patient), (b) underwent hemispherectomy for the treatment of Rasmussen Disease (1 patient), (c) were assessed for reoperation after failure of the first operation (3 patients), (d) presented only subclinical seizures with no SIP (1 patient).

Under UK regulations, no NHS Research Ethics Committee approval was required under section 6 of the Governance Arrangements for Research Ethics Committees (September 2011). The Neuroscience Audit Committee at King's College Hospital has approved this study.

2.2. Electrode placement

The type, number and location of the electrodes were determined by the suspected location of the ictal onset region, according to non-invasive evaluation: clinical history, scalp EEG recordings obtained with the Maudsley system (Fernandez Torre et al., 1999b; Alarcon et al., 2001; Kissani et al., 2001), neuropsychology (Akanuma et al., 2003) and neuroimaging. The selection criteria and implantation procedures have been described in detail elsewhere (Alarcon et al., 2006; Alarcon, 2012).

2.2.1. Subdural electrodes

Subdural electrodes consisted of strips and mats (AdTech Medical Instruments Corp., WI, USA). Each strip consisted of a single row of 4–8 platinum disk electrodes spaced at 10 mm between centres. The disks were embedded in a 0.7 mm thick polyurethane strip which overlapped the edges leaving a diameter of 2.3 mm exposed, and recessed approximately 0.1 mm from the surface plane. Mats contained rectangular arrays of 12, 16, 20, 32 or 64 similar platinum electrodes with 10 mm centre-to-centre distances within rows.

2.2.2. Intracerebral (depth) electrodes

Multicontact flexible bundles of depth electrodes (AdTech Medical Instruments Corp., WI, USA) were implanted stereotactically under MRI guidance. The electrode bundles contained 8 or 10 cylindrical 2.3 mm long platinum contacts separated by 5 mm between centres of adjacent electrodes of the same bundle.

The position of the electrodes was confirmed with post-implantation CT or MRI.

2.3. Electroencephalographic recordings

Recording of intracranial EEG started when the patient had recovered from electrode implantation, usually 24–48 h after surgery. Cable telemetry with up to 64 recording channels was used for data acquisition with simultaneous video monitoring. In 29 patients, the Telefactor Beehive-Beekeeper system (Astro-Med, RI, USA) was used. Data were digitized at 200 Hz and band pass filtered (high pass cut-off frequency at 0.3 Hz and low pass cut-off frequency at 70 Hz). The system input range was 2 mV and data were digitized with a 12 bit analog-to-digital converter (amplitude resolution of 0.488 μV). In the remaining 34 patients, a Medelec-Profile system was used (Medelec, Oxford Instruments, United Kingdom). Data were digitized at 256 Hz and band pass filtered (0.05–70 Hz). The input range was 10 mV and data were digitized with a 22 bit analog-to-digital converter (an amplitude resolution of 0.153 μV). Data were recorded as common reference to Pz or to an intracranial electrode, and displayed in a variety of montages including various scalp, intracranial and average common references to identify the most inactive reference for review in each patient. When common average reference was used, channels showing large spikes or artifacts or responses were removed from the average.

2.4. SIP analysis

The study included 344 seizures (336 clinical and 8 subclinical) recorded from all 63 patients. Visual analysis of the pruned ictal recordings was carried out to identify FIPs and SIPs. As FIP we consider the first sustained ictal change observed at the beginning of seizures recorded in at least one channel, i.e. the patterns previously designated as "sustained ictal onset patterns"

(Jimenez-Jimenez et al., 2015b). A pattern is considered to be "sustained" if it lasts for longer than 1.5 s. FIPs can be EDE, runs of focal fast activity, sharp waves, spikes, theta activity or slow waves. FIPs can be preceded by a transient epileptiform discharge (preceding epileptiform discharge or PED), which does not appear to have prognostic value (Jimenez-Jimenez et al., 2015b) and will be ignored for analysis in the present work. The SIP was the second sustained ictal pattern lasting for at least 1.5 s recorded by any channel after FIP onset, regardless of the location or duration of FIP. Therefore, FIP and SIP can occur in the same channel or in different channels. The terms "first" and "second" ictal patterns refer to the onset of each pattern independently of their duration. If occurring in different channels, FIP and SIP can coexist at the same time, but the onset of SIP must occur after the onset of FIP. If occurring in the same channel, the distinction between FIP and SIP was defined by a change in the EEG pattern among the categories defined in the next paragraph.

The SIPs seen on the EEG were visually classified into: fast activity (FA), spike-and-wave activity, runs of spikes, rhythmic sharp waves, alpha activity, delta activity, theta activity, and electrodecremental event (EDE). In the seizures where the first ictal pattern gradually changed in frequency along time, SIP was considered to start where frequency changed bands (e.g. from FA to alpha). The presence, location, laterality, duration, extent, frequency, rhythm ictal transformation, regularity of each SIP were noted. DJJ and GA carried out the categorization of SIPs while blind to surgical outcome. Patterns were classified according to the recommendations of the International Federation of Societies for Clinical Neurophysiology (Noachtar et al., 1999).

SIPs were considered: (a) *Focal*: recorded by 3 or less neighbouring subdural electrodes, or by 5 or less neighbouring depth electrodes; (b) *Lobar*: if recorded by more than 3 neighbouring subdural electrodes, or by more than 5 neighbouring depth electrodes, in the same lobe; (c) *Multilobar*: if recorded by electrodes in different lobes within the same hemisphere; and (d) *Bilateral:* if recorded by electrodes in both hemispheres. SIP latency was the time difference between the onset of FIP and the onset of SIP.

In order to correlate SIP with surgical outcome, patients were divided into those with a single SIP type and those with more than one SIP type. Among the latter, the most common SIP type was considered for analysis. For quantitative variables (e.g. frequency of fast activity in Hz), the mean of all patient's seizures was used.

2.5. Surgical procedures

Surgery included temporal, frontal, parietal, insular and occipital resections. Tissue was removed and pathology studies performed. En-bloc temporal lobectomies followed an anatomically standardised surgical techniques (Alarcon, 2009). En bloc temporal lobectomy was undertaken at King's College Hospital as originally described by Falconer (Falconer, 1971), later modified to achieve a more complete removal of the hippocampus by use of the principles described by Spencer (Spencer et al., 1984). In effect, between 5.5 cm and 6.5 cm of temporal lobe was removed. In the dominant hemisphere, usually the left, all superior temporal gyrus except the anterior 2 cm was spared. Such a resection would have included at least 50% of the amygdala and 2–3 cm of parahippocampal gyrus and hippocampus. Electrocorticographic intraoperative recordings were carried out and the extent of the resection was occasionally modified according to electrocorticographic findings (Alarcon et al., 1997). In extratemporal procedures, intraoperative electrocorticographic recordings were used to further tailor the resection to remove regions showing pathological slowing and epileptiform discharges (Ferrier et al., 2001). Structural lesions shown on imaging were removed unless functional mapping suggested a significant risk of functional deficits.

2.6. Surgical outcome

Surgical outcome with regard to seizure control was determined at regular postoperative follow up assessments. Surgical outcome was coded according to Engel surgical outcome classification (Engel et al., 1993). Surgical outcome at the longest follow-up available was used for each patient. For statistical analysis, Grade I was considered as "good outcome" and grades II, III or IV as "poor outcome".

2.7. Statistical analysis

Two-tailed χ^2 testing with one degree of freedom with Chi squared Yate's correction was used to compare the proportion of patients with favourable outcome between the groups of patients showing each SIP. Existence of significant differences was assumed if $p < 0.05$. Analysis was carried out with Graphpad (www.graphpad.com/quickcalcs/contingency1.cfm).

3. Results

3.1. Patients

Among all 63 patients, 29 (46%) were female and 34 (54%) were male. The mean age at onset of epilepsy was 10.73 years (SD = 9.07). The average age at resection was 31.8 years (SD = 13.0). The mean follow-up period was 42.15 months (SD = 30.1). Forty-six patients (73.0%) underwent temporal lobe resections, 13 (20.6%) had frontal resections, 1 (1.6%) patient underwent a parietal resection, 2 (3.2%) had occipital resections, and one patient (1.6%) underwent an insular resection. After neuropathological examination, the most common pathology was mesial temporal sclerosis, which was present in 25 patients (39.7%), followed by focal cortical dysplasia which was present in 12 patients (19.0%), 5 patients (7.9%) revealed a dysembryoplastic neuroepithelial tumour, two patients (3.2%) showed heterotopia, and non-specific changes were seen in 12 patients (19.0%). Table 1 shows detailed clinical information for each patient.

3.2. Intracranial electrodes

Among all 63 patients, 20 patients (31.7%) had subdural strips only, 14 patients (22.2%) had depth electrodes only, 19 patients (30.2%) had a combination of subdural mat and strip electrodes, 1 patient (1.6%) had mat electrodes only, 8 patients (12.7%) had a combination of depth and subdural strip electrodes, and one patient (1.6%) had a combination of depth, mat and subdural strips electrodes.

Regarding electrode coverage, 31 patients (49.2%) had electrodes restricted to the temporal lobes, one patient (1.6%) had electrodes restricted to the frontal lobes, 17 patients (27.0%) had electrodes in temporal and frontal lobes, 4 patients (6.3%) had electrodes covering temporal, frontal and parietal lobes, 4 patients (6.3%) had electrodes in temporal and occipital lobes, 3 patients (4.8%) had electrodes in the temporal and parietal lobes, one patient (1.6%) had electrodes covering frontal and parietal lobes, one patient (1.6%) had electrodes covering insula and temporal lobe, and one patient covering temporal, frontal and occipital lobes. Forty-two patients (66.7%) had electrodes implanted bilaterally and 21 patients (33.3%) had unilateral electrodes.

3.3. Topography of resections and surgical outcome

Among the 63 patients recruited, 30 (47.6%) enjoyed Engel grade I, 9 (14.3%) had grade II, 20 (31.7%) had grade III and 4

Table 1
Characteristics of all 63 patients.

Patient	Telemetry duration (days)	Number of Seizures	Electrodes Type	FIP	SIP	Pathology	Resected Lobe	Engel
1	12	2	Subdural	DEE	FA	MTS	Temporal	2
2	7	5	Mat and Subdural	FA	Theta	MTS	Temporal	1
3	20	7	Mat and Subdural	Alpha	Spike-wave	ASTRO	Temporal	3
4	14	2	Depth	FA-DEE	EDE	Tumour	Temporal	3
5	5	2	Depth	FA-DEE	EDE	No changes	Temporal	1
6	20	7	Depth	DEE	FA	FCD	Temporal	4
7	4	5	Subdural	Alpha	Spike-wave	MTS	Temporal	1
8	14	4	Depth	FA-DEE	EDE	Heterotopia	Temporal	2
9	3	3	Subdural	FA	EDE	MTS	Temporal	1
10	11	4	Depth	Sharp-waves	Alpha	MTS	Temporal	1
11	4	6	Subdural	FA	Spike-wave	MTS	Temporal	2
12	13	1	Subdural	FA	Spike-wave	MTS	Temporal	2
13	6	3	Subdural	Delta	Sharp-waves	MTS	Temporal	2
14	6	3	Depth	FA	Spike-wave	MTS	Temporal	1
15	14	3	Mat	DEE	FA	EPNS	Temporal	2
16	12	9	Mat	FA	EDE	FCD	Parietal	1
17	6	1	Mat	FA-DEE	EDE	FCD	Frontal	4
18	8	3	Subdural	FA-DEE	EDE	No changes	Temporal	3
19	9	3	Subdural	FA-DEE	EDE	MTS	Temporal	3
20	5	2	Subdural	Spike-wave	EDE	MTS	Temporal	1
21	5	13	Depth	FA-DEE	EDE	FCD	Frontal	1
22	7	7	Depth	FA	Spike-wave	DNET	Temporal	1
23	8	8	Mat and Subdural	Spike-wave	FA	FCD	Temporal	3
24	20	2	Depth	Spike-wave	FA	Heterotopia	Occipital	1
25	13	2	Subdural	FA	EDE	No changes	Temporal	1
26	10	4	Mat and Subdural	Spike-wave	Alpha	MTS	Temporal	1
27	4	12	Mat	DEE	FA	FCD	Frontal	4
28	8	5	Subdural	Sharp-waves	Spike-wave	MTS	Temporal	3
29	7	5	Subdural	FA	Delta	MTS	Temporal	1
30	8	8	Depth and Subdural	Spike-wave	EDE	FCD	Frontal	2
31	13	4	Subdural	DEE	FA	No changes	Temporal	3
32	9	4	Depth	FA-DEE	EDE	MTS	Temporal	2
33	12	6	Depth	FA	Sharp-waves	FCD	Insula	3
34	7	5	Depth and Mat	FA	Spike-wave	DNET	Frontal	1
35	8	5	Subdural	DEE	Spikes	MTS	Temporal	1
36	3	14	Mat and Subdural	DEE	FA	No changes	Temporal	3
37	7	7	Subdural	Spike-wave	FA	MTS	Temporal	1
38	5	6	Mat and Subdural	DEE	Spike-wave	Heterotopia	Frontal	3
39	6	7	Mat and Subdural	DEE	FA	No changes	Frontal	3
40	6	2	Mat and Subdural	DEE	FA	ASTRO	Frontal	3
41	12	4	Subdural	FA	Sharp-waves	DNET	Temporal	1
42	16	1	Depth	FA	Sharp-waves	No changes	Temporal	1
43	9	5	Depth	Spike-wave	Alpha	MTS	Temporal	1
44	5	4	Subdural	DEE	FA	ASTRO	Frontal	4
45	5	5	Depth and Subdural	FA-DEE	EDE	DNET	Occipital	1
46	6	3	Mat and Subdural	Sharp-waves	EDE	MTS	Temporal	2
47	7	6	Subdural	FA	EDE	No changes	Temporal	1
48	11	3	Mat and Subdural	FA-DEE	EDE	No changes	Temporal	1
49	6	13	Depth	Delta	Spike-wave	MTS	Temporal	3
50	9	11	Subdural	Spike-wave	EDE	MTS	Temporal	1
51	4	14	Depth and Subdural	Alpha	EDE	FCD	Parietal	3
52	7	5	Subdural	FA	EDE	No changes	Temporal	1
53	16	5	Subdural	FA-DEE	EDE	MTS	Temporal	1
54	3	19	Depth	FA-DEE	EDE	No changes	Frontal	3
55	4	5	Subdural	DEE	Sharp-waves	DNET	Temporal	3
56	7	11	Depth and Subdural	Spikes	Delta	MTS	Temporal	3
57	7	8	Depth	FA	Alpha	MTS	Temporal	1
58	8	3	Mat and Subdural	DEE	Alpha	FCD	Frontal	3
59	5	3	Mat and Subdural	FA-DEE	EDE	MTS	Temporal	1
60	14	3	Mat and Subdural	FA-DEE	EDE	No changes	Temporal	3
61	9	4	Mat and Subdural	FA	EDE	FCD	Frontal	1
62	9	4	Subdural	FA	EDE	FCD	Frontal	1
63	9	4	Mat and Subdural	FA	Spike-wave	PIC	Temporal	4

DNET = dysembryoplastic neuroepithelial tumor, FDC = focal cortical dysplasia, MTS = mesial temporal sclerosis, PIC = perinatal ischemic cyst, FIP = first ictal pattern, SIP = second ictal pattern.

(6.3%) presented grade IV after surgery. Among the 45 temporal patients, 23 (51.1%) enjoyed grade I, 9 (20.0%) had grade II, 11 (24.4%) had grade III and 2 (4.4%) presented grade IV. Whereas 15 of the 23 temporal patients with medial temporal onset enjoyed outcome grade I, only 8 of the 22 temporal patients with non-medial temporal onset had grade I (Proportion Test, Z-score = 1.936; $p = 0.026$). Among the 13 frontal patients, only 4 (30.8%) enjoyed grade I, 7 (53.8%) had grade III and 2 (15.4%)

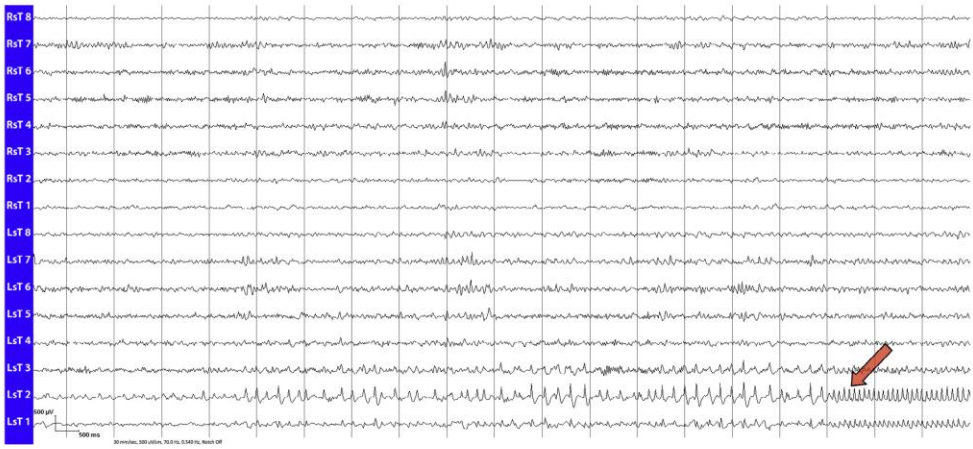

Fig. 1. Example of SIP consisting of focal runs of spikes in a patient with two 8-contact subdural strips (bilateral subtemporal strips), shown in common average reference. Note SIP (arrow) consisting of runs of spikes at electrodes 1–2 of the left subtemporal strip after the seizure had started as spike-wave activity at the same electrodes. RsT = right subtemporal strip, LsT = left subtemporal strip. For each strip, electrode 1 is farthest from the insertion burr hole.

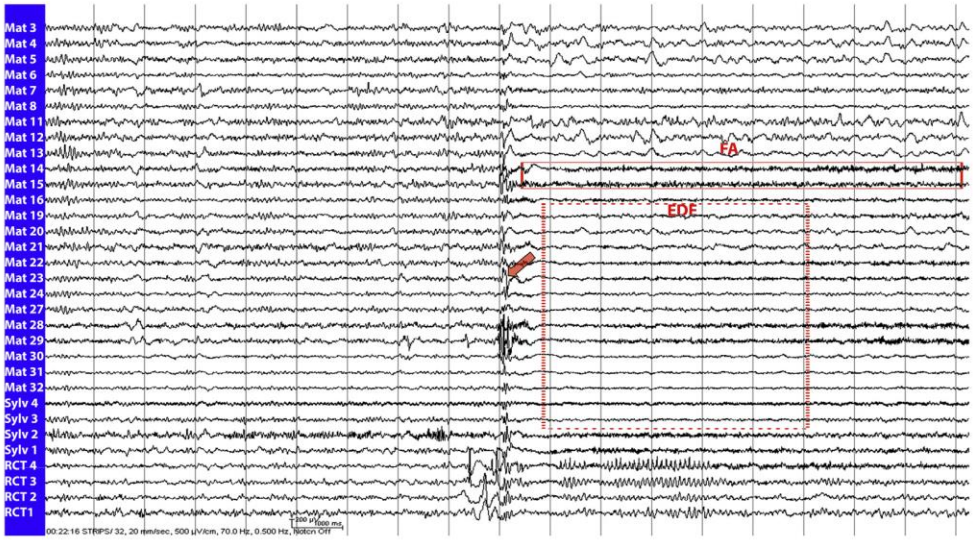

Fig. 2. Example of lobar EDE as SIP (red box) in a patient with a 32-electrode mat over the frontal lobe, one 4-electrode subdural strip (sylvian) and one 4-electrode subdural strip along the centro temporal areas, shown in common average reference. Note a preceding epileptiform discharge (arrow) and sustained fast activity (FA) at 16 Hz arising at electrodes 14–15 of the mat as FIP lasting over 5 s, followed by lobar EDE as SIP (box) involving contacts 19–32 of the mat and 3–4 of the sylvian electrode; lasting for 5 s. Mat = frontal mat; Syl = sylvian subdural strip; RCT = right centro-temporal strip. For each strip, electrode 1 is farthest from the insertion site and 8 is the closest. For the mat, electrode 1 is at the anterior and superior corner. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

presented grade IV. The two occipital resections had grade I. Among the two patients with parietal resections, one had grade I and one had grade III. The only insular patient had Engel grade III. Supplementary Table S1 shows the relation between the location of resection and surgical outcome in all 63 patients.

3.4. Characteristics of SIPs

A total of 344 seizures from the 63 patients were analysed. Representative examples of each seizure onset pattern found are shown in Figs. 1–3. The mean SIP latency was 5.23 s (SD = 6.9). The most common SIP was EDE, which was seen in 26 patients (41.3%). FA was present in 12 (19.0%) patients with a mean frequency of 16.5 Hz (SD = 24.4), spike-wave in 11 (17.5%) patients, alpha activity in 5 (7.9%) patients (mean frequency = 8.5 Hz; SD = 1.07), delta activity in 2 (3.2%) patients (mean frequency = 4.2 Hz; SD = 0.957), sharp-waves in 5 (7.9%) patients (mean frequency = 9 Hz; SD = 1.4), runs of spikes in 1 (1.6%) patient at a frequency of 11 Hz and theta activity in 1 (1.6%) patient at a frequency of 7 Hz.

Among the 45 temporal patients, the SIP was EDE in 18 (40.0%) patients, spike-wave activity in 9 (20.0%) patients, FA in 6 (13.3%), alpha activity in 4 (8.8%), delta activity in 2 (4.4%), sharp waves in 4 (8.8%), runs of spikes in 1 (2.2%) and theta activity in 1 patient (2.2%). Among the 13 frontal patients, the SIP was EDE in 5 patients (38.5%), FA in 5 patients (38.8%), spike wave activity in 2 patients

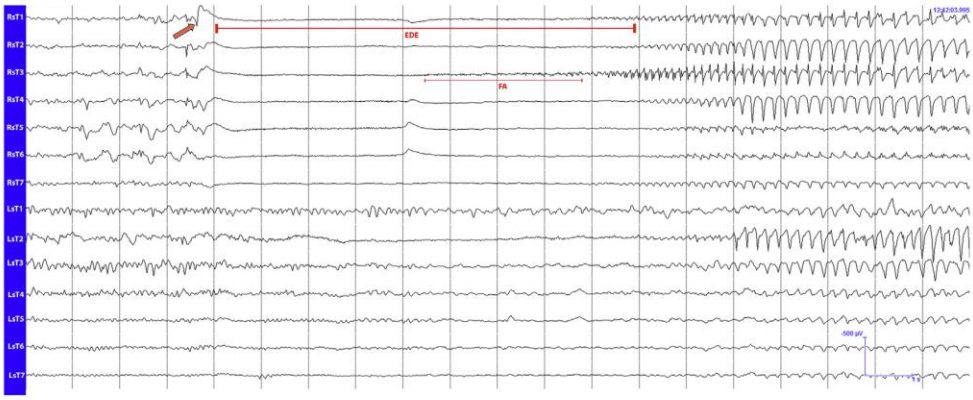

Fig. 3. Example of FA as SIP in a patient with bilateral 7-electrode subtemporal strips. Note a preceding epileptiform discharge (arrow) (Jimenez-Jimenez et al., 2015a,b) followed by diffuse EDE lasting over 9 s as FIP and by FA as SIP at 45 Hz at electrode 3 of the right subtemporal strip for 4 s. RsT = right subTemporal; LsT = left subTemporal. For each strip, electrode 1 is the farthest from the insertion site.

Table 2
Proportion of patients presenting Engel Grade I surgical outcome as a function of SIP pattern.

Pattern	Temporal resections		Extratemporal resections		All resections	
	n/*N*	%	*n*/*N*	%	*n*/*N*	%
Alpha	4/4	100	0/1	0.0	4/5	80
EDE	10/18	66.7	5/8	57.1	15/26	57.7
Delta	1/2	50.0	0/0	0.0	1/2	50
FA	1/6	16.7	1/6	16.7	2/12	16.7
Sharp-wave	2/4	50.0	0/1	0.0	2/5	40.0
Spike-wave	3/9	33.3	1/2	50.0	4/11	36.4
Spikes	1/1	100	0/0	0.0	1/1	100
Theta	1/1	100	0/0	0.0	1/1	100
Total	23/45	51.1	7/18	38.8	30/63	47.6

EDE = electrodecremental event, FA = fast activity.

(15.4%), and alpha activity in 1 patient (7.7%). Among the two parietal patients, the SIP was EDE. Among the two occipital patients, FA was the SIP in one patient and EDE in another. The only insular patient showed sharp-wave activity as the SIP.

Fifty-two patients (82.5%) presented a single SIP type (of which 24 patients had Engel grade I) and 11 (17.5%) had different SIPs in different seizures (among which 6 patients had Engel grade I). No significant differences in outcome were found between the 52 patients with one SIP type and the 11 patients with more than one SIP. In 35 patients (55.6%) SIP had the same topography as FIP.

3.5. Extent of SIPs

SIP was focal in 29 (46.0%) patients, lobar in 15 (23.8%), multilobar in 9 (14.3%) and bilateral in 10 (15.9%) patients. Among the larger group of 45 temporal resections, 25 patients (55.6%) showed

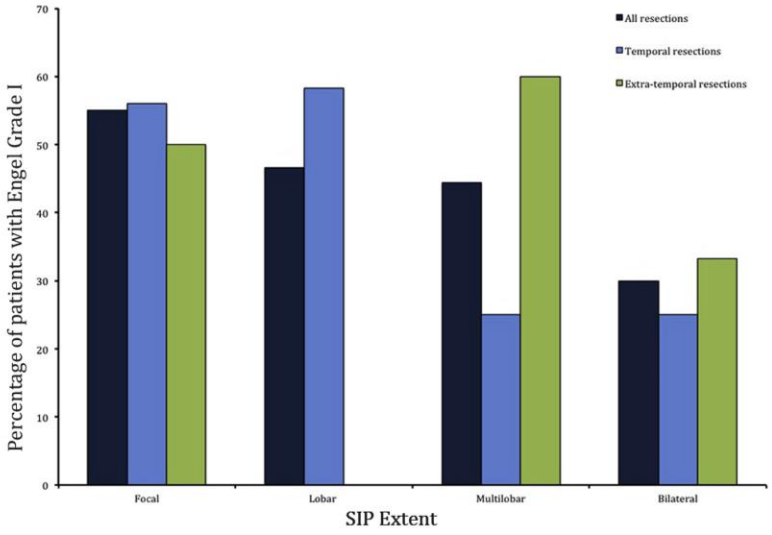

Fig. 4. Relation between SIP extent and proportion of Engel grade I. The histograms represent the percentage of patients who had Engel grade I in relation to SIP extent (focal, lobar, multilobar or bilateral). Histograms are shown for all resections, for temporal and for extra-temporal resections. Note the gradual decrease in the proportion of seizure free patients with SIPs extent. In the extra-temporal group, no lobar SIPs were present.

focal SIPs, 12 patients (26.7%) presented lobar SIP, 4 patients (8.9%) showed bilateral SIP and 4 patients (8.9%) exhibited multilobar SIP.

3.6. Prognostic value of SIPs

Among all patients, EDE was the SIP that showed the highest proportion of patients with Engel Grade I, accounting for 15 (57.77%) of the 26 patients. On the other hand, only 2 (16.7%) patients of 12 presenting FA as SIP showed Engel Grade I. Table 2 shows the proportion of Engel grade I surgical outcome as a function of SIP patterns in temporal, extra-temporal and all resections. EDE was the most common SIP in all subgroups, followed by FA and spike wave. Supplementary Table S2 shows the relation between surgical outcome and SIP in all resections.

Two by two contingency tables were constructed to estimate the association between surgical outcome and different pairs of SIP. This was carried out within the following three groups: all patients, temporal patients and extra-temporal patients. Only the most common patterns within each group were used to perform the following comparisons:

(a) FA versus any other SIP.
(b) FA versus EDE.
(c) EDE versus any other SIP.
(d) Spike-wave versus any other SIP.

Among all 63 patients, two of the 12 patients with FA showed favourable outcome whereas among the 51 patients presenting any other SIP, 28 enjoyed favourable outcome, suggesting that FA was associated with poor outcome ($p = 0.0389$). In contrast, EDE appears to be a predictor of good surgical outcome when compared with FA since 15 of the 26 patients with EDE had favourable outcome ($p = 0.0044$). No differences were found when comparisons were restricted to the smaller populations of temporal or extra-temporal patients. Supplementary Table S3 shows the 2×2 contingency tables with significant associations between Engel outcome scale and SIP in each patient group.

Fig. 4 shows the relation between the extent of SIP and surgical outcome. There is a gradual decrease in the proportion of Engel grade I with the extent of SIP in the complete population, among temporal and among extratemporal patients.

Fig. 5 shows the proportion of patients Engel grade I according to SIP latency. In most patients, SIP latency is shorter than 10 s and in over a half it is shorter than 5 s. However, when latency is longer than 10 s, outcome appears to be better among temporal patients.

No significant differences in the proportion of Engel grade I were found between the 52 patients who presented a single SIP type and the 11 who had different SIPs in different seizures ($p = 0.8618$).

3.7. Evolution of SIPs

The evolution from FIP to SIP was studied in order to estimate the number of times when each SIP occurs after each FIP. The most common SIPs were EDE, FA and spike-wave. In most cases, EDE evolves from a FIP containing FA, either FA only (23.1%) or FA-EDE (53.8%). FA as SIP tends to occur after EDE (75%) whereas spike-wave SIPs tends to occur after FA (54.5%). Supplementary Table S4 shows the number of times when each SIP occurs after each FIP (evolution from FIP to SIP).

4. Discussion

The purpose of this study was to estimate the prognostic value to predict seizure control of the SIP that follows the initial FIP seen at seizure onset. Our findings suggest that the prognostic value of ictal patterns depends on where they occur within the seizure, their spatial extent and latency. As SIP, EDE was associated with favourable outcome whereas FA was associated with poor outcome. More widespread SIPs were associated with poorer outcome. Delayed SIP ($\geqslant 10$ s) appear to be associated with good outcome in temporal lobe epilepsy.

Our report of poor prognostic value for FA may appear puzzling as this pattern is usually assumed to be associated with good prognosis (Lieb et al., 1986; Alarcon et al., 1995; Jung et al., 1999; Kutsy et al., 1999; Lee et al., 2000; Wetjen et al., 2009; Holtkamp et al., 2012; Dolezalova et al., 2013; Jimenez-Jimenez et al., 2015b). However, our present findings suggested that FA does not necessarily predict good prognosis if it appears late in the seizure. This can be explained by the evolution from FIP to SIP. FA tends to be the SIP in seizures starting as EDE, which is predictor for poor outcome as FIP (Jimenez-Jimenez et al., 2015b). This highlights the relevance of adequate electrode sampling to record the initial FA, since FA recorded later in the seizure may not be a marker for good outcome.

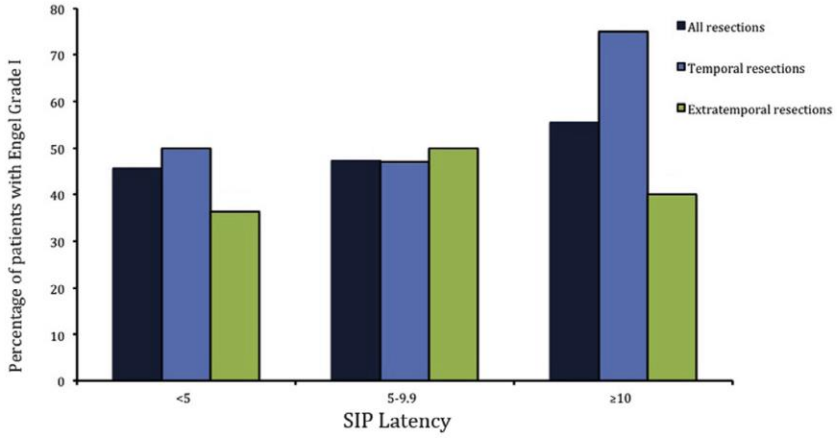

Fig. 5. Relation between SIP latency and proportion of Engel class I. The histograms represent the percentage of patients who had Engel grade I depending on SIP latency (<5 s, 5–9.99 s, $\geqslant 10$ s) Histograms are shown for all resections, for temporal and for extra-temporal resections. Note the increase in the proportion of grade I patients with SIP latency above 10 s in the temporal group.

The more widespread or bilateral SIPs appear to be associated with worse outcome (Fig. 4), possibly because outcome may be worse when propagation starts earlier after seizure onset, contributing to a more widespread SIP. In addition, we found better postsurgical outcome in temporal patients with longer SIP latencies (Fig. 5). These findings suggest that those patients where the FIP remains focal for longer would have better outcome, as initially suggested by the study of contralateral seizure propagation in temporal lobe epilepsy (Lieb et al., 1986).

As many as 17.5% of patients showed different SIPs in different seizures, which restricted the analysis of SIPs to the most common SIP in each patient. This limitation was not present for the analysis of SIP latency where all seizures were evaluated.

In summary, the prognostic value of ictal patterns depends on where in the seizure they occur. As SIP, FA is associated with poor outcome and EDE with good outcome. This is opposite to the interpretation of FA and EDE as FIP. In addition, localised SIPs and delayed temporal lobe SIPs appear to be associated with better outcome.

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Conflict of interest

None of the authors have any conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2015.07.001.

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3 ON-LINE SUPPLEMENTARY DATA

Table S1. Number of patients with each outcome grade according to resection lobe.

Engel Class	I		II		III		IV		Total	
	N	%	N	%	N	%	N	%	N	%
Frontal	4	30.8	0	0.0	7	53.8	2	15.4	13	100
Insula	0	0.0	0	0.0	1	100	0	0.0	1	100
Occipital	2	100	0	0.0	0	0.0	0	0.0	2	100
Parietal	1	50	0	0.0	1	50	0	0.0	2	100
Temporal	23	51.1	9	20.0	11	24.4	2	4.4	45	100
Total	30	47.6	9	14.3	20	31.7	4	6.3%	63	100.0

4 ON-LINE SUPPLEMENTARY DATA

Table S2. Relation between SIP and surgical outcome in all and in temporal resections.

ALL RESECTIONS	I	II	III	IV
SIP	%	%	SIP	%
Alpha (N=5)	80.0	0.0	20.0	0.0
Decrement (N=26)	57.7	15.4	23.1	3.8
Delta (N=2)	50.0	0.0	50.0	0.0
Fast (N=12)	16.7	16.7	50.0	16.7
Sharp-wave (N=5)	40.0	20.0	40.0	0.0
Spike-wave (N=11)	36.4	18.2	36.4	9.1
Spikes (N=1)	100	0.0	0.0	0.0
Theta (N-1)	100	0.0	0.0	0.0
Total (N=63)	**47.6**	**14.3**	**31.7**	**6.3**
TEMPORAL RESECTIONS	**I**	**II**	**III**	**IV**
SIP	**%**	**%**	**%**	**%**
Alpha (N=4)	100	0.0	0.0	0.0
Decrement (N=18)	55.6	22.2	22.2	0.0
Delta (N=2)	50.0	0.0	50.0	0.0
Fast (N=6)	16.7	33.3	33.3	16.7
Sharp-wave (N=4)	50.0	25.0	25.0	0.0
Spike-wave (N=9)	33.3	22.2	33.3	11.1
Spikes (N=1)	100	0.0	0.0	0.0
Theta (N=1)	100	0.0	0.0	0.0
Total (N=45)	**51.1**	**20.0**	**24.4**	**4.4**

5 ON-LINE SUPPLEMENTARY DATA

Table S3. Relation between SIP and surgical outcome. χ^2 = two tailed Chi squared test with Yates correction (1 degree of freedom); * = significant difference

SIP COMPARED	Good	Poor	Statistic	P
ALL PATIENTS				
FA Any other SIP	2 28	10 23	χ^2=4.264	0.0389 *
FA EDE	2 15	10 11	χ^2= 4.053	0.0044*
EDE Any other SIP	15 15	11 22	χ^2= 1.179	0.2779
TEMPORAL PATIENTS				
FA Any other SIP	1 22	5 17	χ^2= 1.889	0.1693
FA EDE	1 10	5 8	χ^2= 1.399	0.2370
EDE Any other SIP	10 13	8 14	χ^2= 0.033	0.8551
EXTRATEMPORAL PATIENTS				
FA Any other SIP	1 6	5 6	χ^2= 0.731	0.3927
FA EDE	1 5	5 3	χ^2= 1.367	0.2423

Good = good surgical outcome (grade I of Engel classification)
Poor = poor surgical outcome (grades II, III or IV of Engel classification)
FA = fast activity
DEE = diffuse electrodecremental event
SIP = second ictal pattern

6 ON-LINE SUPPLEMENTARY DATA

TABLE S4. Seizure pattern evolution. Number of time and proportion of times that each SIP patterns occurs after each FIP pattern.

FIP \ SIP	Alpha	EDE	Delta	FA	Sharp-Wave	Spike-wave	Spikes	Theta	Total
	N=5	N=26	N=2	N=12	N=5	N=11	N=1	N=1	N=63
Alpha	0.0%	3.8%	0.0%	0.0%	0.0%	18.2%	0.0%	0.0%	4.8%
EDE	20.0%	0.0%	0.0%	75.0%	20.0%	9.1%	100%	0.0%	20.6%
Delta	0.0%	3.8%	0.0%	0.0%	20.0%	9.1%	0.0%	0.0%	4.8%
FA	20.0%	23.1%	50.0%	0.0%	60.0%	54.5%	0.0%	100%	28.6%
FA-DEE	0.0%	53.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	22.2%
Sharp-wave	20.0%	3.8%	0.0%	0.0%	0.0%	9.1%	0.0%	0.0%	4.8%
Spike-wave	40.0%	11.5	0.0%	25.0%	0.0%	0.0%	0.0%	0.0%	12.7%
Spikes	0.0%	0.0%	50.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%

4. CHAPTER FOUR

1 Incidence of functional bi-temporal connections in the human brain in vivo and their relevance to epilepsy surgery.

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2 Personal contributions for this publication:

- Review all clinical records for those patients who have been implanted bilateral temporal intracranial electrodes and were operated from November 1999 to January 2010.
- Elaborate a database for entry details of the patients whom fulfilled the inclusion criteria.
- Review all intracranial EEG recordings of the patients (91) included in the study.
- Classify all seizure onsets into the different seizure patterns included for the study.
- Average and review all SPES recordings for all 91 patients and identify different responses to SPES when stimulating medial temporal lobe area.
- Perform the statistical analysis for the study.
- Select and edit different images for including into the manuscript.
- Elaborate all tables for the study.
- Write the initial draft of the manuscript and submit it to respective journal.

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Clinical neuroanatomy

Incidence of functional bi-temporal connections in the human brain *in vivo* and their relevance to epilepsy surgery

Diego Jiménez-Jiménez [a,b,c], *Margely Abete-Rivas* [b,d], *David Martín-López* [a,b,e,f], *María Elena Lacruz* [a,g], *Richard P. Selway* [h], *Antonio Valentín* [a,b,1] *and Gonzalo Alarcón* [a,b,f,*,1]

[a] *Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK*
[b] *Department of Clinical Neurophysiology, King's College Hospital NHS Trust, London, UK*
[c] *School of Medicine, Universidad San Francisco de Quito, Quito, Ecuador*
[d] *Departamento de Neurofisiología Clínica, Hospital Clínico Universitario de Valladolid, Valladolid, Spain*
[e] *West Surrey Clinical Neurophysiology, St Peter's Hospital, Chertsey, UK*
[f] *Departamento de Fisiología, Facultad de Medicina, Universidad Complutense, Madrid, Spain*
[g] *Institute of Medical Epidemiology Biometry and Informatics, Martin-Luther-University, Halle, Germany*
[h] *Department of Neurosurgery, King's College Hospital, NHS Trust, London, UK*

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Epilepsy surgery

ABSTRACT

The incidence of functional connections between human temporal lobes and their latencies were investigated using intracranial EEG responses to electrical stimulation with 1 msec single pulses in 91 patients assessed for surgery for treatment of epilepsy. The areas studied were amygdala, hippocampus, parahippocampal gyrus, fusiform gyrus, inferior and mid temporal gyrus. Furthermore, we assessed whether the presence of such connections are related to seizure onset extent and postsurgical seizure control. Responses were seen in any region of the contralateral temporal lobe when stimulating temporal regions in 30 patients out of the 91 (32.96%). Bi-hippocampal or bi-amygdalar projections were seen in only 5% of temporal lobes ($N = 60$) and between both fusiform gyri in 7.1% ($N = 126$). All other bilateral connections occurred in less than 5% of hemispheres. Depending on the structures, latencies ranged between 20 and 90 msec, with an average value of 60.2 msec. There were no statistical difference in the proportion of patients showing Engel Class I between patients with and without contralateral temporal connections. No difference was found in the proportion of patients showing bilateral or unilateral seizure onset among patients with and without contralateral temporal projections. The

Abbreviations: SPES, Single Pulse Electrical Stimulation; DEE, Diffuse Electrodecremental Event pattern; FA, Fast activity pattern; FA-DEE, Fast activity with Diffuse Electrodecremental Event; SIOP, Sustained Ictal Onset Patterns; PED, Preceding Epileptiform Discharge.

* *Corresponding author*. Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, PO Box 43, London SE5 8AF, UK.
E-mail address: gonzalo.alarcon@kcl.ac.uk (G. Alarcón).

[1] Drs A. Valentín and G. Alarcón are joint senior authors.

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present findings corroborate that the functionality of bilateral temporal connections in humans is limited and does not affect the surgical outcome.

1. Introduction

Anatomical and neuroimaging studies have consistently shown structural connections between both temporal lobes. A component of the fornix crosses to the contralateral hippocampus constituting the hippocampal commissure (Catani, Dell'acqua, & Thiebaut de Schotten, 2013). A recent study with diffusion tensor imaging (DTI) has revealed that 56.7% of 52 healthy volunteers show contralateral temporal connections (Kwon & Jang, 2014). However, it remains unclear if human bilateral temporal connections are functional in vivo. Histopathological samples in normal subjects can identify ventral and dorsal hippocampal commissures, of which only the latter is well defined and sizable in humans (Gloor, Salanova, Olivier, & Quesney, 1993). Lesional and stimulation studies support that hippocampi on either hemisphere process memory independently of each other, suggesting that connections between both hippocampi may not be functionally relevant (Goldstein & Polkey, 1992; Lacruz et al., 2010).

Patients assessed with intracranial electrodes during presurgical assessment of epilepsy provide a unique opportunity to estimate the incidence of functional bi-temporal connections in the human brain in-vivo. Indeed, electrical stimulation has failed to show functional connections between both hippocampi (Wilson, Isokawa, Babb, & Crandall, 1990), or has shown such connections only in a small proportion of patients (Lacruz, Garcia Seoane, Valentin, Selway, & Alarcon, 2007; Lacuey et al., 2014).

Single Pulse Electrical Stimulation (SPES) is used routinely at our centre as part of presurgical assessment for epilepsy in order to identify the topography and extent of hyperexcitable cortex, which might be potentially epileptogenic. Briefly, SPES consists of recording intracranial electroencephalographic responses to cortical stimulation with a brief single electrical pulse. Two main types of cortical responses are evoked by the stimuli, early and late responses. Early responses are recorded in areas around the stimulated cortex but sometimes also at a distance, providing evidence of functional connections between stimulated cortex and the regions where early responses are recorded (Enatsu et al., 2012; Fish, Gloor, Quesney, & Olivier, 1993; Lacruz et al., 2010; Lacuey et al., 2014; Umeoka et al., 2009; Wilson et al., 1990). Late responses are reliable biomarkers of epileptogenic cortex (Flanagan, Valentin, Garcia Seoane, Alarcon, & Boyd, 2009; Valentín, Alarcon, Garcia-Seoane, et al., 2005; Valentín, Alarcon, Honavar, et al., 2005).

Approximately 33% of patients with temporal lobe epilepsy assessed for surgery with intracranial electrodes show bilateral changes at seizure onset, and some of such changes have implications for surgical outcome (Jiménez-Jiménez et al., 2015). However, the nature of those bilateral changes at seizure onset remains unclear. We hypothesise that, if bilateral changes at seizure onset are due to synaptic transmission through anatomical pathways, they should be related to the presence of functional bilateral connections.

In the present study, we estimate the incidence and latencies of human functional contralateral temporo-temporal connections in-vivo in the largest series to date. Furthermore, this is the first study to address whether the presence of such connections is related to bilateral changes at seizure onset or to postsurgical seizure control.

2. Methods

2.1. Subjects

SPES recordings from all 269 patients who had intracranial electrodes implanted for pre-surgical evaluation at King's College Hospital between January 1999 and December 2013 were reviewed. The study included all 91 patients who had intracranial electrodes in both temporal lobes.

Patients were informed of the nature of the study and gave informed consent to undergo SPES. The ethical committee at King's College Hospital (99-017) approved the development of SPES. Single pulse electrical stimulation is now part of the clinical protocol for presurgical assessment of patients with epilepsy with intracranial recordings.

2.2. Electrode placement

The type, number and location of the electrodes were determined by the suspected location of the ictal onset region, according to non-invasive evaluation: clinical history, scalp electroencephalogram recordings obtained with the Maudsley scalp electrode system (Alarcon et al., 2001; Fernandez Torre et al., 1999; Kissani, Alarcon, Dad, Binnie, & Polkey, 2001), neuropsychology (Akanuma et al., 2003) and neuroimaging. All patients with normal neuroimaging were assessed with intracranial electrodes. The selection criteria and implantation procedures have been described in detail elsewhere (Alarcon, 2012; Alarcon et al., 2006). Temporal depth (intracerebral) and subdural electrodes were used as shown in Fig. 1 and described below. The anatomical locations were defined according to (Insausti et al., 1998).

2.3. Subdural electrodes

Subdural electrodes consisted of strips or mats (Ad-Tech Medical Instruments Corp., WI, USA). Each strip consisted of a single row of 4–8 platinum disk electrodes spaced at 10 mm between centres. The disks were embedded in a .7 mm thick polyurethane strip which overlapped the edges leaving a diameter of 2.3 mm exposed, and recessed approximately

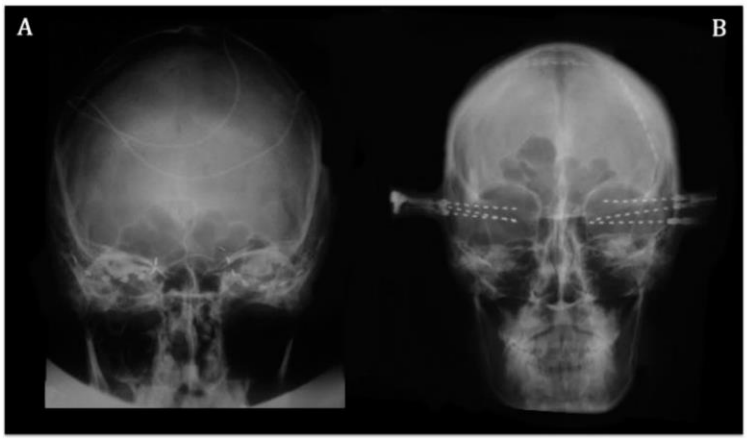

Fig. 1 – Two examples of typical bilateral subtemporal strips and depth electrode (intracerebral) implantations. A) Subtemporal strips are slid under the under-surface of the temporal lobes and record from the lateral cortex, fusiform gyrus and parahippocampal gyrus. B) On each temporal lobe, three depth electrode bundles are implanted stereotactically targeting at the amygdala, anterior and posterior hippocampus. For each bundle, the deepest electrode records from one of these structures, and the most superficial electrodes record from the mid temporal gyrus.

.1 mm from the surface plane. Mats contained rectangular arrays of 12, 16, 20, 32 or 64 similar platinum electrodes with 10 mm centre-to-centre distances within rows. Subtemporal strips of electrodes were inserted through a lateral burr hole and slid under the temporal lobe. The position of each electrode was assessed according to CT or coregistered CT-MRI. Generally, the deepest electrodes in each strip (labelled as 1 and 2) were in contact with the parahippocampal gyrus, electrodes 3 and 4 in contact with the fusiform gyrus, electrodes 5 and 6 in contact with inferior temporal gyrus and electrodes 7 and 8 (most lateral) in contact with the mid temporal gyrus.

2.4. *Intracerebral (depth) electrodes*

Multielectrode flexible bundles of depth electrodes (Ad-Tech Medical Instruments Corp., WI, USA) were implanted stereotactically under MRI guidance. The electrode bundles contained 8 or 10 cylindrical 2.3 mm long platinum electrodes separated by 5 mm between centres of adjacent electrodes of the same bundle. Usually 3 depth electrode bundles were implanted via an orthogonal lateral approach with the deepest electrodes (labelled as 1 and 2) at the amygdala, the anterior or posterior hippocampus according to MRI stereotactic target, and the most superficial electrodes (labelled as 5–7) at the mid temporal gyrus.

2.5. *Electroencephalographic recordings*

Recording of intracranial electroencephalogram started when the patient had recovered from electrode implantation, usually 24–48 h after surgery. Cable telemetry with up to 64 recording channels was used for data acquisition with simultaneous video monitoring. In 40 patients, the Telefactor Beehive-Beekeeper system (Astro-Med, RI, USA) was used. Data were digitized at 200 Hz and band pass filtered (high pass cut-off frequency at .3 Hz and low pass cut-off frequency at 70 Hz). The system input range was 2 mV and data were digitized with a 12 bit analog-to-digital converter (amplitude resolution of .488 μV). In the remaining 51 patients, a Medelec-Profile system was used (Medelec, Oxford Instruments, United Kingdom). Data were digitized at 256 Hz and band pass filtered (.05–70 Hz). The input range was 10 mV and data were digitized with a 22 bit analog-to-digital converter (an amplitude resolution of .153 μV). Data were recorded as common reference to Pz or to an intracranial electrode, and displayed in a variety of montages including various scalp, intracranial and average common references to identify the most inactive reference for review in each patient.

2.6. *Experimental protocol*

SPES was performed between adjacent electrodes using a constant-current neurostimulator approved for use in human subjects (Medelec ST10 Sensor, Oxford Instruments, UK or LeadPoint, Medtronic, UK). Electrical stimulation was carried out with monophasic single pulses of 1 msec duration and current intensity ranging between 4 and 8 mA (4 mA being the intensity most often used). Each pulse was delivered between pairs of contiguous electrodes, every 5 or 10 sec and EEG responses to each pulse were recorded by the electrodes not used for stimulation. No permanent neurological or neuropsychological deficits have been observed associated with SPES. A more detailed description of the experimental protocol for SPES is described elsewhere (Flanagan et al., 2009; Valentín et al., 2002; Valentín, Alarcon, García-Seoane, et al., 2005; Valentín, Alarcon, Honavar, et al., 2005).

The term 'stimulus' or 'stimulation' will be used to designate each single pulse and the term 'series' will be used to designate a batch of several identical pulses applied to the same pair of electrodes, with the same polarity. A series usually comprised 10 stimuli. For each pair of adjacent electrodes, two separate stimulation series were carried out with opposite polarity. Series of opposite polarity might stimulate slightly different regions, since neuronal stimulation is assumed to be greatest at the cathode. The electrodes used for stimulation were not used for recording. In patients with subdural electrodes, all available electrodes were used to stimulate in at least one series. In patients with intracerebral recordings only pairs of electrodes located in grey matter (according to MRI obtained with the electrodes implanted) were used to stimulate. Throughout the paper, the term "contralateral" will refer to the temporal lobe contralateral to stimulation (i.e., the temporal lobe where responses were recorded).

The measured variables were: a) the presence or absence of early contralateral temporal responses when stimulating at each location; and b) the latency of early contralateral responses. The presence of early responses is assumed to provide evidence of connections between the stimulated cortex and the areas where early responses are recorded. Responses to different stimulation locations within the same structure in the same hemisphere in the same patient were pooled together (counted only once for each direction).

2.7. Data analysis

In order to minimise stimulation artefact, responses to stimulation with opposite polarity through the same electrodes were averaged. Cortical responses were identified visually and were considered significant if their amplitude after averaging was at least twice the amplitude of the background activity presence during the 400 msec previous to the stimulus artefact.

In each patient, contralateral (inter-hemispheric) connections were studied when each temporal lobe was stimulated. Thus, for any two regions in contralateral hemispheres, each patient provides two measures, one from right to left and one from left to right. The likelihood of finding functional connections between both regions was calculated as the proportion/percentage of connections found among the number of stimulated hemispheres where such connections could be tested (i.e., in subjects with electrodes implanted in both regions).

Latencies of responses evoked in contralateral structures were studied. Cortical contralateral responses following stimulation artefact were identified visually, and multiple cursors were scrolled through the traces to identify synchronous points and measure latency differences among cursors. Contralateral response latency was measured from the stimulation artefact to the first peak of the first identifiable deflection of the contralateral response. The presence of a response was checked in bipolar montage and in common reference montage with reference to the average of the electrodes from the same strip or bundle. Latencies were measured in the latter montage in order to avoid interference from remote references.

2.8. Seizure onset analysis

Seizure onset of all 40 patients who underwent resection was analysed. Ictal onset pattern was determined by visual analysis of the pruned ictal files of intracranial electroencephalographic recordings. The seizure onset patterns lasting for several seconds were classified as follows (Jiménez-Jiménez et al., 2015): a) Diffuse electrodemental event (DEE), b) Focal Fast activity (FA), c) sharp-waves, d) spike-waves, e) alpha activity, f) theta activity, and g) delta activity. When FA and DEE started within 1 sec, this was classified as h) FA-DEE. These patterns will be generically designated as "sustained ictal onset patterns" (SIOP). Frequently, SIOPs were immediately preceded by a single epileptiform discharge (preceding epileptiform discharge, or PED), which can show a widespread or bilateral distribution. PEDs can precede any type of SIOP and consequently were analysed separately. The term "seizure onset patterns" will include SIOPs and PEDs. A more detailed description of the seizure onset analysis is described elsewhere (Jiménez-Jiménez et al., 2015).

2.9. Surgical procedures

Surgery included temporal resections only. Tissue was removed and pathology studies performed. En-bloc temporal lobectomies followed an anatomically standardised surgical technique (Alarcon, 2009). En bloc temporal lobectomy was undertaken at King's College Hospital as originally described by Falconer (Falconer, 1971), later modified to achieve a more complete removal of the hippocampus by use of the principles described by Spencer (D. D. Spencer, Spencer, Mattson, Williamson, & Novelly, 1984). In effect, between 5.5 cm and 6.5 cm of temporal lobe was removed. In the dominant hemisphere, usually the left, all superior temporal gyrus except the anterior 2 cm was spared. Such a resection would have included at least 50% of the amygdala and 2–3 cm of parahippocampal gyrus and hippocampus. Electrocorticographic intraoperative recordings were carried out and the extent of the resection was occasionally modified according to electrocorticographic findings (Alarcon et al., 1997). Structural lesions shown on imaging were removed unless functional mapping suggested a significant risk of functional deficits. Post-operative imaging was performed in those patients where surgery failed.

2.10. Surgical outcome

Surgical outcome with regard to seizure control was determined at regular post-operative follow up assessments. Surgical outcome was coded according to Engel surgical outcome classification (Engel, Van Ness, Rasmussen, & Ojemann, 1993, pp. 609–621). Surgical outcome at the longest follow up available was used for each patient. Grade I was considered as "good outcome" and grades II, III or IV as "poor outcome". Only those patients with at least one year of follow up were included in this analysis.

2.11. Surgical outcome analysis

Two-tailed χ^2 testing with one degree of freedom and with Yate's correction was used to compare the proportion of

patients with favourable outcome between the groups of patients showing contralateral temporal lobe connections. Existence of significant differences was assumed if $p < .05$. Analysis was carried out with GraphPad.

(www.graphpad.com/quickcalcs/contingency1.cfm).

3. Results

3.1. Subjects and resections

Among the 91 patients included in the study, 45 (49.5%) were female and 46 (50.5%) were male. The median age of SPES assessment was 35.07 (minimum = 10 years; maximum = 29 years). Of the 91 patients, 40 (44.0%) underwent temporal lobe resection and among these, 34 had a follow up longer than 1 year. One hundred and fifty six seizures were studied from the 40 patients who underwent surgery. The median age at resection was 33.2 years (minimum = 15 years; maximum = 55 years).

3.2. Intracranial electrodes

3.2.1. Subdural electrodes

Among all 91 patients, 61 patients (67.0%) had only subdural strips, which included bilateral subtemporal strips in all cases. In addition to the subtemporal strips, 12 patients (13.2%) had one additional unilateral frontal strip, 4 patients (4.4%) had one additional unilateral frontal mat, 3 patients (3.3%) had one additional occipital strip, 1 patient (1.1%) had an additional unilateral frontal mat and a subdural occipital strip, and 1 patient (1.1%) had an additional unilateral frontal strip and one occipital strip.

3.2.2. Depth electrodes

Among all 91 patients, 28 patients (30.8%) had depth electrodes bilaterally implanted in the temporal lobes. In addition to the temporal electrodes, 4 patients (4.4%) had one subdural frontal strip, 3 patients (3.3%) had one subdural occipital strip, and 2 patients (2.2%) had one unilateral frontal depth electrode.

3.2.3. Subdural and depth electrodes

Two patients (2.2%) had a combination of temporal subdural and depth electrodes.

3.3. Presence of contralateral temporal connections

The number and percentage of temporal lobes presenting contralateral temporal responses are shown in Table 1. Responses were seen in a region of the contralateral temporal lobe when stimulating temporal regions in 30 patients out of the 91 (32.96%). Bi-hippocampal or bi-amygdalar projections were seen in only 5% of temporal lobes ($N = 60$) (Fig. 2) and between fusiform gyri in 7.1% ($N = 126$) (Fig. 3). All other connections were seen less than 5% of hemispheres as in Fig. 4.

3.4. Latencies of contralateral temporal connections

Depending on the structures, latencies ranged between 20 and 90 msec, with an average value of 60.2 msec. Table 2 shows the latencies of contralateral connections.

3.5. Seizure onset patterns

Table 3 shows the incidence of each SIOP for the 40 patients who underwent surgery. Patients have been divided into those with and without contralateral temporal connections. Overall, the most common SIOP was FA, which was seen in 14 patients (35.0%), followed by DEE seen in 7 patients (17.65%) and FA-DEE in 5 patients (12.5%). No difference was found in the proportion of patients showing a specific SIOP among patients with and without contralateral temporal projections.

Among the 28 patients without contralateral connections, PEDs were present in 16 patients, were focal in 3 patients, widespread (unilateral involvement of more than one temporal structure) in 12 patients and bilateral in 1 patient. Among the 12 patients with contralateral connections, PEDs were present in 6 patients, were focal in 2 and widespread in 4 patients. Interestingly, no patient with contralateral connections showed bilateral PEDs.

Table 1 – Incidence of contralateral responses to stimulation of temporal lobes.

		Regions showing responses									
		Amygdala		Hippocampus		Fusiform gyrus		Inferior temporal gyrus		Mid temporal gyrus	
		n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Stimulated Regions	Amygdala	3/60	5.0	0/60	0.0	X	X	X	X	0/60	0.0
	Hippocampus	0/60	0.0	3/60	5.0	X	X	X	X	5/126	3.9
	Parahippocampal gyrus	X	X	X	X	4/126	3.1	0/126	0.0	0/126	0.0
	Fusiform gyrus	X	X	X	X	9/126	7.1	6/126	4.7	2/126	1.0
	Inferior temporal gyrus	X	X	X	X	4/126	3.1	2/182	1.0	0/182	0.0
	Mid temporal gyrus	0/126	0.0	0/126	0.0	2/126	1.0	6/182	3.2	8/182	4.3
	Total	3	5.0	3	5.0	19	13.3	14	8.9	15	5.3

n = number of temporal lobes where connection was present.
N = number of temporal lobes where connections were studied.
X = not tested.

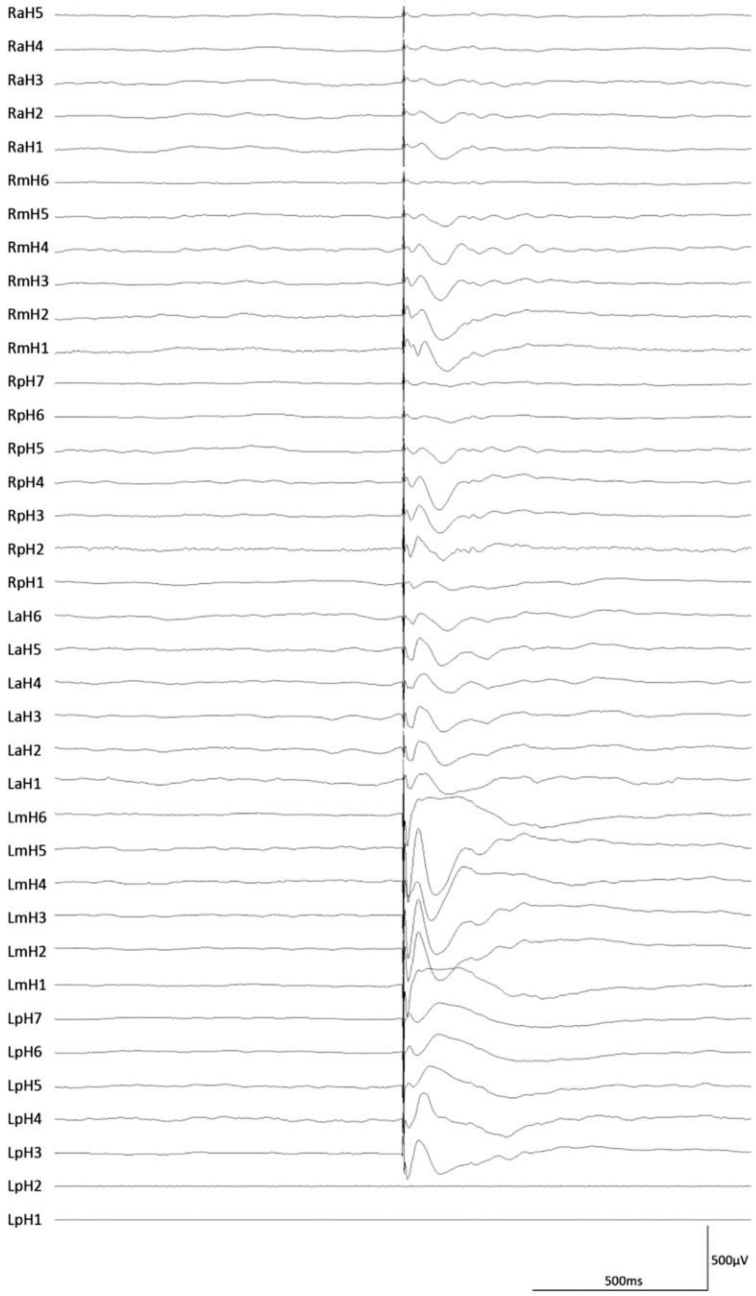

Fig. 2 – Example of contralateral hippocampal response evoked by single pulse electrical stimulation. The patient had bilateral depth electrodes implanted. When stimulating through electrodes 1 and 2 of the left posterior temporal bundle (LpH1-LpH2) there is a response in the contralateral hippocampus (RpH4-RpH2, RmH4-RmH1, RaH1-RaH2) suggesting the presence of functional connections between both hippocampi. The flat horizontal lines show the stimulating electrodes (LpH1-LpH2). For each depth electrode bundle, electrode 1 was the most distal electrode to the insertion burr hole (i.e., the deepest electrode). Recordings are shown in common reference montage. RaH, Right anterior Hippocampus; RpH, Right posterior Hippocampus; RmH, Right middle Hippocampus; LaH left anterior Hippocampus; LmH, Left middle Hippocampus.

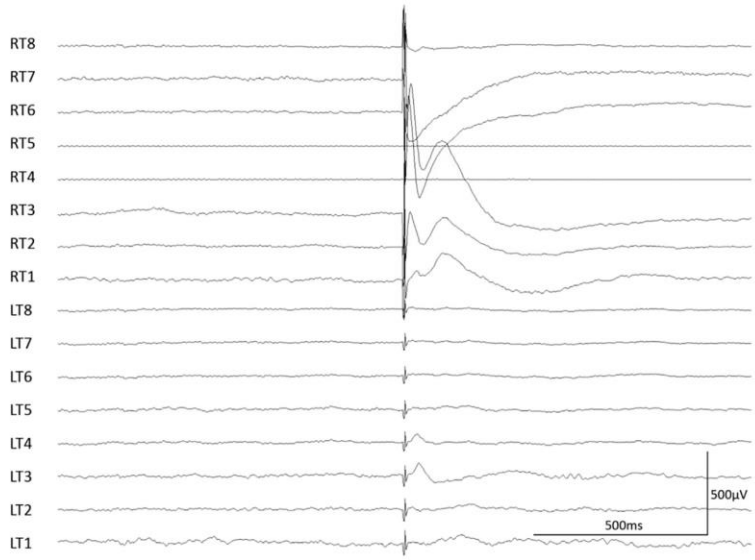

Fig. 3 – Example of contralateral response at the left fusiform gyrus evoked by single pulse electrical stimulation of the right fusiform gyrus. The patient had bilateral subtemporal electrodes implanted. When stimulating through electrodes 5 and 4 of the right temporal bundle (RT5-RT6), there is a response in the contralateral temporal lobe (LT4-LT3), suggesting the presence of contralateral functional connections between both fusiform gyri. The flat horizontal lines show the stimulating electrodes. Recording shown in common average reference. For each strip, electrode 1 was the most distal electrode to the insertion burr hole. RT = Right temporal. LT = Left temporal.

No difference was found in the proportion of patients showing PED or in PED extension among patients with and without contralateral temporal projections.

Table 4 shows the anatomical structure showing seizure onset and PEDs. A substantial proportion of patients showed a lobar onset involving more than one structure. Among the remaining patients, the majority of seizures arose from the hippocampus and parahippocampal gyrus. The largest proportion of PEDs showed a widespread distribution, involving more than one structure. No difference was found among patients with and without contralateral temporal projections, in the proportion of patients showing seizure onset or PED at each location.

3.6. *Prognostic value of contralateral temporal lobe connections*

Surgical outcome from all 34 patients who underwent resection and had a follow up period longer than one year after a temporal resection is summarised in Table 5. Overall, 38.28% of patients remained seizure free after surgery. The median follow up was 21.00 months (minimum = 12 months; maximum = 144 months). Among the 34 patients, 12 showed contralateral temporal connections (30%).

Among the 26 patients without contralateral temporal connections, 10 (38.46%) had Engel Class I whereas among the 8 patients with contralateral temporal lobe connections 3 (37.5%) had Engel Class I. There is no statistical difference in the proportion of patients showing Engel Class I between patients with and without contralateral temporal connections.

4. Discussion

Our findings confirm that the functionality of bilateral temporal connections is limited. Only 5% of amygdala project to the contralateral amygdala. Similarly, 5% of hippocampus is connected to the contralateral hippocampus and 3.9% to the mid temporal gyrus. The highest contralateral temporal projections arise from both fusiform gyri (7.1%) (Fig. 4). These findings are consistent with previous reports from smaller series (Fish et al., 1993; Lacruz et al., 2007; Lacuey et al., 2014; Umeoka et al., 2009; Wilson et al., 1991). Our findings are also consistent with the notion that the temporal lobes on either hemisphere process memory independently (Lacruz et al., 2010). This is in contrast with what occurs with other parts of the limbic system. For instance, the cingular gyrus shows profuse functional connections with contralateral frontal cortex (Lacruz et al., 2007; Rosenzweig, Beniczky, Brunnhuber, Alarcon, & Valentin, 2011; Valentin et al., 2011). The shortest inter temporal latency was between amygdalae, possibly reflecting the shorter distance or callosal propagation. Overall we have found latencies for contralateral bi-temporal connections within the range previously reported (Lacruz et al., 2007; Umeoka et al., 2009).

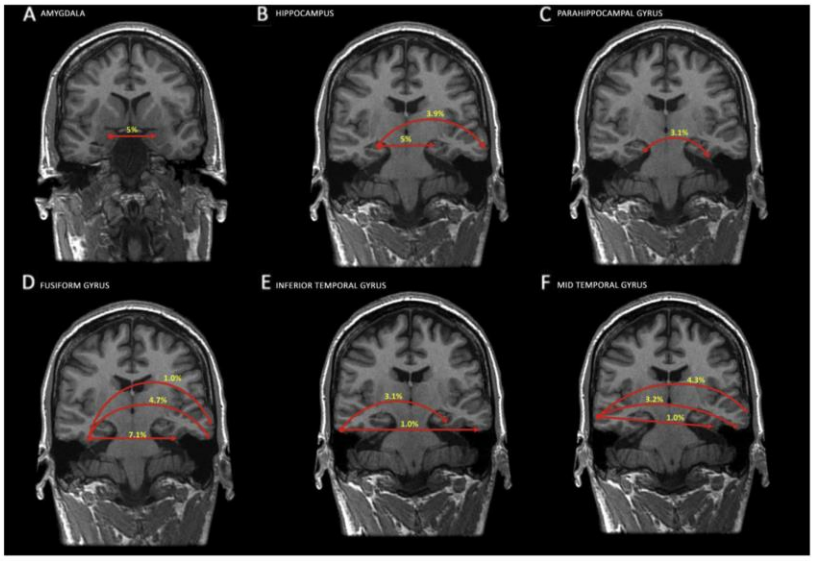

Fig. 4 – Coronal MRI showing void flows from the stimulation site to all identified contralateral temporal responses. The stimulated site is shown next to panel letter. The percentages of hemispheres presenting each projection are shown in yellow. Arrows go from stimulated site to the regions showing responses. Data from all hemispheres from all patients are pooled together as going from right to left. A) Contralateral projections from the amygdala. B) Contralateral projections from the hippocampus. C) Contralateral projections from the parahippocampal gyrus. D) Contralateral projections from fusiform gyrus. E) Contralateral projections from the inferior temporal gyrus. F) Contralateral projections from the mid temporal gyrus.

Table 2 – Latency (msec) of contralateral temporal connections. N = number of temporal lobes stimulated, n = number of temporal lobe with connection.

Stimulated area	Contralateral response	n/N	Median	Minimum	Maximum
Amygdala	Amygdala	3/60	45.75	35.00	70.60
Hippocampus	Hippocampus	3/60	53.61	40.0	58.38
Mid temporal gyrus	Mid temporal gyrus	5/60	61.03	48.0	64.40
Parahippocampal gyrus	Fusiform gyrus	4/126	57.63	20.0	84.21
Fusiform gyrus	Fusiform gyrus	9/126	62.15	40.0	86.99
	Inferior temporal gyrus	8/126	58.50	45.65	70.66
	Mid temporal gyrus	2/126	74.41	59.09	89.74
Inferior temporal gyrus	Fusiform gyrus	4/126	74.88	59.66	85.00
	Inferior temporal gyrus	6/126	58.66	53.73	63.6
Mid temporal gyrus	Fusiform gyrus	2/126	60.61	60.00	61.22
	Inferior temporal gyrus	6/126	63.64	55.00	73.77
	Mid temporal gyrus	8/182	59.94	45.00	77.72

Table 3 – Presence and percentage of each SIOP in patients with and without contralateral connections.

SIOP	Alpha		DEE		Delta		FA		FA-DEE		Sharp -wave		Sharps		Spike -wave		Theta		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	N	%
Patients with connections	1	8.3	2	16.7	0	0.0	4	33.3	1	8.3	1	8.3	1	8.3	1	8.3	1	8.3	12	100
Patients without connections	0	0.0	5	17.9	1	3.6	10	35.7	4	14.3	1	3.6	1	3.6	3	10.7	3	10.7	28	100
Total	1	2.5	7	17.5	1	2.5	14	35.0	5	12.5	2	5.0	2	5.0	4	10.0	4	10.0	40	100.0

Table 4 – Number and percentage of anatomical occurrence of SIOP and PED in patients with and without contralateral temporal lobe connections.

SIOP	Hippocampus		Parahippocampus gyrus		Fusiform gyrus		Inferior temporal gyrus		Lobar		Total	
	n	%	n	%	n	%	n	%	n	%	N	%
Patients with connections	3	25.0	3	25.0	1	8.3	0	0.0	5	41.7	12	100.0
Patients no connections	3	10.7	2	7.1	3	10.7	4	14.3	16	57.1	28	100.0
Total ($n = 40$)	6	15.0	5	12.5	4	10.0	4	10.0	21	52.5	40	100.0

PED	Hippocampus		Parahippocampus gyrus		Fusiform gyrus		Inferior temporal gyrus		Widespread unilateral		Total (excluding bilateral)[a]	
	n	%	n	%	n	%	n	%	n	%	N	%
Patients with connections	0	0.0	2	3.3	0	0.0	0	0.0	4	66.7	6	100.0
Patients with no connections	1	6.3	1	6.3	1	6.3	0	0.0	12	75	16	100.0
Total ($n = 40$)	1	4.5	3	13.6	1	4.5	0	0.0	17	77.2	22	100.0

SIOP = Sustained ictal onset pattern.
PED = Preceding epileptiform discharge.
[a] One patient with no connections had bilateral PED and no patient with connections showed bilateral PED.

Table 5 – Number and percentage of patients with each outcome grade in patients with and without a contralateral temporal lobe connections. Roman numbers refer to Engel surgical outcome classification.

Engel Class	I		II		III		IV		Total	
	n	%	n	%	n	%	n	%	N	%
Patients with connections	10	38.5	4	15.4	7	26.9	5	19.2	26	100.0
Patients with no connections	3	37.5	2	25.0	0	0.0	3	37.5	8	100.0
Total ($n = 34$)	13	38.2	6	17.6	7	20.6	8	23.5	34	100.0

The absence of functional connections between hippocampi is puzzling, as there is ample evidence for the presence of anatomical connections (Lacuey et al., 2014; Lieb & Babb, 1986; Lieb, Engel, & Babb, 1986; Wilson et al., 1990, 1991). There are two commissural systems in primates, responsible of connecting contralateral hippocampi structures: a) the ventral hippocampal commissure, which interconnects both hippocampi; b) the dorsal hippocampal commissure interconnecting both entorhinal cortices. Neurophysiological and neuropathological methods suggest that the ventral hippocampal commissure has virtually disappeared in humans, while the dorsal hippocampal commissure, which interconnects both entorhinal cortices, appears to remain functional (Gloor, 1997; Gloor et al., 1993; Umeoka et al., 2009). We have found that the fusiform gyrus is the temporal structure with the highest proportion of contralateral temporal projections, supporting that the dorsal hippocampal commissure is the most relevant pathway in humans. We found minimal connectivity (5% of temporal lobes) between both amygdalae, in concordance with a previous report using PET (Irwin et al., 2004).

The functionality of bilateral temporal connections affects neither the presence of bilateral changes at seizure onset nor seizure control after surgery. This suggests that the presence of bilateral changes at seizure onset may not be due to rapid propagation through the pathways studied here. The absence of relation between bi-temporal connections and seizure control after surgery further suggests that seizure propagation may not preferentially occur along these synaptic pathways, and consequently, severance of such pathways may not be necessary to achieve favourable outcome. However, analysis of seizure spreading in patients implanted with intracranial electrodes has suggested that the different commissures may be involved in ictal propagation to the contralateral hippocampi (Gloor et al., 1993; S. S. Spencer, Williamson, Spencer, & Mattson, 1987). It is possible that seizures may propagate through anatomical pathways that may not be relevant in normal function.

In conclusion, the present study is novel in two respects:

1) Our series is substantially larger (91 patients) than any previous report. Because the connections described are so infrequent, their presence cannot be estimated in small series. Therefore reporting a large series like ours is crucial for such estimation.
2) This is the first study to address whether the presence of bilateral temporal connections is related to bilateral seizure onset patterns and/or to postsurgical seizure control, which has obvious clinical implications.

Disclosure

None of the authors has any conflict of interest to disclose.

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5. CHAPTER FIVE

1 Discussion

The present thesis has sought to elucidate some aspects of the pathophysiology of seizure onset in focal seizures recorded with intracranial electrodes and its significance to epilepsy surgery.

In the present thesis, I described the different patterns seen at seizure onset and its relation with surgical outcome in a large series (Jimenez-Jimenez et al., 2015b). I found that focal fast activity seen as the first ictal pattern was associated with good surgical outcome. As first ictal pattern, focal fast activity was related to favourable seizure control after surgery whereas diffuse flattening of the EEG was related with poor post-surgical outcome (Jimenez-Jimenez et al., 2015b). Seizures starting with simultaneous fast activity and EEG flattening were correlated to good outcome more weekly than those starting with fast activity. In addition, I have described a discharge that often precedes seizure onset called preceding epileptiform discharge (PED) (Jimenez-Jimenez et al., 2015b). PED can have different spatial extent: focal, lobar and widespread/bilateral. Interesting, PED presence and extent does not seem to affect surgical outcome (Jimenez-Jimenez et al., 2015b). I found that there is no relation between different seizure onset patterns and underlying pathology.

After seizure onset, most seizures comprise a complex constellation of evolving patterns occurring simultaneously or concatenate. Consequently, in addition to

the study of first ictal onset pattern, I also investigated the prognostic value of the second ictal pattern for surgical outcome (Jiménez-Jiménez et al., 2016). When fast activity was seen as the second ictal pattern, it was associated with poor surgical outcome. In contrast diffuse electrodecremental event as second ictal pattern was associated with favourable surgical outcome (Jiménez-Jiménez et al., 2016). In addition, delayed second ictal patterns (≥10sec) appear to be associated with good outcome in temporal lobe epilepsy (Jiménez-Jiménez et al., 2016).

It is difficult to understand the mechanisms for the bilateral EEG patterns (diffuse flattening, preceding epileptiform discharge) seen at seizure onset in focal seizures. In an attempt to establish if such diffuse changes are due to cortical connections, I used single pulse electrical stimulation SPES to study contralateral functional connections of the temporal lobe and their association with bilateral seizure onset patterns and surgical outcome (Jimenez-Jimenez et al., 2015a). Functional connectivity between medial temporal lobe structures was scarce. The highest incidence of contralateral temporal connections was between fusiform gyri. No difference was found in the proportion of patients showing bilateral seizure onset patterns among patients with or without contralateral temporal projections. In addition, there were no statistical difference in the proportion of patients showing Engel Class I between patients with and without contralateral temporal connections (Jimenez-Jimenez et al., 2015a).

In my studies, diffuse electro decremental event was one of the most mystifying ictal patterns, since widespread changes are not expected in focal seizures. Indeed widespread ictal changes can also be recorded during the preictal period (Perucca et al., 2013). The mechanisms of widespread pre ictal and early ictal changes remain unknown.

The presence of widespread iEEG patterns at seizure onset in focal seizures opens a debate for the classical view of a well-defined epileptogenic zone. The later suggests that seizures may arise from a large or widespread network. Neuronal hyperexcitability may reverberate within the network culminating in the onset of overt ictal EEG patterns in particular regions (Alarcon et al., 1995). Moreover, the extension of the network appears to be reflected on the EEG ictal onset pattern. Furthermore, some widespread EEG patterns at seizure onset are associated with worse post-surgical seizure control, suggesting that identification of the network components and their disconnection may be relevant to improve surgical results. If widespread EEG changes result from axonal-synaptic connections, their association with poor outcome would suggest that targeting such connections could improve surgical outcome.

An attempt to explain the flattening seen on the EEG has been provided by spreading depolarization (Leao, 1947). In 1944, Leao induced epilepsy in rabbits by intraperitoneal injection of dial-urethane solution in doses of 0,55 to 0,75cc per kg. Nembutal was used occasionally. He found that minimal electrical stimulation was associated with flattening of the EEG (Leao, 1947). Spreading depression has been defined, as a self-propagating depolarization wave involving

both, neuronal and astroglial mechanisms (Dreier et al., 2012, Leao, 1947, Broberg et al., 2014, Hablitz and Heinemann, 1989). Spreading depression shows an initial depolarization followed by EEG flattening (Broberg et al., 2014, Dreier et al., 2012, Leao, 1947, Hablitz and Heinemann, 1989). Spreading depression has been implicated in the pathophysiology of several neurological disorders, including migraine with aura, epilepsy, and the progression of acute brain injury (Broberg et al., 2014, Dreier et al., 2012).

A recent study in adult Sprague Dawley rats (315–450 g), spreading depression was induced by mechanical (pipette insertion and/or intracranial solute injection) and metabolic (fluorocitrate) factors (Broberg et al., 2014). This study suggested that cortical spreading depression might be involved in generating the electrodecremental events seen on the EEG (Broberg et al., 2014). Thirty minutes after inducing epilepsy in rats, the authors proceeded to record intracranial EEG and described 5 phases on the EEG. First, there was neuronal depolarization during which ripples were observed close to the injection site for the epileptogenic agent. Second, depression of cortical electrical activity was seen which appeared as flattening on the EEG. This depression lasted for 1–2 min. During this phase, the frequency band of suppressed activity was 25–100 Hz. This is then followed by a mixed third phase just after the flattening has recovered, when an abundance of irregular local low frequency spiking appears even though higher frequencies are still suppressed. Fourth, depression of activity was still seen but frequencies started to recover slowly. Fifth, an excitatory process appeared and the EEG started to recover from depression.

This last phase occurred approximately 8 min after a single mechanical stimulus (micropipette injection) (Broberg et al., 2014).

This report is in concordance with the study conducted by Hablitz and Heinemann in rats rendered epileptic by Picrotoxin (50 microM) (Hablitz and Heinemann, 1989). The authors found spike activity and electrodecremental events on intracranial EEG recordings, and concluded that decrement was due to depressed neuronal activity, during which cells repolarize and extracellular potassium levels are restored (Hablitz and Heinemann, 1989). The cortical spreading theory seems to be an interesting concept, which may help solve the present knowledge gap with regards to electrodecremental events. These studies have been conducted in animal models of epilepsy. It remains uncertain whether the same explanation may be responsible for human findings.

Another mystifying pattern is the preceding epileptiform discharge (PED). PEDs were present in 75.4% of patients, and among these, PEDs were widespread or bilateral in 63% (Jimenez-Jimenez et al., 2015b). Interestingly, the presence of widespread or bilateral PED was not correlated with surgical outcome. The physiological and clinical significance of PEDs are unclear, and widespread PEDs are often disregarded in clinical practice. Yet, their association to seizures is obvious, as they occur immediately preceding the EEG onset of nearly every seizure in the same patient. The absence of relation between bilateral PEDs and surgical outcome suggests that PEDs may not be part of the seizures but PEDs may be a condition facilitating seizure occurrence. Single pulse electrical stimulation (SPES) may constitute a novel approach to the study of PEDs.

Responses to SPES can resemble other related physiological waveforms such as interictal epileptiform discharges and K complex (Voysey et al., 2015, Nayak et al., 2014). It would be expected that in areas close to seizure onset, SPES would be able to induce responses similar to PEDs. SPES responses resembling PEDs could confirm whether PEDs are part of the seizure.

Approximately 33% of temporal lobe patients assessed for surgery with intracranial electrodes show bilateral changes at seizure onset (Jimenez-Jimenez et al., 2015b). As stated above, the nature of such changes remains unknown. We hypothesized that if the incidence of bilateral changes at seizure onset is due to synaptic transmission through anatomical pathways, they should be related to the presence of functional bilateral connections. Additionally, removal of such connections should be related with surgical outcome. Recent connectivity studies with neuroimaging seem to support this interpretation. Diffusion tensor imaging (DTI) suggests that patients with mesial temporal lobe epilepsy exhibit decreased connectivity to ipsilateral thalamocortical regions and increased connectivity to ipsilateral medial temporal lobe, insular, and frontal connectivity (Bonilha et al., 2013b). Furthermore, those remaining with seizures after surgery exhibited higher connectivity between structures. However, a study of resting state with functional MRI in temporal lobe epilepsy suggests decreased local and inter-hemispheric functional connectivity and increased intra-hemispheric connectivity compared to normal controls (Maccotta et al., 2013b).

Seizure onset is a complex phenomenon with several patterns that may arise focal in around 31.9%, lobar in around 47.8% and widespread in 20.3%,

frequently involving more than one pattern type at onset (Jimenez-Jimenez et al., 2015b). Identifying a specific pattern in the clinical scenario with such complex features at seizure onset can be challenging. Therefore, we hypothesize that the second ictal pattern that follows the first ictal patter at seizure onset has a prognostic value for surgical outcome. I have shown that the nature of the seizure onset pattern has different prognostic value with regards to surgery. For instance, when diffuse electrodecremental event was present as the second ictal pattern, it was associated with good surgical outcome (Jiménez-Jiménez et al., 2016). The opposite is exhibited when fast activity appears as second ictal pattern (Jimenez-Jimenez et al., 2015b). This surprising finding can be explained by the fact that decrement tend to occur after fast activity, and consequently would be associated with good outcome if occurring as a second ictal pattern.

A recent study using scalp EEG pursued to elucidate the prognostic value of ictal patterns and surgical outcome in 111 seizures from 47 diagnosed with temporal lobe epilepsy (Pelliccia et al., 2013). Authors found that flattening of the EEG was the most common pattern, which was present in 48% of patients, followed by fast activity seen in 22% of patients. Other patterns were less commonly seen (Pelliccia et al., 2013). Unexpectedly, good surgical outcome was seen in 74.4% when flattening of the EEG was the ictal pattern. Good surgical outcome observed with flattening of the EEG may be the result of seizure onset evolution, as fast activity is difficult to record on the scalp.

6. CHAPTER SIX

1 Conclusion

The prognostic value of ictal patterns depends on where in the seizure they occur. Pathology was not correlated to any specific pattern. Additionally, the present findings corroborate that the functionality of bilateral temporal connections in humans is limited and does not affect the surgical outcome. In addition, we found better postsurgical outcome in temporal patients with longer SIP latencies. In temporal lobe patients, we found better postsurgical outcome in patients with longer SIP latencies. These findings suggest that those patients where the FIP remains focal for longer would have better outcome.

7. CHAPTER SEVEN

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