Universidade de Aveiro
2007
Departamento de Electrónica, Telecomunicações e Informática

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Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Doutor em Engenharia Electrotécnica, realizada sob a orientação científica do Professor Doutor João Paulo Trigueiros da Silva Cunha, Professor Associado do Departamento de Electrónica, Telecomunicações e Informática da Universidade de Aveiro

Apoio financeiro da FCT e do FSE no âmbito do III Quadro Comunitário de Apoio.

FCT
Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR

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I dedicate this thesis to my parents, brother, my sister-in-law and my two little nieces.

o júri

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agradecimentos

I would like to express my deepest gratitude to the following people and institutions:

To João Paulo ... for the trust, guidance and independence given to me during these years and km made together. Also for the many wild ideas (including this Ph.D.) that hopefully we will be able to make a reality in the future.

To Prof. Martins da Silva for helping me get inside the EEG, MEG and epileptic brain and being a good listener and partner of many conversations (not always epilepsy) and, of course, many short lunches.

To Prof. Lopes da Silva for the strategic feedback given several times along this work, especially the one given at the beginning of this work to a Computer Scientist with wild ideas in a breakfast table.

To Alberto Leal for the clinical sixth sense for peeking the right patients with the right questions and being the clinical “light-house” along part of this work.

To João Ramalheira, for the many hours in front of an EEG waiting for the right moment (seizure) and the many conversation in front of hipo- and hiper-perfusions.

To Prof. Franscisco Vaz, for the never ending question: “Quando é que está pronta?”. The answer is “Agora”

To Ilídio, who is difficult to put in a GRID that has been a reliable presence in many ways along these years: HISA, Object oriented, agents, rowing, Team-Hos, little red riding hood, agents, GRID…

To Miguel Coimbra, for his thorough review of this thesis (my English “FAQ” and very helpful scientific “testbed”). Hopefully my thesis helped in his Epilepsy understanding and contributed for future “epileptic” projects and shruberies.

To my SIAS colleagues especially those from the early years (Isabel, Gramaxo, Victor, Djo, Relvas, Pedro, Artur) that supported the “chaos” in my brain, asked “eternally” for the end of the thesis and also shared many QUAC QUAC’s. A special mention also for the intelligence community spread from the south to the north further than north.

To all people in the VU MEG Centre and H. St. António who contributed not only in my work and but also in my scientific and clinical growth.

To all people in IEETA and UA that helped me in some way to make possible this work

For all those “non-epileptic”, family and friends, that indirectly supported me during these years.

I also acknowledge the support of the fellowship PRAXIS XXI/BD/19676/99 from Fundação para a Ciência e Tecnologia - Program Praxis XXI.

palavras-chave

Electroencefalograma (EEG), magnetoencefalograma (MEG), pontas, localização de geradores electromagnéticos, espacio-temporal, análise de clusters

resumo

A epilepsia é uma patologia cerebral que afecta cerca de 0,5% da população mundial. Nas epilepsias focais, o principal objectivo clínico é a localização da zona epileptogénica (área responsável pelas crises), uma informação crucial para uma terapêutica adequada. Esta tese é centrada na caracterização da actividade cerebral electromagnética do cérebro epiléptico. As contribuições nesta área, entre a engenharia e neurologia clínica, são em duas direcções.

Primeiro, mostramos que os conceitos associados às pontas podem ser imprecisos e não ter uma definição objectiva, tornando necessária uma reformulação de forma a definir uma referência fiável em estudos relacionados com a análise de pontas. Mostramos que as características das pontas em EEG são estatisticamente diferentes das pontas em MEG. Esta constatação leva a concluir que a falta de objectividade na definição de ponta na literatura pode induzir utilizações erradas de conceitos associados ao EEG na análise de MEG. Também verificamos que o uso de conjuntos de detecções de pontas efectuadas por especialistas (MESS) como referência pode fornecer resultados enganadores quando apenas baseado em critérios de consenso clínico, nomeadamente na avaliação da sensibilidade e especificidade de métodos computorizados de detecção de pontas

Em segundo lugar, propomos o uso de métodos estatísticos para ultrapassar a falta de precisão e objectividade das definições relacionadas com pontas. Propomos um novo método de neuroimagem suportado na caracterização de geradores electromagnéticos – EpiGauss – baseado na análise individual dos geradores de eventos do EEG que explora as suas estruturas espacio-temporais através da análise de “clusters”. A aplicação de análise de “clusters” à análise geradores de eventos do EEG tem como objectivo usar um método não supervisionado, para encontrar estruturas espacio-temporais dps geradores relevantes. Este método, como processo não supervisionado, é orientado a utilizadores clínicos e apresenta os resultados sob forma de imagens médicas com interpretação similar a outras técnicas de imagiologia cerebral. Com o EpiGauss, o utilizador pode determinar a localização estatisticamente mais provável de geradores, a sua estabilidade espacial e possíveis propagações entre diferente áreas do cérebro. O método foi testado em dois estudos clínicos envolvendo doentes com epilepsia associada aos hamartomas hipotalâmicos e o outro com doentes com diagnóstico de epilepsia occipital. Em ambos os estudos, o EpiGauss foi capaz de identificar a zona epileptogénica clínica, de forma consistente com a história e avaliação clínica dos neurofisiologistas, fornecendo mais informação relativa à estabilidade dos geradores e possíveis percursos de propagação da actividade epileptogénica contribuindo para uma melhor caracterização clínica dos doentes.

A conclusão principal desta tese é que o uso de técnicas não supervisionadas, como a análise de “clusters”, associadas as técnicas não-invasivas de EMSI, pode contribuir com um valor acrescido no processo de diagnóstico clínico ao fornecer uma caracterização objectiva e representação visual de padrões complexos espacio-temporais da actividade eléctrica epileptogénica.

keywords

Electroencephalogram (EEG), magnetoencephalogram (MEG), spikes, electromagnetic source imaging, dipole, spatio-temporal, cluster analysis

abstract

Epilepsy is a brain pathology that affects ~0.5% of the world population. In focal epilepsies, the main clinical objective is the localization of the epileptogenic zone (brain area responsible for the epileptic seizures – EZ), a key information to decide an adequate therapeutic approach.

This thesis is centred on electromagnetic activity characterization of the epileptic brain. Our contribution to this boundary area between engineering and clinical neurology is two-folded.

First we show that spike related clinical concepts can be unprecise and some do not have objective definitions making necessary a reformulation in order to have a reliable reference in spike related studies. We show that EEG spike wave quantitative features are statistically different from their MEG counterparts. This finding leads to the conclusion that the lack of objective spike feature definitions in the literature can induce the wrong usage of EEG feature definition in MEG analysis. We also show that the use of multi-expert spike selections sets (MESS) as gold standard, although clinically useful, may be misleading whenever defined solely in terms of clinical agreement criteria, namely as references for automatic spike detection algorithms in sensitivity and specificity method analysis.

Second, we propose the use of statistical methods to overcome some lack of precision and objectivity in spike related definitions. In this context, we propose a new ElectroMagnetic Source Imaging (EMSI) method – EpiGauss – based on cluster analysis that explores both spatial and temporal information contained in individual events sources analysis characterisation. This automatic cluster method for the analysis of spike related electric generators based in EEG is used to provide an unsupervised tool to find their relevant spatio-temporal structures. This method enables a simple unsupervised procedure aimed for clinical users and presents its results in an intuitive representation similar to other brain imaging techniques. With EpiGauss, the user is able to determine statistically probable source locations, their spatial stability and propagation patterns between different brain areas. The method was tested in two different clinical neurophysiology studies, one with a group of Hypothalamic Hamartomas and another with a group of Occipital Epilepsy patients. In both studies EpiGauss identified the clinical epileptogenic zone, consistent with the clinical background and evaluation of neurophysiologists, providing further information on stability of source locations and their probable propagation pathways that enlarges their clinical interpretation.

This thesis main conclusion is that the use of unsupervised techniques, such as clustering, associated with EMSI non-invasive techniques, can bring an added value in clinical diagnosis process by providing objective and visual representation of complex epileptic brain spatio-temporal activity patterns.

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Acronyms

AED	Anti-epileptic drug
BEM	Boundary element models
BOLD	Blood Oxygen Level Dependent response
CBF	Cerebral blood flow
CSF	Cerebro-spinal fluid
DD	Dipole density
DDD	Dipole density distribution
DM	Dipole Model
DSM	Distributed source models
DWI	Diffusion weighted imaging techniques
EC	Eloquent cortex
ECD	Equivalent current dipole
ECOG	Electrocorticography
EEG	Electroencephalogram
EMSI	Electromagnetic source imaging
ExTLE	Extra Temporal Lobe Epilepsy
EZ	Epileptogenic zone
FEM	Finite elements models
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
GOF	Goodness of fit
HH	Epilepsy associated with hypothalamic hamartomas
HRF	Hemodynamic response function
IED	Interictal Epileptiform Discharges
MEG	Magnetoencephalogram
MESS	Multi-expert spike selections
MNI	Monreal Neurological Institute
MRI	Magnetic Resonance Imaging

MRS	Magnetic Resonance Spectroscopy
MTLE	Mesial Temporal Lobe Epilepsy
MUSIC	Multiple signal classification
NAA	N-acetyl aspartate
OLE	Early Onset Occipital Lobe Epilepsy
PET	Positron Emission Tomography
RAP-MUSIC	Recursively applied multiple signal classification
rCBF	Regional cerebral blood flows
SMD	Single moving dipole
SNR	Signal to noise ratio
SPECT	Single Photon Emission Tomography
SPM	Statistical parametric mapping
TLE	Temporal Lobe Epilepsy
VEEG	Vídeo-EEG

1 Introduction

Epilepsy is a chronic condition characterized by spontaneously recurring seizures (Gastaut, 1973). The variety of causes is extensive and includes tumours, congenital malformations, genetic alterations in receptors and channels, and acquired structural abnormalities such as those following trauma or infection (Engel and Pedley, 1998). Epilepsy affects approximately 0.5 – 1 % of the population in industrialised countries (Hauser, 1998), from which approximately 20% continue to have seizures despite adequate anti-epileptic drug treatment; the majority of these cases suffer from localisation-related ('focal') epilepsy (Crawford, 2000).

1.1 Epilepsy surgery: the ultimate objective

The failure of anti-epileptic drug (AED) treatment in about 20% of the patients with epilepsy has brought an increasing interest in surgery as an option in epilepsy treatment. Epilepsy surgery aims to remove the area responsible from seizures and render patient seizure free (Engel, 1993). Surgery is a safe and effective treatment for patients with refractory localisation-related epilepsy, as supported by an extensive controlled trial that showed that surgery improves the chances of being seizure free in comparison to AED treatment (Wiebe et al., 2001). With the modern neurodiagnostic techniques (Duncan, 2002; Richardson, 2003; Knowlton, 2004; Koepp and Woermann, 2005), epilepsy surgery became more cost effective in comparison with the expenses of non-controlled epilepsy and inherent risk of disability and death (Pilcher et al., 1993 ; Sperling et al., 1999a; Engel, 2001; Cascino, 2004).

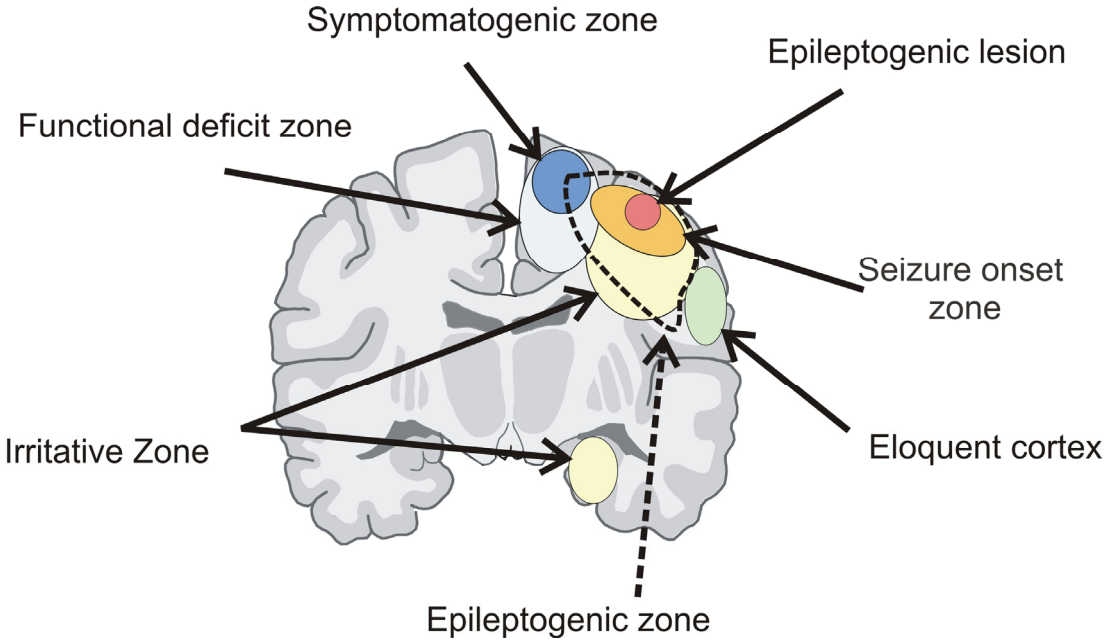


Figure 1 – Relevant zones in epilepsy diagnosis and surgical evaluation

In both the epilepsy diagnosis and presurgical evaluation, the objective is to delineate the area (dashed area) that encloses the epileptogenic zone (EZ). Through the identification of several zones (related with different expression of epilepsy), it is possible to infer the possible locations of the epileptogenic zone and help to plan the surgery procedure that, hopefully, will be able to extract the EZ zone without inducing deficits caused by the resection of deficit related area (eloquent cortex) (the picture is a courtesy of: Christian Vollnar, M.D.)

1.1.1 Finding the epileptogenic zone and eloquent cortex

The main objective of epilepsy surgery is to resect the brain area of the cerebral cortex region that is both necessary and sufficient to generate epileptic seizures - the epileptogenic zone (EZ) (Luders and Awad, 1992 ; Rosenow and Luders, 2001). Regrettably, this zone cannot be spatially delimited precisely nor is static in time, but only through the localisation of brain areas associated to epileptiform manifestations: in semiologic behaviours (e.g. seizures, automatism, behaviour changes), visible in electromagnetic measurements on the scalp (irritative zone) or in brain structure (lesional zone) and other physiological processes it is possible to corner the EZ (Nair et al., 2004). There are six different concepts usually used to describe these different perspectives (Rosenow and Luders, 2001; Richardson, 2003) (Figure 1):

- Irritative zone: area of cortex, which generates interictal spikes;
- Seizure onset zone: area of cortex where clinical seizures are initiated;
- Symptomatogenic zone: area of cortex which, when activated, produces the initial ictal symptoms or signs;
- Epileptogenic lesion: macroscopic lesion which may be causative of the epileptic

seizures by hyperexcitability of adjacent cortex;

- Functional deficit zone: area of cortex not functioning normally in the interictal period;
- Eloquent cortex: area of cortex indispensable for defined cortical functions usually associated to motor and high cognitive tasks (speech, memory).

The eloquent cortex (EC) localisation, in particular, is crucial for detecting overlaps between the EZ and zones responsible for important brain functions (e.g. motor, verbal and memory related functions). This localisation can avoid ill planned resection that might conduce to unrecoverable deficits. Finding the EC may not be as straight forward as mapping specific functions to particular brain regions, as patients with epilepsy may not present typical configuration (Richardson, 2003).

1.2 Epilepsy diagnosis: invasive and non-invasive techniques

The epilepsy diagnosis should use multiple data and analysis techniques where the primary aim is 1) localizing the EZ and EC zones and, in many cases, supporting the surgery option by 2) helping the planning of the surgery resection. Extensive reviews (Siegel, 2004 ; Uijl et al., 2005) offer an overview on the decision making process in epilepsy surgery where the importance of multiple data sources and analysis techniques is stressed out. Two categories of methods and data sources can be used in the evaluation: invasive (that imply a surgical procedure) and non-invasive methods.

Invasive evaluation methods measure electric potentials in the brain through depth electrodes or electrocorticography (ECOG) (Elger and Burr, 1994; Jayakar, 1999). Depth electrodes are placed in depth, near the suspected location to measure the electrical potentials and confirm or dismiss its epiloptogenicity based on the analysis of the electrical brain activity. ECOG similarly to depth electrodes, measures the electrical brain activity in the cortex, but the electrodes are placed in localized areas on the cortex surface (Kuruvilla and Flink, 2003; Blume et al., 2004). By placing electrodes directly on the brain cortex, the signal to noise ratio (SNR) is improved in comparison to traditional scalp electroencephalogram (EEG), as there is no filtering effect caused by the head layers on the signal (scalp, skull and cerebro-spinal fluid - CSF). Consequently, it enables the observation of interictal spikes originated from small cortex patches (less than 6 square centimeters) that are invisible in scalp EEG (Tao et al., 2005).

The non-passive options rely on the inhibition or stimulation of brain areas to infer their specific function/responsibility on brain processes as either normal (e.g. speech arrest, memory alterations, motor activations) or abnormal such as the epileptiform activity (Richardson, 2003; Blume et al., 2004). The most common examples are the electric stimulation and the Wada test (Engel and Pedley, 1998 ; Richardson, 2003). Electric stimulation can be performed with implanted electrodes during surgical evaluation or surgical procedure, enabling a mapping of brain function (combining a stimulation strategy with tests on specific brain functions). The Wada test requires a more complex surgical procedure involving the injection of sodium amobarbital into the internal carotid artery of one hemisphere, which temporarily abolishes the functions of that hemisphere. The induced deficits on both hemisphere may support predictions on the likelihood of postoperative deficits (Lee et al., 2003).

Invasive methods share the risk of any surgery procedure, and by themselves, may not be cost effective as their role is mainly of diagnostic value and not a therapeutic one. For those reasons, invasive procedures are avoided whenever possible and non-invasive methods used as the first option in pre-surgical evaluation protocols (Siegel, 2004 ; Uijl et al., 2005).

A typical example is related with Wada test. Despite its relevance, non-invasive alternatives have emerged with improved diagnosis results, such as magnetoencephalogram (MEG) (Papanicolaou et al., 1999; Hirata et al., 2004; Bowyer et al., 2005) and function magnetic resonance imaging (fMRI) (Kloppel and Buchel, 2005). The later presents comparatively lower costs (Medina et al., 2004).

The use of ECOG and depth electrodes, in contrast with Wada, is still the reference in the irritative zone delineation (Nakasato et al., 1994; Wennberg et al., 1998; Sutherling et al., 2001; Gotman, 2003) and in other methods validation, as it is a precise monitoring tool of very localized brain activity. But due to its limited spatial coverage, the measurements must be taken over areas of interest (Jayakar, 1999; Tao et al., 2005). For that reason their use is usually guided by non-invasive techniques to increase the probability of providing meaningful information. Examples are the combinations with scalp EEG and MEG (Blume et al., 2001; Knowlton and Shih, 2004; Papanicolaou et al., 2005), inverse problem solutions (Assaf et al., 2004), magnetic resonance imaging (MRI) (Kuruvilla and Flink, 2003 ; Shukla et al., 2003), fMRI (Huettel et al., 2004) and SPECT (Thadani et al., 2004).

With the evolution in computer methods and imaging techniques, the relevance of non-invasive methods such as EEG and MEG analysis has increased. Through mathematical and computational methods it is possible to extend simple EEG and MEG tracings associated to localized magnitude variation analysis (e.g. localize phase reversals, identify interictal and ictal epileptiform discharges, slowing) to more precise methods of anatomical localisation of most probable epileptic activity electric generators (Scherg, 1990; Sutherling et al., 1991 ; Baillet et al., 2001). These methods are considered to be part of electromagnetic[1] source imaging (EMSI) approaches (Michel et al., 2004; Wheless et al., 2004). EMSI methods provide a spatial characterisation of brain electrical activity with the high temporal resolution associated to EEG and MEG, which has a special interest in the EZ localisation. EMSI rational is that, by integrating signal extracted features (e.g. interictal epileptiform discharges), anatomical information (e.g. from magnetic resonance) and the most probable localisation of epilepsy related electric generators into a unified framework, it is possible to achieve more accurate information on the EZ localisation.

The focus of the present thesis is to present novel unsupervised contributions based on non-invasive EMSI for the clinical evaluation of epileptic patients.

1.3 Synopsis of the thesis

The initial orientation of this thesis was to study the spatio-temporal nonlinear association patterns in the EEG of epileptic patients following previous related work by J.P. Silva Cunha (Cunha et al., 1994b; Cunha et al., 1994a; Martins da Silva and Cunha, 1994; Cunha et al., 1996; Cunha and de Oliveira, 2000). Due to our group ongoing research activity, the author's research activity focused also in multimodal fusion in clinical environment (Fernandes et al., 2002; Oliveira et al., 2006), which is still a major line of research. This work was relevant to acquire some familiarity with Epilepsy and clinical environment issues.

The génesis of this thesis as it is presented was in 1999 a first contact by F.H. Lopes da Silva through A. Martins da Silva where we were asked to implement a automatic spike detector in MEG to be used at the MEGCenter at V.U in Amsterdam, Netherland. This was

[1] the term "electromagnetic" is used in this thesis in the sense supported by EMSI line of publications. Here, this term refers to the electric and magnetic manifestations produced by brain tissue electric phenomena (Niedermeyer and Lopes da Silva, 1999).

motivated by our line of work in this area with origin in the works of P. Guedes de Oliveira and F.H. Lopes da Silva in early 1980's (Guedes de Oliveira and Lopes da Silva, 1980a; Guedes de Oliveira and Lopes da Silva, 1980b; Guedes de Oliveira et al., 1983).

As a result of this contact, it was arranged a year stay at the MEGCenter under supervision of J.C. de Munck. The initial phase was spent in the familiarisation with MEGcenter team and MEG. As a result of this period several observations were possible: 1) clinicians were not satisfied with commercially available in spike detection for MEG, 2) the final use of an automatic spike detector was ambiguous – several times discussions on whether a spike detector results should match human reviewers or produce detections with stable signatures that produce high goodness of fit source analysis solutions arised - and 3) our experience with limited EEG system (under 32 channels) needed to be adapted to high resolution systems (more than 64 channels), both computational framework and detection methods. The first step, as a result of several discussions with F.H. Lopes da Silva, A. Martins da Silva and J.P. Silva Cunha, was the decision that we needed to define our target, the MEG spike. This characterization resulted in the work presented in section 3.1 where we show that there are difference between EEG and MEG spikes and conclude on some properties of MEG spikes that are statistically different from their EEG counterparts.

A computational framework was implemented to support EEG and MEG processing and the work on EEG/MEG spike detection started. The initial approach was to try use quantified models based in the power concept. These trials were unsuccessfull as no good agreement was found between our quantified models and the expert gold standard. Later, these results motivated the analysis presented in section 3.2 where we try to characterize a expert gold-standard in terms a power based model and draw some conclusions. Due to unrelated factors (entering in a lecturer position at the University of Aveiro) my stay at the MEGCenter was shorthned to 4 months.

The unsuccessful results with MEG spike detection trials motivated us to look for other approaches in the literature. This revision was essential to (re)find 3 studies that were major inspiration in the work that followed: Guedes de Oliveira et al. (Guedes de Oliveira and Lopes da Silva, 1980b), Ramabhadran's et al. (Ramabhadran et al., 1999), Flanagan's et al work (Flanagan et al., 2002; Flanagan et al., 2003). Both Guedes de Oliveira and Ramabhadran work's had a pragmatical approach to the problem oriented to the solution, the localisation of the focus, and not to the "symptom", the spike. Both were based on

simple assumptions and on statistical validation (Guedes de Oliveira et al. in time and space, Ramabhadran et al in space). Flanagan's work presented me to an unknown world of source analysis and made me look at source analysis as the "way" to quantify spike and distinguishing different EEG/MEG activity patterns. During this phase the focus of research moved from spike detection to spatio-temporal characterisation of epileptiform activity to support clinical diagnosis. It is relevant to stress that collaboration with the Neurophysiology department at Hospital Geral de Santo António was fundamental to deviate a scientific oriented mind to a more pragmatical scientific oriented one with clinical awereness, to whom results started to be more relevant if applied in clinical practice.

The beginning of the collaboration with A. Leal M. D. led to a fortunate combination: our scientific interests found a clinician with scientific oriented mind and a keen clinical eye to find and collect interesting models in Epilepsy, some of which were used in the evaluation of our methods (hypothalamic hamartoma related epilepsy and occipital epilepsy). This collaboration was fruitfull (Leal et al., 2002; Fernandes et al., 2003a, b; Fernandes et al., 2005a; Fernandes et al., 2006b; Fernandes et al., 2006a, c). It resulted in two methods proposed in chapter 4 and 5 where scientific ideas were tested and bounded by A. Leal clinical and pragmatic judgement. As results the methods converged to unsupervised approaches with clinical appealing visualisation (not perfect yet). The method proposed in chapter 4 started to focus spatial classification on spike related source analysis solutions by combining a solution similar to Flanagan's spatial filtering with unsupervised statistical cluster analsys. *EpiGauss*, presented in chapter 5, the main contribution of the thesis extended the previous to space and time.

As a conclusion, the author thinks the most import contributions of the present thesis are the results of the proposed future work. In my perspective the current thesis has just deployed the basic framework to be able to address more systematically the complex brain dynamics involved from simple tasks to complex epileptiform activity patterns.

1.4 Contributions of the thesis

In this section we summarize the contributions of the research work presented in the thesis. The major contributions and statements presented are:

- Spike related "clinical" concepts are often unprecise and are not objective. A

reformulation must be done in order to have a reliable reference in quantified spike related analysis processes.

  - In section 3.1, we show that simultaneous EEG and MEG spikes characteristics are different and it is not reasonable to use the same clinical assumption in both EEG and MEG (Fernandes et al., 2004; Fernandes et al., 2005b);
  - In section 3.2, we show that multi-expert spike selections (MESS), although clinically useful and valid, may, in light of objective criteria such as power, present heterogeneous characteristics that may induce a handicap whenever based solely in clinical agreement criteria to define a ground truth, namely when used as references for automatic spike detection algorithms in sensitivity and specificity method analysis;

- The use of statistical approaches to support unsupervised computational methods may overcome some lack of precision and objectivity in clinical inputs. This is illustrated in by two studies for the analysis of epileptogenic electric generators based in EEG.
  - In section 4.4, the use of automatic cluster methods together with dipole models over spikes selections enables an unsupervised classification of the active generators. In the analysis of 4 patients suffering from hypothalamic hamartoma related epilepsy it reproduced previously obtained results in the analysis of clinically identified spike templates using RAP-MUSIC and single moving dipole (Fernandes et al., 2003b, a);
  - In chapter 5, a combined source analysis method, *EpiGauss* extends the method proposed in section 4.4, to accommodate spatio-temporal information. *EpiGauss* combines the advantages of using the time resolution of EEG/MEG and spatial resolution of source analysis methods, with the dipole spatio-temporal information retrieved from individual events sources analysis. Through dipole density analysis and spatial clustering it is possible to present the results in a Brain imaging like manner while providing quantified information. This information can be correlated with clinical expertise and help identifying stable

epileptogenic sources and possible propagation pathways of epileptiform activity. The method was evaluated in 4 patients with hypothalamic hamartoma related epilepsy (in section 5.2) and in 6 patients with Early Onset Childhood Occipital Lobe Epilepsy (section 5.4. and (Fernandes et al., 2006b)).

1.4.1 Related contributions

The work supporting this thesis has been developed at the SIAS group (SIAS,IEETA/University of Aveiro– http://www.ieeta.pt/sias) being a researcher of the group since 1997. The author participated in some related work worth mentioning performed in the epilepsy area, mainly as direct support to related clinical groups.

From the long collaboration with Hospital Geral de Santo António the support in SPECT (Single Photon Emission Tomography), imaging (Ramalheira et al., 1999; Ramalheira et al., 2000) has resulted in a local SISCOM (Subtraction Ictal SPECT CO-registered to MRI) implementation (Fernandes et al., 2002) and, more recently, in an optimized software implementation (result of a master thesis (Oliveira, 2006)) that enabled full autonomy on the clinical SISCOM analysis (Oliveira et al., 2006).

From the collaboration withAlberto Leal M.D. (Hospital Júlio de Matos, Lisbon) and Caselas MRI facilities, with several results published (some examples are (Leal et al., 2002; Pereira et al., 2002; Fernandes et al., 2006a)) has resulted in the first EEG-fMRI setup in Portugal (Fernandes et al., 2005a; Pinto et al., 2005). First clinical trials are now being supported by FCT project EpilBI (POSC/EEA-CPS/60977/2004). These research activities although not part of the present document shows the deepness of the research and development environment that we have in Aveiro that was a great stimulus to this thesis results.

1.5 Thesis structure

In chapter 2, we present the main non-invasive techniques in the epilepsy diagnosis. The focus will be on the brain electric activity characterisation – electromagnetic source imaging (EMSI) – that encloses the main contributions of this thesis.

In chapters 3 and 4, we discuss issues on computational support to EMSI: (1) the selection of relevant electromagnetic events for analysis (chapter 3) and to (2) the methods of inferring the localisation of brain electrical generators (chapter 4).

In chapter 3, we illustrate two examples where clinically accepted definitions may not be enough to ensure a stable and objective ground for quantified analysis. The impact of the absence of a quantified spike definition will be discussed in the context of two EEG/MEG related studies. First, it will be shown that common clinical assumptions on EEG spike morphology are not suitable to characterize MEG spikes (section 3.1) and second, multi-expert spike clinical reference sets may be unreliable as ground truth for spike related computational methods when only defined in terms of expert agreement criteria (section 3.2).

In chapter 4, a review on methods used to infer the localisation of brain electrical activity generators will be presented, together with pre-processing techniques used to improve the quality of the solutions (spike clustering and averaging).

In chapter 4 and 5, we propose two unsupervised methods that use statistical based approach to overcome the lack of objectivity in clinical data, namely in spike selections. In section 4.4, we propose a simple extension of typical EMSI procedures that combines the analysis of individual events generators with statistical spatial clustering based filtering. The method is unsupervised and avoids recurring to clinical inputs in both spike classification and averaging. We evaluated the method in 4 patients suffering of hypothalamic hamartoma related epilepsy. Hypothalamic hamartoma related epilepsy has an accepted localisation of the epileptogenic source which is a good localisation control – the hamartoma itself.

In chapter 5, we present *EpiGauss*, an extension of the previous method (proposed in section 4.4) to accommodate relevant spatio-temporal information. *EpiGauss* combines the advantages of the time resolution of EEG/MEG and spatial resolution of source analysis methods, with the dipole information retrieved from individual events source analysis. Through dipole density and spatial clustering, *EpiGauss* presents the results in a Brain imaging like manner and provides quantified information that may guide the clinical diagnosis. *EpiGauss* evaluation was performed in 4 patients suffering from hypothalamic hamartoma related epilepsy (section 5.2) and in patients with Early Onset Childhood Occipital Lobe Epilepsy (section 5.4).

In chapter 6, a summary on the main contributions is made and perspectives on current and future work are presented.

2 Multimodal non-invasive techniques in epilepsy

The use of non-invasive modalities is the first option in epilepsy centres and ongoing epilepsy surgery programs (Siegel, 2004; Uijl et al., 2005). Despite the existence of numerous non-invasive techniques, the common objective is to characterize epilepsy related activity zones in the brain and to delineate the optimal resection zone that hopefully will enclose the epileptogenic zone (EZ), without inducing impairing deficits (Rosenow and Luders, 2001; Richardson, 2003).

Along this chapter, we will describe the main non-invasive modalities and discuss their role in epilepsy diagnosis according to a broad classification based on the techniques' contributions for epileptic patient clinical characterisation:

- Semiology: patient's seizure motion patterns;
- Brain electric activity: EEG and MEG brain activity;
- Brain morphology: brain structure;
- Brain function: physiologic epileptiform brain function.

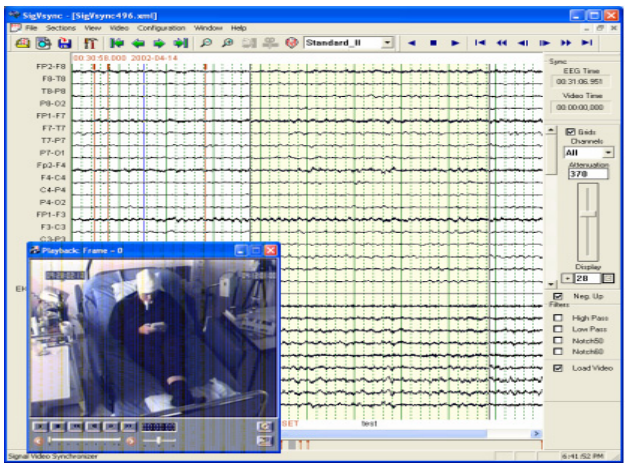


Figure 2 – Video-EEG: synchronized video and EEG

Video EEG systems enable an accurate correlation between semiologic patterns and the brain electric activity changes, relevant in the Epilepsy diagnosis. The SigVSynch VEEG system (above), implemented by our group, is such an example.

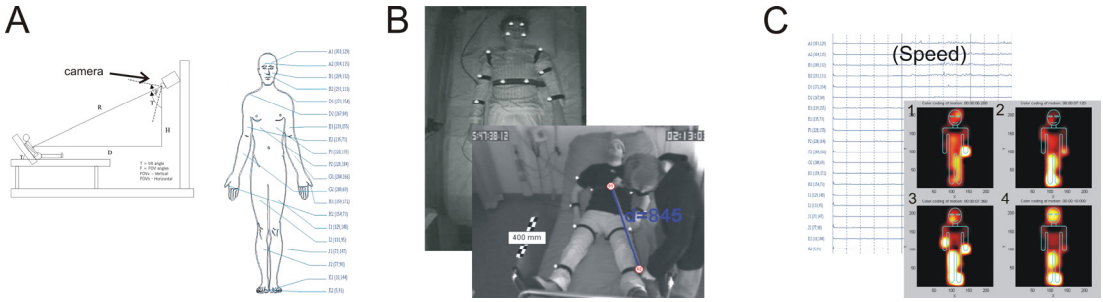


Figure 3 – Movement quantification: extracting information from video

Movement quantification (Li et al., 2002) involves several issues from defining controlled environments (A), devising video processing techniques (B), to methods for result visualization such as tracings, colour maps, etc.

2.1 Semiology: video

The visual observation of epilepsy seizures movement patterns is highly relevant in the clinical diagnosis of epilepsy as altered motion patterns might be clinically associated to possible localisations of the EZ (Bautista and Luders, 2000 ; Rona et al., 2005).

2.1.1 Video in epilepsy diagnosis

In the semiologic study of epileptic patients, video enables the observation of events and allows a detailed analysis of the patient's motor manifestations where the time sequence of events and the occurrence or absence of clinically relevant motions patterns can be identified. By associating EEG with synchronous video both the semiology and brain electrical activity can be related (Cascino, 2002), as illustrated by existing Video-EEG (VEEG) systems (in Figure 2, our group solution SigVSynch). The use of VEEG enables a more accurate correlation between semiology and EEG that can guide in a more precise identification of epileptogenic focus localisation.

For that reason, besides providing clinical hypothesis for EZ localisation, VEEG is essential to distinguish epileptic seizures from pseudo seizures that, without the EEG, may present misleading semiologic patterns (Cragar et al., 2002). These are usually associated with non-epileptic psychological disorders (McBride et al., 2002 ; Uluc et al., 2002 ; Harden et al., 2003; Iriarte et al., 2003 ; Martin et al., 2003; Kellinghaus et al., 2004; Ribai et al., 2005).

Besides the qualitative characterisation, video can also be quantified. Video quantification enables unbiased and reproducible analysis and information extraction, enabling, for instance, more supported clinical decisions and clearer pattern identification.

Recent works by our group show that motion patterns quantification from video is

possible (Li et al., 2002; Cunha et al., 2003) and unbiased information can be extracted and used to characterize them and assist in clinical decision, namely in the distinction of different types of epileptic seizures (Cunha et al., 2003; Meier et al., 2004). The movement quantification involves three typical steps: 1) define a setup involving from camera positions and a human landmark model (Figure 3 (A)), 2) calibrate the setup and extract the markers positions (Figure 3 (B)) and finally 3) process the marker positions and visualize movement quantification. The movement quantification can be presented from tracings (e.g. landmarks position changes, speed) to more elaborated colour maps (Figure 3 (C)).

2.2 Brain electric activity: EEG and MEG

Electrically active tissues bioelectric fields also produce a biomagnetic field (Malmivuo et al., 1997). Based on this principle, it is possible in practice, to obtain a perspective on electrical current dynamics inside the brain by capturing electromagnetic variation patterns generated by brain neurons (Figure 4).

These electromagnetic variations are measured either by electrical potential differentials or current induced magnetic changes. The measurement of electrical and magnetic fields in the brain has been denominated electroencephalography (EEG) and magnetoencephalography (MEG) respectively. The most usual representation of these field variations is as tracings, which represent the electrical or magnetic magnitude changes along time. Historically, EEG is the most ancient and has been performed since 1929 with the first H. Berger's electrical activity registration reports (Gotman, 2001). MEG is more recent and was first performed by David Cohen et al that published their first recordings in 1968 (Cohen, 1968; Crease, 1991).

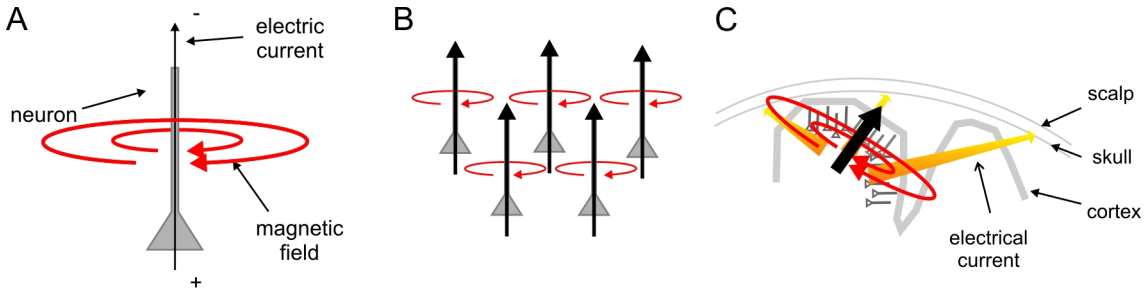


Figure 4 – Electric activity in the brain: from neurons to the scalp

Individual neurons generate electric current that produce magnetic fields (A) that, when simultaneous with others (B), may generate localized variations in both electric potentials and magnetic fields measurable in the surface (C). Adapted from (Engel and Pedley, 1998).

2.2.1 EEG and MEG acquisition

Both EEG and MEG rely on sampling the electric and magnetic fields variations in several locations on the scalp (Figure 5 (E)). EEG is collected through electrodes located in the scalp measuring potential variation in the order of tens of microvolts (Figure 5 (A)). These variations can be acquired with simple and low cost setups (low-cost scalp electrodes and high-impedance and high-gain amplifiers) (Niedermeyer and Lopes da Silva, 1999) (Figure 5 (C)). MEG, on the other hand, has to deal with extremely weak signals, implying the use of very sophisticated (and costly) acquisition technology (Figure 5 (D)). As MEG measures the magnetic induction produced by neural currents in the order of femto Tesla (10^{-15} in relation with the earth magnetic field), the use of special and expensive magnetic shielded rooms and the use superconducting detectors (SQUID - Superconducting QUantum Interference Device) is mandatory to overcome background noise and capture those small variations (Vrba et al., 1999; Knowlton and Shih, 2004) (Figure 5 (B)).

Due to the relation between bio magnetic fields and electric currents, EEG and MEG differ in terms of sensibility and specificity to dipolar patterns, mainly in electric flow direction and orientation variations (Figure 6). Due to spatial and geometrical brain/head configurations, only electric variation measurements can capture both radial and tangential oriented currents in relation to the brain (Nunez, 1995; Malmivuo et al., 1997; Wong, 1998). On the other hand, no magnetic variation can be seen at the head surface coming from radial dipolar currents as their magnetic induced fields are “obscured” by the brain volume and invisible at surface (Nunez, 1995; Malmivuo et al., 1997; Wong, 1998). Nevertheless, despite the differences between electric and magnetic fields, it was experimentally demonstrated that they exhibit very similar patterns as tracings (Malmivuo et al., 1997).

Besides the “blindness” of MEG to radial dipolar sources in the brain (Malmivuo et al., 1997), EEG is affected by the tissues conductivity and their spatial distribution. These have a filtering effect in EEG, inducing a delay and an amplitude change in the acquired signal. As a result, EEG is said to present a “blurred” image of the electrical activity inside the brain (Cohen and Cuffin, 1983 ; Cuffin, 1990 ; Gevins et al., 1991 ; Malmivuo et al., 1997 ; Baumgartner et al., 2000a). For that reason, when not dealing with radial sources, MEG provides a more accurate brain electrical currents characterisation than EEG.

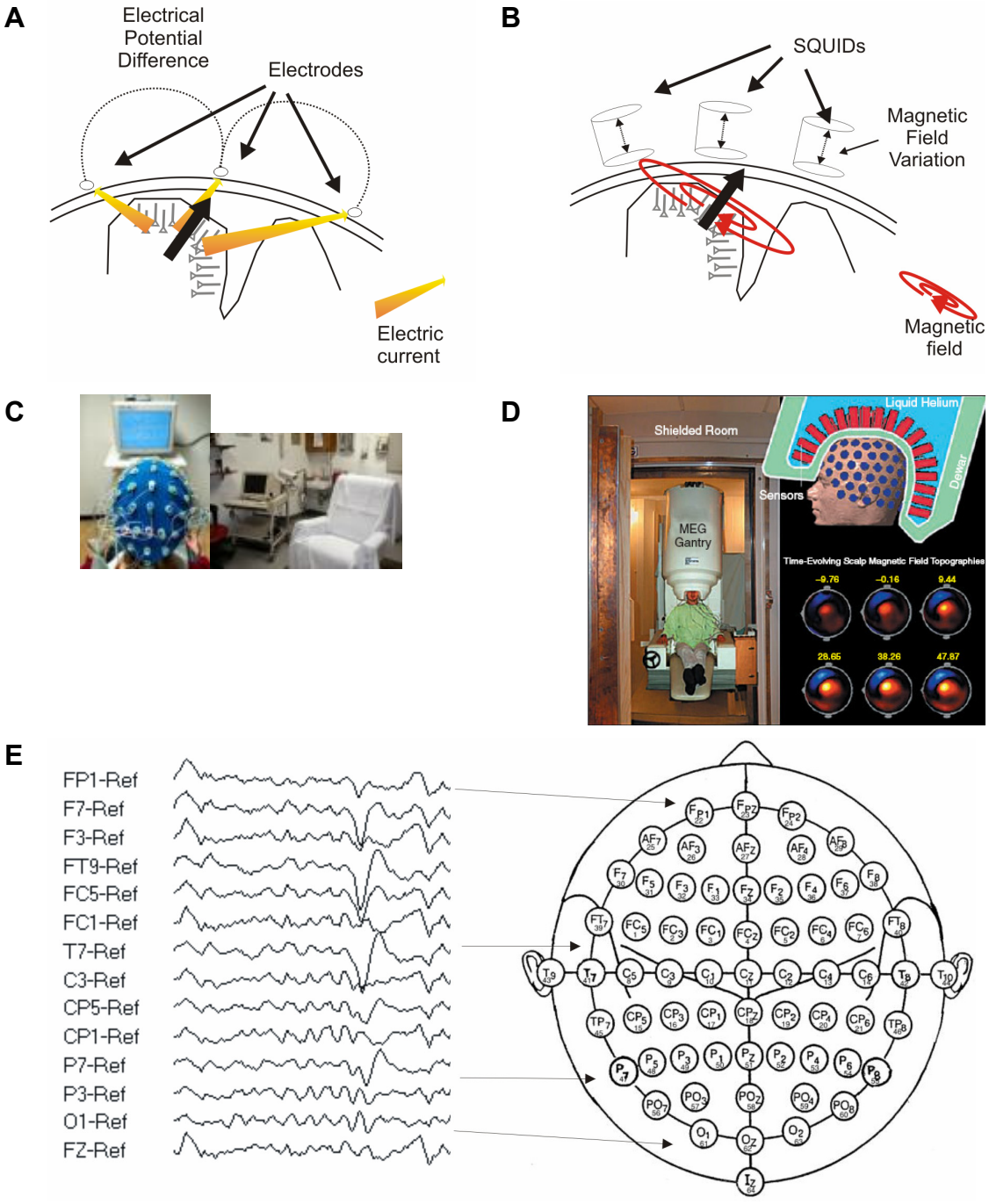


Figure 5 – EEG and MEG: acquisition setups

The acquisition of EEG and MEG is based on sampling electrical/magnetic changes in several places on the scalp through electrodes/sensors (A). In contrast to EEG, which can be acquired through simple setup consisting of a set of electrodes and an amplifier (C), MEG needs special magnetic shielded rooms and superconducting detectors (SQUIDs) with helium cooling (from (Baillet et al., 2001)) (D) to acquire the magnetic variations induced by electrical brain activity (B). Both EEG and MEG are usually viewed as traces representing the electromagnetic variations along time in the sensors positions. Here is presented an example of standard EEG electrode positions system (10-10) and respective EEG traces (E). (A) and (B) adapted from (Nunez, 1995; Engel and Pedley, 1998).

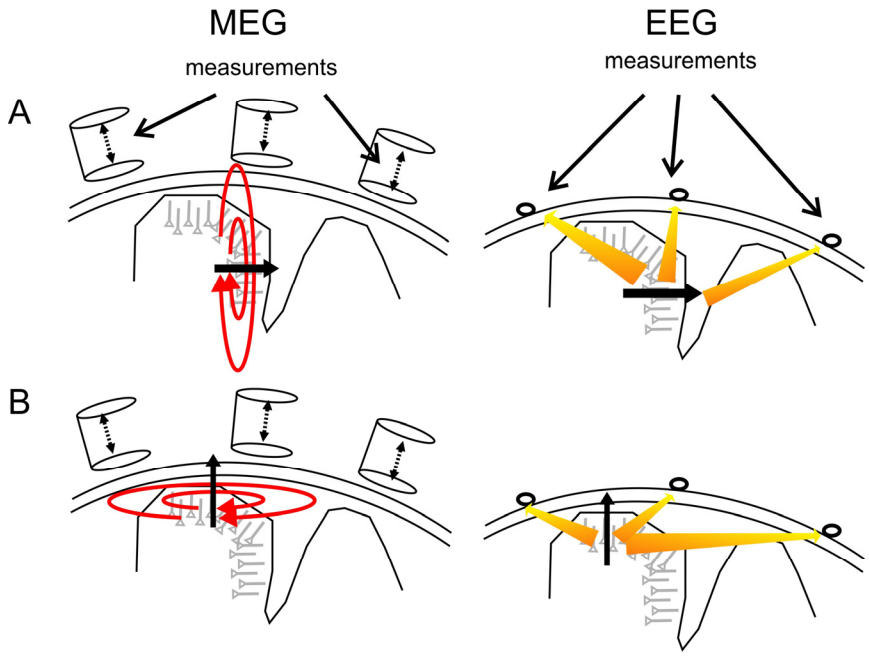


Figure 6 – EEG and MEG: radial and tangencial brain electrical generators

MEG signal is almost unaffected by the several head layers but due to SQUID's sensibility only to radial magnetic field variations, only tangential currents (A) that induce normal magnetic changes can be measured in MEG. Radial currents (B), in contrast, induce magnetic changes tangencial to cortex surface that have a neglible radial contribution. On the other hand, both tangential and radial generators produce signatures measurable in EEG. The EEG's drawback is that both the head layers resistivity and geometrical configuration induce a filtering effect on measurements expressed in a worst signal to noise ratio and time delay between generator changes and changes measured in the scalp. This figure uses the same graphical conventions as in Figure 5 (A & B).

2.2.2 EEG and MEG in epilepsy diagnosis

The role of both EEG and MEG in determing epileptiform activity sources localisation and activity characterisation is well established (Ebersole, 1997 ; Gotman, 2003; Barkley, 2004; Baumgartner, 2004; Bast et al., 2005):

1. Identify the irritative area focus – area of the brain responsible for the abnormal electrical activity;
2. Distinguish between epileptogenic focus and propagation of electrical activity in the brain through the visualization of its spatio-temporal evolution.

Initially, most of the analysis was performed visually, supported by a combination of montages and EEGers mental "reconstruction" of the overall brain activity patterns, where active brain areas and propagation can be inferred (Gotman, 2003 ; Iwasaki et al., 2005).

With the advent of computers, the quantification of EEG/MEG was possible and more sophisticated methods were developed and started to be used, namely frequency domain related techniques (Engel and Pedley, 1998; Niedermeyer and Lopes da Silva, 1999),

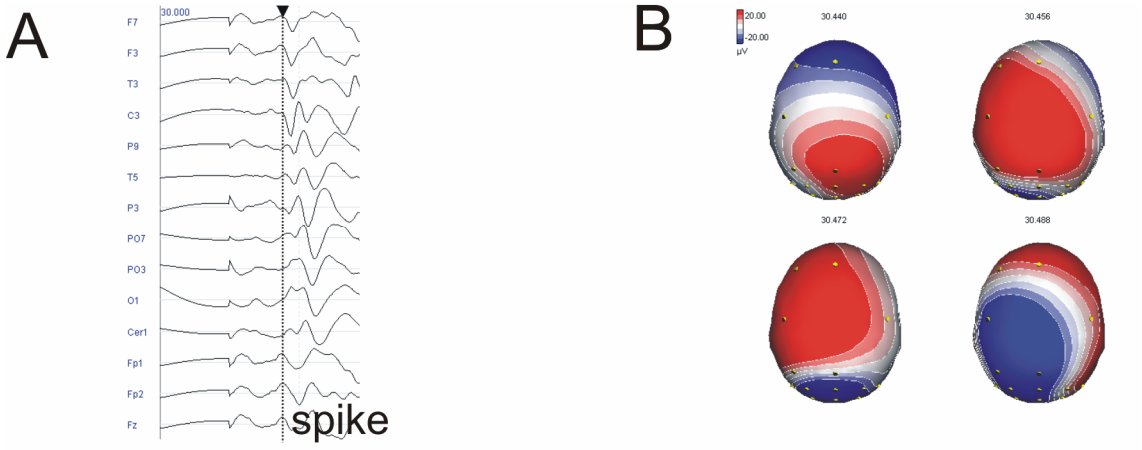


Figure 7 – Events or electromagnetic signature of brain epileptiform activity patterns

Specific brain activity patterns induce electromagnetic variations measurable in EEG and MEG that can be presented in one dimension (one channel through time - a sample of a electroencephalogram is presented in A), in two dimensions as a map (spatial configuration of channels at a given time) or in three dimensions when considering the electromagnetic measurements in time (B). In this figure an epileptiform discharge is illustrated. These electromagnetic patterns are very relevant in confirming the epileptoginicity of brain activity and therefore in epilepsy diagnosis confirmation.

inverse problem (Baillet et al., 2001) and non-linear techniques (Cunha et al., 1994b; Cunha et al., 1996; Le Van Quyen et al., 1998; Elger et al., 2000; Le Van Quyen et al., 2003). The later will be addressed in more detail in chapter 4.

The first contribution of EEG/MEG in clinical diagnosis was through the identification and extraction of brain activity patterns (tracings representing the electromagnetic changes through time in the sensors - Figure 7 (A)) associated to specific clinical condition states (Engel and Pedley, 1998). Different signal processing techniques have been used to enhance these patterns and other specific brain rhythms (Niedermeyer and Lopes da Silva, 1999) such as montages (simple transformations involving mathematical combinations of one or more sensor measures – one example is considering the differences between nearby sensors) or maps (where sensors measurements are represented according to the spatial distributions of the sensors – see Figure 7 (B)) where propagation patterns, locations of high activity or digital signal processing filtering techniques can be more easily spotted.

From the several identified brain activity patterns, some are clearly related with epilepsy - the epiletiform discharges, either during seizures (ictal) or in between them (interictal), these comprise spikes and slow waves (Figure 7). The interictal epileptogenic discharges (IED) presence is considered very sensitive and specific in the epilepsy diagnosis confirmation as shown by the emphasis given to IED in EEG characterisation on epilepsy diagnosis (Engel and Pedley, 1998; Binnie and Stefan, 1999 ; Niedermeyer and Lopes da

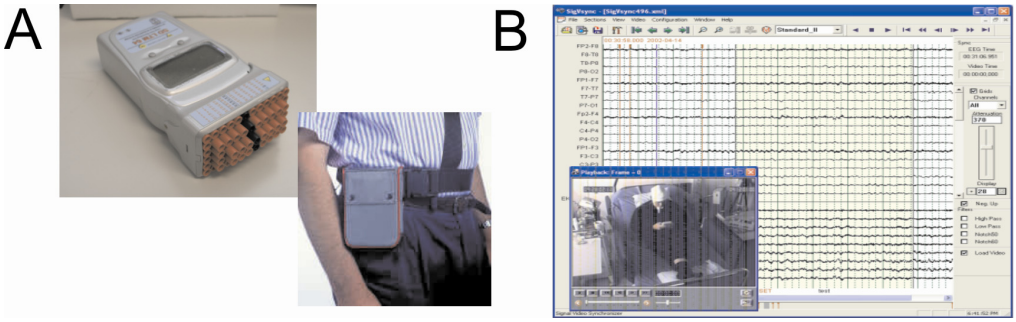


Figure 8 – Ambulatory EEG and long VEEG recordings

Ambulatory EEG systems (A) and long VEEG recordings (B) enable the recording a less controlled context than typical routine EEG, increasing the probability of capturing relevant events, such as seizures, and improve the overall epileptogenic activity characterisation.

Silva, 1999; Ebersole and Pedley, 2003) where the identification of IED, with a consistent clinical history, detects patients with chronic epilepsy with sensitivity between 30 and 90% accuracy. This is reflected in the relevance of EEG related patterns in clinical diagnosis in which they are often the sole discriminating feature between epileptic syndromes (ILAE, 1981; Binnie and Stefan, 1999). However, IED cannot provide an epilepsy diagnosis by themselves and must agree with clinical background. It is known that spikes can be observed in 1-3.9% of healthy subjects (Engel and Pedley, 1998; Ebersole and Pedley, 2003). Also, due to technical issues, like short recordings or poor spatial sampling in the EEG/MEG, it is not possible to make clear epilepsy diagnosis on only few spike occurrences (Engel and Pedley, 1998; Ebersole and Pedley, 2003). Ictal events provide meaningful information worth analysing (Martins da Silva and Cunha, 1994; Gotman, 2003) but as they tend to be scarce and, when observed, exhibit complex signatures (involving spread, focal activity, sometimes with motion related artifacts associated), it is difficult to extract information from ictal events that is conclusive and not misleading (Manford et al., 1996; Foldvary et al., 2001; Gotman, 2003).

2.2.3 Monitoring EEG and MEG

In the absence of epileptogenic activity, ictal and interictal information relevance increases. Strategies like antiepileptic drug deprivation and long time monitoring are used in order to increase the probability of observing epileptogenic patterns. By combining standard EEG with long acquisition times (Schomer et al., 1999), monitoring improves the odds of observing epileptogenic events (seizures and IED) and leads to a more accurate decision on the epilepsy syndrome identification or, in some cases, dismiss the epilepsy hypothesis (e.g. pseudo seizures (Krumholz, 1999 ; Cragar et al., 2002)).

In this context, the EEG compares favourably against MEG since EEG setup is simpler and flexible, adaptable to long acquisitions (in place or ambulatory – as illustrated in Figure 8) and to ictal recordings (Cascino, 2002 ; Pataraia et al., 2004), while MEG's highly complex and controlled acquisition environment does not cope well with uncontrolled motor events, such motor epileptic seizures, or with long acquisition times (Baumgartner et al., 2000a; Stefan et al., 2003 ; Knowlton and Shih, 2004). For these reasons, MEG is not suited for long monitoring and ictal MEG recordings. Despite that, MEG ictal recordings were obtained with consistent localisations when compared with inter ictal findings (Eliashiv et al., 2002 ; Tilz et al., 2002 ; Assaf et al., 2003).

2.2.4 MEG clinical value and its relation with EEG

MEG's clinical applicability and clinical yield have been scarcely addressed, and only recently it started being evaluated in order to assess its true clinical value (Baumgartner et al., 2000a ; Stefan et al., 2003 ; Knowlton and Shih, 2004; Pataraia et al., 2004).

Most MEG studies address the more difficult cases of intractable epilepsy, usually temporal lobe epilepsy (TLE). In lesional TLE, through inverse problem studies estimated MEG generators were found adjacent to lesions visible in MRI scans, as referred in Baumgartner meta-analysis (Baumgartner et al., 2000a). Particularly, in some studies the role of MEG in invasive electrodes placement and surgical planning was relevant (Otsubo et al., 1999 ; Mamelak et al., 2002). MEG might not provide relevant information on its own due to its "blindness" to deep sources and, in some cases, where there is a need to extend the analysis to cortical areas in mesial temporal structure (Baumgartner et al., 2000a; Knowlton and Shih, 2004).

Nevertheless, MEG has a higher sensitivity in lateral TLE and neocortical related disorders (tangential sources) and a potential as a non-invasive method in defining the irritative spike zone (Baumgartner et al., 2000a ; Knowlton and Shih, 2004). In these cases, MEG generators are characterized by "tightly clustered unifocal spikes" and may avoid invasive EEG. In some situations, when no lesion is visible in MRI, these solutions are in agreement with functional imaging identified deficits (Knowlton and Shih, 2004).

Overall some general conclusions on EEG and MEG comparison are consensual:

- MEG is unable to capture deep or radial sources, which are captured by EEG (Malmivuo et al., 1997);

- MEG has better SNR in neocortical areas (Baumgartner et al., 2000a);
- MEG provides clear signal due to the non-existence volume effect, improving the accuracy of localisation of its generators versus EEG. It is relevant to note that MEG models are simpler and less subject to modelling errors as they depend on fewer parameters (e.g. MEG models can depend only on inner skull surface conductivity in contrast with the complete scalp, skull and brain model needed with EEG (Meijs and Peters, 1987; Meijs et al., 1988; Hamalainen and Sarvas, 1989));
- Spike occurrences in EEG and MEG present different timings, in some cases disjoint occurrences with patterns specific to each modality (Zijlmans et al., 2002; Lin et al., 2003 ; Iwasaki et al., 2005). Zijlmans et al. (Zijlmans et al., 2002) described that in some situations, one modality, after a thorough analysis, lead to the identification of "hidden" spike patterns in the other, through averaging.

Overall, as stated in two extensive reviews on the pros and cons of MEG vs. EEG, both Barkley (Barkley, 2004) and Baumgartner (Baumgartner, 2004) draw similar conclusions although departing from, apparently, different sides: EEG and MEG are complementary and should be used together whenever possible and the joint analysis provides information that is not obtainable by either one of them isolated (Yoshinaga et al., 2002). Some authors advocated the combined use of prolonged scalp video-EEG monitoring and short-term MEG recordings for an optimal epiletogenic zone delineation (Stefan et al., 2003; Knowlton and Shih, 2004).

Most of the referred authors defend that MEG should be seen as an auxiliary technique to support cases where standard EEG is only able to reach results that "are either partially localizing or non-localizing" due to, for instance, the difficulty of obtaining "ictal recordings, MEG pecuniary aspects" (Stefan et al., 2003) and the limited contribution MEG versus other modalities such as EEG (Baumgartner, 2004; Pataraia et al., 2004).

Given the EEG and MEG complementary natures, from the theoretical (Malmivuo et al., 1997) to the clinical side (Baumgartner et al., 2000a, b; Stefan et al., 2003 ; Bast et al., 2004; Pataraia et al., 2004; Bast et al., 2005), the consensus is that both modalities should be used whenever possible and be treated as complementary.

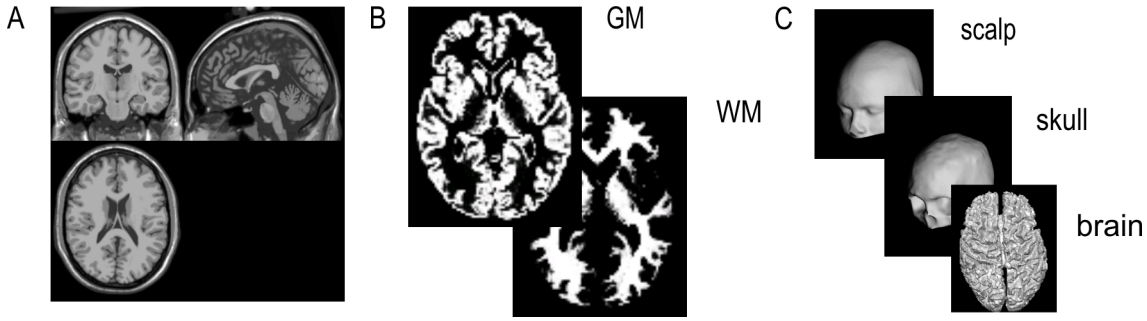


Figure 9 – Magnetic resonance imaging (MRI): an insight on brain morphology.

MRI provides a head structural characterisation (A) where is possible to distinguish several different tissues such as bone, grey (GM) and white (WM) matter (B). From the MRI is also possible to extract different layers namely the scalp, skull and brain that can later be used in further analysis processes, namely source analysis (C).

2.3 Morphology: magnetic resonance imaging

Structural imaging, through magnetic resonance imaging (MRI) (Weishaupt et al., 2003 ; Grant, 2004 ; Tofts, 2004) is gaining enormous relevance in the evaluation of patients with epilepsy. Its increasing spatial resolution has made it possible to associate epilepsy syndromes with specific brain lesions/malformations.

The MRI acquisition principle is based on measuring the radio emission coming from the hydrogen atoms spin orientation when subjected to controlled magnetic gradients (Weishaupt et al., 2003). From the intensities of these radio emissions it is possible to infer the number of protons in a particular "slice" of matter and its relaxation (this is related with changes in protons orientation induced by magnetic gradient changes and the time needed to return to its original orientation). Depending on measured relaxation related parameters, it is possible to infer different tissues/substances signatures, all with a very specific radio emission frequency, namely bone, grey and white matter enabling the extraction of head tissues layers as illustrated in Figure 9. The most common examples are T1, T2 and more recently the fluid-attenuated inversion recovery (FLAIR). Both T1 and T2 are sensible to the tissues' water content, being able to identify differences in body tissues. T1 is good at differentiating the main brain structures (CSF, grey and white matter) from abnormal structures (e.g. lesions and tumours). T2 provides a complementary perspective being more sensible to fat tissues and changes in tissues like neuronal cell loss, presenting visible signatures prior to clear visible T1 changes, namely in hippocampal sclerosis (Van Paesschen et al., 1997). FLAIR is an evolution on T2 with CSF T2 signal suppression, which is more effective at delineating tissue changes like in lesion margins (Wieshmann et al., 1996; Wieshmann et al., 1998; Meiners et al., 1999).

2.3.1 MRI in epilepsy

MRI provides an accurate spatial and morphological brain reference space for data visualization, enabling spatial relations between morphology (in MRI) and other spatial information including SPECT (O'Brien et al., 1999), PET (Kiebel et al., 1997; Cizek et al., 2004) and fMRI (Cohen and Bookheimer, 1994; Heilbrun et al., 2001 ; Salek-Haddadi et al., 2003). This can be achieved through spatial registration of different kinds of information (Crum et al., 2003). Further processing over MRI also enables the extraction of head parametric spatial models (Heinonen et al., 1997; Shan et al., 2002; Akalin-Acar and Gencer, 2004) that can be useful in constraining the electromagnetic source imaging (Stefan et al., 2003; Michel et al., 2004). The MRI has a dual role in epilepsy diagnosis:

1- Enable the detection of morphological malformations/lesions that may be related to epilepsy;
2- Give morphological reference to the head/brain model.

Epilepsy and lesions: identifying lesions and malformations

With the increase in both quality and availability of high-resolution systems, MRI has gained relevance in Clinical Neurophysiology. The improvements in MRI have been translated directly in more accurate localisation of epilepsy related brain lesions (e.g. tumours) and malformations (e.g. mesial sclerosis, dysplasias) initially not identifiable, enabling a significant decrease in numbers of cases of “unknown cause” epilepsies (cryptogenic) and in an increase of successful diagnosis (Guerrini and Carrozzo, 2002 ; Grant, 2004). As a result, high-definition MRI is considered “mandatory” in every pre-surgical evaluation to avoid more extensive studies in case of clear MRI lesions/ malformations identifications. This is emphasized through a direct recommendation of ILAE where MRI role in structural lesions identification is stressed (ILAE, 1997).

Nevertheless, the identification of lesions may not improve directly the surgical outcome where several lesions are likely candidates to surgical resection areas. Such are the cases of malformations or lesions, which present widespread patterns, like focal cortical dysplasias or malformations of cortical developments (Bastos et al., 2002). This is especially true in patients with normal MRI studies and extra temporal lobe epilepsy (ExTLE), which still have bad surgical outcome prognosis in relation to those with an MRI-identified epileptogenic lesion (Cascino, 2001b). For these reasons, in epilepsy, the

Figure 10 – Brain morphology: parametric representations

The use of brain surface parametric representations such as inflated surface (on the right) are useful to enhance and identify brain features which remain "undetected" in traditional axial, sagital and coronal MRI visualization, namely lesions and malformations, such variations in grey matter thickness namely in cortex segmentations (on the left). Examples provided in Caret website http://brainmap.wustl.edu/caret (Van Essen et al., 2001).

use of signal or function related information is crucial to establish the epileptogenicity of detected abnormalities (Grant, 2004).

MRI as brain volumetric model

Alterations and asymmetries in volume of certain brain areas are highly associated to brain dysfunctions which are not always clear-cut cases (lesions or malformations). Such is the case of sclerosis of hippocampal and/or amygdala, among other structures (Van Paesschen et al., 1997 ; Duncan, 2002).

Volumetric 3D T1 MRI enables a good anatomical detail for performing such volumetric measurements and, through comparison of measured values against normal population values and/or symmetry analysis, correlates volume variation patterns with known epileptic syndromes. Due to its close relation with TLE, the hippocampus has been the most addressed structure (Laakso et al., 1997; Salmenpera et al., 2000). A more thorough survey can be found in the reviews of Cascino, Bastos and Duncan (Cascino, 2001b; Bastos et al., 2002; Duncan, 2002). Some studies (Dickson et al., 2001; Kriegeskorte and Goebel, 2001; Memoli et al., 2004) also propose highly illustrative representations such as using parametric surface representations (e.g. artificially inflated brain as illustrated in Figure 10) where changes in local brain areas are enhanced in relation to the overall brain morphology. This is namely the case of sulci or in the grey matter/ cortical surface thickness (Lohmann et al., 2003; Tosun et al., 2004) where localized thickness variation in grey matter can be directly related to development lesions, namely focal cortical dysplasia (Bastos et al., 2002; Guerrini, 2005).

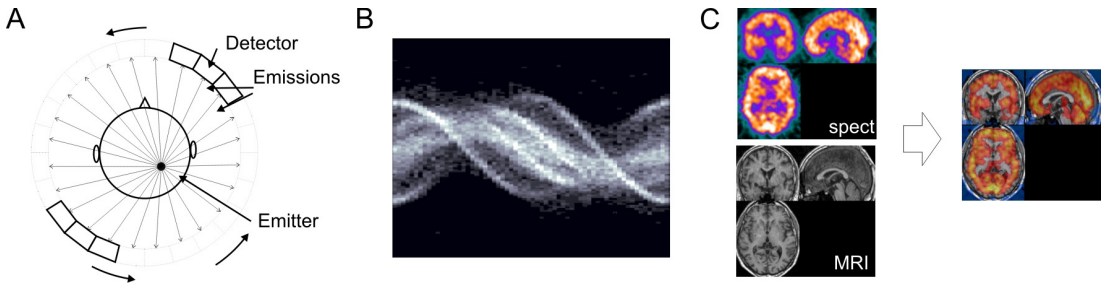


Figure 11 - SPECT and PET: from tracer emission to perfusion volumes

SPECT and PET rely on the radioactive tracers that, when fixated in the brain produce emissions (photons in case of SPECT and positrons in case of PET), can be detected using detectors (A). Through tomographic acquisitions is possible to transform raw emissions measures (B) that, by means of mathematical reconstruction processes, provide a three dimensional tracer perfusion characterisation of the brain. This reconstruction can be represented in a head compatible reference system, namely high-resolution brain MRI (C).

2.3.2 MRI Protocols in epilepsy diagnosis

It is relevant to stress that, for a reliable use of MRI in the epilepsy diagnosis, it is crucial to tailor the protocol to the epilepsy diagnosis specificity in order to ensure the highest specificity and sensitivity to epileptic related signatures (Duncan, 1997; Immonen et al., 2004; Knowlton, 2004). Details can be found in review works and ILAE recommendations (Jack et al., 1995 ; ILAE, 1997 ; Briellmann et al., 2003).

2.4 Function: SPECT, PET and MRI related modalities

Brain activity involves many physiological processes (e.g. blood flow, oxygen and glucose consumption). Both M/EEG and MRI are not suited for the description of such processes: EEG/MEG provides good time resolution but it lacks a clear model relating brain physiological processes and measured electromagnetic variations. On the other hand, MRI offers a good spatial resolution (which is crucial in lesion/malformation detection) but has bad time resolution, and therefore is not able to provide any time related information on brain dynamics.

A series of modalities fill this void in the physiological characterisation of brain processes through indirect observation of biological brain processes. Two main categories exist: 1) one based on tracers, 2) other on MRI based techniques. The tracer techniques are based in tagging the processes biological/chemical by-products, the MRI related rely on measuring electromagnetic fluctuations in the head when stimulated by magnetic gradient, presenting specific signatures that may be correlated to brain processes.

They share properties: 1) poor spatial resolution when compared to MRI and 2) poor, or

no time resolution when compared with EEG and MEG. For that reason, in clinical environments, these are more effective when combined, with both references in space, the MRI (Spencer et al., 1995 ; So, 2000 ; Duncan, 2002) and in time, the EEG/MEG as exemplified in fMRI –EEG studies (Salek-Haddadi et al., 2003).

In the next section we will focus our attention on the following techniques, which have more relevance in non-invasive epilepsy evaluation:

1. Single Photon Emission Tomography (SPECT) and Positron Emission Tomography (PET), both tracer based techniques;
2. Function MRI (fMRI), Magnetic Resonance spectroscopy (MRS) and Diffusion Weighted Imaging techniques (DWI) which are MRI based modalities that are able to characterized different aspects of the brain other than its morphology (Bammer et al., 2005).

2.4.1 SPECT and PET

The principle of tracer techniques is to tag specific biological markers that are closely associated with a specific physiological event. Through specific biochemical design, it is possible, within limitations, to devise tracers that "monitor" specific substances that may be correlated with physiological events, such as blood flow, oxygen intake, glucose consumption or neurotransmitters "activation". By interacting chemically with some biological process by-product, tracers produce variations that can be quantified.

In Epilepsy, both "Single Photon Emission Tomography" (SPECT) and "Positron Emission Tomography" (PET) are the most common tracer techniques. Both techniques rely on measuring emissions of radioactive nature (photons in case of SPECT and gamma radiation as result of positrons annihilation in case of PET) quantified using adequate detectors (Figure 11 (A)). Through the use of tomography acquisition and imaging techniques is possible to extrapolate from the raw emission measurements, a three dimensional tracer perfusion representation of the brain (Figure 11 (B) and (C)).

Both techniques provide maps of relative tracer emission distribution over the brain, from which the local decreases (hipo-perfusions) or increases (hiper-perfusions) in relation to overall brain activation or normal perfusions patterns, can be detected spatially. The clinical interpretation of these variations is highly dependent on the application context and on the technique used.

Single Photon Emission Computerised Tomography (SPECT)

SPECT is a radioactive tracer-based method that is used to image the distribution of cerebral blood flow (CBF) through the fixation of the tracer across the blood-brain barrier. The tracers are injected in the body through an intravenous injection and 70% of the tracer fixates in the brain usually one minute after injection (Duncan, 1997). Due to established relation between increase in regional cerebral blood flows (rCBF) and the occurrences of seizures, it is possible to infer the seizure origin localisation (Newton et al., 1995; Knowlton, 2004; Thadani et al., 2004). In case of an ictal exam, hiper-perfusion (increase in rCBF) is expected near the origin, in contrast with the hipo-perfusion in interictal exams.

The result of a cerebral SPECT acquisition is a volume of rCBF where, from a comparison against the overall global CBF, it is possible to identify regions with a decrease (hipo-perfusions) and increase (hiper-perfusions) in CBF (Figure 12).

The two most common tracers are HMPAO (hexamethylpropylenamine) and ECD (ethyl cysteinate dimer) (Duncan, 1997; Duncan, 2000; Duncan, 2002). The main difference is their stability time prior to injection. HMPAO is considered to be short lived as it gets chemically unstable 30 minutes after preparation whereas ECD is stable for six hours, easing the study of ictal events (Grunwald et al., 1994). After uptake, both allow reliable emission acquisitions for six to eight hours.

Positron Emission Tomography (PET)

PET is similar to the SPECT, where local perfusion variations may be correlated with specific physiological events. But, in contrast with SPECT, it has higher spatial resolution

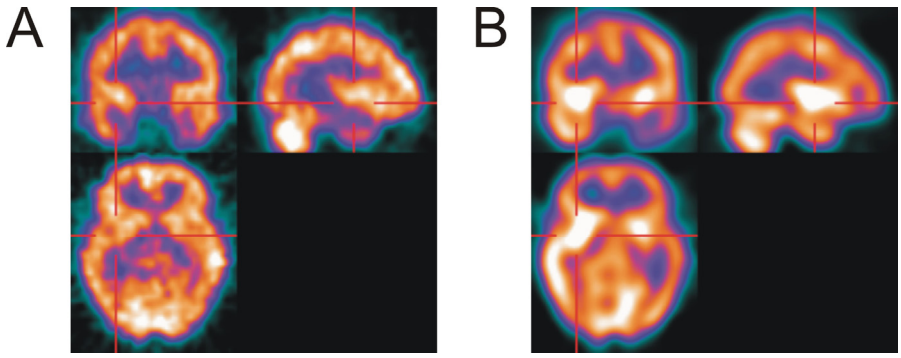


Figure 12 - SPECT changes in perfusions: hipo- and hiper-perfusions.

Local decreases (hipo-perfusions – in A between cross hairs) and increases (hiper-perfusions in B between cross hairs) in SPECT can be identified by visual or quantitative analysis of the reconstructed volume taking into account the overall versus local perfusion configurations and be related to possible abnormal metabolism areas. In case of epilepsy, hipo-perfusions and hiper-perfusions can be correlated with the EZ localisation in epilepsy context.

and can trace physiological events other than rCBF through specific tracer molecules, such as CBF (15O-labelled water), the regional cerebral glucose metabolism (use of 18F – FDG) just to name the most popular ones (Engel et al., 1990; Engel, 1991; Koepp and Woermann, 2005).

Another relevant difference when compared with SPECT is that PET tracers have shorter tracer lifetimes (i.e. two minute half-life of 15O-labelled water) and have a larger stabilization time in the brain (i.e. brain uptake of FDG takes up to 40 minutes). These facts exclude PET as a technique to study quick events such as seizures (Duncan, 1997).

SPECT and PET in epilepsy diagnosis

The main role of SPECT and PET in epilepsy is (Duncan, 2002; Richardson, 2003; Knowlton, 2004; Koepp and Woermann, 2005):

1. To access and measure the physiological response triggered by epileptogenic activity;
2. To improve the localisation of the EZ through correlation of perfusion patterns from ictal, interictal events or other normative perfusion sets.

It was established in the 1980s that a reduced CBF in interictal SPECT is associated to epileptic focus both in adults and children. But it was soon noted that it was not reliable, or at least, did not improve the focus localisation when compared with other clinical available information (Duncan et al., 1997 ; O'Brien et al., 1998; Duncan, 2002). In contrast to PET, due to SPECT's quick stabilization in the brain, SPECT ictal studies have a possible and relevant role in EZ localisation. Similarly to interictal SPECT, the occurrence of local ictal hiper-perfusion is correlated to the origin of ictal events (Duncan et al., 1997) but with a more accurate localisation. As several studies have shown, the accuracy provided by the hiper-perfusion in ictal SPECT is significant, especially in TLE (69 –70%) (Devous et al., 1998). In ExTLE, as seizures are briefer, factors such as the interval between injection and tracer fixation may influence the SPECT namely if it is an ictal or post ictal exam (capturing mostly propagation) (Kaminska et al., 2003; Van Paesschen, 2004). Studies show that in ExTLE the ictal results are worse but, in absence of clear MRI lesions, it provides valuable information for patient evaluation (Harvey et al., 1993 ; Knowlton, 2004).

Since 1998, when O'Brien et al (O'Brien et al., 1998) introduced SISCOM –

"Subtraction Ictal SPECT CO-registered to MRI" - the value of both ictal and interictal exams has increased. With SISCOM, the accuracy in EZ delineation improved both in TLE and ExTLE as shown by several studies, namely against invasive methods (Spanaki et al., 1999a ; Spanaki et al., 1999b; Knowlton, 2004; Thadani et al., 2004). SISCOM implies a more complex procedure (not only simple subtraction of ictal and interictal information) as it includes (1) spatial registration of data, (2) intensity normalization (compensate metabolic differences during different SPECT's acquisitions) and (3) identification of relevant hiper-perfusion, all this to map every information into the same reference – the volumetric brain MRI (Vera et al., 1999 ; Brinkmann et al., 2000 ; Boussion et al., 2002 ; Kaminska et al., 2003).

More recently, SISCOM was extended to accommodate statistical parametric mapping, to identify statistical significant differences between ictal vs. interictal status and/or versus a reference group (Brinkmann et al., 2000; Lee et al., 2000 ; Knowlton et al., 2004 ; McNally et al., 2005).

As ictal events are usually short and brief, together with long PET stabilization times (>40min), PET-based ictal analysis is not feasible. For that reason, PET exams are interictal where, by using different synthesized tracers, it is possible to select specific targets related to specific physiological processes/chemical signatures (Koepp and Woermann, 2005). Most PET studies in epilepsy use FDG that maps the cerebral glucose utilization deficits usually associated to dysfunctional areas. The main problem is that hypometabolisms are not specific to the EZ and can be caused by a series of unrelated brain dysfunctions. For that reason, FDG-PET presents variable results depending on epileptic syndrome (Koepp and Woermann, 2005).

In TLE and ExTLE the overall contribution in epilepsy diagnosis of FDG-PET is similar. Although the hypometabolic area may be restricted to the underlying lesion / EZ suspected zone (Engel et al., 1995), most FDG–PET studies present areas that are diffuse and widespread, usually larger than the pathological abnormality (Hammers et al., 2003), not providing additional sensitivity when integrated with other non-invasive modalities (Gaillard et al., 1995 ; Newton and Berkovic, 1996 ; Duncan, 1997).

Other tracers are used but with less clinical relevance. For instance, the 15O-labelled water maps the CBF with a similar interpretation to SPECT. Currently, research is being done in order to develop other tracers that can map chemical changes in the brain structure

or relate brain structures to physiological changes (Hammers et al., 2003 ; Koepp and Woermann, 2005).

With the advent of high-resolution MRI both SPECT and PET have lost some importance because lesions and malformations can now be better diagnosed, leaving smaller space for the usage of Nuclear Medicine techniques. In this context, both SPECT and PET are recommended in situations where no lesions, or a multitude of lesions, is present, where the MRI analysis is inconclusive and the clinical diagnosis dubious (Duncan, 2002 ; Knowlton, 2004). SPECT, due to its capability to perform ictal exams, still has a complementary role in identifying possible EZ locations where no MRI lesions are detected, (Cascino, 2001b; Duncan, 2002; Cascino et al., 2004a ; Thadani et al., 2004) and in guiding invasive studies (Kaminska et al., 2003).

SPECT and the need for a protocol

SISCOM and other SPECT based methods imply tight protocols to ensure that the data obtained is reliable and useful (Vera et al., 1999; Cascino et al., 2004b; Van Paesschen, 2004). Issues like the tracer, the control of injection timing versus ictal events must be taken into account in order to ensure that an ictal SPECT corresponds to an ictal activation and that an interictal exam is not contaminated by ictal related perfusion. For that reason simultaneous VEEG is essential to determine the relationship between the onset of a seizure and tracer delivery as EEG tracings are still the gold standard for ictal state identification (Cascino, 2001a; Van Paesschen, 2004).

2.4.2 Function Magnetic Resonance Imaging (fMRI)

fMRI is a relatively new MRI based technique that allows monitoring of the brain activation patterns by measuring the magnetic variation induced by changes in the blood flow associated to brain neural activity. The neural activity produces an increase in blood flow (with a delay of about 2 seconds - Figure 13 (A)) richer in oxyhemoglobin to compensate the increase in oxygen consumption. This change in oxyhemoglobin is called the Blood Oxygen Level Dependent response or BOLD effect (Ogawa et al., 1990). The local fluctuations in BOLD induce magnetic variations (Figure 13 (B)) susceptible to be detected through T2-weighted gradient-echo echo-planar imaging (Cohen, 1999) (Figure 13 (C)).

When BOLD activations and deactivations are time related with specific events, they

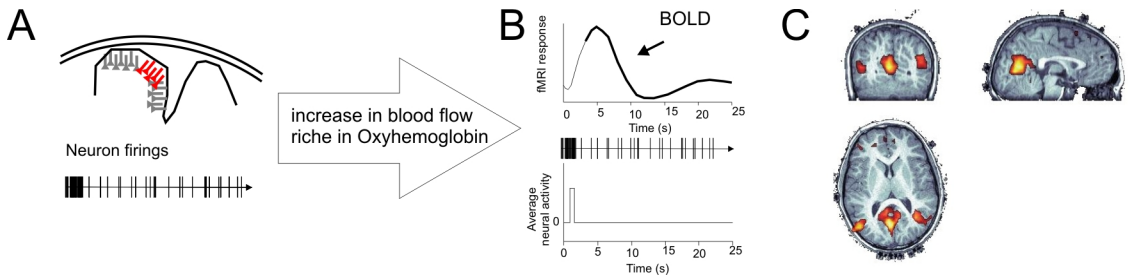


Figure 13 – BOLD effect: measuring blood oxygen levels changes through fMRI

fMRI measures the magnetic changes induced by blood oxygen levels (BOLD) changes fluctuations (B) associated to local neural activity in the brain (A). These fluctuations can be mapped onto the MRI in order to localize active brain areas (C).

can be correlated to the event's related metabolic response in the brain. In epilepsy, BOLD can help identifying the epileptogenic area when associated to clear epileptogenic events and the eloquent cortex responsible for high-level functions (e.g. cognitive, motor), through a proper paradigm. The problem is that BOLD changes are small, in the order of 3-5% from the background MRI imaging signal (Turner and Jones, 2003). It is essential to have a clear model of control/baseline conditions to relate observed variations patterns and specific time events.

For that reason, besides detecting BOLD small variations, fMRI has several problems attached (ranging from purely technical to methodological issues):

- Acquisition timing: one fMRI volume has a time lag between slices that may induce time inconsistencies among slices in the same volume (Benar et al., 2002);
- Motion artifacts: a sequence of fMRI volumes may be affected by the subject's motion. This motion must be corrected in order to be able to compare the spatial temporal change in BOLD across different acquisitions (Liao et al., 2005; Oakes et al., 2005);
- The hemodynamic response function (HRF): there is no unique model for the HRF (Kang et al., 2003; Stephan et al., 2004 ; Friston, 2005) and its relation to a given event or brain area location. This affects the reasoning over the relation between observed BOLD activations and studied events (Handwerker et al., 2004);
- Acquisition time vs. hemodynamic response event: the time resolution of fMRI, although the best in terms of imaging techniques is still poor in terms of hemodynamic activations. For instance, the response for IED is described to be

between 8 to 12 seconds, presenting a typical peak around 4 to 8 seconds (Benar et al., 2002 ; Salek-Haddadi et al., 2003; Turner and Jones, 2003) where most fMRI sequences (in 1.5T) take around 3s to acquire an all head volume. This may compromise the fMRI interpretation depending on the acquisition timing vs. HRF activation stage (Figure 14);

- Establish a clear control to detect activations: the real brain activations patterns behind specific patterns are still unknown, so it is crucial to have clear paradigms/models in order to confirm the hypothesis via fMRI.

Salek-Haddadi et al. present an extensive review on these issues and other fMRI specific details (Salek-Haddadi et al., 2003).

fMRI in epilepsy

In epilepsy diagnosis fMRI represents a trade-off between spatial and temporal resolution and therefore has the role of providing a spatial characterisation of time related activity:

1. Locate the EZ through the correlation of the EEG epileptogenic discharges and their associated BOLD response;
2. Locate the brain areas related to the eloquent cortex functions with special emphasis on cognitive functions to avoid ill-planned surgical resections and possible patient's impairments.

EEG-fMRI related studies

EEG still stands as the reference to detect epileptogenic activity and events in epilepsy. It is established that there is a relation between electrophysiological measures and brain

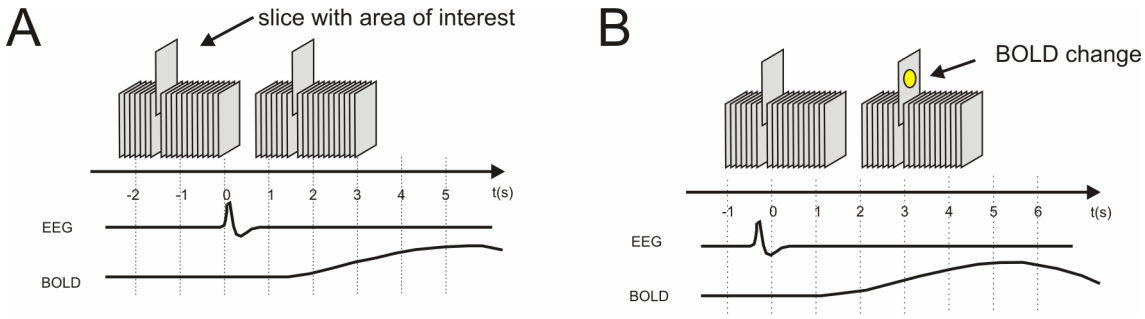


Figure 14 – BOLD change: a moving target for fMRI

The acquisition timing is crucial to describe accurately the BOLD changes. The BOLD response of localized neuronal activation can be missed when fMRI acquisition is not in synch as illustrated in (A) or misrepresented in time due to the delay between neuronal activation and fMRI acquisition (B) (adapted from (Benar et al., 2002))

hemodynamic response (Schomer et al., 2000; Huettel et al., 2004). With the possibility of recording EEG in an MRI environment, associating BOLD variations with EEG patterns (Singh et al., 2003), namely epileptogenic discharges/events appear as the next logical step (Benar et al., 2002; Aghakhani et al., 2004; Kobayashi et al., 2005a). The correlation of electric sources and the brain areas exhibiting BOLD activations can help finding the EZ (Krakow et al., 1999 ; Lemieux et al., 2001a).

The EEG acquired simultaneously with fMRI can be used as paradigm to detect the BOLD activations and to relate the EEG epileptogenic activity to brain areas presenting hemodynamic response.

But in reality, EEG-fMRI combination must deal with new types of artifacts and some methodological issues. When acquiring EEG inside MRI room two new artifacts appear: 1) gradient changes and 2) blood pulse induced artifacts. At some extent solutions for them exist but they are still areas of intense research (Salek-Haddadi et al., 2003).

As standard fMRI acquisition takes approximately 3 seconds for a volume acquisition at a 1.5T MRI, the fMRI time resolution is small in order characterize the BOLD response to an IED (assumed to be about 10-14s seconds with peak at around 4 - 8 seconds) (Benar et al., 2002; Turner and Jones, 2003). This represents a problem on the definition of paradigm model: first, interictal discharges have durations below 200 ms and may not be synchronized spatial-temporally with the fMRI acquisition (as illustrated in Figure 14); second, the lack of a clear model for the HRF of interictal discharges (Dilharreguy et al., 2003) weakens any result analysis associating BOLD and interictal discharges.

Another trend relating E/MEG and fMRI is based on the integration of fMRI activation with the results of electromagnetic source imaging over specific events (not necessarily IED), where fMRI activation can be used to either confirm, guide or improve the sources localisation (Lemieux et al., 2001b; Fujimaki et al., 2002; Toma et al., 2002; Thees et al., 2003; Ahlfors and Simpson, 2004; Schulz et al., 2004; Bagshaw et al., 2005b).

Localisation and lateralization of cognitive function

fMRI is also used in the eloquent cortex (EC) delineation based on selected task induced BOLD responses. It is assumed (supported in neurophysiology knowledge) that tasks invoking specific brain functions are able to activate specific brain areas (e.g. the primary sensory and motor cortex) that produce BOLD variations measurable by fMRI.

The critical issue is the design of tasks that enhance the BOLD activation of specific events in a controlled environment like the MRI acquisition room.

In epilepsy surgery, this assumption is useful to ensure that vital and important functions located in the EC are not affected by the planned surgical resection (Heilbrun et al., 2001 ; Nelson et al., 2002). Tasks related to language and memory functional areas have been designed and shown strong correlation with BOLD activations (Gaillard, 2004). Some examples are applied in language lateralization (Gaillard et al., 2004), semantic decision (Binder et al., 1996), memory encoding and retrieval (Zeineh et al., 2003; Powell et al., 2004), verbal memory tasks (Dupont et al., 2001), just to name a few. For motor related paradigms, video or electromyography (EMG) may provide such a reliable reference, but for high-level and abstract tasks (e.g. involving memory and reasoning) such control might not exist and therefore related analysis is more prone to artifacts and to misinterpretation (false lateralization/localisation obtained) (Jayakar et al., 2002).

Despite several strategies and agreement with invasive tests, such as Wada and electric stimulation, no clear-cut localisation of function is obtained with fMRI. Combined strategies still seem to provide a more complete mapping of eloquent cortex than using fMRI solely (Richardson, 2003).

2.4.3 Magnetic Resonance Spectroscopy (MRS)

Magnetic resonance spectroscopy (MRS) is a non-invasive MRI based technique (Duncan, 1996). MRS allows the measurement of several metabolites through their spectrum signature in a restricted volume in the brain. As some metabolites are correlated with normal and abnormal function in the observed area, their quantification can be used to indirectly infer the normal/abnormal metabolism in the brain. The most relevant one is N-acetyl aspartate (NAA), which is a normal by-product of neuronal cellular metabolism. NAA is a marker of neuronal cell dysfunction, not just volume loss (Theodore, 2004). For that reason, MRS is especially useful in the absence of structural MRI abnormalities and may be able to lateralize TLE when no clear volumetric changes are measured (bilateral atrophy, for instance) (Cendes et al., 1995; Knowlton et al., 1997; Vermathen et al., 1997; Connelly et al., 1998). Other use of MRS is in biological characterisation of tumours (Tedeschi et al., 1997). The problem with MRS is that up to 30% of the acquisitions are not suitable for clinical use: 1) due to artifacts induced by motion and 2) partial volume effect

measure voxels "mixing" the measurements of very specific structure related metabolism (Tedeschi et al., 1997). Despite improvements in spatial resolution through voxel-based grid acquisitions (measures are "taken" voxel by voxel), the spatial definition is still limited (coverage volume and voxel size), implying a strong clinical hypothesis on the focus localisation supported by other multimodal techniques (Duncan, 2002).

2.4.4 Diffusion Weighted Imaging techniques (DWI)

The diffusion weighted imaging techniques (DWI), although promising, are still in early research stages and only now are being assessed clinically. DWI techniques are able to infer the characteristics of cellular tissues (not always visible in normal MRI sequences) by measuring magnetic field variations parameters on the displacement of water molecules (Bammer, 2003). One variant, diffusion tensor imaging (Le Bihan et al., 2001; Sundgren et al., 2004), is able to identify existing damage in structures and major brain pathways, sometimes "invisible" in conventional MRI studies, which can be very useful on relating function alteration with morphological lesions or malformations associated with epilepsy (Eriksson et al., 2001; Rugg-Gunn et al., 2001; Thivard et al., 2006).

2.5 Multimodal techniques in epilepsy diagnosis

We presented several non-invasive modalities where the emphasis was given on their role in epilepsy diagnosis namely in epileptogenic zone (EZ) and eloquent cortex (EC) localisation. Since no specific technique provides an ideal spatio-temporal resolution trade-off (Figure 15), they must be combined for to achieve a better clinical localisation (Duncan, 1997 ; Rosenow and Luders, 2001 ; Duncan, 2002; Richardson, 2003 ; Uijl et al., 2005) and may be used to obtain a multi-perspective characterisation of the brain activity that can be useful in clinical diagnosis and decision (as illustrated in Figure 16) (Rosenow and Luders, 2001; Richardson, 2003):

- Irritative zone: interictal EEG;
- Seizure onset zone: ictal EEG and ictal SPECT;
- Symptomatogenic zone: seizure semiology (VEEG);
- Epileptogenic lesion: MRI, CT, DWI and MRS;
- Functional deficit zone: FDG-PET, fMRI;
- Eloquent cortex: fMRI.

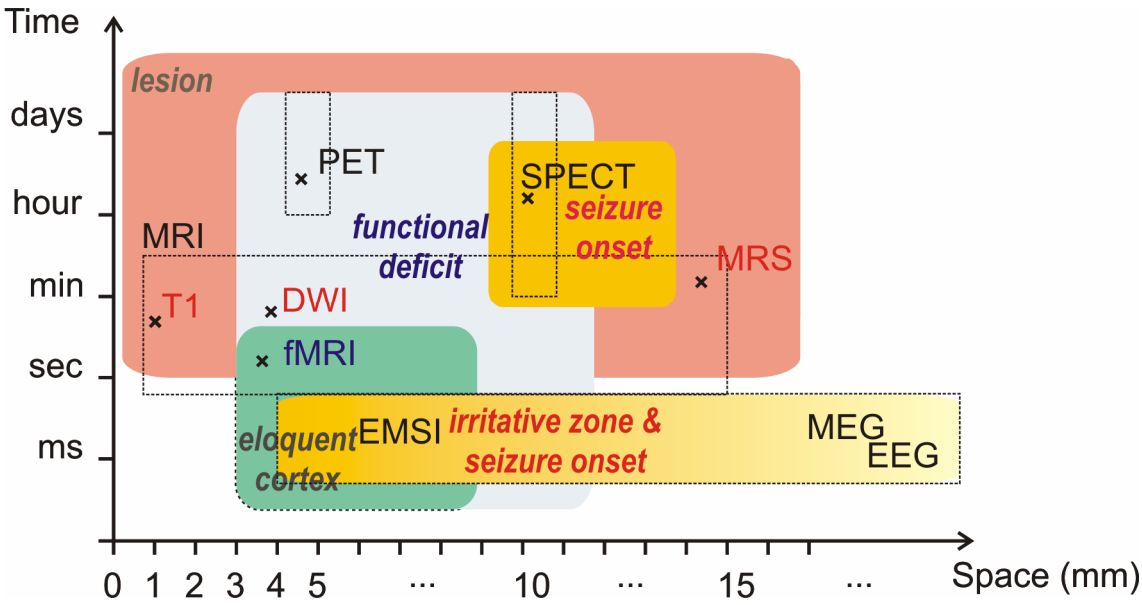


Figure 15 – Spatio-temporal trade-off in non-invasive techniques in epilepsy.

From a spatio-temporal perspective, the non-invasive techniques offer different trade-off between spatial and time resolution in the characterisation of epilepsy. Traditional MRI (T1), and MRS are more suited to characterize the morphology, the PET and SPECT the functional deficits, the fMRI the mapping of brain functions (normal or abnormal) in the brain. In this thesis the focus will be on EMSI, where from the high temporal EEG and MEG resolution, we will try to extract more relevant spatial information as shown in chapters 4 and 5. (adapted from (Churchland and Sejnowski, 1988))

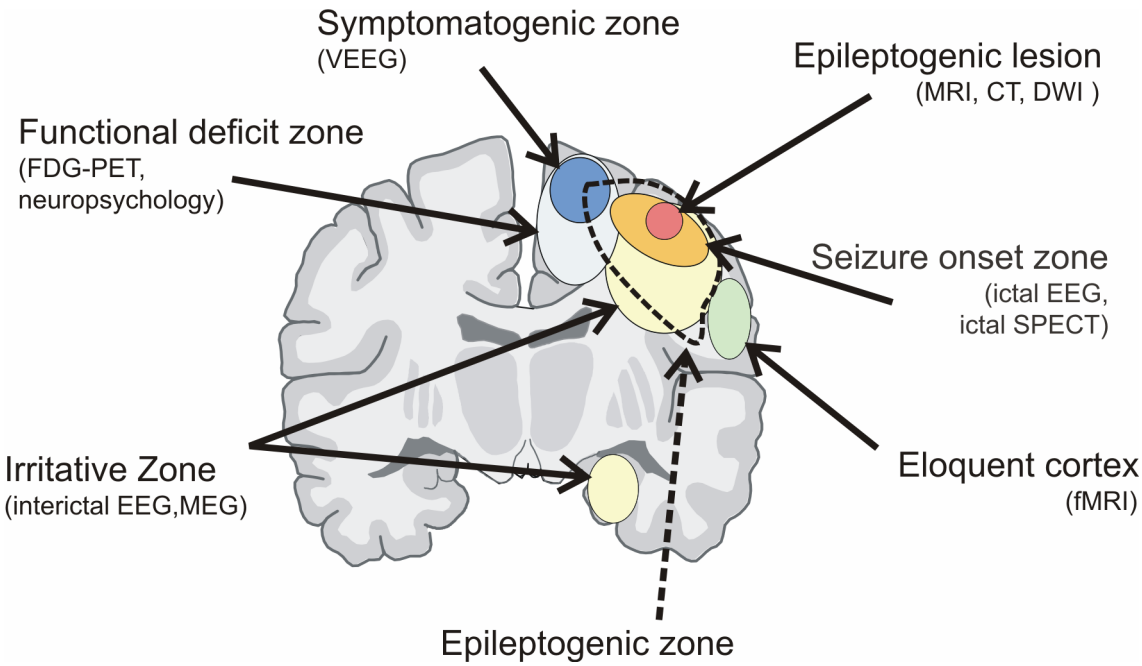


Figure 16 – Non-invasive contributions in epilepsy diagnosis and surgery planning.

Non-invasive techniques provide different perspectives on the epileptogenic zone and eloquent cortex characterisation. These provide helpful contributions in the clinical delineation of relevant brain zones related to the epilepsy syndrome and plan the surgical resection (*dashed line*) hopefully enclosing the EZ without compromising the main task in the EC (the picture is a courtesy of: Christian Vollmar M.D.)

2.6 Electromagnetic source imaging

With the evolution in computer and imaging techniques, the analysis of EEG and MEG has gained a new relevance. Through mathematical and computational methods it is possible to extend simple tracing analysis (e.g. localize phase reversals, identify interictal discharges, slowing) to more precise methods of anatomical localisation of probable epileptic activity generators (Scherg, 1990; Sutherling et al., 1991 ; Baillet et al., 2001). These methods are considered to be part of electromagnetic source imaging (EMSI) methods (Michel et al., 2004; Wheless et al., 2004). EMSI can be seen as a possible non-invasive pathway in the clinical diagnosis of Epilepsy (**Figure 17**). Although EMSI is not a modality on its own, it provides a valuable trade-off between temporal and spatial information when compared to the other modalities and techniques mentioned in this section. By combining high-temporal resolution associated to EEG and MEG in the characterisation of brain activity (Figure 16) together with the spatial information extracted from signal features (e.g. interictal discharges) combined with anatomical information (from MRI) into a unified framework, EMSI is able to provide more accurate information on the localisation of the EZ as illustrated by several studies (Dale and Sereno, 1993; Yoshinaga et al., 1999 ; Shukla et al., 2003 ; Bast et al., 2004; Bast et al., 2005).

The three most critical steps of EMSI are (**Figure 17**):

1. Selection/detection of the relevant patterns as temporal references for analysis (events such IED and evoked potentials responses);
2. Sources/ generators extraction that explain the brain electric activity;
3. Result interpretation by comparing results with observed brain activity and other multimodal related information.

In chapter 3, we show that there is a lack of quantification in relation to spikes either in their intrinsic definition and that a definition reformulation must be done in order to have a reliable reference in quantified spike related analysis processes. We show that simultaneous EEG and MEG spikes characteristics are different and it is not reasonable to use the same clinical assumption in both EEG and MEG. We also show that the use of multi-expert spike selections (MESS) as gold standard, although clinical useful and sound, may induce a handicap when defined solely terms of clinical agreement criteria, namely as references for automatic spike detection algorithms in sensitivity and specificity method analysis.

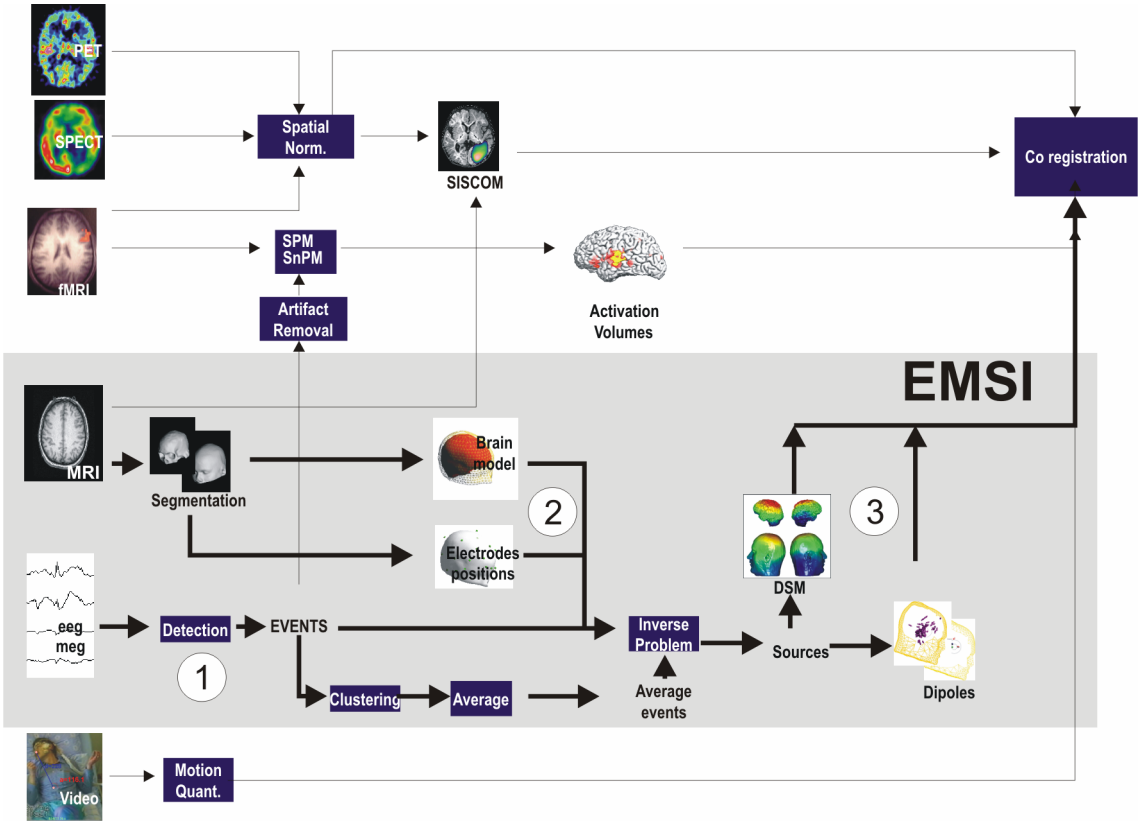


Figure 17 – Electromagnetic source imaging (EMSI) pathway.

The non-invasive diagnosis in epilepsy depends on combining both data sources and processing methods. In this context, the analysis of electromagnetic brain activity signatures provides a valuable trade-off between the time resolution (EEG and MEG) and spatial resolution (from mathematical analysis of electrical current brain generators). This combined approach is an area denominated as electromagnetic source imaging (EMSI). From a perspective of a unified framework, EMSI comprises 3 phases: (1) the selection process of temporal references (events) from EEG-MEG, (2) the extraction of epilepsy related information (sources of activity through inverse problem methods) and (3) the results interpretation in light of clinical and other multimodal information. In this thesis the focus will be in these 3 phases where we will present some considerations and technical contributions.

In chapters 4 and 5, we propose two unsupervised methods that, supported in statistical clustering, try to overcome the inconsistencies induced by clinical inputs. The aim is to provide an overall brain activity characterisation, while maintaining a clear relation with clinical knowledge and expertise. They provide quantified information that be easily visualized and be an added value in the clinical diagnosis process.

In chapter 4, a new method that proposes a new dipole spatial filtering strategy to support source analysis post-processing that combines the analysis of individual events generators with statistical spatial clustering. The method is unsupervised and avoids recurring to clinical inputs in both spike classification and averaging. We apply the method to 4 patients suffering of hypothalamic hamartoma related epilepsy (Fernandes et al., 2003a, b). Hypothalamic hamartoma related epilepsy is a good localization reference as it

has an accepted localisation of the epileptogenic zone – the hamartoma itself (Berkovic et al., 1997; Kahane et al., 2003; Leal et al., 2003).

In chapter 5, the *EpiGauss* method is presented. *EpiGauss* is a combined source analysis method that extends the method proposed in section 4.4, to accommodate spatio-temporal information. *EpiGauss* combines the advantages of using the time resolution of EEG/MEG and spatial resolution of source analysis methods, with the dipole spatio-temporal information retrieved from individual events source analysis. Through dipole density and spatial clustering it is possible to present the results in a Brain imaging like manner and provide simultaneously quantified information that may guide the clinical diagnosis. As a method, *EpiGauss* provides a good insight on the spatio-temporal dynamics of brain activity without the need for specific expert knowledge usually associated with standard EMSI methods. The method was applied to 4 patients suffering from hypothalamic hamartoma related epilepsy (Fernandes et al., 2006a) and 6 patients with Early Onset Occipital Lobe epilepsy (Fernandes et al., 2006b).

2.7 Summary

In this chapter, we presented a review on the state of the art of non-invasive diagnostic techniques used in Epilepsy diagnosis and pre-surgery evaluation with special emphasis on their clinical contributions. An integrated overview of the techniques is provided along three different perspectives: (1) the main contribution to the localisation of the epileptogenic zone (EZ) and eloquent cortex (EC) (summarized in Figure 16), (2) their spatio-temporal resolution trade-off in the EZ and EC characterisation (summarized in Figure 15), and (3) their specific role in epilepsy diagnosis (**Figure 17**) - combination of processing methods and modalities used to support the epilepsy diagnosis and pre-surgical evaluation. Special emphasis is given in the end to electromagnetic source imaging (EMSI), where the thesis main contributions are enclosed (presented in chapter 3, 4 and 5).

3 Electric and magnetic spikes: their usefulness in foci localisation

Since 1929 with the first EEG trials, several EEG features associated to specific brain activity were identified and characterized. Some examples are epileptic discharges (associated to epilepsy) and other rhythmic patterns such as alpha, sleep spindles - associated with specific states of normal brain function (Niedermeyer and Lopes da Silva, 1999). These events present specific spatio-temporal signatures (e.g. temporal duration or the brain area where events were detected) – and are classified, most of the times, according to atlas and accepted definitions (Chartrian et al., 1974 ; Engel and Pedley, 1998; Niedermeyer and Lopes da Silva, 1999).

In epilepsy, ictal and interictal epileptogenic discharges are the most relevant events as they can be associated to the epileptiform brain activity and provide provide clinically relevant information namely on localisation of irritative and epileptogenic zone (EZ)(Ebersole, 1997). Ictal EEG discharges provide meaningful information (Martins da Silva and Cunha, 1994; Gotman, 2003), but due to their complex signature - including spread, multifocal activity and the presence of related artifacts associated - and their scarce occurrence (Manford et al., 1996; Foldvary et al., 2001; Gotman, 2003), their role in epilepsy diagnosis is usually secondary in relation to the more common interictal epileptiform discharges (IED). IED, besides being more common, can be easily identified by specialists (or by trained technicians under supervision), through EEG/MEG visual inspection. Typically, the localisation information extracted from clinical analysis in IED is “coarse”, comprising laterality (right, left) and associated brain areas (frontal, temporal, central, parietal, occipital) information, despite the existence of more sophisticated EEG/MEG quantification and processing methods (Engel and Pedley, 1998).

This is also true for the IED associated concepts (spikes, sharp waves, background) that, since the first accepted definitions, in spite of signal processing evolution, remain highly subjective, as illustrated by (Chartrian et al., 1974):

*"**Background activity** - Any EEG activity representing the setting in which a given normal or abnormal pattern appears from which such pattern is distinguished. Comment: not a synonym of any individual rhythm such as the alpha rhythm.*

(...)

***Sharp wave** – A transient, clearly distinguished from background activity, with pointed peat at conventional paper speeds and duration of 70-200 msec, i. e., over 1/14 – 1/5 sec. approximately. Main component is generally negative relative to other areas. Amplitude is variable. Comments: (1) Term does not apply to (a) distinctive physiologic events such as vertex sharp transients, lambda waves and positive occipital sharp transients of sleep, (b) sharp transients poorly distinguished from background activity and sharp-appearing individual waves. (2) Sharp-waves should be differentiated from spikes, i. e, transients having similar characteristics but shorter duration. However, it is well to keep in mind that this distinction is largely arbitrary and serves primarily descriptive purposes. Practically, in ink-written EEG records taken at 3 cm/sec, sharp waves occupy more that 2 mm of paper width and spikes 2 mm or less C.f. Spike*

(...)

***Spike** – A transient, clearly distinguished from background activity, with pointed peak at conventional paper speeds and a duration from 20 to under 70 ms, i.e., 1/50 to 1/14 sec. approximately. Main component is generally negative relative to other areas. Amplitude is variable. Comments: (1) EEG spikes should be differentiated from sharp waves, i.e., transients with similar characteristics but longer durations. However, it is well to keep in mind that this distinction is largely arbitrary and serves primarily descriptive purposes. Practically, in ink-written EEG records taken at 3 cm/sec, spikes occupy 2mm or less of paper width and sharp waves more than 2mm. (2) EEG spikes should be held in clear contra-distinction to the brief unit spikes recorded from single cells with micro-electrode techniques. C.f. Sharp wave"*

The current spike and related definitions are ambiguous, inexact and often recursive (examples are *underlined* in the previous quotation) therefore they are unreliable references. However, in practice, when objective definitions are needed (e.g. in automatic spike detection solutions), most of the time the solution lies in recurring to "proprietary" spike definition, based in clinician selections (Guedes de Oliveira et al., 1983 ; Koffler and Gotman, 1985 ; Principe and Smith, 1985 ; Davey et al., 1989 ; Gabor and Seyal, 1992 ; Wilson et al., 1999 ; Black et al., 2000 ; Acir and Guzelis, 2004) or in some intrinsic signal characteristic associated to IED (Witte et al., 1991 ; Sartoretto and Ermani, 1999 ; Fernandes et al., 2000; Goelz et al., 2000 ; Latka et al., 2003 ; Adjouadi et al., 2004).

This is also true when combining EEG and MEG, where the lack of objective EEG IED

definitions raises doubts on the adequacy of using clinical EEG knowledge in MEG. Several studies (Merlet et al., 1997; Baumgartner et al., 2000b ; Yoshinaga et al., 2002; Zijlmans et al., 2002 ; Stefan et al., 2003 ; Baumgartner, 2004 ; Pataraia et al., 2004; Stefan et al., 2004; Iwasaki et al., 2005) have shown that IED in EEG and MEG seem to differ either in morphology, time synchrony or localisation accuracy. The existence of non synchronous patterns of occurrence, in part explained by EEG and MEG different susceptibility to head layers and to the configuration of underlying brain electrical activity sources (Cohen and Cuffin, 1983 ; Malmivuo et al., 1997; Yoshinaga et al., 2002 ; Bast et al., 2004 ; Pataraia et al., 2004; Bast et al., 2005), raised doubts on whether we are indeed observing similar shape events in EEG and MEG (Zijlmans et al., 2002).

This has consequences when trying to establishing ground truth for spike definition, either as an objective quantification or through building a spike reference to be used EEG and MEG spike related analysis.

We illustrate this in section 3.1, where we show that we cannot consider that the EEG knowledge on IED can be applied directly into the MEG analysis, despite the apparent similarities (Malmivuo et al., 1997; Merlet et al., 1997). This will be demonstrated by the statistical differences found in the paired analysis over the morphological properties of synchronous EEG/MEG IED (published by our group in the Journal of Clinical Neurophysiology (Fernandes et al., 2005b)). We show (section 3.2.) that, despite recurrent use of multi expert spike selections (MESS) as gold standard reference in spike related studies, this may be misleading. MESS may present heterogeneous characteristics that, in some cases, may induce a handicap whenever used as spike ground truth based solely on clinical agreement criteria, namely when used as reference in automatic spike detection method sensitivity and specificity analysis. (Wilson and Emerson, 2002; Zijlmans et al., 2002).

3.1 What does an epileptiform spike look like in MEG?[2]

For more than 30 years epileptiform spikes and on-going EEG activities have been identified based on well-established operational definitions (Chartrian et al., 1974) .

[2] Published as Fernandes, J.M., Martins da Silva, A., Huiskamp, G.M., Velis, D.N., Manshanden, I., De Munck, J.C., Lopes da Silva, F.H., Cunha, J.P.S. (2005b). What Does an Epileptiform Spike Look Like in MEG? Comparison Between Coincident EEG and MEG Spikes. J Clin Neurophysiol 22, 68-73.

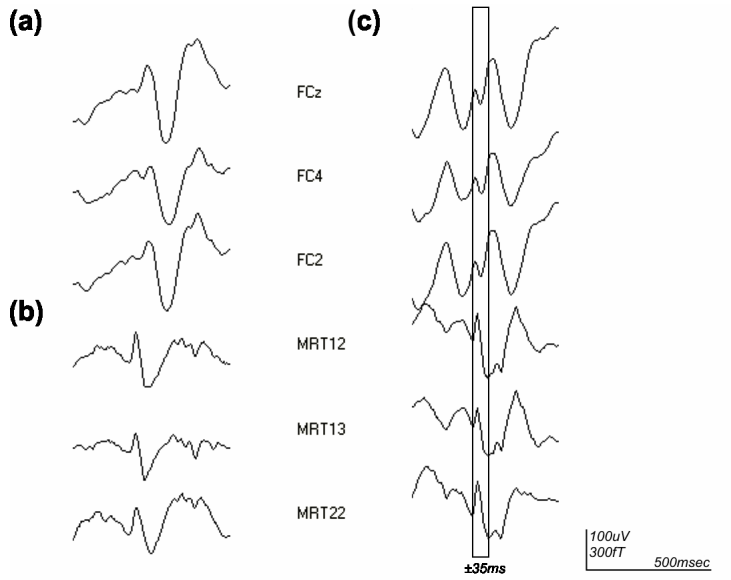


Figure 18 – Spikes in EEG and MEG: examples

Examples taken from pat3: (a) EEG epileptiform event (b) MEG epileptiform event on same area (c) Coincident events in EEG and MEG within a +/- 35 ms time window (from (Fernandes et al., 2005b))

Despite of progressive use of Magnetoencephalography (MEG) and the extensive work on the characterisation of electrical and magnetic events of cerebral origin, corresponding definitions with respect to epileptiform events recorded on MEG are not yet available. This question merits being investigated with respect to the general aim of advancing the clinical applicability of the MEG and in order to develop automatic recognition algorithms for such magnetoencephalographic events.

Recent studies reinforce the need of such operational definitions both in the clinical laboratory (Zijlmans et al., 2002) and in the field of computer-based detection algorithms. The latter have been developed and implemented in clinical practice in the EEG field (Carrie, 1972; Gotman and Gloor, 1976 ; Guedes de Oliveira et al., 1983; Frost, 1985; Gotman, 1999), but not yet in the MEG field. Nevertheless, in a number of investigations the localisation of interictal spikes sources based on MEG, or MEG and EEG recordings, has been carried out (Sutherling et al., 1988a; Sutherling et al., 1988b ; Sutherling et al., 1991 ; Ebersole, 1997 ; Merlet et al., 1997 ; Ossenblok et al., 2003 ; Van't Ent et al., 2003).

The basic question of our study is: can we use the same definitions of epileptiform spikes that are commonly used in EEG, for MEG recordings?

To answer this question we performed a quantitative comparison of coincident EEG and MEG events (within a +/- 35 ms window) that were selected by a senior clinical neurophysiologist as characteristic EEG epileptiform spikes. A parametric description of the morphology of the epileptiform MEG and EEG events was made.

Patient	Age (Sex)	Clinical Features	Time (s)	Channels EEG/MEG
Pat1	21 (F)	Complex Partial(CP), left temp. focus. Six months after recordings: surgery. Confirmed mesial temporal sclerosis, Wyler grade 3. Seizure free (Engel 1a) one year later.	900	64 / 150
Pat2	39 (F)	CP, right frontal parasagittal region. Starting after drainage right frontal lobe cerebral abscess.	300	45 / 150
Pat3	27 (M)	CP seizures, right frontal region, secondary generalisation. Pharmacoresistant epilepsy starting after bacterial encephalitis and right frontal lobe cerebral abscess. Magnetic ressonance: right frontal gliosis. EEG/CCTV irritative zone right frontal (RF) and central. Ictal EEG high voltage RF slow wave. Pathology confirmed right frontal gliosis and seizure free (Engel 1a).	300	33 / 147

Table 1 – Spikes in EEG & MEG: data sets characterisation

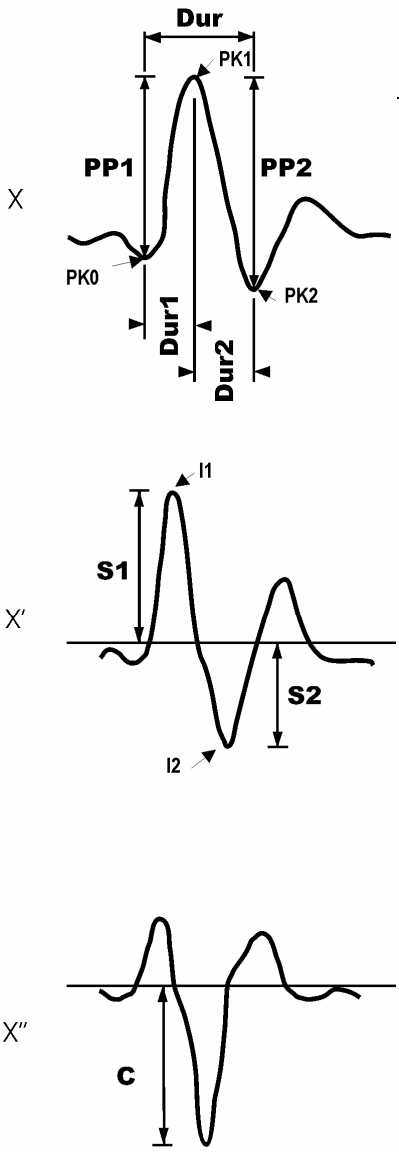
3.1.1 Materials and methods

Data

The data was acquired at the MEG Centre of the Vrije Universiteit Medical Centre, Amsterdam, using a whole-head helmet MEG system (VSM MedTech Ltd., Coquitlam, BC. Canada) consisting of 151 MEG channels and 64 EEG channels (Vrba et al., 1999). EEG was recorded with a 10-10 system and a common average reference. Simultaneous EEG and MEG data of three patients suffering from drug-resistant epilepsy were recorded. The datasets acquired at 625Hz, lasted 25 minutes. The data was band-pass filtered between 1 and 50Hz. The data sets used have the properties described in Table 1.

Protocol

A senior clinical neurophysiologist (AMdS) selected segments of waking EEG with on-going background activity and with epileptiform spikes from the EEG records of the patients. In order to characterise the normal background activity, epochs were selected from frontal and occipital EEG derivations. Background was characterized by quantifying the frequency and amplitude within different frequency bands, according to the international glossary (Chartrian et al., 1974). More than 10 seconds of background segments were selected for each data set.



Name (Variable)	Description
Dur (DUR_T)	Time difference *PK2-PK0* in seconds
Dur1 (DUR1)	Time difference *PK1-PK0* in seconds
Dur2 (DUR2)	Time difference *PK2-PK1* in seconds
Dur2/Dur1 (DUR2_DUR1)	$\frac{Dur2}{Dur1}$
$\hat{X}$, $\hat{X}'$ and $\hat{X}''$	Standard deviation in EEG background segments in X, X' and X'' respectively
PP1 (PP1)	$PP1 = \frac{\lvert X(PK0) - X(PK1)\rvert}{\hat{X}}$
PP2 (PP2)	$PP2 = \frac{\lvert X(PK1) - X(PK2)\rvert}{\hat{X}}$
PP2/PP1 (PP2_PP1)	$\frac{PP2}{PP1}$
I1 and I2	$I1 \in]PK0, PK1[$ and $I2 \in]PK1, PK2[$ $\forall I \in]PK0, PK1[, \lvert X'(I1)\rvert >= \lvert X'(I)\rvert$ $\forall I \in]PK1, PK2[, \lvert X'(I2)\rvert >= \lvert X'(I)\rvert$
S1 (S1)	$S1 = \frac{\lvert X'(I1)\rvert}{\hat{X}'}$
S2 (S2)	$S2 = \frac{\lvert X'(I2)\rvert}{\hat{X}'}$
S2/S1 (S2_S1)	$\frac{S2}{S1}$
Sharpness or C (SHARP)	$C = \frac{\lvert X''(PK1)\rvert}{\hat{X}''}$

Figure 19 and Table 2 – Spikes in EEG & MEG: spike model and parameters

Spike parameters are defined for the original signal (X), its first derivative (X') and its second derivative (X''). (Figure and table adapted from (Fernandes et al., 2005b))

The presence of epileptiform spikes in the EEG and MEG was carried out by visual inspection of all derivations, mainly in the area of the epileptogenic focus (Ebersole, 1997) with locations described on Table 1 (data sets characterisation). Since the EEG data was

		N	Mean	Min	Max	Standard Deviation
DUR_T (s)	EEG	120	0.053	0.030	0.074	0.012
	MEG	120	0.047	0.016	0.082	0.014
SHARP	EEG	120	7.80	0.92	51.82	7.34
	MEG	120	38.43	5.96	172.21	29.40
PP2_PP1	EEG	120	12.60	0.73	89.67	15.45
	MEG	120	7.75	0.03	68.97	9.62
S2_S1	EEG	120	7.57	0.47	99.15	12.25
	MEG	120	7.00	0.06	75.13	11.02
DUR2_DUR1	EEG	120	0.47	0.10	1.80	0.28
	MEG	120	0.65	0.11	6.00	0.68

Table 3 – Spikes in EEG & MEG: descriptive statistics

used as reference, we selected for analysis only the MEG transients with a spike-like configuration that occurred within a -/+ 35 ms window in relation to any EEG spike identified (as illustrated by Figure 18). The EEG spikes were within the accepted definition of interictal epileptiform spikes according to Chartrian et al., 1974 (duration between 20 and 75ms).

As described in (Guedes de Oliveira et al., 1983), the spikes were selected and their morphologic parameters (described in Figure 19 and Table 2) were normalized relative to the background characteristics in the same signal. This selection process resulted in 120 pairs of EEG and MEG events occurring within the same time window of 80 ms.

The morphologic parameters extraction was performed using a computational tool, written in C++, used also to compute the mean, minimum and maximum values and the corresponding standard deviations.

Statistical methods

The null hypothesis was that coincident EEG spikes and MEG transients had the same statistical characteristics. To test this hypothesis a paired t-test was performed for each parameter. Since parameters were, in general, not normally distributed a LOG (base 10 logarithm) transformation was applied. To verify the assumptions of the paired t-test (the paired difference should be normally distributed), we applied standard normality tests,

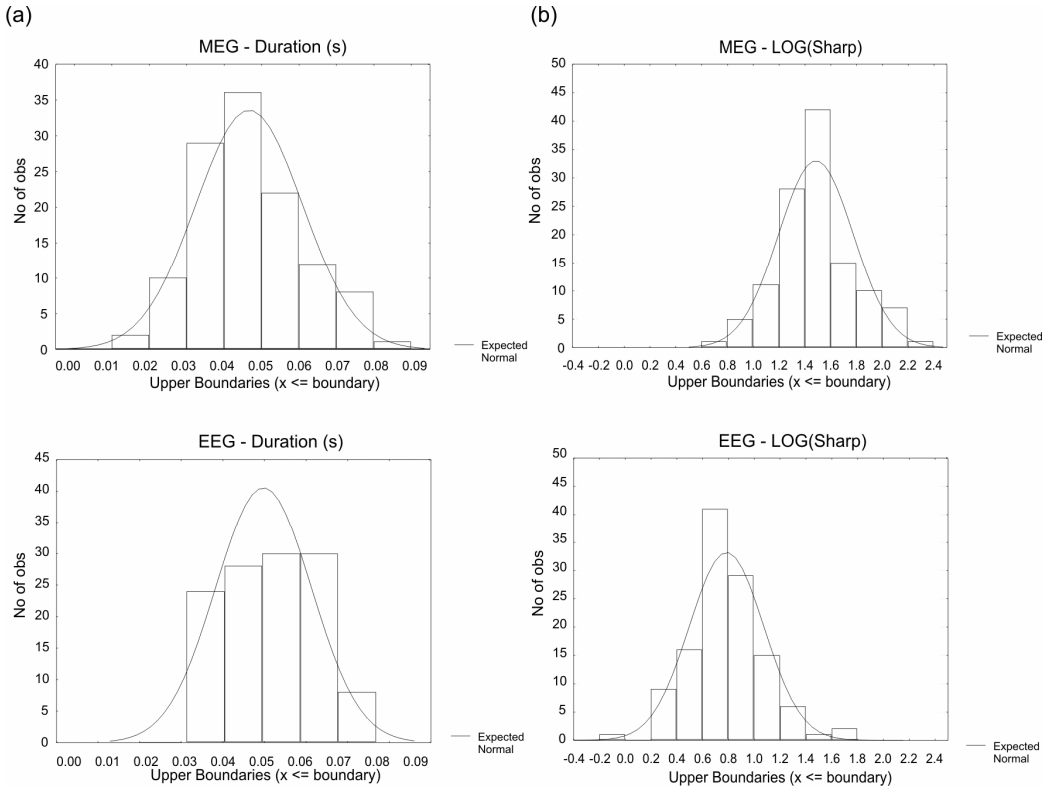


Figure 20 – Spikes in EEG and MEG: duration and sharpness histograms

Histograms of the duration (a) and sharpness (b) of 120 EEG and MEG simultaneously recorded spikes (adapted from (Fernandes et al., 2005b))

namely the Kolmogorov-Smirnov one-sample D statistics (Chakravarti and Roy, 1967) and the Shapiro-Wilks' W test (Shapiro and Wilk, 1965) for each parameter paired difference (Armitage, 1971). For all parameters the required assumptions were met.

3.1.2 Results

The results of the computational analysis of the parameters of the EEG spikes and MEG transients are presented in Table 3. The statistical results are presented in Table 4. We can clearly deduce that, for values of p less than 0.01 (99% confidence interval), the hypothesis that the parameters had the same distribution was rejected.

The obtained results show clearly that inter-ictal epileptiform spikes recorded in EEG and MEG transients, occurring within the same 70 ms window, share some properties but differ statistically in characteristics such as duration, sharpness and shape.

In summary, MEG spikes are sharper than EEG spikes and their duration is shorter as it is illustrated by the comparison of the histograms illustrated in Figure 20. In addition the shape, defined as the ratio between the amplitudes of the rising and the decaying flanks of

	N	P (paired t-test)	EEG =MEG	Means
DUR_T	120	p<0.01	rejected	EEG>MEG
LOG(SHARP)	120	p<0.01	rejected	EEG<MEG
LOG(PP2_PP1)	120	p<0.01	rejected	EEG>MEG
LOG(DUR2_DUR1)	120	p<0.01	rejected	MEG>EEG

Table 4 – Spikes in EEG & MEG: paired t-test - statistics over spikes metrics

the spike (PP2/PP1), is different between both kinds of spikes.

The main conclusion is that MEG spikes are, in average, shorter and sharper than simultaneously occurring EEG spikes.

3.1.3 Discussion

MEG and EEG epileptiform spikes are generated by non-stationary dipolar sources and, because the neuronal activity underlying spike generation propagates over the cortex, the electrical potential recorded at the surface has a prolonged duration when compared with the cortical (source) generator. This can be explained taking into account that an activation front, such as it occurs during a spike that propagates with a certain velocity, is seen from a distant point in the volume conductor, attenuated in amplitude and in a more dilated time scale (Lopes da Silva and van Rotterdam, 1993). However the corresponding magnetic field reflects the direction of the intracellular current densities with a tangential orientation to the cortical surface, and the contribution of the volume currents is much less important, although a propagating activation front will also be reflected in a MEG waveform dilation with respect to the cortical waveforms. The differences between EEG and MEG may be accounted for, on the one hand by the different effects of the volume currents and, on the other, by the fact that EEG and MEG have different sensitivities to tangential and radial components of the sources. In general, we may assume that the source of a given epileptiform spike propagates along a cortical gyrus, going from a fissure to the crown of a gyrus. In such case, the MEG event will reflect mainly the tangential or fissural components while both tangential and radial (corresponding to the crown of the gyrus) components will contribute to the EEG. Consequently the MEG signal would correspond to a more spatially limited and geometrically simpler propagating source. Therefore the EEG signal would be more dilated in space and less sharp. These assumptions may be

tested by model simulations.

In the present analysis we focused on the epileptiform spikes recorded simultaneously in both the EEG and in the MEG within a rather short time window. It will be interesting to investigate this question using longer time windows in order to determine whether epileptiform spikes appear as single events both in EEG and MEG or not. Preliminary observations suggest that often one single EEG spike seems to correspond to a burst of MEG spikes usually with low amplitudes.

To the best of our knowledge there are no other studies where comparison between the waveforms of EEG and MEG epileptiform spikes were done systematically. However the differences that we found in spikes were also noted by Merlet et al. (Merlet et al., 1997) in duration between MEG and EEG spikes and are also put in evidence graphically in a recent study by Baillet et al (Baillet et al., 2002).

On a clinical perspective the findings reported here reinforce the need for a definition of epileptiform events in MEG. Such characterisation would increase the objectivity on the epileptiform events selection in MEG analysis, that seem to be more dependent on the observer experience than in common and objective criteria, as suggested by Zijlmans et at (Zijlmans et al., 2002).

As a consequence, both visual and automatic spike detection in MEG should take into account the differences between EEG and MEG transients and should be done according to a criteria adapted to the MEG and not simply based on traditional EEG evaluation.

3.2 On the usefulness of multi expert spike selection

Since the initial spike based studies in the 70's, the common practice, is to establish a clinical spike ground truth based the consensus between 2 or more reviewers - the gold standard (Gotman and Gloor, 1976 ; Lopes da Silva et al., 1977 ; Pfurtscheller and Fischer, 1978 ; Frost, 1979 ; Guedes de Oliveira and Lopes da Silva, 1980a ; Ktonas et al., 1981 ; Guedes de Oliveira et al., 1983 ; Wilson and Emerson, 2002). By comparing datasets with a gold standard set it is possible to access how well the dataset agrees with clinical consensus. Gold standards are useful in detection methods evaluation. Usually a two parameter "evaluation" - sensitivity and specificity – is used to perform a quantified analysis on the agreement between detections and the gold standard (Wilson, Harner et al. 1996). A method with high sensitivity (detects most of the clinical consensus detection)

and high specificity (avoids "wrong" detections or false positives) models well the clinical gold standard.

With recent advances in both acquisition and computational methods the relevance of such references has increased, namely in the design and evaluation of automatic detection algorithms. For instance, in EEG/MEG spike related studies, with high spatial resolution (up to 256 channels or more) and long monitoring sessions the clinical identification of epileptiform spike patterns has an increasing complexity and therefore more prone to human errors (Wood, Black et al. 2004), although these errors may not undermine the clinical decision when contextualized with other available information (Engel and Pedley 1998). This overwhelming amount of clinical information makes the establishment of a reliable and objective spike reference even more pressing. Nonetheless the errors in clinical identification represent a major hindrance for the building of reference sets for spike, and may affect negatively the accuracy of such sets in the evaluations based on traditional sensitivity and specificity criteria.

Several questions have to be taken into consideration. First, the definition of a spike has remained rather subjective since the 1970's (Chartrian, Bergamini et al. 1974) and is highly dependent on the reviewer experience; the term expert reviewer is often used as a symbol of authority that justifies the validity of any identification. Nevertheless, there are no objective criteria regarding epileptiform spike morphology that are generally accepted (Zijlmans et al., 2002; Fernandes et al., 2005b). Second, there is a large variability in the performance of several clinical experts so that the reliability of clinically defined reference sets is limited.

In the present study, we characterize a multi-expert spike selection identified by a group of experts. This "gold standard" consists of 1804 spikes that were identified in EEG, in MEG or in both by at least one of three experienced EEG reviewers.

According to an apparent literature consensus, power representations of EEG and MEG may provide good estimates of the occurrence of ictal and interictal events (Skrandies, 1989 ; 1990; Litt et al., 2001; Van Drongelen et al., 2003 ; Gigola et al., 2004; Esteller et al., 2005; Harrison et al., 2005).

In this study, we will analyse a multi-expert spike selection (MESS) in terms of expert agreement and of power patterns in both EEG and MEG. The power pattern analysis will be supported in a simple power based metric evaluation. This is based on the assumption

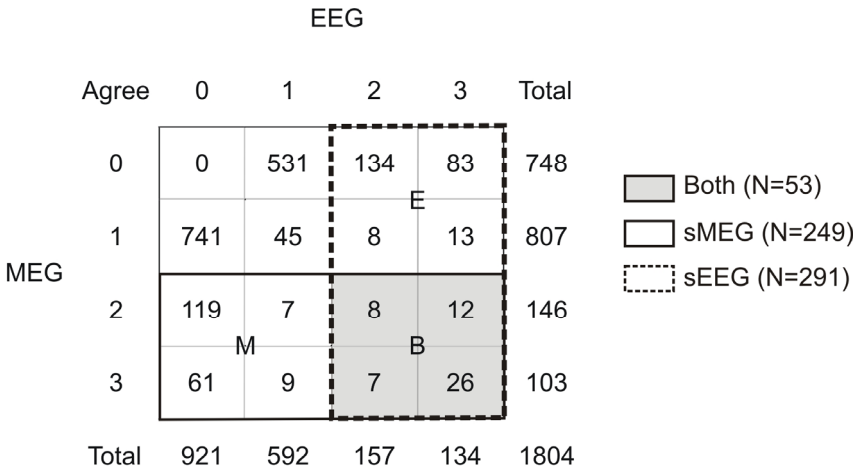


Figure 21 – MESS: Spikes selection in function of expert agreement

The EEG, MEG and Both sets are defined in terms of expert agreement. The Both set includes spikes detected by at least 2 experts in EEG and MEG, sEEG spikes detected in EEG by a least 2 experts and sMEG spikes detected in EEG by a least 2 experts. The table shows the count of detection in each category where the sets are graphically enhanced. The spikes in class E are only detected in EEG, spikes in M only detected in EEG and spikes in B detected in both EEG and MEG.

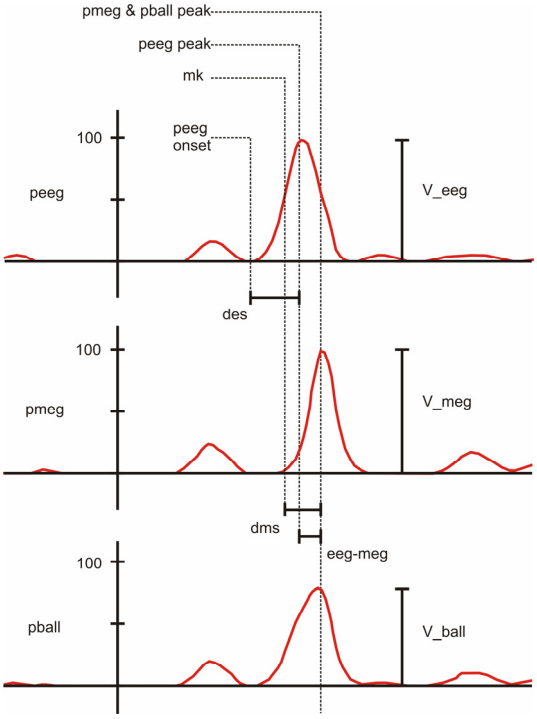
that epileptiform brain activity may induce power changes in EEG and in MEG. We also characterise the relation between reviewer's agreement and observed power pattens, discussing the results and possible consequences of using MESS as ground truth, namely in the evaluation of sensitivity/specificity of an automatic algorithms.

3.2.1 Materials and methods

Data

The data sets were acquired at the MEG Centre of the VU Medical Centre, Amsterdam, using a whole-head helmet MEG system manufactured by CTF Inc. (VSM Med Tech Ltd., Coquitlam, BC, Canada), consisting of 151 MEG channels and 64 EEG channels (Vrba et al., 1999). EEG was recorded at 625 Hz with two setups: a 10- 20 (31 channels) and 10-to-10 system (64 channels) with a common average reference. An overall of 135 minutes of simultaneous EEG and MEG from nine patients with drug-resistant epilepsy was acquired and analysed. Spikes were detected by experts independently in EEG and in MEG resulting in a total of 1804 spikes identified by at least one expert in either EEG, MEG or both.

The data sets used have the properties described in (Zijlmans et al., 2002) and summarized in Figure 21.



Metric	unit	Description
v_ball	0-100 %	pball relative power peak amplitude
v_eeg	0-100 %	peeg peak relative amplitude
v_meg	0-100 %	pmeg peak relative amplitude
eeg-meg	Ms	Time between peeg and pmeg peaks
des	Ms	peeg peak slope duration
dms	Ms	pmeg peak slope duration

Figure 22 and Table 5 – MESS: power model and metrics description

For each event, the peaks in instantaneous squared power nearer the initial marker (mk) are selected in both EEG (peeg) and MEG (pmeg). From the average of instantaneous power2 in EEG and MEG, pball is calculated and the pball peak amplitude extracted (v_ball). The duration of the rising slope of the peak are extracted in EEG (des) and MEG (dms). From the peak reference the distance between EEG and MEG peak is calculated (eeg-meg).

Protocol

All events identified were considered and originated 3 expert based spike selections: sEEG (identified by 2 experts or more in EEG), sMEG (identified by 2 experts or more in MEG) and Both (identified by 2 experts or more in EEG and MEG). For all spikes in each of these multi-expert spike selections (MESS) a coded classification was established to each event according to the following rule (as in Figure 21):

E – only identified in EEG

M – only identified in MEG

B – identified in EEG and MEG (within a +/- 35 ms interval)

For each detected event with time of occurrence mk a signal window of [mk-0.5s , mk+0.5s] was extracted and band-pass filtered (4 – 70 Hz) in order to remove low frequency background oscillations. For each signal window, EEG and MEG power representations were scaled within the interval [0,100]. In this process the power maximum value in the studied intervals was mapped into 100 and a measure of relative power characterisation of the time window obtained. To avoid artefacts and high frequency noise

		overall			sEEG			sMEG			Both		
		N	Mn	Std	N	Mn	Std	N	Mn	Std	N	Mn	Std
v_ball	(%)	1804	35.6	32.0	291	37.9	32.8	249	41.0	32.1	53	48.0	0.0
v_eeg	(%)	1804	37.4	40.2	291	39.9	42.0	249	43.5	40.9	53	51.8	0.0
v_meg	(%)	1804	40.1	40.4	291	43.0	42.5	249	44.8	41.4	53	50.4	0.2
des	(ms)	1804	29.0	13.5	291	30.0	14.5	249	29.3	13.7	53	32.6	11.2
dms	(ms)	1804	27.3	11.8	291	26.8	11.6	249	26.4	10.7	53	30.4	14.4
eeg_megs	(ms)	1804	-0.3	14.0	291	-1.0	15.3	249	1.1	15.0	53	-1.9	-59.2

Abreviations : N – number of observations, Mn-Mean, SD – standard deviation

Table 6 – MESS: descriptive statistics

the squared power representation were smoothed using a Barlett triangular filter (10 samples window). The highest power peak nearer the marker mk (within +/150ms) was used to define an adjusted time of occurrence for each event and used to extract the model related features (as illustrated in Figure 22). Three instantaneous power based representations were calculated for each sample in the interval (Figure 22).

- peeg – overall EEG scaled relative power representation
- pmeg - overall MEG scaled relative power representation
- pball = (peeg + pmeg) / 2

The pball metric was used to provide a balanced overall power estimate in both EEG and MEG. The wave morphologic parameters were described according to the model metrics presented in Figure 22 and Table 5. The metrics were extracted using a computational tool developed in our lab, written in C++.

To study the relationship between expert agreement and power metric a statistical analysis was performed to assert the influence of the different levels of agreement (1 expert and consensus of 2 or 3 experts) in EEG and MEG in the spike selection power characteristics.

To study the relationship between EEG and MEG spikes based on power patterns a bivariate histogram comparison between values of relative power peaks in both EEG and MEG spikes (Figure 23) was performed. A k-means cluster analysis method (Bishop, 1995) was used to split the data according to different clusters of related spikes (KMeans). The k-means analysis consists of a cluster algorithm with the goal to divide a set of objects into K clusters such that some metric relative to the centroids of the clusters is minimized.

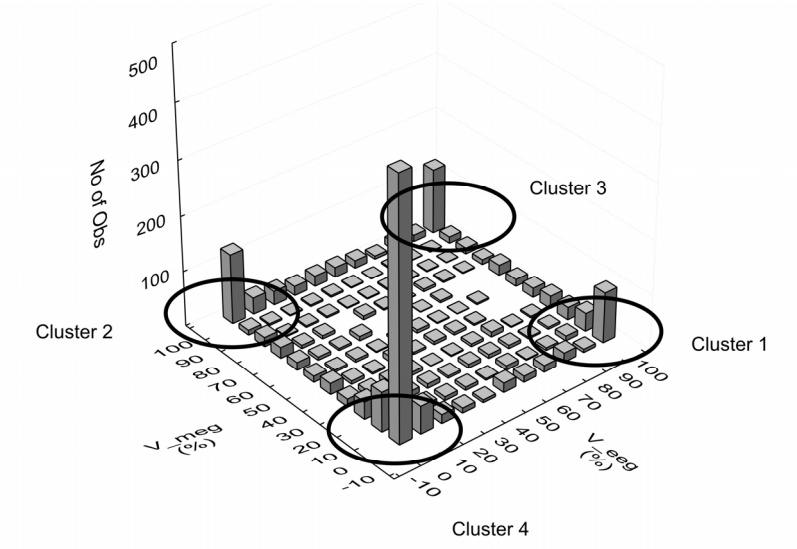


Figure 23 – MESS: bivariate histogram between peeg and pmeg:

Four clear agglomerations are observable. These agglomeration were clearly identified by the k-means clustering method (K=4): cluster 4 for spikes exhibiting low relative power (RP) in both EEG and MEG (bottom), cluster 1 for low RP in EEG and high RP in MEG (right), cluster 2 high RP EEG and low RP in MEG (left) and finally cluster 3 for high RP in both EEG and MEG (on the top).

In the present study, each spike was characterized by its relative power in EEG and MEG and the Euclidean distance metric used. K value selection was performed after histogram topological analysis.

Statistical analysis

To study the discriminant potential of the spike power metrics we analysed the observed patterns statistically. A preliminary test on the normality of the metrics was done using standard normality tests: the Kolmogorov-Smirnov one-sample D statistic (Chakravarti and Roy, 1967) and the Shapiro-Wilks W test (Shapiro and Wilk, 1965) with the null hypothesis that metrics had a normal distribution.The Kruskall-Wallis test (KW) (Siegel and Castellan, 1988) was used in the analysis of variance of between compared groups. It was used to characterise 1) the influence of expert agreement in EEG and MEG and 2) of the KMeans classification in relation to the MESS metrics. The KW is a nonparametric alternative to oneway between groups ANOVA where the null hupothesis is that the different groups were drawn from the distribution or from distributions with same median. Classifications with KW presenting $p < 0.05$ where considered to discriminate statistically different categories.

			EEG (%)			MEG (%)			Both		sEEG		sMEG	
Cluster	N	%	RP	Mn	SD	RP	Mn	SD	N	%	N	%	N	%
1	363	20%	H	86.3	17.8	L	17.8	16.0	11	21	62	21	58	23
2	374	21%	L	14.8	15.6	H	89.3	15.6	9	17	63	22	54	22
3	276	15%	H	90.8	14.9	H	91.7	13.7	16	30	49	17	47	19
4	791	44%	L	7.0	9.9	L	9.0	12.2	17	32	117	40	90	36
Total	1804								53		291		249	

Abreviations : N - number of observations, E- EEG , M- MEG, B- EEG & MEG , RP – relative power, L - Low relative power, H - High relative power, Mn – Mean, SD – standard deviation

Table 7 – MESS: KMeans vs. expert based classification

3.2.2 Results

None of the of metrics exhibited a normal distribution.

The analysis of the variance (KW) over spike metrics in relation to levels of expert agreement in EEG and MEG found that the following metrics were separated in statistically different groups of agreement level (consensus of 1,2 or 3 experts as illustrated in **Figure 24**): in both EEG and MEG: delay between EEG and MEG power (eeg-meg), overall relative power (v_ball) and EEG relative power (v_eeg); in MEG: MEG relative power(v_meg); in EEG and MEG: : overall, EEG and MEG relative power (v_ball, v_eeg and v_meg, respectively) and duration of power peak in both EEG (des) and MEG (dms).

From the observation of the bivariate histogram of the overall spike population (corresponding to spike identified by at least one expert in EEG, in MEG or both) (Figure 23) four clear peaks are visible. Therefore a value of K=4 was used in our clustering (Figure 23): cluster 1 (20%) with high relative power EEG and low relative power in MEG (Figure 23 right); cluster 2 (21% of the spikes) exhibiting low relative power in EEG and high relative power in MEG (Figure 23 left); cluster 3 (15%) for high relative power in both EEG and MEG (Figure 23 upper peak) and cluster 4 (44%) for low relative power in both EEG and MEG (Figure 23 bottom peak). Thus it is worth stressing that 791 of 1804 spikes (44% of total spikes) of the presented average relative power in both EEG and MEG below 10% in relation to the maximum power in the corresponding time interval.

The four clusters identified by the “K-Means” characterized graphically together with the overall population of identified spikes in both relative power patterns and time (Figure

23). From the KMeans classes analysis (Table 7), w**e** **o**bserved relative power metrics variance in KMeans classes clearly more stable and smaller than the overall MESS (Table 6). From the same analysis it is possible to observe that about 40% of all the expert based spike selections were also classified by KMeans in cluster 4, exhibiting low EEG and MEG power spikes.

The analysis of the variance (KW) over KMeans classification over the 6 metrics described in Figure 22 and Table 6 found that the discrimant metrics ($p<0.05$) were relative power related metric (i.e. EEG relative power (v_eeg), MEG relative power (v_meg) and EEG/MEG average relative power (v_ball)) and power peak slope duration in EEG and MEG (i.e. des and dms respectively) and the non-discriminant was the difference between the time of occurrence of EEG and MEG (eeg-meg) despite the low p value of 0.06. The pair-wise chi-square analysis of Kmeans classification with sEEG, sMEG and Both spike classifications was inconclusive in the independence hypothesis for sEEG and sMEG (presented $p>0.05$) and significant for Both set.

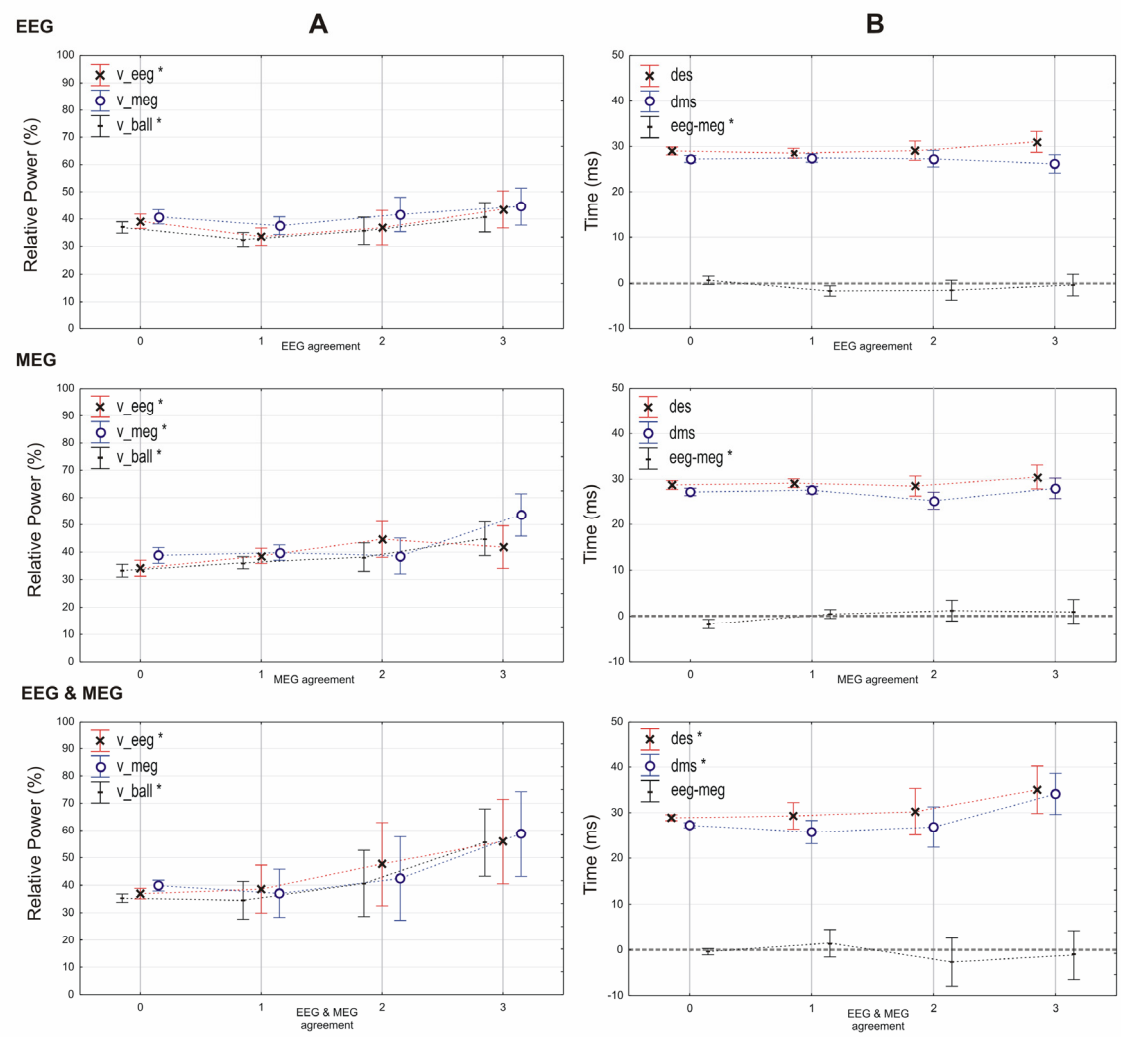
3.2.3 Discussion

The results show that when considering EEG (sEEG) and MEG (sMEG) independently, an increase in consensus identifies spike classes where differences in delays between EEG and MEG peaks and changes in power change are significant (KW $p<0.05$). Curiously, EEG consensus tends to identify, in average, spikes where power MEG peak preceeds the EEG one, whereas in MEG the opposite happens. The clinicians' sensitivity in MEG selections to both EEG and MEG power variations may support previous observations that pointed EEG events concomitant with MEG spikes detections to present a sharper transient therefore less prone to be signaled as a spike (Zijlmans et al., 2002).

The Both set analysis supports the claim of clinicians' sensitivity to power variations both in EEG and MEG, where an increase in expert consensus tends to identify spikes larger and with higher power amplitude.

Several studies performed comparisons between EEG and MEG using a whole-scalp neuromagnetometer (Zijlmans et al., 2002 ; Lin et al., 2003; Iwasaki et al., 2005). All studies perform blind EEG, MEG revision.

(1) Analysis of variance of metrics vs levels of reviewers's agreement



(2) Analysis of variance of metrics vs Kmeans

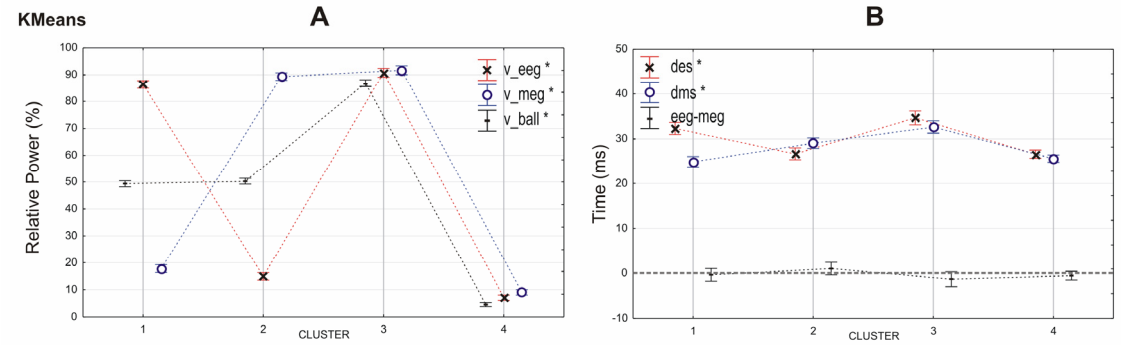


Figure 24 – MESS: Analysis of variance of spike selections

The analysis of variance (Kruskall-Wallis ANOVA) on the influence of (1) the levels of agreement in EEG, MEG and both and (2) on the KMeans classification versus the metric model presented in Figure 22 and Table 6. The significant results for a given metric are signaled with (*) on the graphs ($p<0.05$). The means were weighted by the number of observations. The spreads denote 95% confidence interval. The lines denote the average values. For relative power (A), squares are related to EEG relative power at peak (v_eeg), empty circle to MEG relative power at peak (v_meg) and full circle to average EEG and MEG relative power at peak (v_ball) values. In time related metrics (B), cross relates with EEG onset peak duration (des), empty circle with MEG onset peak duration (dms) and small rectangle to the time lag between EEG and MEG peak (eeg-meg).

Only Zijlmans et al. (Zijlmans et al., 2002) addresses specifically the expert agreement issues but their results cannot be used to assert any conclusion on the validity of MESS. In contrast to our study, Zijlmans et al. aim was to establish the validity of combined approach proposed to ensure a reliable spike selection based on experts for use in source modeling. The study used kappa analysis and template match approach in order to filter "unequivocal" spikes types – consensual spikes between experts (kappa>0.5) grouped according to template.

Both Lin el al. (Lin et al., 2003) and Iwasaki et al. (Iwasaki et al., 2005) addressed the clinical advantages of using interictal EEG vs. MEG spike. Most of their analysis was centred on localization yield. Lin et al. used dipole modeling as localisation reference, while Iwasaki et al. besides source analysis based localization also used, in most cases, surgery outcome as clinical ground truth. In relation to spike selections, they only characterize numerically the numbers and percentages of spikes types - present only in EEG (E), only in MEG (M) or in both (B) - and establish hypothesis on their results. To compare the population relation between EEG and MEG, Lin uses a spike detection index to characterize the E, M and B spikes proportions. While both studies used accepted EEG criteria when detecting "unequivocal" EEG spikes - sharp transient clearly different from background activity with an "epileptiform" morphology and a logical spatial distribution (Chartrian et al., 1974; Cobb, 1983) - in MEG they follow different approaches. Iwasaki et al. applied the same EEG criteria in MEG while Lin et al. used a two steps validation in the MEG selections: first, it only accepts detections MEG spikes that appear in 3-5 spatially closed channels and second, valid detections must present clear dipolar pattern with ECD solutions with a goodness of fit >80% located. In EEG, several montages were used to detect the spikes. Therefore, their results are not comparable.

In contrast to the previous studies, our objective was not to compare the clinical yield between EEG and MEG neither propose a spike filtering method but to establish an objective characterisation of a MESS. The use of a simple power method allowed us to analyse a set of spikes identified by experts in EEG and MEG and to discriminate the existence of 4 clusters that besides being statistically significant, exhibitspecific power related signatures. To associate spike with power peaks is intuitively sound and in agreement with the traditional spike definition where spikes are described as sharp transients that stand out of the surrounding background (Chartrian et al., 1974). In other

studies such approach have been used in order to characterize and detect epileptiform events (Skrandies, 1989 ; 1990; Litt et al., 2001; Van Drongelen et al., 2003 ; Gigola et al., 2004; Esteller et al., 2005; Harrison et al., 2005). For instance, power maxima were already associated with high signal-to-noise ratio epochs and stable activation of brain activity generators (De Munck et al., 2001a).

However, despite power based metrics usefulness to characterize epileptiform spikes, the downside is that overall power may mask complex spatio-temporal spike events. That is the case of localized activations or propagation involving one or more brain areas as illustrated by Ossadtchi et al (Ossadtchi et al., 2004). Ossadtchi showed that stable and localized generators might present apparently unstable signatures with apparently low signal-to-noise ratio. Further work, supported in source analysis, must be done to clarify the relevance of low power signal-to-noise ratio events found in these multi-expert spike selections, namely if they have intrinsically low signal-to-noise ratio, and therefore unreliable, or if the low signal-to-noise ratio is the result of complex spatio-temporal spike related generator interactions, that, due to noise or time power cumulative effect are hidden in the midst of overall brain power changes.

3.2.4 Conclusions

Clinically identified data sets of epileptiform spikes, used without any carefull spatio-temporal context, do not appear to constitute a good spike gold standard reference when based solely in terms of clinical agreement criteria. The results suggest that a gold standard characterisation must contain further information other that clinical agreement, for instance with respect to the localisation of epileptogenic zones obtained independently as it has been shown in several studies (Lantz et al., 2003; Lin et al., 2003; Schwartz et al., 2003; Van't Ent et al., 2003; Ossadtchi et al., 2004; Iwasaki et al., 2005).

Other results suggest the need to use spatio-temporal characterisation such potential maps and spike clustering (Lantz et al., 2003; Van't Ent et al., 2003), component analysis (Schwartz et al., 2003; Ossadtchi et al., 2004), inverse problem solutions (Baillet et al., 2001) combined with overall power features to be able to characterize objectively and distinguishing relevant spike related activity (e.g. propagation involving several localized generators) from noise or non related measured brain activity. Nevertheless we should note that source localisation accuracy is also considered a relative concept, since it depends on

solving the inverse problem that, as generally known, is ill-posed.

3.3 Summary

In this chapter we discussed the impact of the lack of objective definition of clinical entities, more specifically in relation to the spike concept. First, we demonstrated that extensions of EEG definitions to MEG might be abusive as they are morphologically different (Fernandes et al., 2005b). Second, we show that multi-expert's spike selections, although clinically relevant, may be unreliable ground truth for quantified spike characterisation whenever used as spike ground truth based solely in terms of clinical agreement criteria namely as reference either for validation and evaluation of automatic spike detection methods.

4 Inverse problem: a statistical aidded spatial filtering and clustering approach

With evolution in computer and imaging techniques, the analysis of EEG and MEG has gained a new relevance. Through mathematical and computational methods it is possible to extended simple visual "brain waves" analysis (e.g. localize phase reversals, identify interictal discharge, slowing) to more precise methods of anatomical localisation of most probable epileptic activity electric generators (Scherg, 1990; Sutherling et al., 1991 ; Baillet et al., 2001). These methods are considered to be part of electromagnetic source imaging (EMSI) methods (Michel et al., 2004; Wheless et al., 2004). EMSI methods provide a valuable trade-off between temporal and spatial information on brain electrical activity (as seen in chapter 2) when compared to the other modalities, with high temporal

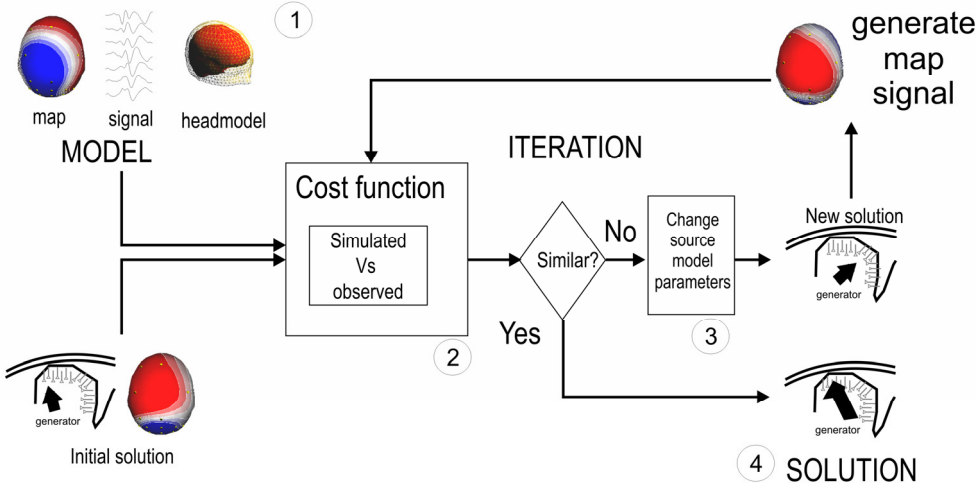


Figure 25 – Inverse problem: an iterative process

To determine the source localisation responsible for the activity in the brain or obtain a map characterisation of overall brain activity (4) is the main objective of the inverse problem. The solutions are obtained commonly through iterative minimization algorithm that, based on a brain model, the observed signal (1) and on a set of operations, explores the various possible brain activity configurations (3). A cost function (2) that penalizes less reliable solutions, can be used to improve the inverse problem results.

resolution associated to EEG and MEG. This is of special interest to EZ localisation.

The main objective of EMSI is to find the active electric generators in the brain responsible for the electromagnetic measures taken at a limited number of points (electrodes) in the scalp or cortex. Unfortunately, EMSI methods do not provide unique generators characterisations since there is no unique characterisation of a given state as different configurations of sources (number, location and direction) can produce the same activity observed at the scalp (Nunez, 1981; Ebersole, 1997 ; Benar et al., 2005).In this chapter a small introduction on EMSI methods is provided and related issues discussed with focus on the EMSI dependence on the clinical events input that support the source analsys process. We propose a simple method supported in unsupervised statistical analysis that tries to overcome data quality / reliability issues and provide unsupervised guidance in results interpretation.

4.1 Mathematical formulation of inverse problem

Mathematically, the inverse problem can be presented as an equation depending on four parameters (Figure 26):

- F is the function that models the contributions of the sources (X) in each individual channel (electrode);
- Y is the measured electromagnetic variations time series (Y) captured at the surface (scalp);

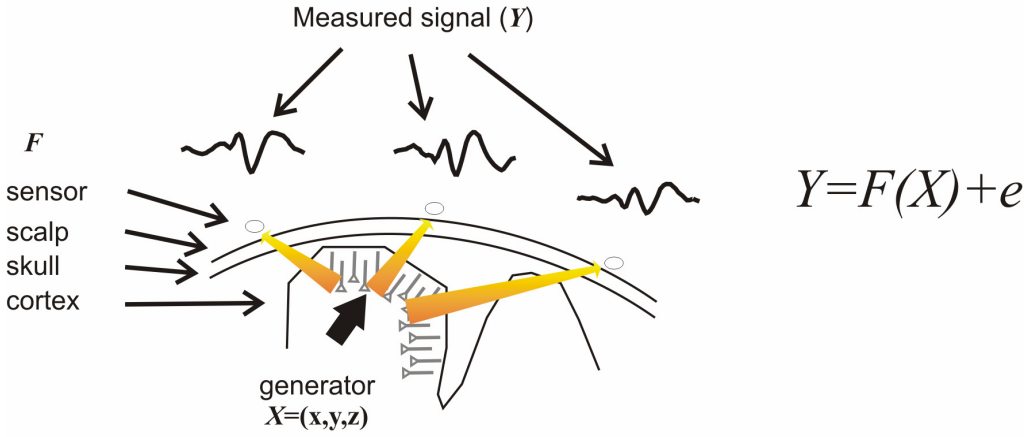


Figure 26 – Inverse problem: a mathematical equation

The Inverse problem solution consist on finding the best source configuration (X) that produces the measured signal (Y), as result of the propagation of the activity to the scalp by traversing the head. Function F models both the sensors and the influence of the different head shells (spatial and electrical properties). As in any measurement processes it is assumed that additive noise (e) is present in the measured signal.

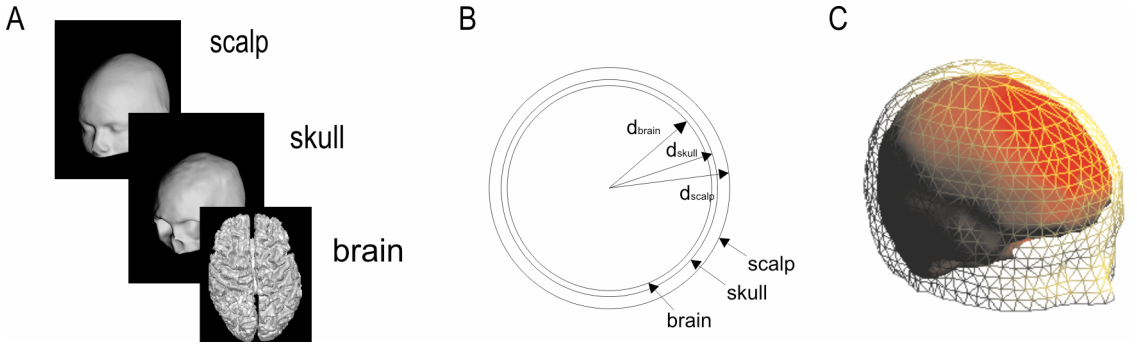


Figure 27 – Head models: from head to spherical and realistic models

The head is constituted by several concentric layers comprising scalp, skull and brain (A). In spherical models (B) the series of concentric brain layers are modelled as concentric spheres with a centre (common to all layers), a radius (dbrain, dskull and dscalp) and respective electrical resistivity (adapted from (Sun, 1997)). In contrast, realistic model (C) from a segmentation of morphology of the head (usually MRI) produce mathematical parameterised surfaces representing each layer.

- the noise (e) that affects the measurement;
- the X is the unknown source configuration that, depending on the method, may be characterized by different parameters/features.

The main aim of the inverse problem is to determine possible generator configurations (X) able to generate the measured activity (Y) in the brain (modelled by F).

This equation has an infinite number of source configurations (X) that generate the same measured EEG and MEG signal (Y) (Hamalainen and Sarvas, 1989; De Munck et al., 2001a) because it is mathematically undetermined. For that reason, the "best" mathematical solutions can be found, usually, through iterative mathematical methods which look for the most reliable solution by imposing constraints according to established criteria (head model, conductivities, and spatial configuration of generators) (Figure 25). The most common option is the least mean squares method (Press et al., 2002).

4.1.1 Head model: the main constraint

The head/brain model is the most important part of the inverse problem equation (Figure 26). First, spatial properties of the head restrict the space of available solutions (brain activity is inside the head in the cortex) and second, the head structure (including tissues) has influence in the electromagnetic measurements on the scalp (Malmivuo et al., 1997). Due to complexity of the head volume, simplified models are often used where two features are of particular relevance:

- spatial characterisation
- electromagnetic properties

Typically the head is modelled as several concentric compartments (Figure 27 (A)): scalp, skull, cortex (the most common) where, depending on the compartment, we can find differences not only on spatial but on physiological properties, namely conductivities.

Since the 1980's simpler representations of the head were used based on simple mathematical approximations using concentric spheres (spherical model) (example in Figure 27 (B))(Nunez, 1981 ; Berg and Scherg, 1994 ; Yvert et al., 1997)

Spherical models are simple to model and estimate (radius for each different layers easily extrapolated from "conventional" proportions) using estimates of the electric properties of each layer (Sun, 1997).

With the advance in computers (processing and capacity) and the evolution of Brain Imaging such as MRI, it started to be manageable to use more accurate and complex head models (one example is presented in Figure 27 (C)). Through segmentation methods (Heinonen et al., 1997; Van't Ent et al., 2001 ; Shan et al., 2002 ; Smith, 2002) it is possible to obtain different head layers (usually represented as 3D meshes that "enclose" each head volume) with a more accurate spatial description. The use of these models brought an increase in the accuracy of inverse problem solutions, when compared with the spherical models (Cuffin, 1990; Cuffin et al., 2001b, a). These models derived from MRI segmentation are often called realistic models (Cuffin, 1995; Zanow and Peters, 1995).

Comparisons between realistic and sphere models have been conducted in EEG (Menninghaus et al., 1994 ; Silva et al., 1999 ; Cuffin et al., 2001a ; 2001b). Results seem to confirm that realistic models offer better accuracy than spherical ones, but imply complex and time consuming procedures (segmentation, electrode position, mathematical computations). For this reasons, spherical models provide a quick way of "looking" into possible generators before starting with more serious analysis using realistic models. This is especially true in MEG, where the volume effects are almost non-existent (Malmivuo et al., 1997 ; Van den Broek et al., 1998 ; Baumgartner et al., 2000a; Baumgartner, 2004).

A compromise between these two approaches is the use of average brain models or atlas based models where all the *a priori* known parameters are pre-calculated according to an average brain spatial model and standard electrode positions. These can be used either in the absence of patient MRI or in preliminary analysis, where time consuming tasks such as segmentation should be avoided. This approach has the advantage of allowing approximated solutions co-registered to brain structure and assess the need for further and

more complete (and time consuming) analysis, including the use of an individual realistic model. The use of brain templates also enables specific template related optimisations that may translate, for instance, in faster calculations. (Pascual-Marqui et al., 2002; Saletu et al., 2005 ; Schimpf et al., 2005).

4.1.2 Head conductivity modelling

Head tissue conductivities models are also essential to model the electromagnetic (essentially electric) properties of the head (Malmivuo et al., 1997). Since the 1960's (Geddes and Baker, 1967) absolute and relative conductivity of different head layers have been established. For several studies, the skull conductivity was assumed to vary between 40 to 90 times of the ratio of conductivity of brain versus scalp (Geddes and Baker, 1967; Homma et al., 1995). Since then, these values have been used as brain conductivity canonical tables. Recently, studies provided more precise measures (Ferree et al., 2000 ; Goncalves et al., 2000 ; Akhtari et al., 2002) that contradict the previous values and show different relations between the head layers. This fact reinforces the need to customize, when possible, the conductivity models to each specific head (Goncalves et al., 2000; Goncalves et al., 2003a).

The most common approaches to model the electrical properties of the brain are the finite elements models (FEM) (Pohlmeier et al., 1997 ; Vanrumste et al., 2001)) and boundary element models (BEM) (Fuchs et al., 2001 ; Van't Ent et al., 2001). These are two different mathematical modelling strategies that integrate both spatial and conductivity data in order to simulate the brain volume and its complex structure. The BEM approach assumes a spatial model delimiting each head compartment (boundaries) and assumes homogeneous conductivies between consecutive layers. In contrast, FEM takes into account local conductivities for its head electric model, which implies more complex and computationally demanding calculations in contrast to BEM models. For simplification, usually a coarse tri-dimensional grid is used for spatially sampling the FEM model local properties.

4.1.3 Position and number of sensors

Another important parameter in the inverse problem is sensor positions. This is needed to accurately model the spatial relationship between sensor and brain activity generators.

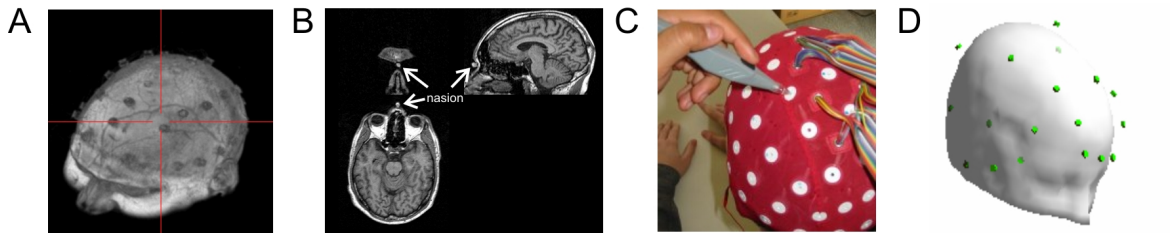


Figure 28 – Sensor: extracting positions on the scalp

The accuracy in sensor positions improves the source analysis results quality. Several methods exist to perform such task: direct identification of sensor in high-resolution MRI (A), interpolation from anatomic markers extracted from MRI (like nasion, sometimes marked by markers like vitamin E) (B), extraction using radio frequency digitizers on the scalp (C) among others. The end result can be used in inverse problem where sensor positions are co-registered with head models (as illustrated in (D))

For that reason, issues like sensor number and location are relevant, as discussed and shown by Michel et al. (Michel et al., 2004). With high-resolution MRI the extraction and identification of sensor position is easier (sometimes using contrast markers such as vitamin E) and ensures spatial consistency between the brain and the sensors location. Another approach, specific to MEG, is able to extract sensor positions through the measurement of magnetic variations versus a fixed reference (De Munck et al., 2001b). Such principle is also used in solutions not specific to MEG, through the use of digitizers and a radio frequency reference (as illustrated in Figure 28).

Some examples of clinical application of previously referred methods are described in both Bast et al. and Pataraia et al. studies (Bast et al., 2004; Pataraia et al., 2004). To avoid tagging all the individual electrodes, some interpolation methods were proposed that extrapolate from a limited set of sensor locations or anatomical references, the remaining sensor locations with reasonable accuracy, which is useful in clinical practice (De Munck et al., 1991; Le et al., 1998).

4.2 Generator models: brain electric sources characterisation

The concept of generator or source is central to the inverse problem. A generator is a spatial abstraction of localized brain electrical activity that is responsible for part/overall of measured brain activity electromagnetic signature. Two types of generator models are commonly used:

- Dipolar models – where the brain activity is the result of the interaction of a finite number of generators (usually few) with precise locations and electric current orientation.

- Distributed source models also referred as imaging based – where no precise modelling is made on the brain activity generators. The target is to obtain the overall electromagnetic characterisation of the brain activity, which might help in finding the underlying brain activity electrical generators.

4.2.1 Dipole model or equivalent dipole model

As summarized by Waldorp (Waldorp, 2004), equivalent current dipoles (ECD) are electrical current abstractions that model the current generated by individual cortical neurons (pyramidal cells) as vectors. Dipoles localisation is in the electrical activity centre of gravity and its orientation is the sum of the individual electric currents orientations (Figure 29). Dipoles are flexible as they allow the modelling of all possible source configurations with a limited number of positions and associated current orientation (Nunez, 1981; Peters and De Munck, 1989).

Dipole based methods assume that a finite and small number of localized sources (dipoles) are responsible (may explain) for a given measured signal (Williamson and Kaufman, 1990 ; Gotman, 2003). The objective is to find the dipole configuration that minimizes the error between the measured and explained signal by the dipole configuration. This is achieved by exploring iteratively the possible dipole configurations (by changing the number of dipoles, location, orientation and magnitude). Iterative methods such as least squares (Press et al., 2002) supported on problem related heuristics and constrains are used to obtain reliable solutions. Thorough and extensive reviews on the

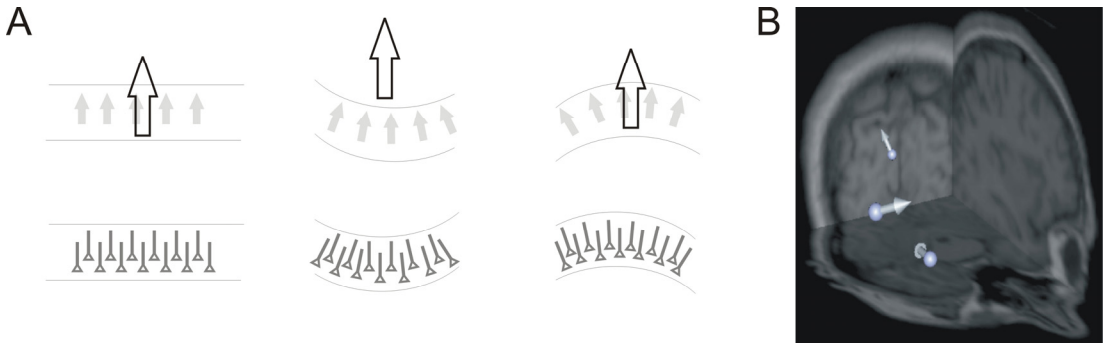


Figure 29 – Source models: equivalent current dipole

Dipoles are a mathematical abstraction of electric activity in localized brain area. Dipoles are represented as vectors with orientation and magnitude, as sum-up of individual localized contributions. However, when interpreting dipoles, it must be considered that (A) different neuron layers configurations share similar dipole representations. When co-registered with MRI, dipoles provide an estimated on the generator position in the brain (B)

existing methods are provided by Baillet et al. and Michel et al. (Baillet et al., 2001 ; Michel et al., 2004).

Simpler dipole model methods only determine instantaneous dipole solutions for given time instants. Examples are the fixed dipole model that assumes the source is fixed in space with varying amplitude or the rotating dipole model that assumes that the source is fixed and can rotate. Spatio-temporal methods extend previous approaches by introducing time in the generator characterisation. They obtain dipole temporal characterisation by simple application of the instantaneous dipole models at each latency in a time interval (Scherg and Von Cramon, 1986) or by using more sophisticated solutions, where dipoles are obtained as the result of location restrictions combined with global spatio-temporal search strategies (De Munck, 1990; Mosher et al., 1992 ; Mosher and Leahy, 1998; Huizenga et al., 2002). Examples are:

- MUSIC and RAP-MUSIC (Mosher et al., 1992 ; Mosher and Leahy, 1998) – look for sources in a pre-established 3D grid and looking for the most probable ones. RAP MUSIC – recursive MUSIC applies the same reasoning over the non-explained signal by MUSIC (Mosher and Leahy, 1998).
- Spatio-temporal multiple source analysis (MSA) – locate iteratively generators through the ECD probes along time and space, trying to explain residuals between measured and model (Scherg et al., 1999).
- Beam forming – local directional filtering of the dipole sources (SAM) is another approach, that besides spatial localisation restrictions constrains the direction of dipole solutions (Sekihara et al., 2001 ; Sekihara et al., 2002)

4.2.2 Distributed source models

Distributed source models (DSM), try to capture its overall brain spatio-temporal variations (Figure 30) instead of finding clear and localized generators as dipoles that explain the brain activity. As sources are not independent, DSM supporters argue that it is not reliable to completely identify all the active generators accurately, being preferable to characterize the overall activation patterns in order to infer from its structure (dipolar maps or hotspots) possible generators. By minimizing the error between the observed brain patterns of activity and the “blurred” activity characterisation, it is possible to obtain brain maps where most probable locations of generators are identifiable (Baillet et al., 2001).

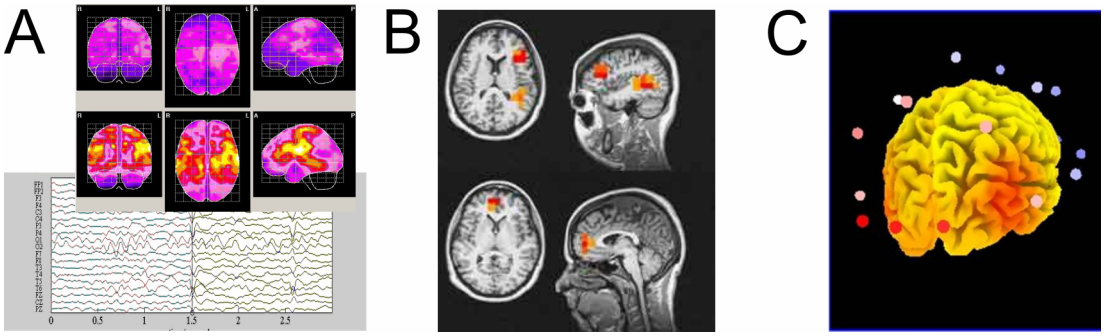


Figure 30 – Source models: distributed source modelling

Distributed source models methods described the overall brain activity as probabilistic maps associated with specific time periods. Extreme values can be associated with the most probable localisations of the activity sources (A) and results are often co-registered over MRI (B) and visualized in three dimensions (C). Examples provided in LORETA website http://www.unizh.ch/keyinst/NewLORETA (Pascual-Marqui et al., 1999).

Some DSM methods obtain such maps by looking for generator configurations while keeping specific brain activity intrinsic properties:

- Cortical distributed source models, try to estimate the amplitudes of a dense set of dipoles distributed at fixed locations within the head volume (Dale and Sereno, 1993).
- Bayesian based methods (Baillet and Garnero, 1997 ; Trujillo-Barreto et al., 2004), by taking into account temporal ("smooth" source evolution) and spatial (brain model) constrains, try to build a probabilistic map that gives the likelihood of a given location being responsible for the observed activity.
- Laplacian weighted minimum norm (LORETA) (Pascual-Marqui et al., 1999) where the map is constrained by assuming it has a smooth spatial distribution (obtained by minimizing the laplacian).
- Epifocus (Grave de Peralta Menendez et al., 2001) assumes the existence of only one focal source in the map solution.
- Minimum norm (Hamalainen and Ilmoniemi, 1994) tries to find solutions that require minimum energy maps.

4.2.3 Different ways of constraining the source analysis

Besides the spatial and functional constraints obtained with the help of MRI or physiological knowledge about brain activity, functional imaging techniques have been

recently used to improve the spatial constraining of possible generator localisation. The hypothesis is that the activation on fMRI is correlated with the epileptogenic activity, and should be spatially linked with the active electric generators. This hypothesis can support the use of the spatial fMRI activations as spatial constrains in source analysis besides brain cortex spatial model (Liu et al., 1998 ; Trujillo-Barreto et al., 2001 ; Grave de Peralta Menendez et al., 2004). However, a recent work by Bagshaw et al (Bagshaw et al., 2005b) questions the validity of such approach by showing that source localisation results may not be spatially overlapped with the associated BOLD response. In this case using fMRI activations as spatial constraints will mislead the source analysis process (Ahlfors and Simpson, 2004).

4.2.4 Accuracy and error estimation

It is important to stress the need to characterize a solution's performance. A typical mathematical approach to this problem is using a measure that compares the real and solution induced electromagnetic fields: the goodness of fit of the solution (GOF), expressed in a percentage, where 100% is the perfect mathematical fit of the solution. However GOF is a mathematical characterisation of an undetermined problem, and a good GOF may not be translated directly to a clinically sound solution. For that reason, relying on clinical judgment and invasive recordings (Kobayashi et al., 2005b) is essential in order to avoid "misleading" solutions. Darvas et al (Darvas et al., 2005) provides a short but thorough review dipole models accuracy assessment.

4.3 Issues of the inverse problem

As seen in the previous sections, inverse problem methods are highly dependent on multiple factors (Michel et al., 2004):

- Head models: spherical, realistic (Cuffin, 1990 ; Menninghaus et al., 1994).
- Conductivity model: BEM / FEM (Pohlmeier et al., 1997; Fuchs et al., 2001) and conductivity (Pohlmeier et al., 1997 ; Goncalves et al., 2003b).
- Sensors: number and location (Michel et al., 2004)
- Data quality: signal-to-noise ratio (SNR) of events.

While the first two issues are method related, the data quality issue is transversal to all of them. For that reason, generic solutions are employed, both as pre-processing and post-

processing, to improve the data related issues in the inverse problem results regardless of the methods specificities. Pre-processing is centred in improving the data quality, including critereous selection and averaging, while post-processing focus is on improving the quality of inverse problem solutions, either by excluding unreliable ones or inferring safer targets from the raw solution set.

4.4 Spatial filtering of dipoles and dipole clustering

Due to noise in electromagnetic measurements or variable background activity, even with sophisticated signal processing filtering techniques, sometimes it is not possible to obtain sharp event signatures. This negatively influences the data SNR and the inverse problem solution quality (Stephen et al., 2003).

Clinical event selections, usually obtained through visual analysis of specific event morphology over are dependent on reviewers experience and difficult to reproduce as illustrated, for example, by Wilson and Emerson review paper (Wilson and Emerson, 2002). For that reason, clinical classification should be combined with multiple information such as maps or source analysis (e.g. (Lantz et al., 2003; Schwartz et al., 2003; Van't Ent et al., 2003; Ossadtchi et al., 2004) in order to provide a quantified and reliable clinical reference.

Averaging similar events is one way of improving the SNR of a data set. As demonstrated in several studies, the averaging of several measured instances of the same brain activity can reveal and enhance EEG related spatial temporal features (time–locked) that were hidden by background activity and/or noise (Yoshinaga et al., 1993; Zijlmans et al., 2002).

This may explain the popular use of averaging of related event EEG/MEG before performing any kind of source analysis (Torres, 1967 ; Rosadini et al., 1974 ; Thickbroom et al., 1986 ; Yoshinaga et al., 1993). However, averaging events implies the existence of a clear event morphological model - to define a similarity criteria - and temporal model common to all events - to establish common time reference - to allow the event alignment without inducing temporal inconsistencies prior to average. This usually requires skilled EEGer intervention in the process.

For that reason, the usage of automatic methods to separate and grouping interictal discharges (IED) using similarity models – spike clustering - is appealing option as it

eliminates the human repetitive task and increases the separation objectivity (Wood et al., 2004), placing the human in a validation and/or a control role through parameter settings (Wilson et al., 1999; Guess and Wilson, 2002). Typically automatic spike clustering consists of statistical clustering methods that are customized to specific event models and classifications, through the use of simple features from simple amplitude and wave slope (Wilson et al., 1999) to more complex spatio-temporal patterns over all available channels of given events (Van't Ent et al., 2003). Lewicki's review on generic spike sorting gives a complete overview on the spike sorting/classification research area (Lewicki, 1998).

The problem with performing the events average is that, besides implying spike grouping by increasing the SNR of spikes (through related spikes averages), averaging reduces events individual amplitude variations and affects the spatial characterisation of the average generator by "hiding" the spatial variance associated to each individual event (Ochi et al., 2001a). For that reason, using individual events in source analysis can provide comparable localisation accuracy (Ochi et al., 2001a ; Chitoku et al., 2003) through the structure of individual IED sources in time and space. From individual event solutions, besides inferring spatial spread of the activity in time, we are able to filter solutions by combining spatial information and known patterns of brain activity, namely artifact related sources/background and IED (Kobayashi et al., 2001 ; Flanagan et al., 2002 ; Chitoku et al., 2003; Flanagan et al., 2003).

Coupled to these observations, the discussion on whether to use average or individual events in source analysis has been a recurrent issue in the literature for several years. Observations were made by several studies using both approaches but no clear conclusion as been reached (Tseng et al., 1995; Ochi et al., 2001a ; Ochi et al., 2001b ; Kobayashi et al., 2002 ; Yoshinaga et al., 2002 ; Chitoku et al., 2003 ; Bast et al., 2004 ; Ossadtchi et al., 2004 ; Whittingstall et al., 2004 ; Kobayashi et al., 2005b).

The objective of the study presented in this chapter is to propose an unsupervised method to support clinical diagnosis based on independent events source analysis combined with a statistical cluster approach. The method is applied in the characterisation of 4 patients suffering from hypothalamic hamartomas related epilepsy. The epilepsy associated with hypothalamic hamartomas (Valdueza et al., 1994) constitutes a syndrome with peculiar seizures, usually refractory to medical therapy, and exhibiting multifocal spike activity in the scalp EEG, in which the origin of spike activity is localized in the

subcortical region in the hamartoma neighbourhood (Munari et al., 1995). The objective was to use the hypothalamic hamartomas clear epileptogenic source localisation to compare the quality and source analysis result accuracy based in a single moving dipole when using (1) average spike events and (2) individual spike events (this study was presented in (Fernandes et al., 2003b, a)).

4.4.1 Material and methods

Data

The evaluation was performed over a population of 4 patients suffering from epileptic seizures related with hypothalamic hamartomas. This population was already addressed in in the study by Leal et al. (Leal et al., 2002) where its findings point the hypothalamic hamartoma vicinity to be the source of the epileptogenic activity in agreement with previous papers, namely (Munari et al., 1995; Berkovic et al., 1997; Kahane et al., 2003) . The summarized clinical characterisation is found in Table 8.

Methods

The interictal EEG data was obtained during video–EEG monitoring (Telefactor Beehive; Zwolle, the Netherlands), lasting from 6 to 48 h. The sampling frequency was 200 Hz and a set of 27 scalp electrodes was used for patient 1, while 32 electrodes were used for all other patients. The EEG was inspected visually using an average reference montage and spikes with a clear distinction from the background and no artifacts were selected for further analysis. A visual classification of spikes was performed, based on the morphology and spatial topography at the peak. As many as three different topography classes were defined to represent all the spike types present in the record of each patient. All EEG epochs were high-pass filtered with a time constant of 0.16 s and a low pass filter of 35 Hz. The spikes for each class were then averaged after synchronization by the peak at the channel with the highest spike amplitude.

Pat	Age (y)	Sex	Background EEG	Spk Activity	Seizure types	Spk	Spk Types
Pat 1	25	M	Slow (7Hz)	Fr/Tp (+R)	PC & As	102	3
Pat 2	11	M	Slow (7.5Hz)	Fr (+R)	Gl, Da & As	47	2
Pat 3	5	F	Normal	Fr (no lat)	PC & tonic	32	2
Pat 4	2	F	Normal	Temporal (R)	Gl & PC	26	2

Tp – Temporal, Fr – Frontal, Gl – Gelastic, PC – Partial Complex, As – astatic, Da – dacristic, Spk – Spike, R – Right

Table 8 – Dipole filtering & clustering: clinical dataset characterisation

Source analysis (moving dipole model) was performed over the interictal spikes using 1) the average spike and 2) the isolated spikes. For both average and isolated spikes the dipole location with best goodness of fit (GOF) were selected, and a comparison performed against each other and against recursively applied multiple signal classification (RAP-MUSIC (Mosher and Leahy, 1998)) reported on a previous publication (Leal et al., 2002). The results of this study are illustrated in Figure 32 where both the RAP-MUSIC and single moving dipole results on average spikes templates are presented.

For enhancing the spatial structure in the individual spikes a statistical cluster analysis method based on Gaussian Mixture Models (Harris et al., 2000) was applied. The cluster method identified dipole spatial agglomerations.

These were later colour coded for visualization (as in Figure 33.).

For each patient the average dipoles and individual dipole cloud locations are presented, mapped on the respective head model (as in Figure 33). The two circles represent the hamartoma vicinity. The first encloses the hamartoma; the second represents a 2 cm vicinity sphere around it.

Source analysis

For the independent dipole solutions, no prior verification on the dipole model was performed over each individual event. To ensure spatial sampling for performing the dipole clustering a minimum of 30 valid dipole solutions was set. For that reason no strict GOF threshold was fixed, and, in contrast with other studies such as (De Munck et al., 2001a; Ochi et al., 2001a ; Chitoku et al., 2003 ; Lin et al., 2003 ; Bast et al., 2005), the GOF threshold value depended on the number of available dipole solutions and on the established spatial sampling limit. As result the GOF threshold varied from 70% to 95%.

	Spk	GOF> 70%	Total (added)	GOF> 70%
Pat 1	102	102	102 (0)	102
Pat 2	47	44	47 (0)	44
Pat 3	32	23	98 (75)	63
Pat 4	26	26	183 (157)	165

Table 9 – Dipole filtering & clustering: dipoles characterisation

In the cases where the number of spike related dipoles above a 70% GOF was below 30, a new spike selection was performed, in order to improve the spike / dipole sampling. This process is described thoroughly in the method section

Table 9 and Figure 31, illustrate the variability in all patients between dipole solutions and their GOF.

To ensure reasonable spatial sampling for performing the dipole clustering a minimum of 30 valid dipole solutions was set and, in patient 3 and 4, a looser spike selection criterion was employed in order to increase the number of spikes and improve the number of dipoles with a GOF over 70%.

4.4.2 Results

In all 4 patients (Figure 33 and Figure 34), the clouds of dipoles mapped the areas pointed by the spike average dipole solutions and agreed with prior clinical findings and hypothesis that points the hamartoma to be the source of epileptogenic activity: 1) the dipole clouds agree with EEG, RAP-MUSIC and average spike moving dipole locations; 2) the spatial spread of the dipole clouds agrees with the direction from dipole solutions in onset to peak of the spike average analysis in RAP-MUSIC and average spike moving dipole.

The statistical clustering was able to identify the main clusters in areas enclosing spike sources types (onset and spike peak) but missed several visible and/or suggestive agglomerations of dipoles. In patient 1 and 2, despite the fact that dipole agglomerations were located near the average events sources (type I in patient 1, type II in patient 2) no cluster was identified by this analysis. In patient 3, there is a group of dipoles that suggest a frontal spread in the hamartoma vicinity, but no cluster was detected. In patient 4, a cloud in the central area is identified as a whole, enclosing the hamartoma neighbourhood. Visually the dipole cloud seems to suggest the existence of two structures in this big cluster group: one around the hamartoma (frontal) and a more central one. The later suggests propagation from the hamartoma to the occipital area.

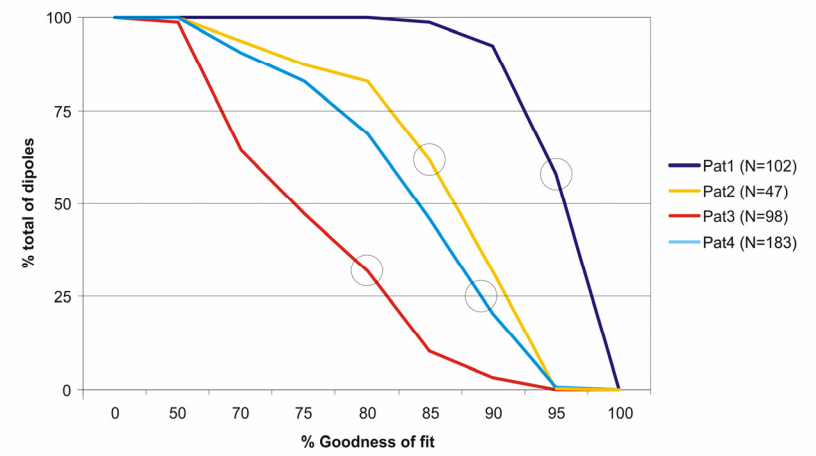


Figure 31 – Dipole filtering & clustering: dipoles goodness of fit distribution

All patients exhibited different dipoles GOF distributions and for ensuring a minimum dipole spatial sampling (at least 30 dipole) different thresholds were used for each patient (circles indicate the 30 dipoles level in relation to total the number of dipoles). A fixed high threshold strategy, for GOF theshold higher than 90%, in the same cases, like in patients 2 and 3, would compromise the dipole sampling limit.

4.4.3 Conclusion

The proposed method, based on the combined use of individual events dipole analysis and a cluster approach, was able to reproduce the clinical diagnosis findings on EEG focus and prior source analysis results (RAP-MUSIC and average spike moving dipole) in our previous study (Leal et al., 2002), identifying and separating the generators without any clinical input. Clinicians take typically more than 30 minutes to perform this separation procedure that is now spared with the propose method.

The localisation hypothesis on the generators position extracted from the dipole agglomerations on generators localisation and on possible propagation patterns were in agreement with the events and clinical analysis and were also comparable with both the analysis over average events and with RAP-MUSIC (Leal et al., 2002) with an increased spatial characterisation. At same time, they provided added information on the spatial spread of the epileptogenic brain activity associated with the hypothalamic hamartoma.

Cluster analysis provided an unbiased method for retrieving a structure from dipole agglomerations without any previous spike selection and identified clusters were consistent with the clinical diagnosis (EEG findings) and prior source analysis results (RAP-MUSIC and average spike moving dipole).

The relaxation of typical pre-requisites of dipole analysis (e.g. stable dipolar maps, good SNR) did not induced loss of accuracy as attested by the agreement found in both averaged

and unaveraged approaches. This option had major benefits: 1) avoided exhaustive events pre-processing visually performed by the clinician, 2) increased the brain source spatial sampling and 3) allowed a more accurate control between the dipole spatial sampling and GOF threshold in the analysis stage. The later was especially relevant, as in contrast with typical usage of static and a strict threshold on the GOF (as illustrated by (De Munck et al., 2001a)), the use of an adaptable GOF filter avoided situations with few or no dipole solutions for analysis in the studied populations. For that reason a looser 70% of GOF criterion was adopted.

The drawback was the sensitivity of cluster analysis to spatial sampling, as illustrated in patient 3 and 4 where visually identified dipole agglomerations were not identified. Nevertheless, in both cases, the visual clusters presented a reduced number of dipoles. No study was performed in order to assert the relationship between this empirical observation and the limited spatial sampling or on the specific characteristics of the used cluster analysis method.

As a final note, our results also support the studies of Chitoku et al. (Chitoku et al., 2003) and Ochi et al. (Ochi et al., 2001a), that show that the process of using average events may conduct to a decrease in the spatial resolution on the dipole solutions and of Kobayashi et al. (Kobayashi et al., 2002) and Yoshinaga et al. (Yoshinaga et al., 1993) where the usage of individual sources is compared favourably against several other localisation methods.

4.5 Summary

In this chapter, we presented an overview on the inverse problem: the mathematical formulation, the generator models, and the methods.

In this context, we proposed an unsupervised EMSI method, based on the combined use of individual events dipole and cluster analysis that was able to reproduce the clinical diagnosis findings on EEG focus and prior source analysis results (RAP-MUSIC and average spike moving dipole) in our previous study (Leal et al., 2002), identifying and separating the generators without any clinical input for separating spike types that saves clinician time, making this approach more “clinician friendly” than others used nowadays.

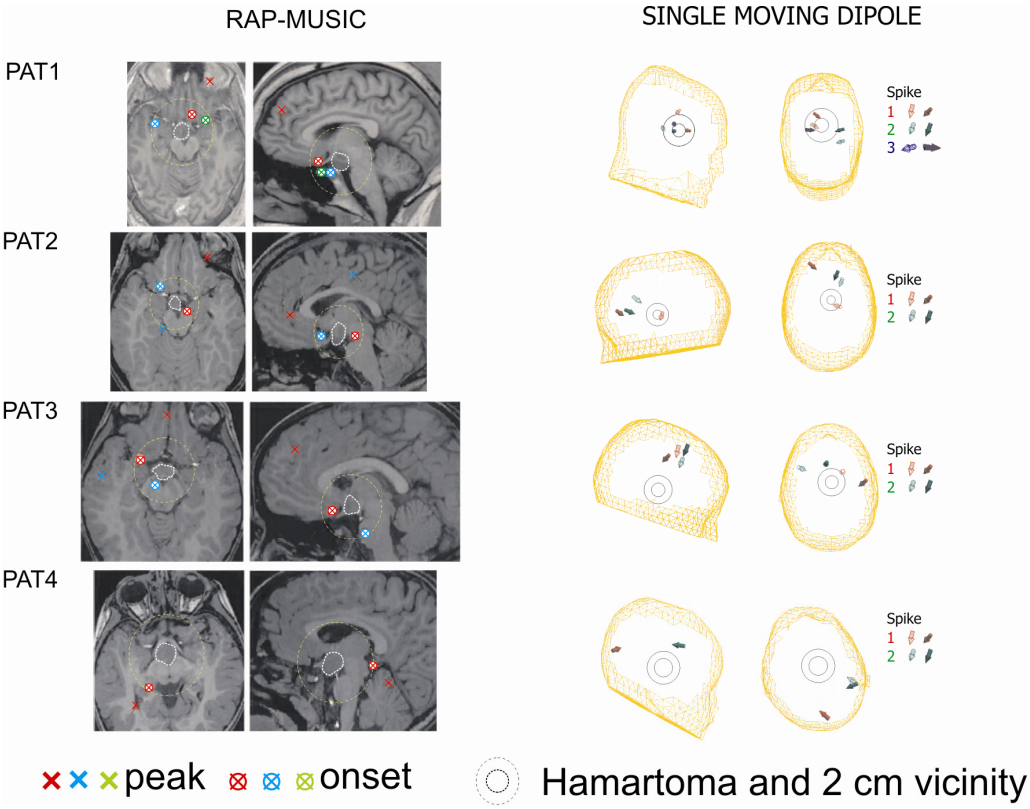


Figure 32 – Dipole filtering & clustering: RAP-MUSIC and SMD solutions

The characterisation of patients by RAP-MUSIC and single moving dipole (SMD) methods. In both methods spike templates are colour coded (type I is spike 1 in red, type II is spike 2 in green and type III is spike 3 in blue). RAP-MUSIC solutions are projected on the axial and sagital planes through the hamartoma centre. The SMD are co-registered over a realistic head model. Concentric circles outline the hamartoma (adapted from (Leal et al., 2002))

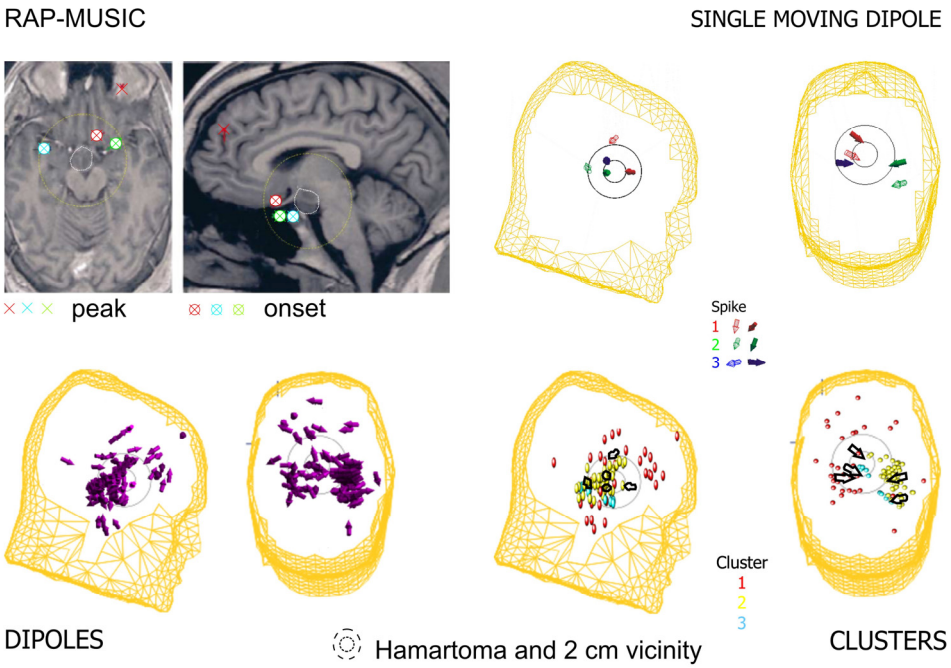


Figure 33 – Dipole filtering & clustering: Detailed description of patient 1

Both dipole clouds and cluster analysis were able to separate spatially the sources identified by RAP-MUSIC and single moving dipole (SMD) in the average spike types analysis (as in Figure 32) – outlined in black over clusters. Dipole cluster are colour coded (in red dipoles non classified or noise). Dipoles presented in best GOF latency. Concentric circles outline the hamartoma.

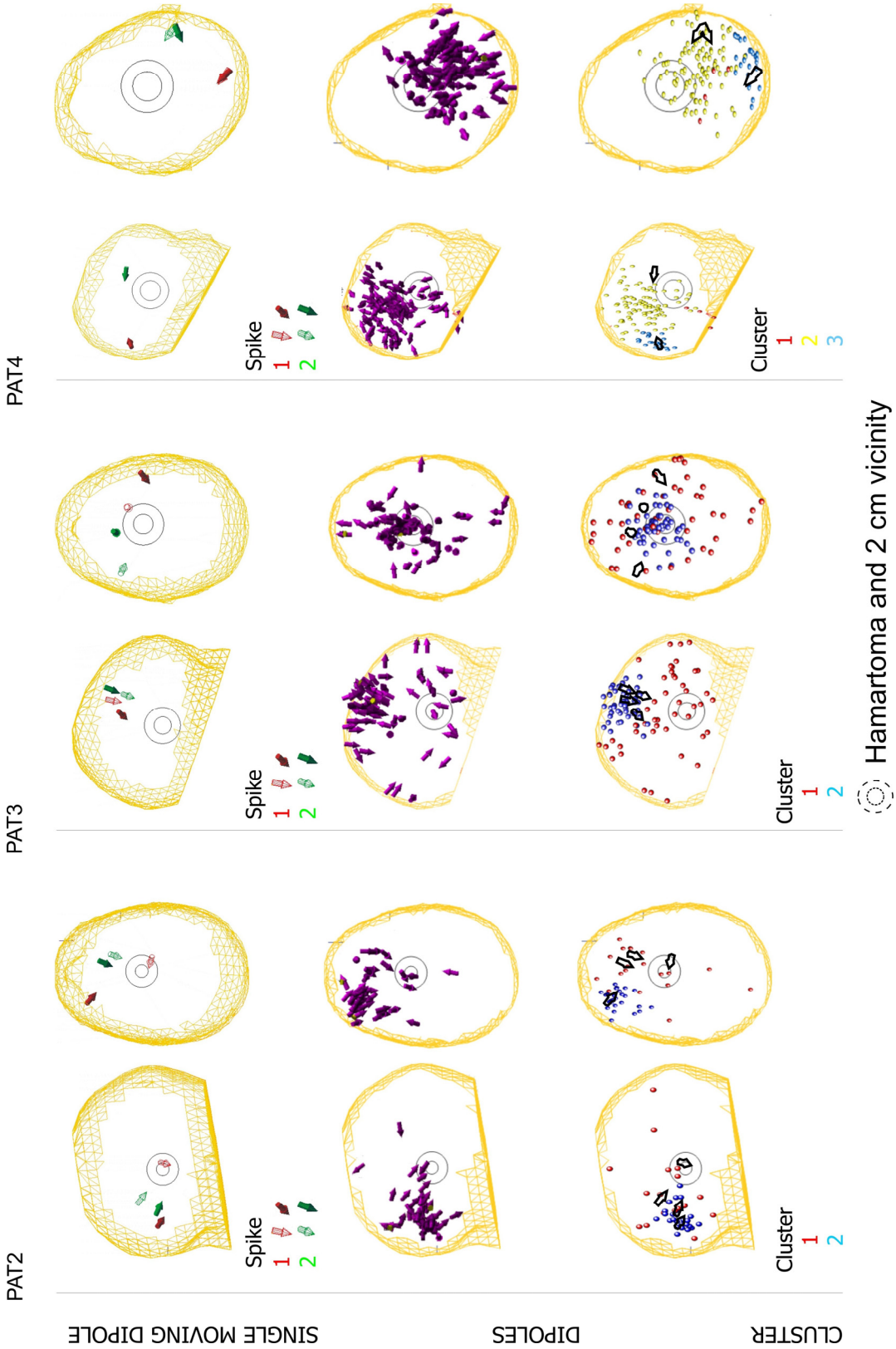


Figure 34 – Dipole filtering & clustering: dipole clouds and clusters results

The dipole characterisation of patient 2, 3 and 4 is presented according to Figure 33. In all patients both cluster agglomeration and cluster analysis provided an unbiased method for retrieving a structure individual dipole analysis that was able to separate the generators identified by both RAP-MUSIC and single moving dipole.

5 *EpiGauss*: a contribution for brain dynamics analysis

The characterisation of the spatio-temporal dynamics of epileptiform brain activity is relevant in the clinical diagnosis of epilepsy. Through the analysis of the scalp EEG, the epileptogenic area can be identified with reasonable accuracy (Ebersole, 1997; Barkley and Baumgartner, 2003; Ebersole and Pedley, 2003; Gotman, 2003). In this context, source analysis can provide further spatial-temporal characterisation of the epileptiform activity related to irritative area (Ebersole, 1997; Baillet et al., 2001; Gotman, 2003). Among the existing source analysis methods, the simplest and most popular model is the single moving dipole (Cuffin, 1985 ; De Munck, 1990 ; Scherg, 1990 ; Baillet et al., 2001 ;

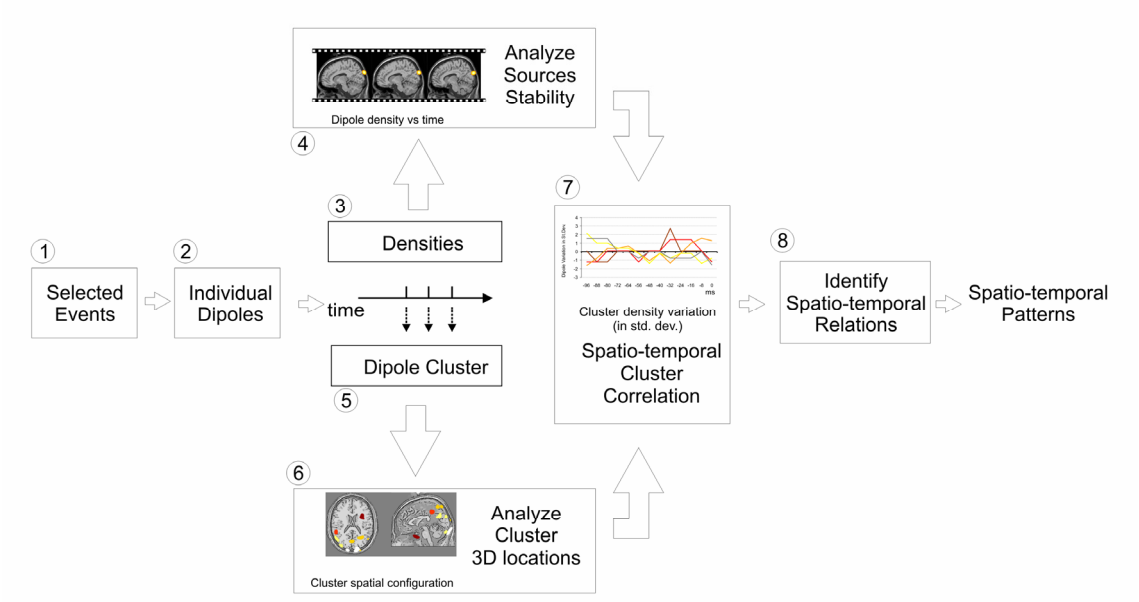


Figure 35 – *EpiGauss*: method layout

For each event (automatically or manually selected) – (1), single moving dipole is fitted (2). From each sample, dipole densities distributions (3) are calculated and their maxima co-registered with the standard head model used in the dipole analysis (4). Cluster analysis is applied (5) to the dipole solutions identifying spatio-temporal dipole clusters (6). The clusters are co-registered with the head model (using a maximum intensity projection) and their density variations (7) are presented as a plot as standard deviations in relation to cluster own average density (y axis) through time (x axis). By combining the cluster spatial configuration (6), the overall density distributions (4) with the spatio-temporal relation between cluster (7) it is possible to identify inter-cluster spatio-temporal relations (8) that may help to infer propagation or activations limited in space and time.

Michel et al., 2004). Dipole models are based on the equivalent current dipole concept, an abstract representation of the mathematical centre of gravity of electric activity (represented as a vector with the orientation and magnitude of the sum of the active electric currents). Dipole models assume that only a few sources are active at a given moment, which can be modelled by a finite (one or more) number of dipoles.

Nevertheless, dipole results may be misleading as dipolar solution only present a mathematical solution (not unique) that explains a given electrical configuration (Ebersole, 1997; Baillet et al., 2001; Gotman, 2003; Michel et al., 2004). For this reason the translation of the dipole solutions to specific brain areas associated to irritative activity has to be done carefully by experts to avoid misinterpretations of the results (Gotman, 2003). This includes being able to verify the reliability of the solutions, their number and stability in the clinical background context through the use of goodness of fit heuristics (Baillet et al., 2001 ; Michel et al., 2004).

The concept of dipole density plot, introduced by Vieth et al. (Vieth et al., 1992; Vieth et al., 1993), extended the simple dipole model adding to discrete dipole solutions a spatial density characterisation. Dipole density plots were used to localize focal abnormal activity (Vieth et al., 1993) and to compare spontaneous slow and fast activity in different brain conditions, such as ischemia and amnesia (Stippich et al., 2000) or schizophrenia (Sperling et al., 1999; Sperling et al., 2002). Dipole density plots were extended to dipole density distributions (DDD) where dipole counts inside a 3D grid mapped into MRI were replaced by 3D convolution with a Gaussian kernel to each dipole location (Sperling et al., 1999). DDDs provide smoother and continuous spatial description of dipole densities. Through DDDs several studies used absolute and relative density maximum to estimate the generators location involved in different brain activity scenarios (Brockhaus et al., 1997 ; Diekmann et al., 1998 ; de Jongh et al., 2001 ; De Munck et al., 2001 ; Fehr et al., 2001 ; Huppertz et al., 2001a ; Fernandez et al., 2004) .

In this chapter we present *EpiGauss* (Fernandes et al., 2006b; Fernandes et al., 2006a), a new unsupervised method that combines both single moving dipole model and dipole density information with 3D spatio-temporal dipole cluster analysis. In this way, spatio-temporal dipole characteristics can be correlated with the scalp EEG events and used to identify visually related spatio-temporal brain activations, namely to estimate localized sources and propagation pathways. The results obtained with *EpiGauss* are co-registered

within a standard 3D MRI head model and are presented in the form of volumes of spatio-temporal dipole density time courses that reflect the dynamics of dipole densities and provide a probabilistic representation of the brain activity. *EpiGauss* results can be used in statistical parametric mapping (SPM) to compare with results obtained using other modalities (Friston et al., 1998).

In this chapter we present the *EpiGauss* method and its application in two different studies: the first approaches a group of 4 patients suffering from hypothalamic hamartoma related epilepsy (section 5.2) and the second addresses a groupd of 6 patients with Early Onset Childhood Occipital Lobe Epilepsy (section 5.4).

5.1 Method

5.1.1 Dipole analysis

In *EpiGauss*, for each selected event, a time reference is selected according to a pre-established event model to be used as time reference. In this study, the focus was on the analysis of epileptiform spikes. The spike onset phase was selected as target and instantaneous power maxima of the spike used as zero time reference. The spike onset phase is the suitable time interval to study the spatio-temporal genesis of spikes (Merlet et al., 1996; Scherg et al., 1999; Huppertz et al., 2001b; Lantz et al., 2003). For each spike, we analysed the 80 ms preceding the spike instantaneous power maximum (the interval of -80ms to 0 ms). The overall alignment process was fully automatic and performed by a computer program we wrote in C++ language.

Single moving dipoles were fitted to each individual event, using a standard realistic head model based on the MNI average brain (Evans et al., 1992; Evans et al., 1993) during the studied interval. The resulting dipoles were analysed in terms of dipole density distributions and of dipole spatio-temporal agglomerations. To identify these dipole agglomerations a statistical cluster analysis method was used. This analysis was in successive equality spaced time intervals of 8 ms (Figure 35 (1)). Dipole calculations were performed using the ASA software and the standard realistic head model and electrode locations contained in it (ASA software, ANT, Enschede, The Netherlands).

5.1.2 Dipole density distributions

For each patient, several DDDs (Vieth et al., 1992; Diekmann et al., 1998) were

calculated from the individual dipole solutions found in the previous phase of the method using a 3D spatial Gaussian kernel with full width half height of 15mm (standard deviation approximately 6 mm) at the position of each individual dipole location. The selection of the full width half height of 15mm was based on several studies that estimates the spatial accuracy of dipole models over EEG using spherical or realistic head models, which ranged from 3 to 17 mm (Zanow and Peters, 1995; Leahy et al., 1998; Krings et al., 1999; Cuffin et al., 2001a ; 2001b; Huppertz et al., 2001b).

For each analysed time sample, an individual DDD were calculated and the spatial location of the volumes of maximum density identified (the third quartile on dipole density distribution was used as a threshold) (Figure 35 (3)). From the co-registration of the maxima location of dipole density for each time sample (Figure 35 (4)) it is possible to follow the trajectories of dipole density maxima along time and identify possible stable sources (spatially limited concentration of maxima at successive time latencies) or help establishing a time relation involving different active brain areas that can be associated with possible propagation pathways. This can be illustrated either as trajectories projections over the head model or as 3D videos showing high dipole density areas changes along time (as illustrated in **Figure 36**).

5.1.3 Cluster analysis

A clustering method based on Gaussian Mixture Models ((Harris et al., 2000) - available in http://www.st-andrews.ac.uk/~wjh/klustawin) was applied on all computed dipole solutions in the studied intervals (no time of occurrence or goodness of fit selection criteria was applied). The clustering method assumes that a mix of clusters, all presenting a Gaussian-like configuration, forms the data. The method finds iteratively the most reliable cluster configuration in terms of number of clusters, cluster shape and overall spatial cluster configuration. The cluster parameters were the default for the method implementation, except the maximum cluster configuration where the maximum of 5 was considered. The best score cluster classification was selected from 100 iterations of the algorithm (method criteria), with number of clusters equal to the mode of all solutions. Clusters presenting multifocal spatial configuration were discarded as noise.

The dipole clusters are characterized according to three different perspectives:

- Cluster spatial configuration where cluster maxima densities are co-registered to

the head model using the maximum intensity projection of the cluster maxima densities (**Figure 35** (6));

- Dipole cluster density variations, where clusters density variations in time (in the x axis) is plotted in standard deviations (in the y axis) in relation to their average density in the analysed interval (Figure 35 (7)). Through identification of localized periods of activity (peaks in density variations) or significant variations (above 2 standard deviations in relation to average density in the time interval analysed) it is possible to map EEG changes through cluster related brain areas;
- Significant relations between cluster density variations and spatial relation between clusters may identify the existence of spatio-temporal dependencies between dipole clusters and may suggest propagation.

5.1.4 *EpiGauss* Interpretation

From the joint analysis of the cluster spatial configuration (**Figure 35** (6)), the cluster density variation plot (**Figure 35** (7)), relation analysis between cluster density variations and dipole density maxima spatio-temporal trajectories in time (**Figure 35** (4)) it is possible to infer spatio-temporal limited events, spatio-temporal relation between active brain areas and to suggest possible propagation pathways (as illustrated in **Figure 36**).

As shown in previous studies (Filipe et al., 1989; Wong, 1990; Bertashius, 1991; Cunha et al., 1991; Martins da Silva and Cunha, 1994) correlation analysis infers time dependencies that can be associated to brain activity propagation pathways. In *EpiGauss* the same reasoning was applied to study the inter-cluster density variation correlations. This is possible by combining the cluster densities time courses and their spatial relation. As illustrated in **Figure 36** it is possible to identify related clusters propagation by combining the linear correlation r (or *Pearson*'s r) (Press et al., 2002) between clusters temporal dipole density variation with their spatial features. In the present study, only inter-cluster correlation values above 70% were considered in the analysis.

Dipole density maxima spatio-temporal trajectories, although not translating directly the location of the brain active generators, give a probabilistic representation of the sum-up of individual active generators along time. The trajectories provide a spatio-temporal characterisation of the evolution in time of the "strength" of each clusters in terms of dipole density fluctuations.

These changes can help identifying:

- stable sources – cluster with stable dipole density mapped by dipole density maxima trajectory for limited time may point to a relevant brain activity source;
- fluctuaction in activity between clusters related brain areas, complementing dipole density correlation information – cluster density variations consistent with changes in dipole density maxima trajectories may a point to a shift in brain activity.

To illustrate the method results we will use a patient with Early Onset Childhood Occipital Lobe Epilepsy (Ferrie et al., 1997; Lada et al., 2003 ; Taylor et al., 2003; Ferrie et al., 2006). The detailed clinical characterisation can be seen in Table 11 – patient 1. *EpiGauss*'s results (Table 12 and **Figure 36**) suggest the hypothesis of propagation from occipital poles to occipital parietal areas where the EEG focus was identified.

This is supported by apparent propagation between cluster 3 and 5 (occipital poles) to cluster 2 and 4 (occipital parietal areas) which is reasonable: 1) cluster are located in both areas ,2) cluster 2 densities are negatively correlated cluster 3 densities (linear correlation r=-0.8 delay=0ms) and 3) cluster 2 maximum densities occurs first. Also propagation from cluster 2 to 4 (linear correlation r=0.9, delay=16ms) is plausible as, besides being spatially close, their density peaks are in sequence (-16 ms and 0 ms). The dipole density maxima trajectories do not contradict these hypotheses, involving the identified cluster areas in the same temporal sequence. These findings are not easy to extract directly from the EEG - illustrated by cluster related spike averages (**Figure 36** - E) – even when guided by the information extracted from the dipole density analysis.

5.2 Discussion and conclusion

EpiGauss method aims to be simple and usable in clinical environment and present objective contributions for clinical use:

- depends on reduced inputs, namely EEG event detections or pre-calculated dipole solutions as (x,y,z) locations;
- is an unsupervised method as it uses:
  - objective time references (spike power maxima) for event alignment;
  - single moving dipole model, a model with no *a priori* assumptions;
  - unsupervised cluster analysis to classify results;
- saves time by eliminating the spike separation needed in other methods;

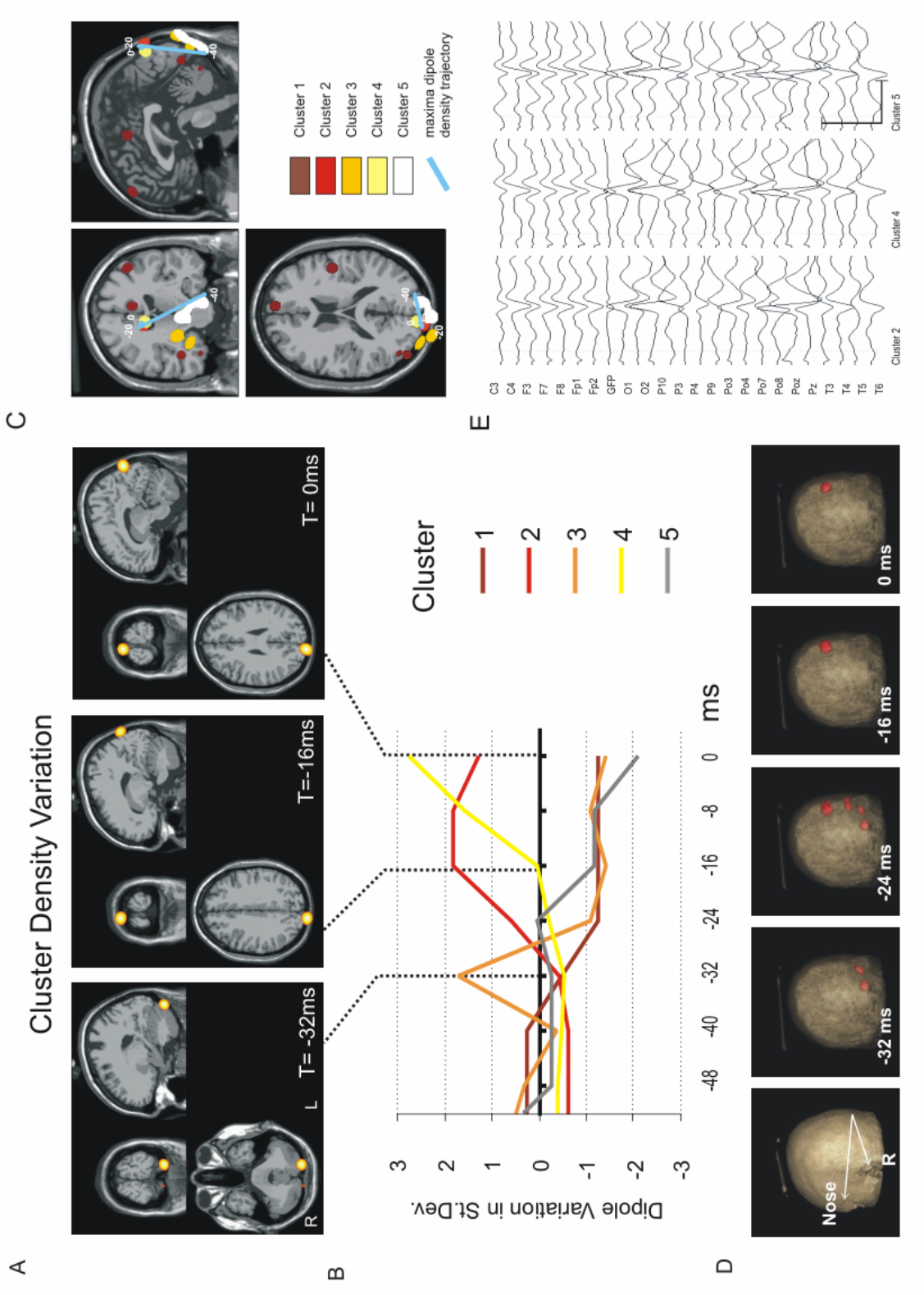


Figure 36 – *EpiGauss*: results illustration

Cluster dipole density variations in time (B) when related with overall dipole densities maxima trajectory (A) may be used to support spatio-temporal hypothesis over the cluster configurations. By associating clusters positions with specific dipole density maxima in time it is possible to identify stable sources and possible propagation pathways. The combination of clusters and the overall dipole densities maxima either as trajectories (C) or as 3D video (D) - where areas of high density can be observed through time - enables more intuitive analysis. Cluster dipole density variations can also be used to infer intra- and inter-cluster features (B) namely through linear correlation (*Pearson's* r). The EEG scale horizontal in (E): 200ms vertical: 200 μV.

- provides quantified and objective information:
    - Clusters with spatial and temporal information – the overall dipole density and the dipole densities in time;
    - Correlations coefficients and time lag relating cluster in time and space;
- intuitive visualization using dipole densities presents results in a familiar way for Brain Imaging users.

By being based on simple and objective time references, on reduced inputs, on single moving dipoles and accompanied by intuitive visualization, *EpiGauss* is able to reduce user interactions saving time. Naturally *EpiGauss* automation (involved several options that will be discussed next) suggests that it may be a good approach in exploratory EEG analysis. *EpiGauss'*s results can also be a complement to be integrated with other information (electrophysiological information from EEG, morphological from MRI and clinical) in order to understand more complex spatio-temporal brain activity patterns. With support of a computational framework, more intuitive visualization can also be used to observe the spatio-temporal patterns as movies in three dimensions.

Through the use of a simple event model with a reliable time reference (the spike power maxima) it was possible to establish clear time reference for overall spatio-temporal brain activity characterisation based on single events analysis. At the same time, the use of such time reference allowed a fully automated and unsupervised analysis process and event alignment which is useful in a clinical environment.

The use of a standard model - the MNI standard head model (Evans et al., 1992; Evans et al., 1993) – represents a tradeoff between *EpiGauss*'s clinical usability and the use of personalised realistic head models. The increase in accuracy obtained through personalised head model is neglible when contextualized with *EpiGauss*'s independence on both the existence of MRI and expertise to segment the realistic head model.

Single moving dipole usage in *EpiGauss* as a sampling method to characterize spatial fluctuations of brain electrical activity along time has the advantage of providing simple solutions (individual dipole) that can be used to obtain a probabilistic characterisation - through dipole densities - and to capture spatio-temporal source structure - through cluster analysis finding related dipole agglomeration. The use of individual single dipole solutions also enables a clear map between EEG events and dipole solutions. This allows relating all dipole information (e.g. dipole densities, dipole locations, cluster maximum densities) with

EEG events that, combined, can be later interpreted and used in clinical diagnosis, namely relating events with active brain ares in space and time. On the other hand, single moving dipole model is recurrently referred to be suspectibile to misrepresent complex sources configurations (Ebersole, 1997). Our assumption is that, if the selection of events is representative of the overall brain electrical activity, single moving dipole solutions will reflect the weight of active sources along time and provide probabilistic description that will be further enhanced by the combination of both dipole cluster and dipole density maxima. For these reasons, *EpiGauss* statistical stability is highly dependent on the dipole sampling and on the number of events analysed.

EpiGauss's use of dipole densities represents an evolution on the discrete dipole characterisation. Dipole densities, provide a 3D smoothed spatio-temporal histogram of dipole densities in contrast to the discrete characterisation in Ossadtchi et al.. Besides enabling the extraction of features, such as quartiles, modes or maxima, densities can be used as intuitive references in the identification of areas of interest and in the intra and inter subject density comparisons (Sperling et al., 1999b; Stippich et al., 2000; Sperling et al., 2002). Examples are Z-scores based filtering and statistical parametric mapping (SPM) with other statistical maps namely those used in fMRI (Friston et al., 1998). This DDD *EpiGauss* usage is a step ahead from previous studies (Vieth et al., 1992 ; Vieth et al., 1993 ; Brockhaus et al., 1997 ; Diekmann et al., 1998 ; De Jongh et al., 2001 ; De Munck et al., 2001a ; Fehr et al., 2001; Huppertz et al., 2001b ; Fernandez et al., 2004) where high dipole densities were only associated to areas of interest related with the studied activity.

When compared with other EMSI methods used to characterise brain active generators associated to epileptiform events, *EpiGauss* is an unsupervised method that only relies on single moving dipole and cluster analysis to obtain a probabilistic spatio-temporal characterisation from dipole solutions – dipole clusters and dipole densities. Being unsupervised, is a good approach in exploratory EEG analysis and a complement to be integrated with other information (electrophysiological information from EEG, morphological from MRI and clinical) in order to understand more complex spatio-temporal brain activity patterns. With support of a computational framework we have developed, more intuitive visualization can also be used to observe the spatio-temporal patterns as movies in three dimensions.

Similarly to other methods (Lantz et al., 2003; Schwartz et al., 2003; Ossadtchi et al., 2004), *EpiGauss*, is able to identify features that can be directly interpreted by clinicians based only on clinical expertise and not on technical skills. These features can help identifying and explaining more complex spatio-temporal patterns. Nevertheless, in contrast with other studies (Lantz et al., 2003; Schwartz et al., 2003), based on reasoning over probabilistic maps that characterize overall brain activity, *EpiGauss* employs the single moving dipole solutions as a discrete and biased sampling method towards the fluctuations of the epileptiform brain activity centre of gravity.

EpiGauss probalistic characterisation is similar to distributed source model methods (Michel et al., 2004) such as LORETA (Pascual-Marqui et al., 1999), minimum norm (Hamalainen and Ilmoniemi, 1994), LAURA (Grave de Peralta Menendez et al., 2001) or EpiFOCUS (Grave de Peralta Menendez et al., 2001) among others. But, in contrast to distributed source models, *EpiGauss* provides a probabilistic spatio-temporal characterisation of brain activity avoiding any mathematical manipulation or parametrisation. Distributed source models tend to be highly dependent on mathematical operations, without any physiological basis, to ensure convergence on usable solutions and, as suggested by Michel et al. (Michel et al., 2004), obtained solutions should be taken with caution. Some examples are assumption on smoothness (Pascual-Marqui et al., 1999), energy distribution (Hamalainen and Ilmoniemi, 1994), spatial constraints (e.g. activity limited to cortex surface (Hamalainen and Ilmoniemi, 1994)) or the existence of localized focal activity (Grave de Peralta Menendez et al., 2001)).

Our results reinforce the role of EEG and source analysis in the extraction of spatio-temporal features from brain activity. Although the current trend in spatio-temporal characterisation of the brain epileptiform activity is based on fMRI studies (sometimes combined with EEG) (Salek-Haddadi et al., 2003), EEG on its own still provides a superior time resolution in comparison with fMRI (Benar et al., 2002; Salek-Haddadi et al., 2003), with enough spatial resolution for diagnose and a clear epileptogenicity criteria . This is not true in functional techniques such as fMRI, where, besides the absence of a clear model relating BOLD effect and electrical brain activity (Benar et al., 2002; Bagshaw et al., 2004; Handwerker et al., 2004; Bagshaw et al., 2006), the analysis results involves an high degree of expertise (Friston et al., 2000; Gotman et al., 2004; Marchini and Presanis, 2004; Kobayashi et al., 2005a).

Pat	Age (y)	Sex	Spk Activity	Seizure	Spk (N)	Spk Types
1	25	M	Ft/Tp (R)	PC & As	110	3
2	11	M	Frontal (R)	G, Da & As	49	2
3	5	F	Fr (NI)	PC & tonic	34	2
4	2	F	Tp (R)	G & PC	26	2

Pat – patient, Spk – spike; Localisation: Fr – Frontal, Tp – Temporal, R – Right, L – Left, NI – No lateralization; Seizure type: PC – Partial Complex, G – Gelastic, As – Astatic, Da – dacristic

Table 10 – *EpiGauss* & HH: clinical da taset characterisation

5.3 Hypothalamic Hamartoma: the focus localisation[3]

In this section, *EpiGauss* is used to study the epileptiform brain activity in 4 patients suffering to hypothalamic hamartoma related epilepsy by analysing the spatio-temporal patterns on the onset phase of detected interictal spikes.

The epilepsy associated with hypothalamic hamartomas (HH) (Valdueza et al., 1994; Nguyen et al., 2003) constitutes a rare syndrome with peculiar seizures, usually refractory to medical therapy, presenting multifocal spike activity in the scalp EEG. HH has the peculiarity of providing an optimum validation model as it is established that the only origin of epileptiform activity is the hamartoma itself (Berkovic et al., 1997; Kahane et al., 2003; Leal et al., 2003). In this study, four patients with HH related epilepsy that were already studied previously by our group (Leal et al., 2002) were evaluated using *EpiGauss* method.

5.3.1 Datasets

The interictal EEG data was obtained during video–EEG monitoring (Telefactor Beehive; Zwolle, the Netherlands), lasting from 6 to 48 h. The sampling frequency was 200 Hz and a set of 27 scalp electrodes was used for patient 1, while 32 were used for all other patients. The EEG was inspected visually using an average reference montage and a total of 219 spikes with a clear distinction from the background and no artifacts were

[3] Published as Fernandes, J.M., Leal, A.J.R., Cunha, J.P.S. (2006b). EpiGauss: spatio-temporal characterization of epiletogenic activity applied to hypothalamic hamartomas. In:Campilho, A., Kamel, M. Eds, Image analysis and recognition, International conference ICIAR 2006 *Lecture Notes in Computer Science* 4142, Springer, Berlin, pp 680-690.

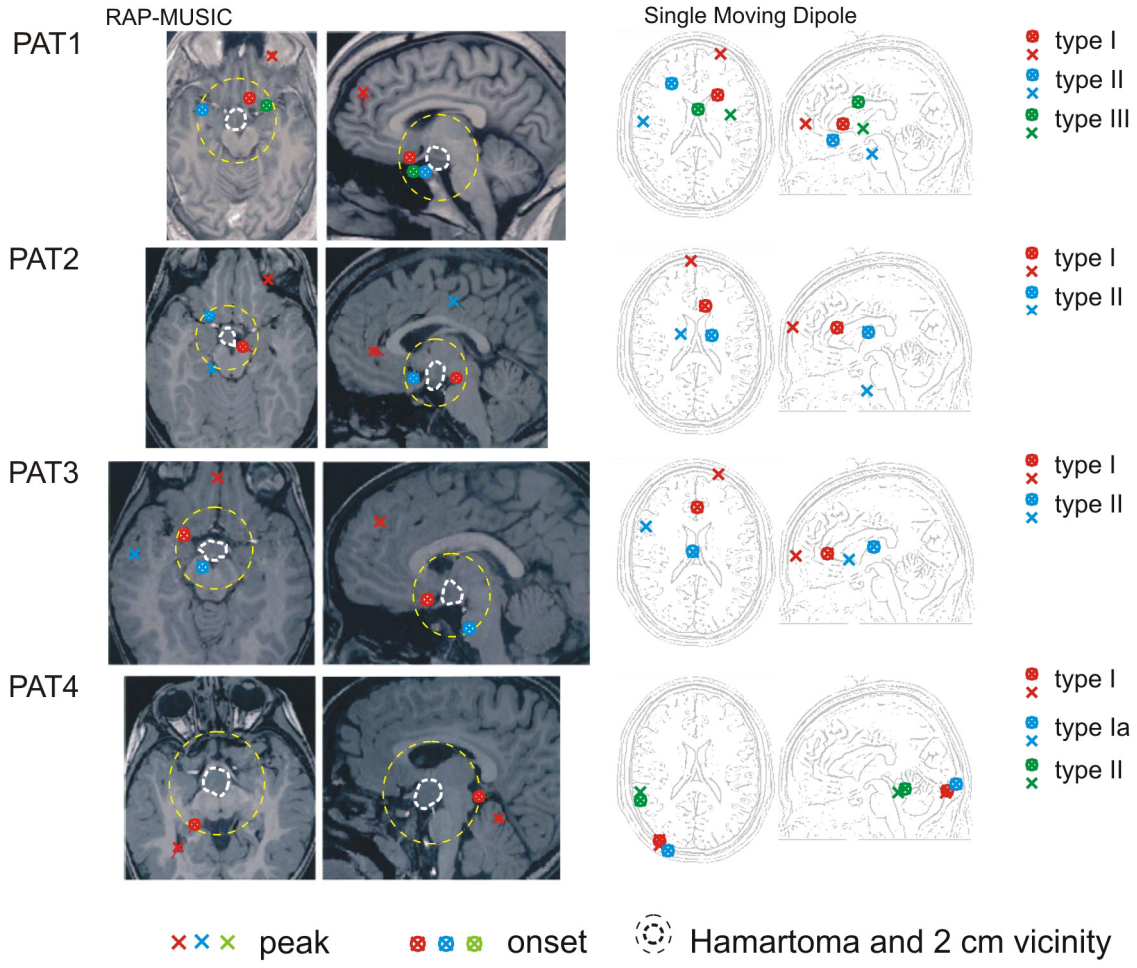


Figure 37 - *EpiGauss* & HH: RAP-MUSIC and single moving dipole analysis.

In both the RAP-MUSIC and Single Moving Dipoles (SMD) solutions of the spike type averages the sources are presented at the onset (with circle) and peak (no circle) of the spike. In the RAP-MUSIC the sources are co-registered over the patient MRI and in the SMD over the standard head model used (adapted from (Leal et al., 2002)).

selected by a senior EEGer (AL) for further analysis. The clinical and dataset characterisation can be found in Table 10.

A visual classification of spikes was performed, based on the morphology and spatial topography at the peak. This visual selection resulted on the identification of a set of multichannel spikes that were divided into different spike type classes organized according to their topography as previously reported (Leal et al., 2002). Instantaneous power profile was then computed and their maxima were used as *EpiGauss* time reference. Averages of each spike type classes were generated using this time reference. For each individual spike and spike type averages, Single Moving Dipole model (SMD) were fitted using a standard head model (ASA software, ANT, Enschede, The Netherlands) during a 100 ms interval

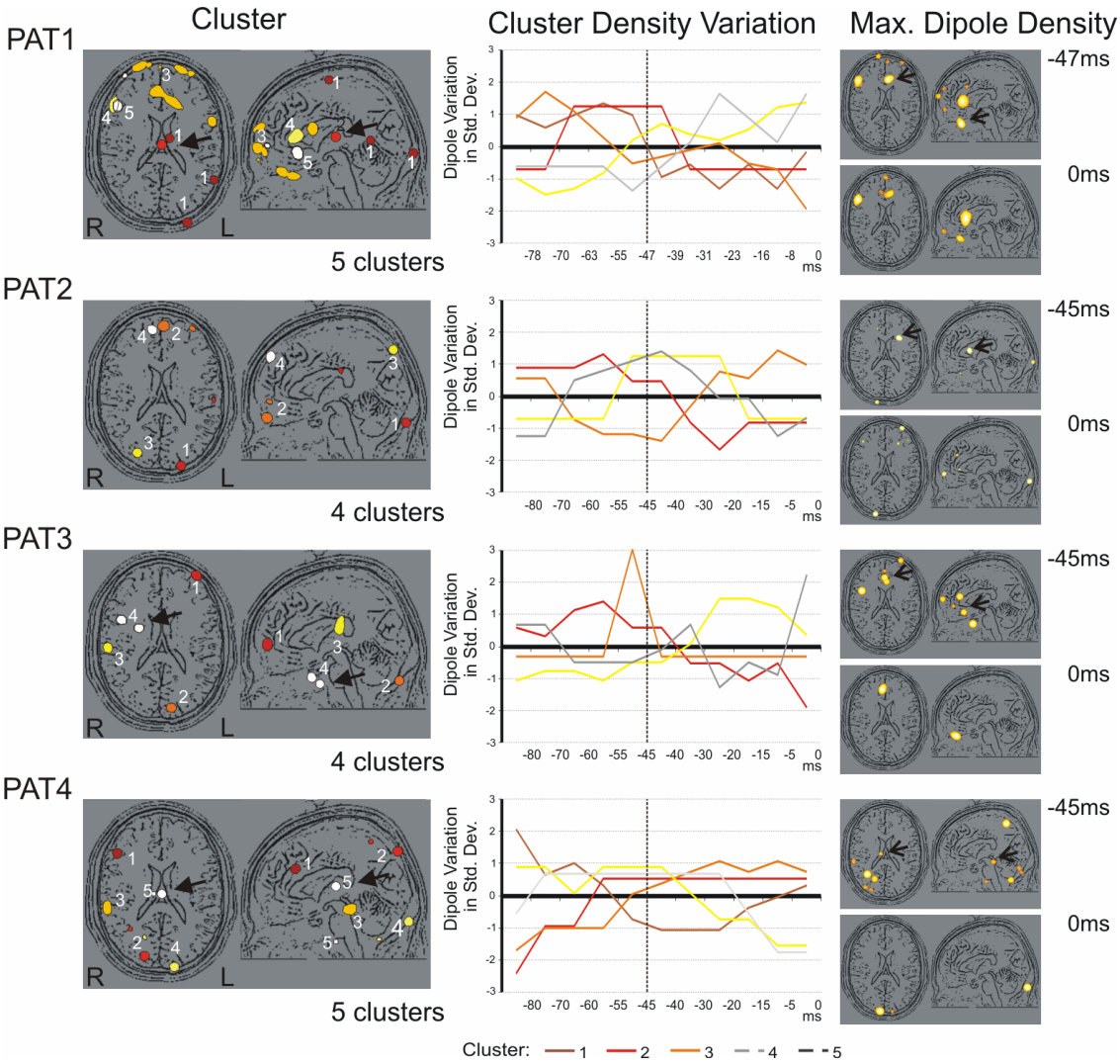


Figure 38 – *EpiGauss* & HH: patients spatio-temporal characterisation.

From the cluster spatial distribution and their dipole density (DD) variation patterns it was possible to infer propagations between occipital polar area and parieto and high occipital areas in all patients (more clear in patients 1 and 2). In multifocal patients clear inter hemispheric propagation was detected. From the overall DDs, posterior occipital lobes maximum DD was observed in all patients (between -64 ms and -32 ms before the spike power peak – t=48ms shown) regardless of the specific propagation patterns observed in each patient independently of the main activity observed in the EEG (t=0ms). These maximum were clearly mapped by dipole clusters in all cases. Also propagation along the occipital parietal was observed (more clear in patients 1 and 2). To note that the use of an head model for adults in a group of children (average 4.8 years) was taken into account in the spatial analysis of both clusters and dipole densities.

enclosing the onset spike phase to the highest EEG instantaneous power latency nearer the spike peak (-100 ms to 0 ms at power peak). The resulting dipoles were analysed according to the *EpiGauss* method. The analysis was done in successive intervals of 8 ms.

5.3.2 Results

The result from the SMD and RAP-MUSIC analysis (Leal et al., 2002) are presented in Figure 37 while the *EpiGauss* results on the same patients are presented in Figure 38. In patient 1, a deep source (cluster 2) was found. The frontal (cluster 3) and temporal (cluster 4 and 5) locations of the clusters agree with the observed spike activity and with both SMD and RAP-MUSIC results: cluster 3 captures the apparent propagation observed in type I and III spikes, cluster 4 and 5 the ones of type II.

In patient 2, a stable deep activity is detected between -60 ms and -20 ms. Cluster 2 suggests a strong propagation to the frontal left area starting at -30 ms. Cluster 4 identifies activation in the frontal area in between -60 ms and -20. The clusters findings agree with the EEG and both SMD and RAP-MUSIC results (cluster 4 describes type I and cluster 2 the type II spikes). Although the analysis of the cluster and dipole densities identified a stable deep source, a consistent spatio-temporal cluster in the respective location was not found.

In patient 3, a deep source is active around -45 to 40 ms. Cluster 4 suggests a later propagation to surface after -15ms. A later frontal activation is observed (cluster 1 and later density increases at 0ms). The clusters agree with the EEG, SMD and RAP-MUSIC: cluster 3 and 4 describes type I and cluster 1 the type II spikes. The time activations in cluster 1, 3 and 4 suggest independence between temporal right and frontal left areas.

In patient 4, a deep source is found between -80 ms and -20 ms as cluster 5. The analysis suggests an early activation in occipital (cluster 4) and occipital parietal (cluster 2) areas followed by activity in the right occipital temporal areas (cluster 3). As in the previous cases, the clusters agree with the EEG, SMD and RAP-MUSIC results: cluster 2/4 describe type I/Ia and cluster 3 the type II spikes.

Although in some cases the deep source was not clearly captured by the identified clusters (patient 2) from the observation of the dynamics on dipole density along time all patients exhibited deep activations around –45 ms before spikes power maximum with later spread to surface. The clusters at surface (Figure 38) identified the observed spike activity location (Table 10) and were also in agreement with the previous source analysis results. In all four patients the clusters characterized consistently the sources found in the scalp EEG by RAP-MUSIC and SMD of average spike type sources (Figure 37).

5.3.3 Discussion and conclusions

The *EpiGauss* was used in the characterisation of epileptiform brain activity in patients suffering from HH related epilepsy through the analysis of the onset phase of interictal spikes. Despite its rare occurrence (Nguyen et al., 2003), HH related epilepsy provides one of the clearest models both for source location and propagation pathways of epileptic electrical activity. First, it is well established that the only epileptiform brain activity source is the hamartoma itself (Berkovic et al., 1997; Kahane et al., 2003; Leal et al., 2003) and second, it provides a clear propagation hypothesis: from the HH to the scalp EEG localized focus.

In all the four patients, *EpiGauss* localized origins in deep source consistent with the HH location, active around –45 ms before the spike peak occurrence with later propagation to the surface. The surface clusters were in agreement with the spike activity observed in EEG.

EpiGauss was compared with two different source analysis methods: SMD on average of spike types and RAP-MUSIC (Leal et al., 2002). For a reliable comparison, SMD results were used as common reference between RAP-MUSIC and *EpiGauss* results, and therefore they were recalculated using the same standard head model. The *EpiGauss* results are consistent with the locations found in RAP-MUSIC and SMD spike types in every patient. This was confirmed by comparing the clusters spatial characterisation with EEG findings, RAP-MUSIC and SMD results over average spikes types.

5.4 Occipital Lobe Epilepsy: a stable source in occipital pole

In the this section we want to assert if *EpiGauss* is able to provide an added value in source localisation and propagation information in relation to traditional EEG visual inspection in 6 children suffering of Occipital Lobe Epilepsy (OLE) (Ferrie et al., 1997; Lada et al., 2003 ; Taylor et al., 2003; Ferrie et al., 2006). OLE is an epileptic syndrome with a clear clinical and semiological characterisation but with heterogeneous EEG activity patterns, therefore, the ideal target to perform a thorough *EpiGauss* comparison with EEG visual analysis results. The analysis was focused on the spike onset phase where, according to several studies (Merlet et al., 1996; Scherg et al., 1999; Huppertz et al., 2001a; Lantz et al., 2003), most of the spike related propagation occurs.

		Pat 1	Pat 2	Pat 3	Pat 4	Pat 5	Pat 6
	Sex	M	M	M	M	M	F
	Age	4 y	6 y	6 y	4 y	4 y	5 y
Interictal EEG							
	Duration (min)	79	81	84	71	63	73
	Focal	Yes	Yes	Yes	No	No	No
	Localisation	Oc Post	Par Oc	Oc L	Fr, Tp Post L	Oc R, Ct R, Oc L	Oc L, Oc R, Par
	Spikes	273	326	224	230	260	332
Seizures							
	Onset	3 y	4 y	6 y	4 y	2 y	2 y
	Symptoms	V, N, Dc	V, Dc, H, Sl	Ed, Dc	V, H, Dc	Dc, V, Ed	V, Dc, Ed, Sl
	Duration	> 30 min	> 20 min	>10 min	> 20 min	> 15 min	
	Total number	> 5	1	1	3	> 5	6

Abbreviations: V- Vomiting, Dc - Decreased Consciousness, H - Decreased tone, Sl - Speech loss, Ed - Eye deviation, N – Nystagmus, Oc – Occipital, Fr – Frontal, Par – Parietal, Ct – Central, R – Right, L – Left, P – Posterior

Table 11 – *EpiGauss* & OLE: patient clinical characteristics

5.4.1 Datasets

We studied six children (5 male) with an average age of 4.8 years, with Early Onset Childhood Occipital Lobe Epilepsy (Ferrie et al., 1997; Lada et al., 2003 ; Taylor et al., 2003; Ferrie et al., 2006). Early Onset Childhood Occipital Lobe Epilepsy (OLE) is an epileptic syndrome where children present characteristic semiological pattern but a heterogeneous scalp EEG analysis with multifocal spike activity without a consistent spatial topography. For each patient, 1 hour sleep EEG was acquired at 500Hz (10-20 system plus PO3, PO4, PO7, PO8, POz). A total of 451 minutes of EEG was acquired (average 75 minutes per patient). EEG was filtered with a time constant of 0.3 s and low pass filtered at 70Hz and an average montage used in EEG review. Spikes were visually identified in the occipital area, the EEG clinical focus area, resulting in a total of 1644 spikes (average of 274 spikes per patient). The complete patient characterisation is summarized in Table 11.

5.4.2 Results

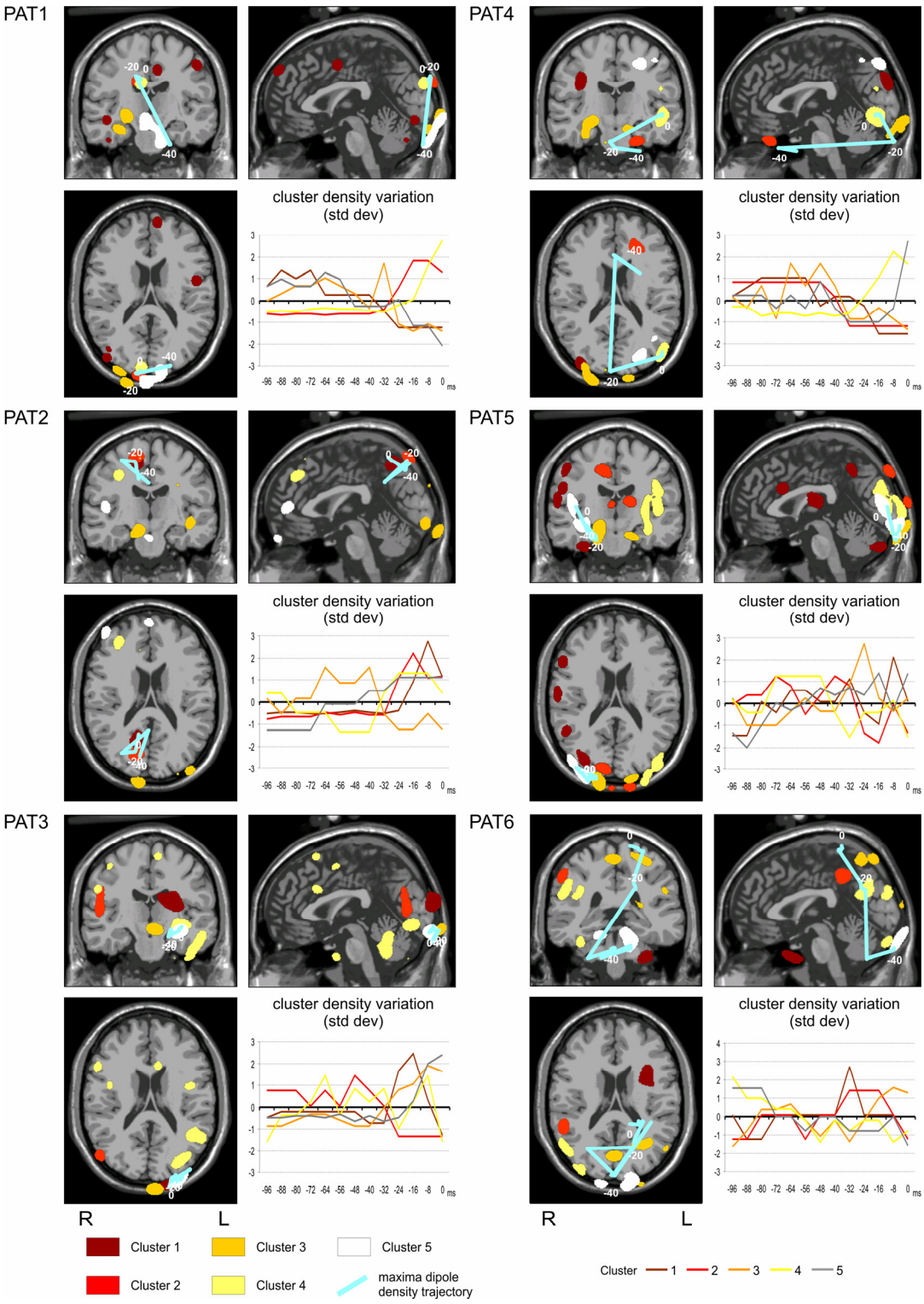


Figure 39 – *EpiGauss* & OLE: patients spatio-temporal characterisation

In all patients the occipital pole, mapped by clusters, was considered as a possible origin of propagation (-64 to -32 ms prior to spike peak) to parieto and high occipital areas. The findings were in agreement with the changes in the overall dipole density maxima in posterior occipital lobes, regardless of the specific EEG patterns observed. Dipole density maxima are represented as trajectories co-registered the head model and clusters (only the 40 ms preceeding the spike peak are shown - -40, -20 and 0 ms time are marked). Results presented as in **Figure 36**.

	Dipole density	EEG Visual inspection	Clusters Area & Laterality	Propagation	Linear correlation r (*)	
Pat1	Oc Ct Sup	Oc Post	Oc Sup (2R,4R), Oc Pol (3R,5Bil)	3->5 -> 2->4	3,2 (-0.82 d=0ms) 4,5(-0.79 d=0ms) 3,5(0.71 d=8ms)	5,2(-0.84 d=8ms) 2,4(0.99 d=16ms)
Pat 2	Par Oc	Par Oc	Par Ct (1R,2R), Oc Pol (3Bil), Par Fr (4R), Fr (5R)	3 -> 2 -> 1 4<->5	1,2(0.98 d=-8ms) 2,4(0.75 d=-8ms) 2,5(0.78 d=-8ms)	2,3(-0.74 d=-8ms) 3,4(-0.85 d=0ms)
Pat 3	Oc L	Oc L	Oc Par (1L), Oc (2R), Oc Pol (3L,5L),	1->5 2->5 3->5	1,5(0.92 d=8ms) 2,3(-0.92 d=0ms)	2,5(-0.93 d=8ms) 3,5(0.95 d=8ms)
Pat 4	Oc Difuse	Fr, Tp Post L	Oc Sup (1R,5L), Oc Inf (3Bil,4L), Tp (2L)	2 -> 4 -> 5 1->3	1,2(0.92 d=-16ms) 1,4(-0.89 d=0ms)	1,3(0.77 d=16ms) 2,4(-0.97 d=16ms)
Pat 5	Oc Difuse	Oc R, Ct R, Oc L	Oc Pol (3Bil), Oc High (2Bil,4L,5R)	2 <-> 3	2,3(-0.70 d=-8ms)	
Pat 6	Oc Par Difuse	Oc L, Oc R, Par	Tp (1L), Oc Par (4R), Oc Pol (5R), Par High (2R,3L)	4/5 -> 2 -> 3	4,5(0.79 d=-8ms)	

Abbreviations: Oc – Occipital, Pol – Polar, Fr– Frontal, Par – Parietal, Ct – Central, Tp – Temporal, Ms – Mesial, Post – Posterior, R – right, L – Left

(*) pairs of clusters that present correlation higher than 70%. The pairs of cluster are presented followed by the value of the maximum correlation value and the respective delay in ms

Table 12 – *EpiGauss* & OLE: dipole density and cluster characterisation

Three patients exhibited clear focal EEG activity in the occipital region while the others were multifocal EEG (occipital and central/parietal regions). The individual propagation patterns inferred from the joint analysis of the cluster dipole density variation and the cluster spatial configuration are described in Table 12 and in Figure 39.

From the analysis of the overall dipole densities maxima spatial variations, the involvement of the posterior occipital lobe was common to all patients as illustrated in Figure 39. This suggests that this is a common area in the OLE patients studied despite the different observed propagation patterns to other areas (parietal and temporal). In all patients, overall dipole densities maxima were mapped by dipole clusters. Based on a more detailed analysis we were able to identify possible propagation patterns.

In patient 1, the dipole density maxima trajectory spatial variations and the clusters suggest propagation from the occipital pole activity (mainly on right side) (clusters 3,5) to occipital superior areas (clusters 2,4). This could be identified based on the negative correlation and correlation delays between cluster group formed by clusters 2 and 4 versus the group of clusters 3 and 5. This is also supported by the move of the dipole density maxima from the occipital pole to the occipital superior area which indicates a change of the center of mass of electric activity between these two areas. As cluster 1 included activity in several brain areas it was not considered in the analysis.

In patient 2, we identified possible propagation from occipital pole (cluster 3 around -32ms) to right occipital parietal areas (from clusters 2 to 1). This is supported by the negative correlation between cluster 2 and 4 vs. cluster 3. From the dipole density maxima trajectory, the activity in the right occipital parietal areas seems to be predominant in the 40 ms preceeding the spike peak. An activation in fronto parietal areas is also observed around -40 ms (increase in dipole density in clusters 4 and 5) which is negative correlated with the occipital pole activity (cluster 3).

In patient 3, activity in the right occipital area (cluster 2) and the left occipital pole area (cluster 5 to 3) was present. The activity on the left side is dominant from the analysis of dipole density maxima trajectory, where activity centre of mass is located in the 40 ms preceeding the spike peak. This left occipital activity involves the poles (cluster 3 and 5) and the higher occipital areas (cluster 1) corroborated by the positive correlation between cluster 3 and 5, their spatial closeness. The dipole density maxima trajectory also suggests that cluster 3 and 5 represent the same occipital polar activity. As cluster 4 included activity in several brain areas it was not considered in the analysis.

In patient 4, two different propagation patterns are identifiable. The first starting in left temporal area (cluster 2) to occipital pole (cluster 4) and then to higher left occipital areas (cluster 5). The second pattern involving the left side from occipital superior area (cluster 1) to occipital left pole (cluster 3). The negative correlation between cluster 1 and 4 together with their spatial characteristics suggests that these propagation paths are independent. The analysis of the dipole density maxima trajectory corroborates the hypothesis propagation from temporal to occipital area and within the occipital poles, predominantly on the left side.

In patient 5, despite the diffuse occipital activity observed involving the occipital poles

and high areas in both hemispheres suggested by the negative correlation between cluster 3 (occipital poles) and 2 (occipital high areas), from the dipole density maximum spatial variations the activity on the right side (cluster 5) seems to be dominant in relation to the left (cluster 4). As cluster 1 included activity in several brain areas it was not considered in the analysis.

In patient 6, propagation from both right occipital (cluster 4) and occipital polar areas (cluster 5) to the left parietal area (cluster 3 and 2 around -32 ms) may be suggested. A propagation to right parietal area may be inferred through the cluster dipole density peak spatio-temporal relation between cluster 2 (-24 ms) and 3 (-8 ms). The analysis of dipole density maxima trajectories corroborates these findings by showing an change in trajectory from the right (-40 ms) side to the left to occipital parietal area (-20ms). An activation in the temporal area (cluster 1 around -32 ms) seems to be unrelated in the context of the dipole density spatial changes, involving mainly occipital and parietal areas.

5.4.3 Discussion and conclusions

Our initial question was on the added value of *EpiGauss* method in the epileptiform brain activity characterisation through source localisation and propagation related information when compared with standard EEG visual analysis.

In an apparently heterogeneous group of patients with OLE comprising both focal and multifocal patients (Table 12), *EpiGauss* was able to identify reliable patterns that sugest propagation between occipital poles (around 40 ms prior to spike peak) and surface EEG focus (located mainly in parieto or high occipital areas) in all patients, which was not clear in visual EEG analysis. Furthermore, in multifocal patients, active areas of brain in both hemispheres were also enhanced by *EpiGauss*. With the help of dipole density maxima trajectory it was also possible to corroborate the apparent inter-cluster propagation. These consistent relations between EEG focus and spatio-temporal *EpiGauss* sources also support previous studies (Merlet et al., 1996; Scherg et al., 1999; Huppertz et al., 2001a; Lantz et al., 2003) that point that the spike onset phase to be the best suited time interval to analyse and explain the genesis of the occurrence of spikes observed in scalp EEG.

The results agree partially with the few attempts to apply source analysis to characterize OLE (Kanazawa et al., 2005 ; Yoshinaga et al., 2005) where dipolar sources were described in mesial occipital and rolandic regions. With *EpiGauss*, we established strong

hypothesis on possible temporal relation between similar areas to those described in the mentioned studies, through temporal relation between clusters in similar locations, and through inference of patient specific patterns relating occipital parietal and activity in occipital poles. This constitutes a clear contribution to the study of OLE and indicates that our method may be used to perform similar studies in other groups.

5.5 Summary

In this chapter, we presented the main contribution of this thesis, the *EpiGauss* method. *EpiGauss* method, although only based in scalp EEG, is provides an added value in the spatio-temporal characterisation of brain activity, namely in the identification of possible propagation pathways as illustrated by both examples (Hypothalamic Hamartoma related epilepsy and Early Onset Occipital Lobe Epilepsy). Through the combination of several existing solutions (dipole modelling, dipole density) with a statistical clustering analysis layer (the novelty of the method) and a simplified clinical decision process, *EpiGauss* is able to:

- be used current clinic without specific expertise other than clinical and a good degree of automation – all results were obtained using scalp EEG monitoring setup without any human intervention in the analysis process;
- provide intuitive way of identifying possible propagation and stable sources – results agree with scalp EEG analysis and identify possible propagation pathways;
- provide complementar information – *EpiGauss* results are co-registered with MRI and provide maps that can be used in further analysis, namely SPM.

6 Conclusions

The delineation of the epileptogenic zone is the most important task in the context of epilepsy diagnosis. The use of a multimodal approach based on non-invasive techniques is often the most accessible and recommended option. Besides the great evolution in the imaging fields, the diagnosis based on the characterisation of brain electrical activity is still unavoidable: first due to its simple representation and accessibility and secondly due to EEG and MEG high temporal resolution. With the use of electromagnetic source imaging, it is possible to complement the temporal description with a spatial characterisation of the electrical activity brain generators. Nevertheless, to achieve an integrated computational framework that can aid the clinical diagnosis, some issues must be considered: first, clinical concepts such as spikes must be quantified to avoid ambiguities and to be able to build reliable references for computational methods (section 3.1 and 3.2); second, methods should avoid user specific expertise in the absence of such objectivity. In this thesis we have shown that, regardless of existing ambiguities, the combination of statistical methods (cluster analysis) with simple electromagnetic source imaging models (single dipole model) enable unsupervised approaches, such as *EpiGauss* (chapter 5), that provide a good spatio-temporal characterisation of the epileptiform brain activity, in such a way that is both reliable and clinicaly useful from early diagnosis stages, as it presents results in a natural representation for Brain Imaging users and shares some interpretation principles with most functional imaging techniques such as SPECT/PET or fMRI.

6.1 Major contributions

In this last chapter we summarize the major contributions of the research work presented in this thesis:

- Spike related "clinical" concepts are often unprecise and are not objective. A reformulation must be performed in order to have a reliable reference in quantified spike related analysis processes.
    - Clinical spike definition is subjective and must be reformulated in order to be a reference in quantified analysis processes, namely automatic spike detection methods. In section 3.1, it is shown that EEG and MEG spikes differ significantly and that it is not reasonable to use the same clinical assumption for both modalities analysis (Fernandes et al., 2004; Fernandes et al., 2005b).
    - Multi-expert spike gold standards based only in expert agreement may not be a reliable reference and may need further characterisation other than simple expert agreement. In section 3.2, we show that the use of a multi-expert spike selections (MESS) as a ground truth may be misleading whenever based solely in clinical agreement criteria.
- The combination of statistical methods such as cluster analysis may improve the source analysis results interpretation, providing unsupervised clinical guidance in the clinical interpretation of the source analsys results.
    - The use of automatic cluster methods together with dipole models over spikes selections eliminates the event separation task used in other approaches providing an unsupervised classification of the active generators (section 4.4 and (Fernandes et al., 2003b, a);
    - *EpiGauss*, an extension of the previous method proposed in section 4.4 that to accommodates relevant spatio-temporal information. *EpiGauss* combines the advantages of using the time resolution of EEG/MEG and spatial resolution of source analysis methods, with the dipole spatio-temporal information retrieved from individual events source analysis. The method combines dipole modelling, dipole density with a statistical clustering analysis layer and may provide an objective characterisation of the spatio-temporal changes in brain activity, namely by providing a good insight on stable sources and possible propagation patterns (chapter 5)..
    - *EpiGauss* was able to confirm prior analysis results on hypothalamic

hamartoma related epilepsy (in section 5.2 and (Fernandes et al., 2006a)) and contribute to a new relevant clinical observation in Early Onset Childhood Occipital Lobe Epilepsy by identifying a consistent active sources in the occipital pole in 6 patients comprising both focal and multifocal nature EEG (section 5.4. and (Fernandes et al., 2006b)).

6.2 Perspectives, current and future work

The spatio-temporal characterisation of epileptic syndromes is crucial in the epileptic patient's care. This thesis focus is a new EMSI contribution in that direction. *EpiGauss* method, although based only in scalp EEG, is able to contribute to a better spatio-temporal patterns characterisation in a clinical environment through the identification of stable active brain sources and possible propagation pathways. This was illustrated in both examples: the hypothalamic hamartoma related epilepsy (HH) and Early Onset Childhood Occipital Lobe Epilepsy (OLE).

This work points to the opposite direction of the current literature trend to move from basic neurophysiology (EEG, MEG and source analysis) to fMRI. fMRI is attractive since it can combine spatial and temporal information with a underlying physiological processes - the BOLD effect (Ogawa et al., 1990). But, as described in section 2.4.2, low temporal resolution and the absence of a clear model that correlates the BOLD variations and brain activity as brought a new impetus to EEG and source analysis through the EEG-fMRI studies, where EEG is used as control/paradigm for fMRI interpretation. This evolution is illustrated by the recent research lines of well-known groups (for example the Monreal Neurological Institute - MNI (Benar et al., 2002; Benar et al., 2003; Bagshaw et al., 2004; Gotman et al., 2004; Bagshaw et al., 2005a; Bagshaw et al., 2005b; Kobayashi et al., 2005a; Bagshaw et al., 2006)).

In this context, most recent source analysis related studies, besides specific methods proposals and/or improvements, are related with fMRI (exemplified by MNI line of work among other groups), centred on the EEG and MEG combined studies (some examples (Stefan et al., 2004; Bast et al., 2005; Pataraia et al., 2005)) or on the source analysis issues from validation to specific method improvements (some examples (Ranken et al., 2004; Trujillo-Barreto et al., 2004; Bowyer et al., 2005; Darvas et al., 2005; Kobayashi et al., 2005b; Rodriguez-Rivera et al., 2006)) and not centred in proposing methodological

frameworks to clinically deploy/integrate source localisation methods as is the case of *EpiGauss*.

Following this rationale, the next planned steps for the work in this thesis are to perform a more thorough validation on *EpiGauss* to assert 1) its localisation accuracy, 2) its propagation characterisation usefulness by comparing with established propagation physiological models, namely those related with human motion and 3) the relation between *EpiGauss* results and brain underlying physiologic activity through comparison *EpiGauss* results and BOLD activations using EEG-fMRI.

Current candidates to be used as accuracy controls should be 1) specific brain rythms (either spontaneous or evoked) with well known generator localisations, such as alpha rythms (Nunez, 1995; Nunez et al., 2001) or evoked potentials (Chiappa, 1997) and 2) specific epileptic syndromes where the irritative zone is well delineated or where invasive studies provide reliable localisation of the focus. Currently we are focusing in lesional epilepsy candidates to epilepsy surgery with intracranial monitoring. Epilepsy candidates with intracranial monitoring will allow an accurate assement of the *EpiGauss* localizing accuracy compared with the actual intracranial irritative area. Ictal studies with *EpiGauss* also constitute an area of interest and will be performed whenever possible. Preliminary studies were performed and present promising results with one patient with HH related epilepsy where *EpiGauss* identified a consistent cluster within the hamartoma area, clearly distinguishable from other found clusters, in contrast with weaker signature found in some patients in the HH interictal studies (section 5.2).

The same models used to provide a localisation controls constitute good propagation models. Such is the case of epileptic patients, where both the irritative zone and EEG focus localisation is known and evoked potentials with accepted physiological models. Both models provide clear propagation pathways (from known origin to the EEG focus or specific brain area associated with propagation models) and allow a spatio-temporal hierarchisation between involved brain areas.

At same time, relating *EpiGauss'* results with BOLD fMRI activations will provide physiologic characterisation of a brain activity, whenever an EEG-fMRI acquisition is possible.

The comparison of ictal movement quantification versus synchronized EEG spatio-temporal characterisation using *EpiGauss* is also an important target. Since the first

movement quantification of epilepsy seizures in 2D (Li et al., 2002), relating human motion and electrical brain activity was an atractive problem but difficult due to sampling frequency differences (more 200 Hz in EEG vs 25 Hz (25 fps) in movement quantification from common video setup). With the perspective of a full 3D movement quantification system with sampling frequency reaching hundreds of hertz (Cunha et al., 2006), we plan to correlate both measures in 1) current accepted models of motor areas and related pathways and in 2) epileptic seizures by combining EEG, movement quantification and *EpiGauss* spatio-temporal characterisation of EEG.

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