Contribution of seizure semiology to diagnosis and anatomo-electrical localisation of epilepsy

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Abstract

Epileptic seizures, characterised by paroxysmal disturbance of brain electrical activity, are recognisable by temporary change in clinical state (for example motor signs, behavioural modification or altered conscious level), temporally associated with the cerebral discharge. While analysis of such clinical seizure signs ("semiology") formed the main basis of epilepsy study from the late 19th century onwards, understanding of the neural basis of semiological expression has advanced relatively little, in comparison to other aspects of epilepsy research. Analysis of ictal clinical signs is today considered essential for diagnosis of epilepsy, offering clues to underlying anatomical localisation and pathophysiology; however, paradoxically, the cerebral substrate of semiological signs remains incompletely understood in many cases and its localising value is therefore debated. Characterising the anatomo-pathophysiological basis of seizure semiology is especially important in the context of epilepsy pre-surgical evaluation, even more so when no radiologically visible lesion is present, since semiological analysis, if validated for a given seizure type, offers crucial localising information. For pharmacoresistant focal epilepsies in which surgical treatment might be possible, a number of cases require intracranial EEG recording. The method of stereoelectroencephalography (SEEG) is particularly useful as this allows simultaneous exploration of multiple, distant brain structures using stereotaxically placed multi-lead electrodes with concurrent video recording. The data thus acquired help form a three dimensional view of spatio-temporal seizure dynamics. Using SEEG it is therefore possible to undertake detailed analysis of semiological patterns and to study their temporal relation to the abnormal electrical cerebral activity occurring in brain networks during seizures. Epileptic seizures characterised clinically by transient cognitive dysfunction, behavioral change and complex motor signs are particularly challenging to analyse and categorise semiologically; indeed any paroxysmal behavioral disturbance must also be analysed with regards to whether it is actually caused by an epileptic discharge or not, since other forms of pathology, particularly psychogenic nonepileptic seizures (PNES), may be difficult to distinguish from epileptic seizures on a purely clinical basis, and require video-EEG recording for confirmation. This issue is particularly pertinent for prefrontal and parietal lobe seizures, which pose specific challenges for electroclinical analysis. PNES have a different and as yet poorly defined neurobiological basis compared to epileptic seizures. However growing understanding of the brain networks underlying emotional dysfunction, complex motor behaviour and altered consciousness, in particular data derived from intracranial studies of epileptic seizures, can help to further knowledge of how altered activity within these neural networks might interact with psychological and other factors in the pathophysiology of PNES.

Through detailed observation of multiple epileptic seizures across a large population of patients, it can be appreciated that similarities exist in both clinical pattern and anatomical organisation of seizures. The existence of semiological patterns is in favour of the hypothesis that specific neural circuits underlie some forms of behavioural expression, and thus reinforces the validity of pursuing this line of investigation in epileptic seizures.

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List of Figures

List of Published Works Included in Thesis

First or last author works (= joint first author), listed according to their order of discussion in dissertation*

Contribution to the Articles Included in this Thesis

Article	Article name	My role	Significance of work
1	Emergence of semiology in epileptic seizures	Id, M, D, W	Only existing review of this subject, co-written with a leading expert in the field
2	SEEG in presurgical assessment of MRI-negative epilepsy	Id, M, D, W, C	The first major overview of a large series of SEEG in the MRI era; the first paper to examine the role of SEEG in MRI-negative epilepsies; an influential and widely-cited paper that has probably contributed to increasing use of SEEG in many international centres and has paved the way for subsequent studies of other investigation modalities in MRI-negative epilepsies
3	MRI-negative prefrontal epilepsy explored by SEEG	Id, M, D, W, C	A detailed case study illustrating the principles discussed in Article 2
4	Frontal lobe seizures: From clinical semiology to localization	Id, M, D, W	The largest published series of FLE explored with SEEG. The first study to demonstrate correlations between semiological patterns and anatomical localisations using SEEG. The first study to demonstrate the existence of a rostro-caudal gradient in semiological expression of frontal seizures
5	Prefrontal seizures manifesting as motor stereotypies	Id, M, D, W, C	The first paper to detail the rationale for applying the term stereotypy to frontal seizure semiology
6	Gamma knife radiosurgery of paracentral epilepsy	Id, M, D, W, C	One of very few studies describing GK in extra-temporal epilepsies. The only published GK series of paracentral epilepsies. The first paper to discuss semiological evolution as a post-intervention effect of GK
7	Outpatient video EEG recording in the diagnosis of non-epileptic seizures: a randomised controlled trial of simple suggestion techniques	Id, M, D, W, C	The first study to look at suggestion in a randomised approach in PNES. The first to highlight PNES in a medical setting as a predictor for capturing seizures on video-EEG. The first study of suggestion methods to explicitly inform patients that we expected to record PNES
8	Use of short term video EEG in the diagnosis of attack disorders	Id, M, D, W, C	A follow-on larger series to Article 7, confirming the same results in a much larger group and overcoming the problem of the under-powering of the previous study
9	Nonepileptic seizures: An honest approach to provocative testing	Id, M, D, W, C	A contribution to (still ongoing) debate in the epileptological literature as to the ethics of using suggestion in provoking PNES
10	Parietal seizures mimicking psychogenic nonepileptic seizures	Id, M, D, W, C	A response to a major review highlighting the previously under-recognised risk of misdiagnosing parietal seizures as PNES.

Id: Original idea and/or principal role in formulating concept; M: Method design; D: Data collection and/or analysis; W: Writing of article; C: Corresponding author

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I would particularly like to thank Patrick Chauvel for supervising this work during its final phase, and Dr Aline Russell for early EEG training and support.

I would finally like to thank my family, in particular my husband Stéphane, my children Luke, Harry and Mark, and my parents James and Mary.

Declaration

The results presented in this thesis are my own work except where there is an explicit statement to the contrary.

Aileen McGonigal

Abbreviations

BA	Brodmann's area
EEG	Electroencephalography
EZ	Epileptogenic zone
FCD	Focal cortical dysplasia
FLE	Frontal lobe epilepsy
FLS	Frontal lobe seizure
GK	Gamma knife radiosurgery
ILAE	International League Against Epilepsy
MRI	Magnetic resonance imaging
PNES	Psychogenic nonepileptic seizures
SEEG	Stereoelectroencephalography
Video-EEG	Simultaneous recording of EEG (usually surface EEG) and video of patient

1 Introduction: electrophysiology and the clinical expression of epileptic seizures

Epileptic seizures, characterised by paroxysmal disturbance of brain electrical activity, are recognisable by transient change in clinical state (for example motor signs, behavioural modification or altered conscious level) that is temporally associated with the cerebral discharge. This discharge can be measured using electroencephalography (EEG) with either surface or depth electrodes. In the pre-EEG era, analysis of clinical seizure signs ("semiology") formed the main basis of epilepsy study[1], along with post-mortem pathological analysis of brain lesions associated with epilepsy. Neuroimaging has allowed increasingly precise definition of structural and functional (e.g. metabolic) brain abnormalities in patients with epilepsy[2, 3]; but because of the variable and often complex relation between the region of primary organisation of ictal (seizure) discharge and any underlying anatomical lesion, it remains necessary to integrate all available data, including clinical and electrophysiological methods, in order to delineate the epileptogenic zone (EZ); that is, the region of primary organisation of seizure discharge. This is especially true when epilepsy surgery is being considered.

While semiology remains an important component of epilepsy evaluation, our understanding of the neural basis of semiological expression has advanced surprisingly little, despite accessibility of increasingly more precise methods of studying cerebral function[4], probably because the role of semiology is seen as relatively less crucial in the context of available EEG, neuroimaging and other data. In this thesis, I will examine how clinical expression of seizures is related to their cerebral organisation, how this knowledge helps with diagnosis and localisation of epileptic seizures, and how this line of study offers a means to advance our understanding of epilepsy. The work presented here makes use of electroelectroencephalographic data interpreted in conjunction with simultaneous video recording of seizures (video-EEG), particularly from direct intracerebral recording using stereoelectroencephalography (SEEG), thus allowing study of the neuronal networks involved in the partial epilepsies described here and in production of different semiological patterns during seizures.

2 The paradox of clinical semiology

Over recent decades, thinking on the value of seizure semiology has been rather dichotomous, as evidenced by the numerous and often contradictory contributions to this subject in the literature. On one hand seizure semiology is classically regarded as the key to localisation of dysfunction within the nervous system, in the same way as for clinical signs in other neurological diagnoses[5]. It is widely accepted that analysis of ictal clinical signs is essential for diagnosis of epilepsy and that this process offers clues to underlying anatomical localisation and pathophysiology[6, 7]. This premise is indeed the cornerstone of the major classification system of seizures and epilepsies developed by the International League Against Epilepsy (ILAE)[8, 9], which has evolved over the last 25 years and now includes specific documentation of definition of terms used to describe semiological features[10].

However in contrast to this principle, a large body of work derived from studies of epileptic patients undergoing evaluation for epilepsy surgery, has highlighted the difficulties inherent in using semiological data to infer likely zone of seizure onset. While certain semiological signs or constellations of signs are rather clearly recognisable and characteristic, even pathognomonic, of certain forms of seizure and thus in some cases of certain types of epilepsy (such as mesial temporal lobe seizures in mesial temporal lobe epilepsy[11], or focal clonic seizures in contralateral primary motor cortex epilepsy[12]), on the other hand some signs and patterns are rather considered of uncertain localising value or even potentially mislocalising[13]. This latter situation includes semiological patterns or signs that are particularly variable or difficult to analyse because of their complexity, such as those seen in prefrontal seizures[14]. The notion of misleading localising information comes particularly from observations in which a similar clinical expression (such as “hypermotor” behaviour) has been found to occur in seizures arising from different brain localisations[15-17], or even in non-epileptic pathologies[18]. For these more complex seizure types there is a significant gap in our understanding of the relation between cortical seizure organisation and clinical expression. Indeed lack of progress in understanding the neural basis of production of clinical signs, in the context of many such

"negative" semiology studies, has led to debate on whether the analysis of semiological features of certain types of epileptic seizure is actually useful in localising the anatomical zone of seizure production[19, 20]. This lack of certainty produces particular challenges in the clinical context of epilepsy presurgical evaluation, with for example acknowledged difficulty in some cases of distinguishing between temporal lobe and extra-temporal lobe seizures[19]. Progressing to more precise sub-lobar localisation is considered even more challenging, especially in extra-temporal epilepsies, of which frontal lobe epilepsy is widely considered the most difficult[21]. This difficulty is particularly marked when no visible lesion is present on magnetic resonance imaging (MRI) to serve as a guide to anatomical localisation[22] and the issue of MRI-negative epilepsies (no visible lesion) will be discussed in more detail below.

Apart from signs arising from epileptic discharge within primary cortex, where there is a more or less linear relation between electrical activity and clinical expression, more complex patterns of signs arise from abnormal activity within a distributed network of several brain regions, whether local or widespread[4, 23-25]. The issue of how to accurately observe, categorise and evaluate the importance of different semiological components is particularly pertinent for epileptic seizures in which the pathological cerebral discharge is organised within widely distributed networks involving associative cortex, notably prefrontal and/or posterior parietal regions[21, 26-28]. As well as complex motor signs and behavioural change there may be altered consciousness or responsiveness that present specific challenges for objective evaluation[29-31]. In such seizures, relations between clinical manifestation and electrical disturbance are typically complex and non-linear[30], with seizure propagation pathways that might be distant and multi-directional, so that anatomical localisation becomes very challenging[4]. Existing classification of semiological signs is to some degree inadequate for characterising such seizures[10, 27].

As well as current limitations in knowledge of the cerebral substrate of many clinical seizure patterns, there are also methodological difficulties related to seizure observation. Given the short time period for occurrence of these signs, which are usually multiple and appear successively or simultaneously (a seizure usually being a paroxysmal disturbance of behaviour lasting from a few seconds to a few minutes depending on seizure type), the clinical difficulties of accurate

observation and evaluation of seizure semiology are thus significant. Even with modern synchronised video-EEG methods, in which the relevant segment can be replayed as many times as necessary in order to visualise the clinical features and their relation to EEG changes, the core method of interpretation of seizure semiology remains entirely subjective, relying on the observational skills and experience of the doctor reviewing the recording, as well as other technical and environmental factors such as video quality and presence or absence of appropriate peri-ictal examination by trained staff (which contribute to the "granularity of the seizure scene"[4]). The process of analysing seizure semiology is thus both highly operator-dependant and situation-dependent, giving rise to problems of inter-observer variability that are known to be particularly marked for seizures of the complex behavioural sort[32, 33]. I would also suggest that bias may occur due to specificities of the perceptive processes of the seizure observer: for example, increased attention paid to emotional faces[34], or more difficulty in perceiving "nonsense" or non goal-directed motor behaviours[35, 36]. This aspect of semiological analysis has not so far been studied systematically and is a potential area of future research. Issues pertaining to optimal conditions for analysing semiology are relevant not only for assessment of localising signs of epileptic seizures but also for distinction between epileptic and non-epileptic events[32, 37] and in more detailed semiological analysis of psychogenic non-epileptic seizures (PNES)[38]. The most reliable results are obtained in specialised recording units with trained staff, allowing for optimal seizure recording conditions and especially benefitting from the advanced pattern-recognition abilities of expert seizure observers who may more readily and more accurately make sense of a complex clinical picture and its relation to EEG data. This whole domain of seizure analysis remains however relatively under-examined, and it can be imagined that future studies on semiology will more strongly emphasize the complementary value of objective and quantitative approaches to semiological evaluation[39-44].

Despite limitations as discussed above, detailed observation of multiple epileptic seizures across a large population of patients shows that similarities do exist in both clinical expression and anatomical organisation of seizures, even for the most complex patterns[4, 45]. Seizure propagation takes place within pre-existing neural networks that have, at least in theory, somewhat predictable structural

and functional connectivity[46, 47]. The fact that semiological patterns repeat within patients and may have similarities between patients is consistent with the hypothesis that specific neural circuits underlie some forms of ictal behavioural expression[21], and thus reinforces the validity of pursuing this line of investigation. The type of discharge and the relations between different structures within the network, in terms of degree of synchronisation[30, 48] or desynchronisation[49, 50], are highly likely to play an important role in clinical seizure expression[4]. Examples of this in terms of the mechanisms of altered consciousness in seizures and ictal fear-related complex motor behavior will be discussed below. Intracranial EEG provides a high spatio-temporal resolution of brain electrical activity, which can be compared with clinical signs recorded on time-locked video. Adequate methodology for investigating cerebral substrates of seizure semiology should permit simultaneous evaluation of multiple brain structures with a high spatio-temporal resolution, time-locked with clinical seizure signs as recorded on video. This is particularly pertinent when examining ictal complex behaviour since it is necessary to be able to sample various structures within distributed cortical networks, in particular frontal lobe. In human subjects this process is clearly limited to patients undergoing presurgical evaluation, with inevitable constraints on choice of sampling sites, according to the clinical question to be resolved. While methods of recording from cortical surface (subdural grids and strips) may be extremely useful in answering specific clinical questions, these do not however allow simultaneous recording from multiple distant structures, deep structures cannot readily be assessed and some regions such as orbitofrontal cortex may not be explored because of anatomical constraints[51]. In the context of study of semiology, the SEEG is the optimal method available today allowing sampling of cortical networks. As well as progress in understanding of epilepsy, this approach also offers a means to advance knowledge of the physiological and pathophysiological basis of aspects of consciousness[30, 52] and certain motor behaviours[53], since epileptic seizures recorded with intracerebral electrodes provide a unique model for studying cortical function and dysfunction in vivo[54]. Specific examples of neural substrates of semiological patterns in epileptic seizures, as elucidated using SEEG, are discussed below in sections 4 and 5: alteration of consciousness and fear-related behavior.

3 Stereoelectroencephalography: 4-D electrophysiological investigation of the epileptic brain

The main body of work presented in this thesis utilises the SEEG method in a context of epilepsy presurgical evaluation, of which some general methodological comments can be made. This is the clinical and electrophysiological method of brain exploration developed by the team of Bancaud and Talairach in the Hôpital Sainte Anne, Paris from the 1960's onwards[55], and continued notably by Patrick Chauvel[56] in France and the late Claudio Munari[57] in Italy, and their pupils (Figure 1).

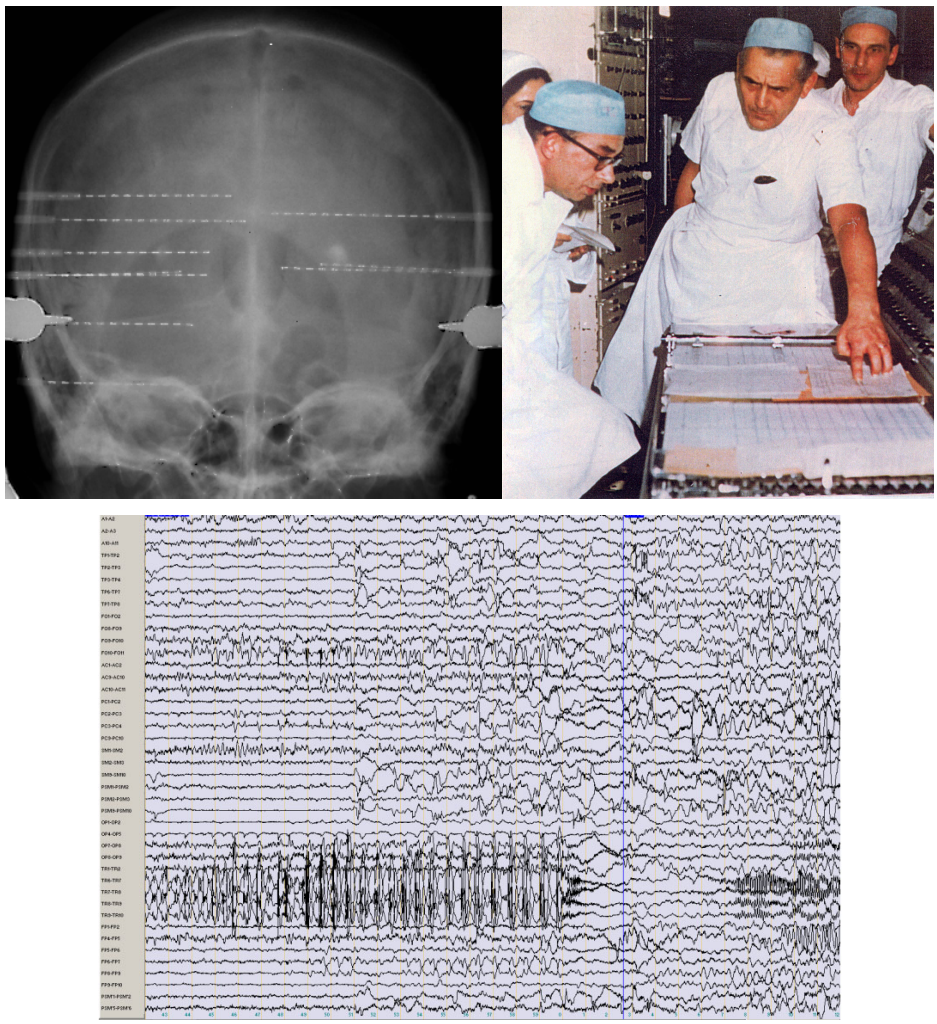

Figure 1. Intracerebral recording using stereoelectroencephalography (SEEG). **Top left panel**: Skull radiography showing position of SEEG electrodes after implantation. Electrodes are here implanted orthogonally, bilaterally, reaching medial brain structures. The individual recording contacts on each electrode can be seen (10 or 15 depending on electrode length) can be seen. The Talairach stereotactic frame, used during implantation, can be seen on the exterior of the skull. **Top right panel**: Neurophysiologist Jean Bancaud (left) and the neurosurgeon Jean Talairach (centre) interpreting an SEEG trace printed on paper (1970's). **Bottom panel**: Typical SEEG trace seen on a modern computer screen.

The SEEG method offers a high-resolution view of temporal and three-dimensional spatial dynamics of epileptic activity, which can be compared in real-time with clinical seizure evolution. Electrode placement in specific anatomical structures is dependent upon the pre-established hypotheses of probable zone of seizure onset and propagation, and allows simultaneous recording from medial and lateral brain structures at multiple sites. Electrodes, numbering between 5 and 15 depending on individual case characteristics, are placed during general anaesthesia. Use of the Talairach stereotactic frame from the 1960s onwards was a pioneering technique allowing precise anatomical positioning in the pre-MRI era[58, 59]; more recently other frameless methods of SEEG implantation based on multi-modal planning and robot-assisted surgery have been developed[60, 61] (Figure 2).

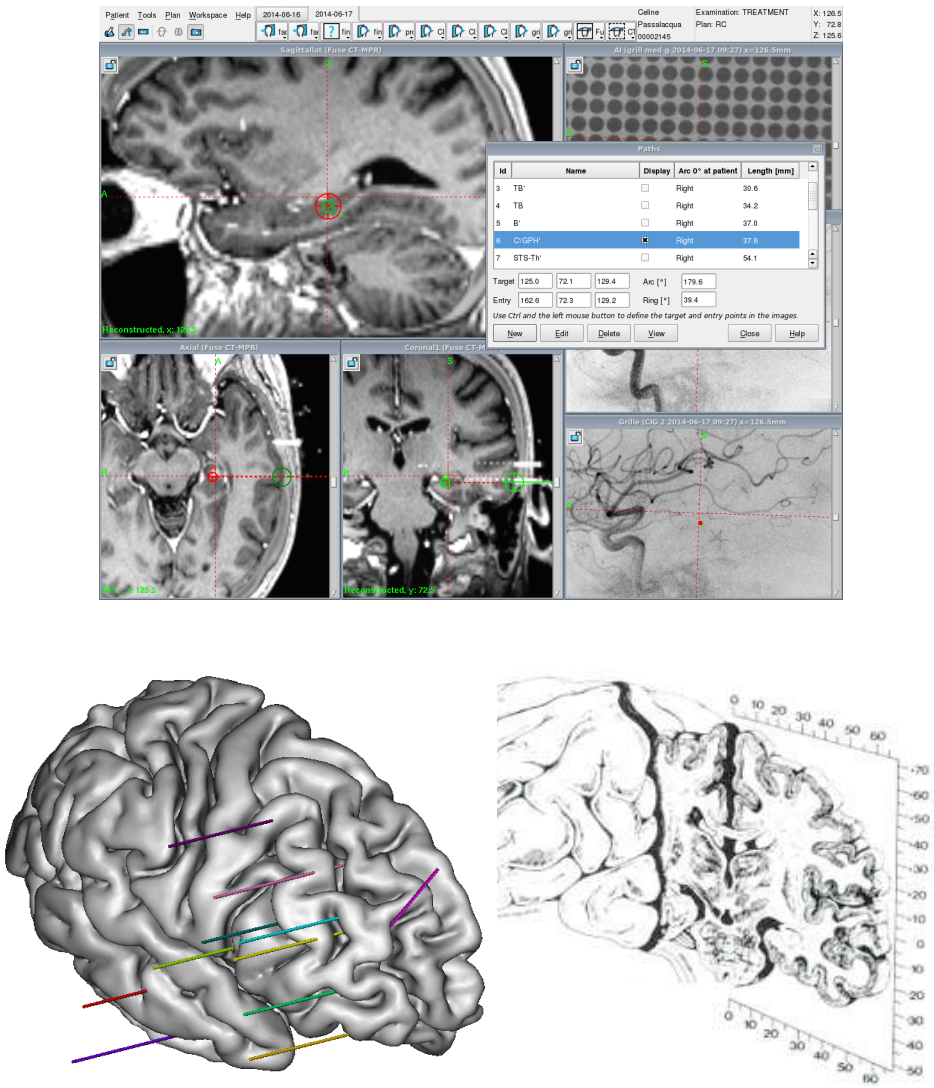

Figure 2. Modern MRI and angiogram visualisation of electrode trajectory (**top panel**) and computerised planning of electrode trajectory (**bottom panel**).

Electrodes may readily be placed in brain regions generally inaccessible by other means of intracranial recording (subdural grids or strips), including orbitofrontal cortex, insula[62] and subcortical structures[63, 64]. Planning of trajectory takes into account cerebral vasculature in order to minimise bleeding risk, which is around 1%[60, 65]. Indeed risks of SEEG, in terms of major complication rate (significant symptomatic haematoma and/or infection) are consistently lower (consistently 2-3% across studies[51, 60, 66]) than those associated with subdural grids, which range from 6.5%[67]-13.5%[68] in the subdural series with the best safety profile. Recording takes place in the video-EEG telemetry department during a 4-10 days recording period. Interictal activity and ictal activity are analysed, ideally including multiple habitual seizures, as well as results of stimulation studies of selected electrode contacts. Various methods of EEG signal analysis[24, 50] may also be employed to quantify signal frequency and epilepsy network dynamics. The region of primary organisation of ictal discharge (that is, the epileptogenic zone (EZ) as defined by Bancaud and Talairach)[55] and subsequent propagation pathways are correlated with the anatomical positions of the relevant electrodes maximally displaying abnormal activity, and clinical seizure signs as they evolve over time: hence, the formulation of "anatomo-electrical-clinical correlations"[55], which is the core feature of the SEEG method (figure 3).

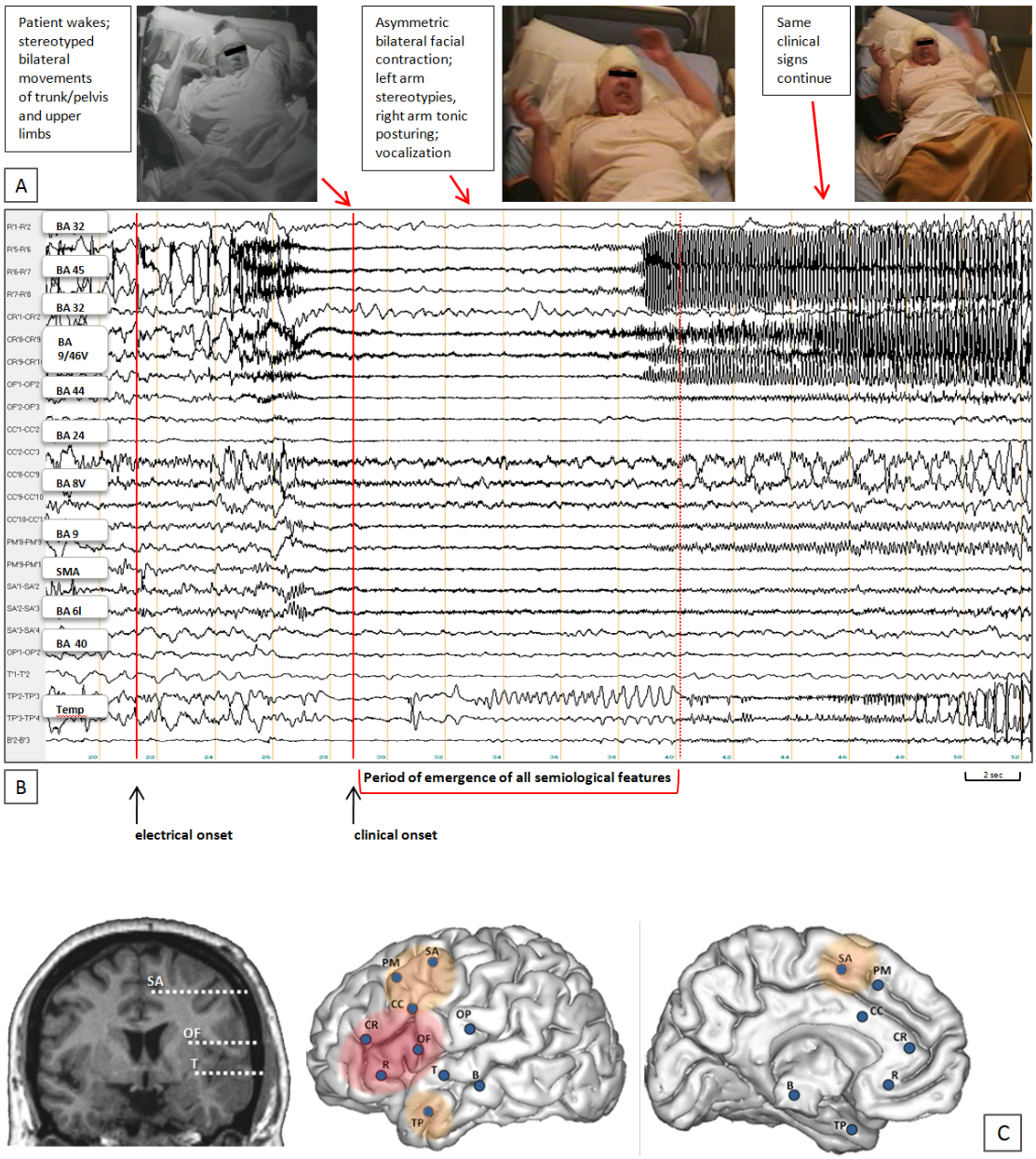

Figure 3. Anatomo-electro-clinical features of a patient with frontal lobe epilepsy. **Panel A**. Semiology is characterized by non-integrated gestural motor behaviour with proximal stereotypies of pelvis, trunk and left upper limb, elementary motor signs (asymmetric bilateral facial contraction, tonic/dystonic posture of right upper limb) and vocalization. **Panel B**. Ictal SEEG shows increasing synchrony, rhythm and amplitude of interictal spikes and superposition of a low voltage rapid discharge at electrical onset in the ventro-lateral prefrontal cortex (BA 45, BA 9/46V, BA 44; red-colored in box C), followed at clinical onset by a less tonic low voltage fast activity involving premotor and posterior lateral prefrontal areas (BA 8V, BA 9, SMA and lateral BA 6; orange-colored in box C) and by a rhythmic slower activity in the temporo-polar region (orange-colored in box C). **Panel C**. Coronal view of patient's T1 MRI with 3 implanted electrodes and lateral and medial view of all implanted depth electrodes on a 3D reconstruction of the neocortical surface of the brain. Regions showing major involvement in the generation of the ictal discharge are colored in red and regions showing minor involvement in orange. BA: Brodmann area. Electrodes labels: B = Hippocampus; CC = BA 8V (external contacts), BA 24 (internal contacts); CR = BA 9/46V (external contacts), BA 32 (internal contacts); OF = BA 44; OP = BA 40; PM = BA 9 (external contacts), pre-SMA (internal contacts); R = BA 32 (external contacts), BA 45 (internal contacts); SA = lateral BA 6 (external contacts), SMA (internal contacts); TP = temporal pole; T = superior temporal gyrus.

This overall process leads to delineation of the epileptogenic zone (EZ) and enables a zone of surgical resection to be proposed, if appropriate to the case, with the exact relation of the EZ and optimal ultimate surgical resection being highly dependent on the electroclinical characteristics of individual cases[69].

SEEG is of course somewhat less well suited than subdural grids or strips to studying electrical signal over contiguous areas of cortex, such as may be desirable when performing functional cortical mapping for motor function over the cortical convexity. It is possible (although not routine) to combine SEEG and subdural methods, providing complementary electroclinical data in selected cases[70]. SEEG is nevertheless the increasingly preferred means of intracranial recording[51] for many leading centers performing presurgical assessment, being especially relevant in extra-temporal and non-lesional MRI-negative cases[66]. In the context of the work presented here, SEEG is undoubtedly the best available method of studying neural correlates of complex semiology involving behavioural change, for the reasons described above.

4 Neural substrates of semiological patterns studied using SEEG

This section describes some specific examples of how SEEG may be used to explore the neurobiological basis of epileptic seizures, and relates directly to the topic of **Article 1** in this thesis (Emergence of Semiology) as well as referring to **Article 4** (Frontal lobe seizures: From clinical semiology to localization). Article 4 will also be further discussed in a subsequent section.

4.1 Altered consciousness in epileptic seizures

Studies using SEEG have contributed to understanding the role of specific neuronal networks that may be disrupted when altered consciousness occurs during epileptic seizures. The two main components of consciousness are *wakefulness* and *awareness*, of which the latter is most relevant to epileptic seizure semiology. The notion of awareness may be further separated into subjective, experiential phenomena of consciousness; and objective signs of

response to environment and other people. It is this second category (external signs of altered responsiveness) that is more readily studied in the clinical context. Clearly, analysis of conscious level in seizures is challenging; an operational approach, using objectively measureable changes in patients' contact with the environment and the examiner, as well as their memory for events occurring during the seizures, has been proposed, with various consciousness ratings scales having been validated[52, 71, 72] and applied in a clinical research context.

From a neuroscientific perspective, consciousness has been conceptualized in various ways, taking into account the neural networks that remain active in the absence of specific cognitive tasks, whose organisation appears to underlie the awake brain's baseline state, described as the "default mode network" (DMN)[73]. From functional imaging data[74], this network has been shown to involve posterior mesial structures including precuneus and posterior cingulate, as well as lateral parietal, dorsolateral prefrontal and ventromesial prefrontal cortex. This network is markedly deactivated in conditions of altered vigilance including sleep and anaesthesia; and may also be altered in some neurological conditions that are associated with altered awareness including persistent vegetative state[75], Alzheimer's disease[76], attention deficit disorder[77] and epileptic seizures[73]. Indeed all types of epileptic seizures affecting consciousness, whether seizure organisation is generalised (e.g. absence seizure) or partial (e.g. temporal lobe seizure), appear to produce this clinical sign via effects on the same network of brain structures[31]: the upper brainstem and medial thalamus; the anterior and posterior cingulate, medial frontal cortex, and precuneus; and the lateral and orbital frontal cortex and lateral parietal cortex. This clearly overlaps significantly with what has been termed the DMN.

Another model for thinking about the neural basis of consciousness was derived from a theoretical computational model called the global workspace[78-80], which has become accepted across many disciplines as a useful framework and has been particularly employed as a basis for thinking about consciousness in epileptic seizures. According to this model, which has been developed and refined including with data from functional neuroimaging and neurophysiology, the multitude of available incoming perceptual information will reach conscious

awareness only if three conditions are met[81, 82]: the information must be detected by cortically represented systems (such as visual, auditory or memory processing), corresponding to "modules" or "local experts" [83]; this information must then be "amplified" by a higher level of cortical processing dominated by prefrontal cortex; and lastly the information is then "broadcast" throughout a widely distributed network characterised by coherent neural activity within many different brain structures. In this model the vast majority of cognitive processes do not therefore reach conscious awareness; priority for reaching conscious access is given to stimuli that are new, threatening or highly relevant to an active goal or process[83]. The likely core neural basis for this model is the thalamo-cortico-thalamic circuit, with connections to specialised cortical regions, notably executive attentional processing in prefrontal regions and sensory processing in posterior regions. The anatomical distribution of this network overlaps with that described as underlying the DMN; but while it has been suggested that the DMN is primarily involved in self-awareness or self-referential processes[84] (this aspect being particularly associated with mesial fronto-parietal structures), the global workspace is considered to encompass all incoming perceptual information from self and from the environment, and centres on the degree to which this is made available to the rest of the brain (that is, the process of conscious access)[85].

It has been postulated that hypersynchronisation may be a direct pathophysiological mechanism of altered consciousness, through reduction of the diverse repertoire of highly differentiated neural states normally present in the alert state[86]. The relevance of studying epileptic seizures in this context is that when transient, reversible alteration of consciousness occurs, components of its neural substrate may be studied using SEEG signal analysis to investigate interdependencies between altered electrical activities in different anatomical structures. It is also pertinent that epileptic seizures are themselves characterised by altered synchrony between various brain structures[87]. It can be hypothesised that loss of consciousness will occur during an epileptic seizure only if a large enough volume of cortical tissue within critical areas is involved by a hypersynchronised discharge, which disrupts normal local functioning and/or deactivates distant structures necessary for regulation of attention, perception and vigilance.

In terms of the global workspace model, it is predicted that cortico-thalamic pathways should be particularly affected, with certain cortical regions such as prefrontal and parietal cortex playing a specific role[88] in acting at the "modular" level of the global workspace model[83].

Study of temporal lobe seizures that were investigated by our team using SEEG, notably with exploration of thalamic structures, demonstrated altered synchronisation of cortico-thalamic networks[52, 64], to a degree that was directly related to the level of the patient's altered responsiveness as measured objectively by clinical ictal examination. A subsequent study of parietal epilepsy also highlighted the role of parietal lobe structures in these "consciousness networks"[89]. Finally the SEEG series of frontal lobe epilepsies presented in this thesis[27] showed a higher incidence of altered consciousness in prefrontal as compared to premotor or precentral epilepsies[27, 90] in keeping with clinical observations previously made by Bancaud and Talairach[91]. Indeed a subsequent study by our group using signal analysis of SEEG data in frontal seizures confirmed and refined this finding[78], showing that greater levels of synchrony between prefrontal and parietal structures were found in seizures with a more marked degree of altered consciousness. This finding is thus in keeping with the notion that the global workspace mainly involves an associative fronto-parietal network. The fact that prefrontal much more than premotor areas were associated with altered consciousness is also an expression of the hierarchical organisation of frontal lobe function[92, 93], whereby integration of progressively higher order commands within the action-perception cycle[93] depends on interactions between increasingly associative cortical structures. In the frontal lobes this is organised along a rostro-caudal gradient[94], the highest order regions lying most rostrally, with somatotopic connections to relevant parietal associative cortex.

4.2 Fear-related ictal behaviour

One of the most strikingly characteristic semiological pictures in epileptic seizures is that of apparent fear-related behaviour, expressed with explosive, hyperkinetic movements. Vocalization with an emotional quality (such as screaming, shouting or wailing), and verbalization including swearing, may also occur. Fearful and/or aggressive facial expression is often a very striking feature.

Bancaud and Talairach, using stereo-electroencephalography to analyze seizures via anatomo-electrical-clinical correlations, were the first to emphasize the role of the anterior cingulate gyrus in the generation of complex motor activities and affective manifestations such as expressions of fear[95] [96], and subsequent observations confirmed this[97-100]. The clinical aspect is in keeping with previous descriptions including the original observation of "orbitofrontal seizures"[101, 102] as well as other early case reports of similar semiology associated with mesial prefrontal seizure activity[14, 103, 104] As confirmed in the SEEG series of frontal seizures presented in this thesis[90], seizures were reproducibly organised within a ventromesial prefrontal network involving mesial posterior orbitofrontal cortex (BA 14 and 25), anterior cingulate region (BA 32) and sometimes, temporal pole (Fig 1). Indeed stimulation studies during SEEG, using small electrical currents to test the reactivity of specific electrode contacts and their role in the epileptogenic zone (a standard part of the SEEG method) could trigger exactly the same fearful behavioral semiology when certain regions of the anterior cingulate or orbitofrontal cortex were stimulated, thus confirming their role in seizure organisation. The role of these ventromesial prefrontal structures, and their paralimbic connections (especially amygdala) in emotional processing of fear in normal subjects and in patients with brain lesions has been clearly defined by Damasio and others[105, 106].

The electro-clinical pattern described in this series also resembles what has been termed "type 1 hypermotor seizures (HMS1)"[107] in a published series that reflects interest in the notion of hypermotor or hyperkinetic seizures as a specific clinical entity[15]. However, in the frontal seizures paper included in this thesis, ictal movements associated with fearful behavior were in fact not invariably hyperkinetic. Indeed rather than agitated movements, some patients presented what appeared to be defensive behaviour (hiding face in hands or in pillow, or "freezing" in fear), as also observed in a previous study[98]. This seems to suggest that the affective component of fear (and/or anger) may be a more relevant semiological characteristic in this group than the specific pattern of motor behaviour. This could indeed be in keeping with the notion of a cingulate area for fear avoidance[108]. Clinical seizure expression in ictal fear-related behavior may well be influenced by individual internal and external factors (e.g.

patient personality, environmental conditions); this will be further discussed in a later section.

Finally, ictal fear-related behavior has been studied using signal analysis from SEEG data, with the important finding that desynchronisation occurred between the ventromedial prefrontal region and associated structures of the paralimbic network at the time of onset of clinical signs[49], particularly between orbitofrontal cortex and amygdala. It is hypothesized that this functional decoupling produces disruption of normal control mechanisms of emotional behaviour.

5 Neural substrates of semiology: the importance of considering both temporal and spatial features of electrical seizure discharge

The two examples of complex semiological features of epileptic seizures described above (altered consciousness and fear-related behaviour) thus demonstrate the relevance of SEEG when trying to better understand their underlying neural mechanisms. Seizure semiology can be seen as an emergent property of a dynamic, non-linear system with self-organising properties, in a similar way to the properties of the electrical discharge that underlies its production[87]. As such, attempts to understand correlations between (mainly cortical) electrical activity and clinical signs must take into account both the anatomical spread of seizure and the timescale over which changes occur.

It can be noted that, as mentioned above, by studying SEEG signals and their correlations in different structures at different times in the seizure, fear-related behaviour is associated with sudden *reduction of synchronisation* in the epileptogenic network, whereas altered consciousness is associated with *increased synchronisation* within the epileptic neural network. This difference in synchronisation pattern may be partly explained by the frequency of seizure discharge, since fast gamma band epileptic discharges (as seen in the fear-related seizures) tend to produce desynchronisation, whereas epileptic discharges in a slower, more physiological range (as seen in many seizures with altered consciousness) often lead to hypersynchronisation[4]. Other examples of

seizure semiology associated with hypersynchronisation within a distributed network are déjà vu[109, 110] and ictal humming or singing[48, 111].

This indeed highlights the importance not only of *spatial* (localisation) aspects of seizure organisation in understanding the emergence of semiology, but also its *temporal* aspects (e.g. discharge frequency, latency and synchronisation effects). Temporal aspects of seizure organisation have tended to be neglected in previous studies of seizure semiology, which have often concentrated on searching for "localising value" of semiological features, and often (perhaps inappropriately in some cases) searching for a linear, one-to-one association between a particular semiological sign and a particular cortical region[20]. Indeed in the majority of previous studies, even those with detailed semiological analysis and intracranial EEG data, only structures involved at seizure onset are typically considered[112], rather than taking a more dynamic approach to seizure discharge as it evolves throughout the longer period of appearance of semiological signs (as termed the "early spread network" by Bancaud). This is indeed a crucial point, illustrated in Figure 4: seizure onset is characterised by the transition from preictal rhythmic spiking to the appearance of a fast low voltage discharge (gamma band) in frontal pole and pre-cingulate regions, which then develops over at least 20 seconds, with no clinical sign being observed; it is only when the seizure spreads to anterior premotor regions and orbitofrontal regions, with a theta-range discharge, that the semiology emerges. It thus seems logical to analyse both seizure onset and early seizure spread patterns. This aspect of dynamic analysis of seizure evolution was likely crucial in the frontal seizures studies included in this thesis (Articles 3, 4 and 5), in being able to demonstrate correlations between semiological and electrical patterns, and helps to explain the many "negative" results in previous studies[112].

6 Interaction of seizure discharge with normal brain networks: influence on seizure semiology and interictal function

The question of why some patients with fear-related behaviour in seizures should present a more aggressive pattern of behaviour and others a more defensive pattern, as described above, is an interesting topic for reflection. Another example of variability in semiological expression is our observation that

semiology of the most anterior prefrontal seizures was more likely to be affected by the environment and the presence of an examiner than was the semiology of more posterior prefrontal or premotor seizures[27]. For example, seizures involving the frontal pole and lateral orbitofrontal cortex could be associated with retained awareness including eye contact, laughing in a social context and conversation with the examiner, including echolalia[27, 53]. This likely relates to the role of the most anterior prefrontal regions in social cognition[113] and as such could be seen as another reflection of the hierarchical organisation of the frontal lobes[92]. Seizures involving prefrontal regions, much more than other brain regions, often show an "idiosyncratic" appearance, perhaps reflecting the patient's underlying personality, with great variation between individual patients. That differences in semiological expression may occur between individuals with ostensibly similar electrical seizure organisation in both spatial and temporal aspects, suggests that additional factors are brought into play. These might conceivably involve intrinsic factors related to the patient's personality or cognitive profile, and extrinsic factors in terms of environmental conditions at the time of the seizure (e.g. enclosed space, approach of examiner, perceived degree of threat of approaching person (male versus female), cultural factors, whether patient is in bed or standing up at the time of seizure onset, and so on.). This aspect of interactional factors affecting behavioural expression evokes the notion of "embodiment" in social psychology, which assumes that thoughts, feelings and behaviour are grounded in sensory experiences and bodily states, necessarily prone to environmental influence[114]. It may also be related to the concepts of "coping style"[115] and "behavioural syndrome"[116] as studied in animal and human subjects, which help to explain individual variation in behavioural types, and which are influenced by genotype, development, early experiences, social support, etc. The idea that such factors might influence expression of seizure semiology could of course be relevant not only to behavioural expressions during epileptic seizures but also the phenomenology of psychogenic non-epileptic seizures (further discussed below).

As well as ictal semiological expression, the factors that tend to trigger seizures could also be influenced by these variations in internal and external conditions between patients. For example, in some forms of epilepsy, seizures are triggered by stressful situations[117]. A subgroup of such patients with temporal lobe epilepsy (TLE), whose seizures were typically triggered by emotional factors,

showed altered interictal cognitive function with an attentional bias towards threatening stimuli[118]. In such cases the epileptic pathology, because of its localisation in mesial temporal networks that are directly involved in emotional processing (paralimbic network, especially the amygdala), is the major cause of the abnormal emotional and cognitive processing in these patients, with pre-existing biological or psychological profile likely also playing a role (since not all patients with TLE manifest an emotional component). The perception of stressful situations in these patients is likely to be heightened, as illustrated by the attentional bias mentioned above; and because emotional processing occurs within the same network involved in seizure production (especially the amygdala and its connections), an increase in stress response can "tip the balance" within this unstable network and provoke a seizure.

To summarize, for a given individual, epileptic seizures can thus be seen to interact with cognitive networks that influence the interictal state and triggering of seizures, and which continue to function, at least partially, during the seizure; and these are likely influenced by both intrinsic (e.g. personality) and extrinsic (environmental) factors. How these factors interact to influence seizure semiology, and how they might impact on interictal psychological, cognitive and social function, is an intriguing and understudied aspect of epileptology.

7 Additional commentary on papers included in thesis (articles 2-6)

7.1 Validation of the SEEG electroclinical method as a tool for localization in lesional and non-lesional epilepsy (articles 2 and 3)

Despite advances in neuroimaging, using best practice imaging protocols up to 50% of patients evaluated in tertiary epilepsy surgical centres still have normal or non-contributory imaging results[119]. In addition, a given radiologically visible lesion may not necessarily be concordant with other clinical data[120]. The detection of "false positives", that is, clinically irrelevant lesions, may become more frequent with increasing resolution of structural imaging[120] and there are likely to be natural limits to the contribution of more sophisticated imaging in

improving our ability to localise the EZ. Thus, it remains necessary to maximise the information drawn from all available non-imaging data, including seizure semiology[4, 13], in the context of presurgical evaluation. Better understanding of this is also essential if progress is to be made in understanding seizure organisation[121, 122]. Indeed semiological and electrophysiological data can contribute to better *a posteriori* radiological determination of anatomical abnormalities using post-processing methods, by reducing the size of the field to be imaged and focussing on a specific brain region that has been identified by electro-clinical data[3, 123].

Such patients with so-called "MRI-negative epilepsy" present particular challenges for presurgical evaluation, since necessarily assessment of likely localisation of the EZ relies much more heavily upon the other available non-invasive investigations[124-126], and upon clinical seizure semiology. Comparing accuracy of SEEG in this MRI-negative group to those with a radiologically visible and probably epileptogenic lesion, therefore presents a means of indirectly validating the accuracy of the electroclinical hypotheses, including semiological data. Since a high rate of localisation was achieved in this study (Article 2 of this thesis), with no difference between the 2 groups, the SEEG method (this having indeed been developed in the pre-MRI era) was shown to be highly effective and independent of radiological lesional status. These findings are therefore an indirect validation of the accuracy of the pre-implantation hypotheses based on clinical semiology and non-invasive data, since electrode placement is entirely dependant upon this step, as well as of accuracy of analysis of SEEG data itself.

In terms of surgical outcome, a high proportion of seizure-free patients in the MRI-negative group proved to have focal cortical dysplasia. The positive surgical outcome in this subgroup of MRI-negative FCD is in marked contrast to the much poorer results reported in contemporary studies using subdural grids[22]. One explanation may be the ability of SEEG to record from FCD located in the depth of sulci, a characteristic anatomical location for the development of this type of malformation. In our series dysplasia cases often showed a characteristic pattern of subcontinuous rhythmic spiking in the pre-ictal and interictal period[127]; this is in keeping with others' observations and the pattern can be considered an electrophysiological signature of FCD, indicating that electrode localisation is within or very close to the lesion[128] (figure 4). Such observations have

contributed to increasing use of SEEG in preference to subdural grids for exploration of suspected FCD in MRI-negative cases[51].

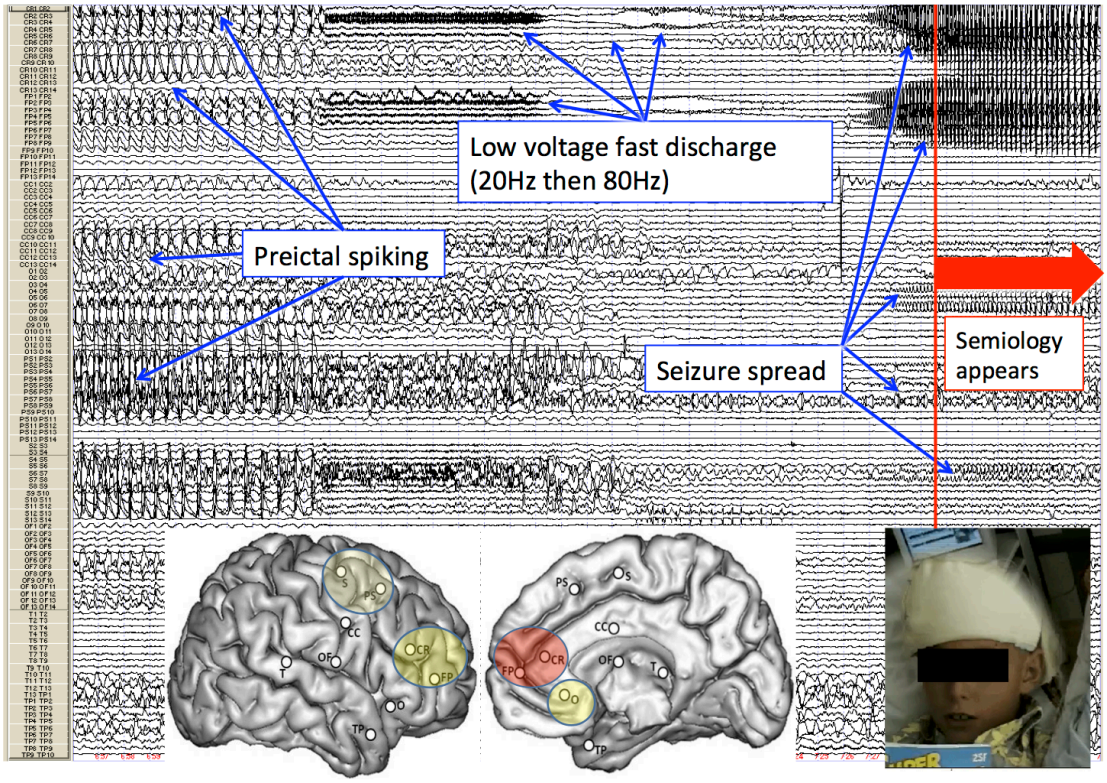

Figure 4. Example of a prefrontal seizure recorded with SEEG, in a patient with MRI-negative cortical dysplasia. Preictal rhythmic spiking precedes the onset of a low voltage fast discharge (gamma band), recorded from a relatively focal region of right anterior prefrontal cortex including the frontal pole (maximal in electrodes CR and FP). The appearance of clinical signs occurs several seconds after the fast discharge, at which time slower rhythmic discharges (theta band) are also seen in anterior premotor regions and anterior cingulate gyrus. Identical seizures could also be triggered in this patient by stimulating electrodes CR and FP.

7.2 From semiology to localisation in frontal seizures (article 4)

Frontal seizure patterns in terms of semiology may be extremely difficult to analyse since these are typically complex, variable and often expressed as very brief seizures, in which multiple signs may appear simultaneously or in rapid succession. It has indeed been commented that distinguishing between different subgroups of frontal seizures according to anatomical localisation is perhaps impossible[20]. However clinical experience dictates that a certain degree of resemblance can be recognised between patients, lending support to the notion that specific sub-systems within frontal lobes might underlie different clinical seizure patterns, and thus that a classification of frontal lobe seizure (FLS) could be possible[129]. It is recognised that, while seizure expression in frontal lobe

epilepsy (FLE) might be very variable between patients, there nevertheless exists a high degree of reproducibility for a given patient's seizures[130], suggesting that specific circuits underlie clinical expression of the pathophysiological discharge[21].

This study demonstrated that clear relation exists between clinical seizure pattern and cerebral organisation of seizure discharge, and that this is demonstrable using the SEEG electroclinical method. This was true for all types of frontal seizures over a heterogeneous population, including the most complex behavioral expressions. The methodological approach was particularly important here and differed from previous studies, particularly in choice of semiological categories and the use of direct comparison of the evolving clinical sequence with SEEG data, and this probably played a crucial role in being able to demonstrate correlations. A particularly novel finding is that of the rostrocaudal gradient of semiological expression, which has never previously been demonstrated for epileptic seizures. Increasingly complex, highly integrated behaviors, with more distal repetitive movements, often involving emotional expression and/or interaction with the examiner, were observed in progressively more rostral localisations of the epileptogenic zone. Such an observation is in keeping with current neuroscientific thinking on frontal lobe function[94] and reinforces the validity of further pursuing this line of investigation in frontal seizures. Confirming these results in an even larger group of patients would help to reinforce validity but could also give a "higher resolution" view of semiological subtypes.

7.3 Proposal for a conceptual framework for categorising complex motor behavior in frontal lobe seizures: ictal stereotypies (article 5)

A striking methodological challenge when attempting to classify frontal lobe seizures using semiology is the need for accurate observation, description and categorisation of motor behaviour. Indeed this step seems to be essential to the ultimate demonstration of correlation between clinical semiology and specific frontal lobe regions[27], and its abstruse nature is probably reflected in the "negative" results of previous FLE studies[112]. An example is the use of the generic term "automatism" to group together many diverse forms of ictal

behaviour[112], and the lack of any specific anatomical or physiological substrate implied when employing this[10]. The presence of repetitive motor behaviour may not uncommonly be observed in FLS, evoking the term "stereotypies", defined by Ridley[131] as excessive production of one type of motor act necessarily resulting in repetition. The challenges and importance of accurate definition of this clinical entity have recently been highlighted[132]. The relevance of stereotypies in the context of the present research question is that over the past decade, their neuronal substrate has been gradually elucidated through animal[133] and human[134] models of repetitive behaviours seen in various pathologies[135, 136]; there is convincing evidence that specific cortico-striatal circuits underlie such behaviours, being the same neural pathways as those involved in physiological motor learning that are necessary to encode motor sequences. Frontal lobe cortex is topographically connected to striatal structures[137]. This provides a clear conceptual framework for investigating in detail the relation between motor behaviour patterns and seizure organisation.

These observations therefore indicate a localising value for different forms of ictal stereotypies in prefrontal seizures, since distal stereotypies were associated with more anterior prefrontal lobe localisation and proximal stereotypies with more posterior prefrontal lobe involvement. More complex and more distal motor stereotypies were sometimes associated with verbal stereotypies, expressed in a context of integrated behavior[27], which occurred in the most anterior prefrontal localisations. This again is an indication that seizure organisation in frontal lobe epilepsy follows a hierarchical "structure", whereby the more complex, integrated ictal behaviours are associated with seizure involvement of progressively more anterior, or rather more rostral prefrontal structures.

That repetitive movements and behaviours, sometimes qualitatively similar to those observed in other neurological conditions[138], may also occur in the course of frontal lobe seizures, evokes the possibility that specific cortico-striatal circuits, driven by an epileptic discharge in their cortical component, underlie semiological production[53]. This challenges the traditional assumption that "epileptic automatisms" should be considered as a separate entity[132] when classifying stereotypies. It also calls into question the notion that automatisms occurring during seizures are due to a general loss of cortical control over subcortical structures[139] in favour of a possibly more direct and network-specific

action driven by the cortical epileptic activity. Further work should aim to characterise in more detail different sub-groups of ictal stereotypies, with a view to discerning to what degree clinical expression is dependant on specific cortical structures, and to what degree the same clinical pattern might be elicited by different cortical inputs acting on the same subcortical system.

7.4 Alteration in semiology as a marker of responsiveness to gamma knife radiotherapy (article 6)

An interesting aspect of semiology is its dynamic aspect. Seizure semiology is characterised by rapid evolution in time, being a direct function of the temporo-spatial dynamics of electrical activity within brain networks. In the context of successful epilepsy surgery, when these brain networks are physically disconnected and removed from the rest of the brain by cortical resection, seizures disappear or at least dramatically reduce in frequency[140]. In failed surgery, immediate relapses typically show similar semiology[22] whereas later relapses can show altered semiology. The explanation for this observation remains to be fully elucidated but might include different clinical expression by a residual part of the original EZ because of altered connectivity following surgery. However a different pattern of post-operative evolution of semiology, that showed a very gradual disappearance of the motor component of seizures was observed in cases of paracentral epilepsy treated by gamma knife radiosurgery (GK). GK is an alternative surgical treatment used in some cases of focal epilepsy[141, 142], especially in brain structures not readily amenable to microsurgery[143]. The majority of cases treated for focal epilepsy using GK have been mesial temporal lobe epilepsies[144-146] or epilepsy related to hypothalamic hamartoma[143]. The role of GK in focal extra-temporal epilepsies remains to be determined. Given its ability to treat highly focal regions and deep structures, there is growing interest in the potential of using GK for certain extra-temporal cases deemed inoperable by conventional surgery[147].

It is noteworthy that a therapeutic effect was produced very gradually in these patients, with (somewhat surprisingly, given the efficacy of the treatment in 2/4 patients), no visible tissue alteration on MRI, and preceded ultimate reduction in seizure frequency. This seems to fit with the suggested mechanism of a neuromodulatory, rather than a destructive effect, of GK[141, 148] and implies that improvement was due to microscopic changes at the glial/neuronal/white

matter cortical levels not visualizable on MRI. The somewhat unexpected semiological evolution observed here has not previously been highlighted, including in the various studies on GK in temporal lobe epilepsy[145, 148], and its neuropathophysiological basis remains to be elucidated. Observation of semiological modification prior to reduced seizure frequency has been made in other patients in our centre with focal extra-temporal epilepsy, including one insular and one parietal (unpublished observations, in preparation) and thus does not seem to be specific to paracentral epilepsy. Seizure semiology could be considered here as a dynamic marker of response to gamma knife radiosurgery, offering both a clinical indicator and an intriguing domain for further research. More work requires to be done to optimise patient selection for GK, since factors such as cortical region, focality of EZ and discharge type may play a role in responsiveness to this treatment.

8 Differential diagnosis of complex motor behaviour and/or altered consciousness: role of video-EEG in distinguishing epileptic seizures from psychogenic non-epileptic seizures (PNES) (commentary on articles 7-10)

The above discussion has dealt so far with complex patterns of motor behaviour and/or altered consciousness that arise because of an epileptic discharge within the cortex. However when evaluating any form of paroxysmal behavioral disturbance in the clinical setting, a first step is to assess whether it is actually caused by an epileptic discharge or not, since other forms of pathology, particularly psychogenic nonepileptic seizures (NES), may be difficult to distinguish from epileptic seizures on a purely clinical basis[149], and require video-EEG recording[150] for confirmation. This presents an important clinical challenge, the difficulty of which is reflected in high rates of delayed and erroneous diagnosis of attack disorders[149].

8.1 Use of suggestion techniques to increase yield of video-EEG recording of PNES (articles 7-9)

In order to achieve optimal patient care and to minimise the risks of

inappropriate treatment due to diagnostic error, reliable and practicable means of diagnosis are required[149]. Recording of habitual events of video-EEG is the gold standard[149] but access to this relatively expensive resource[151] may be limited, contributing to diagnostic delay. Suggestion methods have long been employed to maximise the chance of recording typical events in patient with suspected PNES, but some previous studies have been criticised for the use of sometimes invasive and essentially dishonest means of suggestion (e.g. an injection of normal saline, telling the patient that it will induce an epileptic seizure) and this area remains rather controversial[152, 153].

The findings of the randomised study included in this thesis indicate the clinical utility of simple suggestion methods in allowing recording and thus definitive diagnosis of PNES[149]. Diagnosis was robust since no diagnosis of PNES was later revised to epilepsy. A similar yield of around 40-50% overall diagnostic yield of PNES has been shown using similar suggestion techniques in larger groups[149, 154]. An important aspect of the methodology was the use of as honest an approach as possible, in contrast to some previous studies: patients were told that PNES were suspected and that the goal was to record these, which nevertheless did not appear to reduce recording yield[155].

The question of how suggestion may act to trigger PNES in susceptible patients is an interesting one. Within the general population different individuals have a greater or lesser tendency to what has been termed “hypnotic suggestibility”, measurable by several validated scales[156]. A high level of suggestibility has long been considered a feature of hysteria[157], nowadays conceptualised as functional (or somatoform) disorders[158]. Patients with PNES have been described as showing high hypnotic suggestibility[159]; however, it has been highlighted that dissociative tendencies may perhaps represent a more important factor[160] in explaining their apparently suggestible profile. From the work of Charcot, Janet and Freud came the idea that hypnosis, hysteria and dissociation are closely linked; this notion remains current today, and has begun to be tested scientifically[156, 161, 162]. Suggestion is also a component of the increasingly well-studied placebo effect[163, 164], that is, a “psychobiological phenomenon attributable to the overall psychosocial therapeutic context”[164], which encompasses expectation of a certain outcome. In our studies of PNES, the setting is the video-EEG recording and the expectation (of the patient and of the doctor) is that there is a greater chance than usual that a seizure will occur. It is interesting that, in patients in

our study in whom suggestion during video-EEG provoked an event, there was a prior history of events occurring in medical settings[165], indicating an implicit degree of increased baseline suggestion caused by the situational context for this subgroup. The increased tendency to suggestibility in patients with PNES has been conceptualised as an expression of an unstable, poorly flexible cognitive-emotional system[166]. In the context of patients presenting PNES during video-EEG, it seems likely that specific vulnerability traits that are characteristic of this population contribute to whether or not attacks are triggered in specific settings. These could include altered arousal[166], increased anxiety[167], dissociative tendencies[168] and emotion-focussed coping strategies[160]. This echoes to some degree the factors that may also influence seizure production in patients with epilepsy whose seizures are triggered by emotional factors, as discussed earlier[118].

8.2 Parietal seizures mimicking psychogenic non-epileptic seizures (article 10)

Diagnostic confusion is particularly evident when trying to distinguish non-epileptic seizures from epileptic seizures characterised by complex behavioural features as described above. The classical epilepsy type associated with this diagnostic difficulty is that of frontal lobe seizures, particularly of the "hypermotor" kind[149, 169]. However parietal epileptic seizures are probably an under-recognised and possibly more important source of diagnostic error in this regard.

Parietal seizures typically do not show prominent hypermotor features[170, 171] but rather complex sensory illusions often associated with partial or complete alteration of consciousness, that may follow a waxing and waning pattern[26], often without clear surface EEG change in the early part[26, 28, 171]. The semiological picture observed in this series of parietal seizures could evoke the "pseudosyncope"[38, 172] type of PNES in some, or the "dystonic attack" type as described by Hubsch and colleagues[38]. The waxing and waning evolution of clinical signs observed in our cases is especially pertinent given that this feature is typically associated with NES rather than epileptic seizures[38]. It has been highlighted that analysis of semiology as well as history and EEG is crucial when making a positive diagnosis of NES[149] and this seems especially true in episodes

characterised by complex behavioral semiology. Parietal seizures, and not only frontal seizures, should be considered within the differential diagnosis of NES[173].

9 Conceptualising pathogenic mechanisms of complex motor behaviour and altered consciousness in PNES

Despite similarities in clinical aspect, the complex motor behavior and altered consciousness produced during epileptic seizures and those produced during PNES certainly do not have the same neurobiological mechanism, since in PNES no electrical modification of cerebral origin is visible on scalp EEG[174]. In rare cases of PNES recorded during intracranial EEG investigation in patients with epilepsy[175], similarity in semiology of both types of event (epileptic and non-epileptic) has been noted, with no seizure discharge in the cases considered to be PNES; although the limited number of data, including SEEG sampling issues, probably limits the conclusions that can be drawn from this particular study. Previous studies of patients presenting both epileptic seizures and PNES have noted similar semiological features between both attack types in about a third of subjects[176, 177]. Semiological analysis of PNES may certainly provide a useful basis for identifying patient subgroups and may thus facilitate study of the diagnostic, prognostic and eventually pathophysiological significance of different PNES subtypes[38]. On the other hand, evaluation of semiological data in PNES is hampered by methodological difficulties, especially in terms of subjective semiology since this depends largely upon interpretational judgments, which are inevitably prone to bias. Subjective semiology in PNES indeed remains a relatively poorly described area[38, 174, 178]. One important issue that has been identified for functional neurological symptoms in general, and which is almost certainly true for PNES, is the varied way in which patients might experience symptoms of dissociation, and their difficulties in describing this[179].

What mechanisms might be hypothesized to explain the seizure patterns seen in PNES? A certain degree of reproducibility for the semiology of PNES for an individual patient can often be seen clinically. Studies looking at categorising PNES semiological subtypes over a series of patients note that individual patients usually (but not always) present seizures that fall into the same category, e.g. hypermotor attacks[180]. However more precise examination of reproducibility of motor semiology in PNES would require detailed and ideally quantitative video

and/or accelerometry methods, recording multiple seizures per patient over a series of patients; to my knowledge such a study has not so far been performed. If reproducibility for specific motor sequences (including parameters such as rhythmicity and amplitude of movements, for example) was demonstrated, this could be an argument in favour of a specific learned motor pattern that becomes progressively reinforced over time in patients with motor PNES. This notion seems close to the mechanisms involved in stereotypy production, in various neurological conditions[134], and in some epileptic seizures[53], as previously discussed. Indeed this would fit with the conceptual pathogenic model proposed by Baslet, in which the particular baseline emotional and cognitive profile of patients with PNES leads to events being triggered by subconsciously perceived (emotional) stimuli, leading to what Baslet terms "deployment of pre-wired behavioral tendencies"[166]. Whether or not the pattern of movements or altered consciousness seen in PNES are really "pre-wired" can be debated; but in any case the repetition of these behaviours over time could certainly lead to their becoming ingrained and automatic via physiological processes of motor learning including "chunking"[135]. As has been proposed for other functional disorders including conversion paralysis[161] and psychogenic movement disorders[181], a disruption of higher control networks involving especially prefrontal structures may affect movement initiation, movement conceptualization and experience of volition[161, 182]. The effect of emotional stimuli (testable by experimental paradigms involving perception of happy or fearful faces, for example) may directly influence motor control programmes through altered connectivity patterns between structures involved in emotional processing (e.g. amygdala) and structures involved in motor control (e.g. supplementary motor area) as has been demonstrated in other motor conversion disorders[182]. To apply this theoretical model to motor PNES, a pre-conscious stimulus could thus trigger the stereotyped behaviour pattern of PNES through an interaction between emotional and motor networks, for example via abnormal connectivity involving salience and executive networks[183].

In the case of PNES characterised primarily by altered consciousness, it could likewise be supposed that alterations occur in the networks responsible for maintaining awareness of self and the environment. The nature of altered consciousness in PNES is even more challenging to evaluate and study than that of epileptic seizures[184], and seems to be qualitatively quite different, both in

terms of level and content[72]. Around a third of patients with PNES in one series described complete loss of consciousness and another third described partial awareness but being unable to react[178]. One interesting theory to try and understand this clinical phenomenon incorporates the notion of altered perception of agency and bodily consciousness. This has been proposed in the context of fMRI study of paroxysmal psychogenic movement disorder, in which right temporo-parietal hypoactivation was demonstrated[181]. This brain region is known to be involved in self-awareness and has been proposed as a centre for integration of bodily self-consciousness, drawing on data from studies of out-of-body experience[185, 186]. This region is also of course involved in networks subserving consciousness, as discussed earlier with regards to epileptic seizures.

A number of recent studies have employed analysis of resting state connectivity in patients with PNES to try to elucidate possible pathophysiological mechanisms involved. Studies of interictal brain connectivity in patients with PNES using fMRI[187, 188] have shown complex and widespread alterations in resting state structural and functional connectivity, including increased coupling in fronto-parietal regions[189]. Studies using high density interictal EEG have also shown altered connectivity implicating fronto-parietal[190] and possibly basal ganglia[191] dysfunction, postulated to be a neurobiological correlate of dissociation. A study of brain metabolic resting state from our team, in a group of patients with PNES, indicated reduced hypometabolism in right parietal and anterior cingulate regions[192]. While methodological limitations restrict the conclusions that can be drawn by these different studies, the data overall points to pathological functioning in the baseline (interictal) state of multiple, multi-level distributed networks involved in many different aspects of cognitive processing. Further work could aim at refining such connectivity studies, looking at specific subgroups of patients with PNES (for example controlling for psychiatric comorbidities, dissociative tendency, semiological seizure type, duration of seizure history, aetiology and so on). Information on the pathophysiological mechanisms of seizure organisation, semiological and interictal dysfunction in epilepsy (from SEEG and other sources) seems particularly valuable when attempting to think about the possible mechanisms of PNES, because of the paroxysmal nature of both disorders, and because of phenomenological overlap in clinical presentation.

10 Conclusions

The above studies demonstrate that analysis of seizure semiology, analysed in conjunction with EEG data, allows meaningful investigation of cerebral substrate of ictal signs, both in epileptic and psychogenic, non-epileptic seizures. Moreover this approach provides a scientific framework in which to investigate cerebral organisation of seizures, and thus eventually characterise cerebral substrates of specific behavioral or cognitive features occurring during seizures. The methodological challenges are however significant, especially in terms of current approaches to analysis and categorisation of clinical signs, which necessarily involve a high degree of bias. In addition inevitable bias of SEEG electrophysiological data in epilepsy arises from the fact that electrode placement, performed in a clinical context, depends directly on first having correctly predicted likely brain systems and structures involved for a given patient's epilepsy, and must necessarily limited to the minimal number of sites necessary for clinical evaluation. It can be imagined however that future progress in semiological analysis, perhaps using more quantitative methods, coupled with progress in imaging and electrophysiological analysis could lead to significant shifts in current understanding (figure 5).

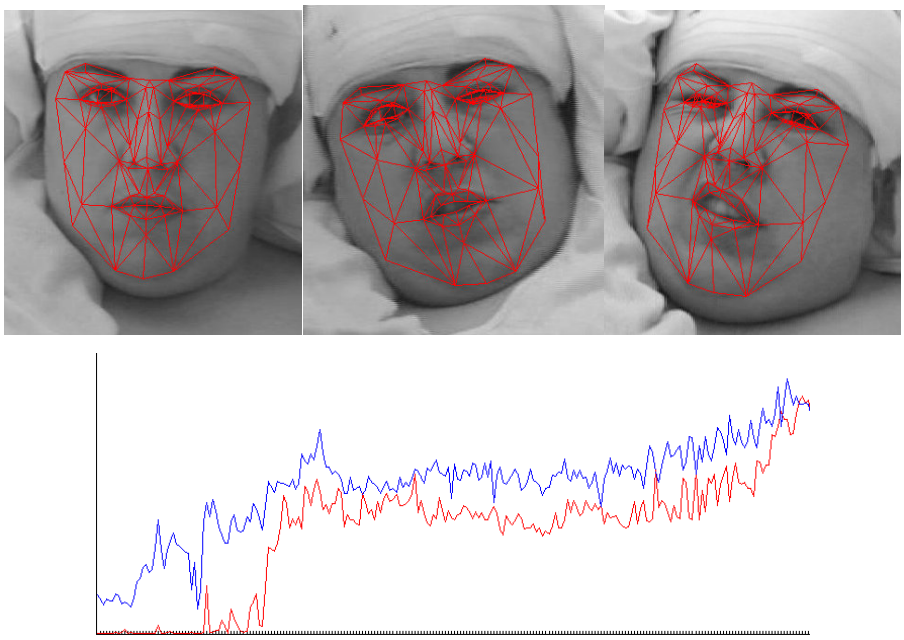

Figure 5. Quantative approaches to semiology could provide new means of analyzing motor behavior and its relation to underlying electrical activity. Patient's facial expression during frontal lobe seizure analysed using parameterized face mask specifically developed for model-based coding of human faces[33]. **Top panel**. The left image shows a neutral view and the two other images are taken during the seizure. **Bottom panel**. Evolution of facial parameters during a frontal lobe seizure. The time is on the x-axis. The red curve is the left opening of the mouth and the blue one is the right opening of the mouth.

Better interactions between neuroscientists and clinicians, for example in the study of complex movements and repetitive behaviour, could help develop mutually beneficial research directions, both in epilepsy and in PNES.

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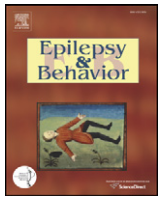

Review

Emergence of semiology in epileptic seizures ☆

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ABSTRACT

Semiology, the manifestation of epilepsy, is dependent upon electrical activity produced by epileptic seizures that are organized within existing neural pathways. Clinical signs evolve as the epileptic discharge spreads in both time and space. Studying the relation between these, of which the temporal component is at least as important as the spatial one, is possible using anatomo-electro-clinical correlations of stereoelectroencephalography (SEEG) data. The period of semiology production occurs with variable time lag after seizure onset and signs then emerge more or less rapidly depending on seizure type (temporal seizures generally propagating more slowly and frontal seizures more quickly). The subset of structures involved in semiological production, the "early spread network", is tightly linked to those constituting the epileptogenic zone. The level of complexity of semiological features varies according to the degree of involvement of the primary or associative cortex, with the former having a direct relation to peripheral sensory and motor systems with production of hallucinations (visual and auditory) or elementary sensorimotor signs. Depending on propagation pattern, these signs can occur in a "march" fashion as described by Jackson. On the other hand, seizures involving the associative cortex, having a less direct relation with the peripheral nervous system, and necessarily involving more widely distributed networks manifest with altered cognitive and/or behavioral signs whose neural substrate involves a network of cortical structures, as has been observed for normal cognitive processes. Other than the anatomical localization of these structures, the frequency of the discharge is a crucial determinant of semiological effect since a fast (gamma) discharge will tend to deactivate normal function, whereas a slower theta discharge can mimic physiological function. In terms of interaction between structures, the degree of synchronization plays a key role in clinical expression, as evidenced, for example, by studies of ictal fear-related behavior (decorrelation of activity between structures inducing "release" phenomena) and of déjà vu (increased synchronization). Studies of functional coupling within networks underlying complex ictal behavior indicate that the clinical semiology of a given seizure depends upon neither the anatomical origin of ictal discharge nor the target areas of its propagation alone but on the dynamic interaction between these. Careful mapping of the ictal network in its full spread offers essential information as to the localization of seizure onset, by deducing that a given network configuration could only be generated by a given area or group of areas.

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1. Introduction

Clinical semiology is the manifestation of epilepsy. Significant advances in the comprehension of the epileptic diseases, at least in seizure structure, were achieved long before the advent of electrophysiology and neuroscience, notably in the second part of the 19th century by Herpin [1], Gowers [2], and Jackson [3]. In this era, the only available approach to the investigation of epilepsy (apart from postmortem brain examination) was, of course, through direct observation of seizures, allowing the formulation of hypotheses regarding their pathophysiological basis that show remarkable accuracy in light of the modern understanding of epilepsy [3–7]. The ability to use this clinical information alone to categorize seizures and to form such hypotheses of underlying disordered brain function indicates that semiology is not an epiphenomenon but rather a hallmark of this peculiar disorder in the brain. Decades later, the advent of EEG recording led to a second major step in the advancement of seizure understanding, just as important as semiological observation but more readily quantifiable: the identification of an electrical marker of neuronal dysfunction. The resulting dialogue between these two identifiers of epilepsy, that is, clinical signs and

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pathological electrical activity, has remained at the center of clinical evaluation and, consequently, clinical research.

Among the pioneering concepts of John Hughlings Jackson, one of the most important is represented by his term "discharging lesion" to designate the brain functional process at the origin of seizures. Once the electrical counterpart of this process was discovered some 40 years later, it seemed legitimate to merge both clinical and electrical aspects of seizure expression into a single entity. The time markers of epilepsy rhythms, thus, became labeled according to a presumed binary relation between observable clinical features and measurable electrical activity. The first axiom has been that there are periods of time characterized by abnormal electrical activities without clinical manifestations, which define interictal activities [8]. The second axiom is that there is a dependency of clinical signs and symptoms on electrical activity.

The observed dependency of clinical semiology on electrical activity could have well been a simple coincidence or an epiphenomenon. Taking examples from other neurological conditions, the presence of a sensorimotor deficit in stroke or cognitive impairment in neurodegenerative disease is not necessarily due to the EEG slow waves that may be observed in these situations. However, in epileptic seizures, the causal relation between electrical abnormality and production of ictal signs is real. What has led to establishing the link between semiology and electrical discharge in epilepsy is certainly the observation that "auras" and full seizures could be induced by electrical stimulation of the cerebral cortex, with frequencies in the same range and likely time correlation of the two phenomena [9]. Intracerebral recordings allowed demonstration that abnormal electrical activity preceded the onset of a clinical manifestation [10,11]. Nevertheless, this precession alone did not ipso facto demonstrate linear causality. Again, Jackson, reasoning in terms of his hypothetical "discharging lesion" and unencumbered by the (as yet unknown) physical electrical discharge, had well anticipated the debate in envisaging how this discharge might remotely activate or inactivate the normal regions of the brain.

2. Localizational reductionism

With technical advances in the field of imaging and the rapid development of epilepsy surgery to remove the cerebral lesion that has become visualizable by radiological means, emphasis has been increasingly placed on localization. Curiously, two trends have evolved in parallel. On the one hand, some papers have seriously questioned the capability and, therefore, the utility of clinical semiology as compared with morphological techniques in localizing the epileptogenic zone [12,13]. The presence of a radiological lesion is regarded as a heavily weighted piece of evidence in favor of the zone of seizure origin more or less independent of clinical seizure presentation [14,15], leading to less emphasis on detailed semiological analysis, especially in mesial temporal lobe epilepsies [15]. Indeed, the better prognosis in epilepsies treated by resection of MRI-visible lesions compared with those with no such lesion [16–19] and the apparent lack of ability to predict outcome based on seizure semiology [20] continue to influence selection of patients for presurgical evaluation. This has almost certainly led to potentially operable cases being excluded from intracranial exploration on the supposed basis of likely poor outcome [21]. On the other hand, enthusiasm for classification has induced an opportunist concept of "localization-related epilepsies", with inevitable confusions between seizures and epilepsies and between the epileptogenic zone (misunderstood as seizure-onset zone) and its clinical expression. The ILAE 1989 classification [22] is particularly informative from that perspective, providing a ready-to-use compendium of signs and symptoms supposed to support a lobar localization. Such a compendium was in fact drawn from the SEEG experience at that time [23], but in the interests of simplicity and practicality, contrived to constrain an evolving sequence of manifestations within anatomical lobar limits. It could be considered that, unfortunately, this commendable effort led to the opposite effect, being inaccurate and often misleading. Why do we imagine that the propagation of an epileptic discharge should respect "lobar" boundaries? Since anatomical systems are based on neural connections between structures rather than spatial proximity [24], it seems logical that the propagation of seizure discharges should occur within existing brain wiring patterns, albeit in a pathophysiological context.

3. Anatomo-electro-clinical correlations and the network concept

From the patient's point of view, semiology is the experience of their epilepsy. In order to understand what semiology represents in terms of its localization within brain structures, it is crucial not to neglect the time dimension of a seizure. Many studies have failed to demonstrate any significant localizing value for isolated signs or symptoms, taking either the lesion or the region of surgical resection as a point of reference [12]. On the other hand, attributing entire sequences of ictal signs to paroxysmal activity in the area of seizure onset [25] is also misleading. The anatomo-electro-clinical method proposed by Bancaud and Talairach [10,26], which was of course developed in the pre-imaging era, is robust whether or not a radiologically visible lesion is present [27]. Rather uniquely amongst means of intracranial recording, SEEG allows appreciation and documentation of temporo-spatial relations in seizure spread, including across distant structures. It is essential to remember here that there is a time lag of variable duration between electrical onset (usually in the form of rapid discharge) and the appearance of the first clinical sign; indeed this time lag (discharge preceding clinical onset) is considered an essential criterion for ensuring the accuracy of localization of the epileptogenic zone as measured by SEEG [10,28]. This is an especially important point given the substantial number of intracranial EEG studies devoted to analysis of discharge pattern at seizure onset (especially fast discharge, see [29] for review) compared with the much smaller number of reports of electro-clinical correlations as they occur during semiological expression of seizures. Time lag between electrical and clinical onset may vary from milliseconds to seconds, depending on the brain regions involved. The time window between clinical onset and full expression of clinical signs is also variable. This "period of installation", when symptoms and signs emerge slowly and progressively (for example in medial temporal seizures), or rather rapidly (for example in frontal seizures), is the critical time window for analysis in order to understand the relationship between clinical semiology and anatomical localization.

The fact that electrical activity at seizure onset cannot alone explain emergence of semiology is quite easy to understand. Functional neuroimaging has extensively documented the fact that any observable behavioral trait or any definable cognitive process is underlain by co-activation/deactivation of (often distant) cortical areas organized as a network [30]. It would indeed be odd if paroxysmal behavioral or cognitive dysfunction due to seizures did not share this basic principle. The relationship between semiology of a given seizure and the so-called "seizure onset zone" therefore cannot be other than complex, since this critically depends on the cortical system in which the seizure develops. The following paragraphs will discuss how seizure localization, propagation, type of discharge, and interaction between structures within the epileptogenic network influence semiological expression.

4. Hard-wired connections and localization

Let us look at the cerebral cortex and how it is organized. In terms of the primary sensory areas (somatosensory, auditory, visual, olfactory, gustatory), there are very few intermediate synapses between the peripheral receptors and the cortex. In other words there is a fairly simple and direct linear relation between clinical signs and seizure discharge arising from primary sensory cortex. Therefore, there is no apparent reason that hallucinations or illusions should not be localizing. This relation has been confirmed for the visual modality through intracranial stimulation and surgically treated case studies [11,31]; for example elementary hallucinations such as colored circles, twinkling stars or

moving flies in left superior visual field quadrant would indicate a discharge in the right infra-calcarine cortex [32–34]. Such elementary hallucinations do not arise within spontaneous seizures beginning in structures distant from visual cortex. More complex visual phenomena such as altered color perception of the current scene (dyschromatopsia) or metamorphopsia, are not associated with onset in primary visual areas but rather imply temporal or occipito-temporal seizure organization with discharge in one of the visual associative areas [35]. Interestingly, epileptic discharges act as interfering noises in cabled and hierarchical systems. Placed at the cortical entry, they will be "interpreted" by the downstream areas as signaling a new object (hallucination), but occurring more distantly in the visual network within the "interpreter" sites the current scene will be distorted or denatured (illusion) [36].

The same disorganization has been evidenced for auditory hallucinations and illusions. Indeed Jackson had already identified elementary auditory hallucinations (which he called "crude sensations") as localizing to the "superior temporo-sphenoidal convolution" through comparison between clinical seizure semiology and subsequent post-mortem examination of the brain [37]. Stimulations (or seizures) limited to the tip of Heschl's gyrus (primary auditory cortex) induce abnormal additional noises such as buzzing or engine sounds perceived in the contralateral ear, whereas a similar discharge in the lateral part (secondary auditory cortex) provokes incoming environmental sounds that are heard louder or fainter, or with waxing or waning modulations [38] (Fig. 1). Illusions can also be produced by stimulations of planum temporale or anteriorly in superior temporal gyrus (STG) (Brodmann's area (BA) 22).

The same principle of producing hallucinations or illusions in the somatosensory system is applicable when ictal discharge onset site changes from primary SI to more posterior (area 5 or 7) or inferior parietal (parieto-opercular SII) regions [39,40]. The synaptic proximity to the periphery guarantees a topologic organization of the symptoms in reference to the topographic maps in these sensory areas, confirmed by cortical stimulation studies [41,42]. Thus a retinotopic, tonotopic, and somatotopic distribution as well as a clear lateralization is respected for seizures arising from the primary sensory areas [11,42].

Since Jackson's era, a grossly similar observation has been achieved for the efferent motor systems. Generation of cortical myoclonus in primary motor cortex is an example that thoroughly demonstrates this topographic wiring [43–45]. Moving away from the primary to the secondary motor area, observation of the signs of local seizure or stimulation provides important data to consider regarding the mechanisms of semiology. Firstly, the topologic character of the motor behavior is less marked; secondly its complexity is greater; and finally inhibitory, namely negative components, appear intermingled with positive ones, or occur as isolated signs. SMA seizures are a perfect illustration of this integrative level of organization. The most commonly observed pattern consists of tonic asymmetric posturing of various types, with more or less pronounced head deviation and arm flexion that is generally contralateral to the ictal discharge, while arm raising and fencing posture occur rarely. However seizures arising from SMA, especially in its rostral part (pre-SMA), consist only of a simple arrest of speech, followed or not by a quavering vocalization, and arrest of movement or subtle leg repositioning. When the examiner raises the patient's arms, they gradually drop back down to their original position. This inhibitory or negative phenomenon occurs with involvement of certain dorsal or ventral premotor areas [46–48], which have been named "negative motor areas". Whether the resulting inactivation effect comes from direct subcortical (brain stem or spinal cord) projection or is mediated through primary motor cortex relay is not clear, and the two mechanisms may operate in parallel.

However another explanation could account for such a phenomenon, since not only negative motor manifestations occur in seizures

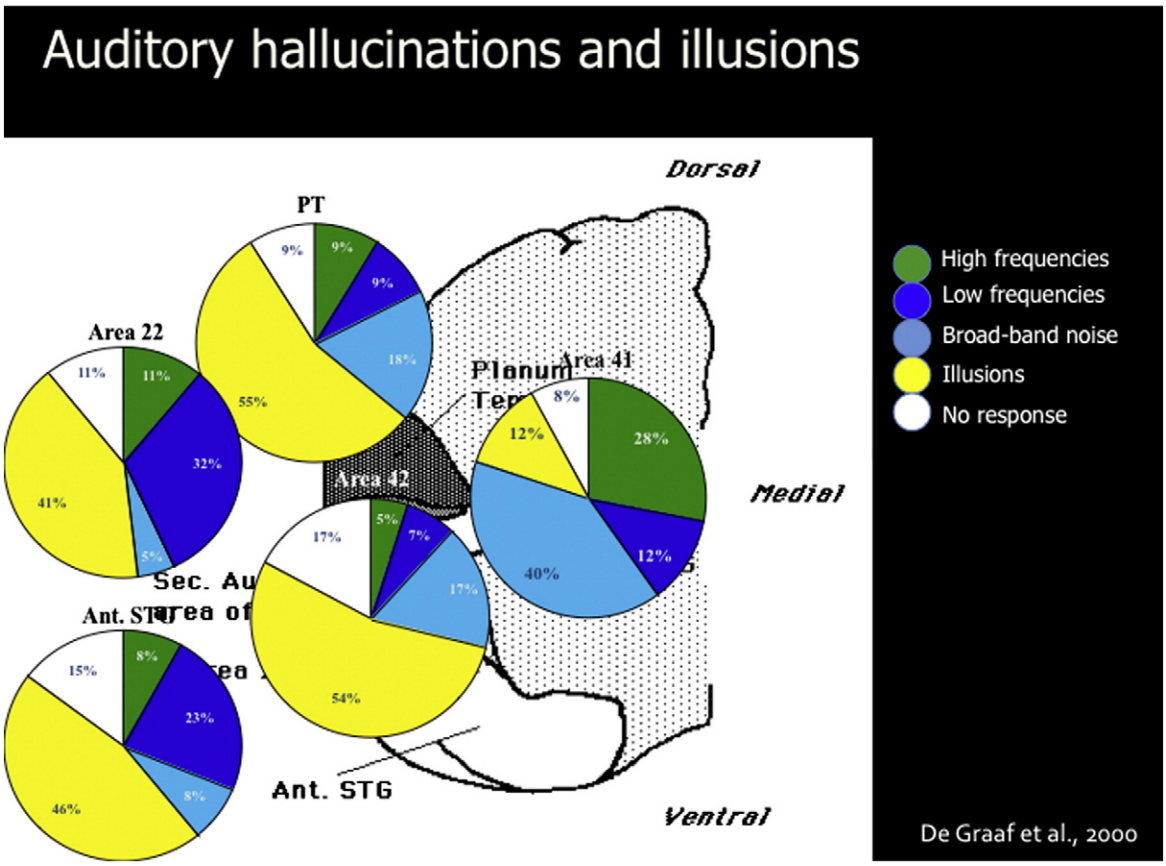

Fig. 1. Results of stimulations of the superior temporal gyrus and planum temporale (from [38]). Stimulation of the medial transverse gyrus of Heschl produced auditory hallucinations in 80% of the patients, most being high-frequency or broadband noise. Stimulation of the lateral transverse gyrus, as well as of anterior superior temporal gyrus or planum temporale led to more illusions (41-55%). From medial to lateral sites, the type of hallucinations changed from high- to low-frequency noises.

starting within these "negative" areas. This critically depends on discharge frequency, as demonstrated in a parent sign, negative myoclonus [48–50]. In a given region of the primary motor cortex, while a phasic discharge superimposed with a fast oscillation leads to a local myoclonic jerk [43], an oscillatory discharge of higher frequency leads to an arrest in maintaining a posture or accomplishing a voluntary movement (Fig. 2). Therefore the semiological expression at the periphery is crucially influenced by the discharge frequency as well as anatomical localization of the seizure.

5. Early Spread Zone

Another factor, often linked to frequency, is the initial extent or spread of ictal discharge. This can be easily observed in motor seizures. Both spatial extent and frequency of the discharge interact to transform a sub-clinical paroxysmal discharge into a clinical seizure in secondary or tertiary areas, and clonic or myoclonic into tonic seizures in primary motor area [51]. Cortical myoclonus, of any type, results from an MI efferent volley. Even though studies using back-averaging might have led to the belief that an EEG spike is the causal event for jerking [52], the few intracerebral recordings published [43,53,54] have stressed the lack of constant time correspondence between spikes and jerks, and especially the presence of fast activities superimposed on phasic, high-amplitude sharp waves. On the other hand, isolated spikes in MII and MIII never result in myoclonus. While premotor areas have been implicated in the pathophysiology of juvenile myoclonic epilepsy [55], hyperexcitability of central cortex has been evidenced through high-amplitude somatosensory evoked potentials (HASEP)[56–58]. As mentioned above, a discharge that remains limited to a part of area 6 (medial or lateral) produces quite different clinical semiology from a discharge that immediately spreads out to neighboring areas. The sub-areas of premotor cortex and the precentral motor cortex are tightly interconnected, so that tonic discharges tend to invade this ensemble of areas as a whole in the different types of tonic-postural seizures [43,51]. The anatomical extent of this "early spread zone" [59,60], and the frequencies developed during the time window just after seizure onset, thus critically determine the clinical features of a given seizure as compared with another one arising from the same region. The early spread zone can therefore be considered as the organic link between the epileptogenic zone and the emergence of semiology.

For the same reasons, the characteristics of early spread determine production of hallucinations or illusions in the sensory and cognitive cortical systems. If visual or auditory areas are instantly invaded by a fast activity, there will be no conscious "perception" of the abnormal or distorted experience [61]. Either positive (production of signs) or negative (functional arrest) features can thus dominate the semiological picture in seizures affecting the same brain regions. Whether this difference in expression is mediated mainly through signal frequency or rate of spread is not yet understood. Therefore, the modes of spread should be analyzed.

6. Inter-areal and trans-areal propagation of ictal discharge

A classical model of seizure propagation is the 'march'. Though Jackson is credited with its historical description, he highlighted that it was in fact Bravais who first proposed the notion of stepwise invasion of neighboring areas by ictal discharge [62]. Progressive somatotopic engagement of limb musculature results from such a march as it develops in motor cortex. Considered as a canonical manifestation of seizures of central origin, march of motor signs is however rarely observed [43]. As discussed above, oscillatory frequency and initial spatial extent of early discharge are the factors that determine the form of clinical semiology, such that, for example, tonic (high frequency) discharges in motor cortex will tend to cause tonic seizures and clonic (lower frequency) spike discharges will likewise give rise to clonic jerks.

An interesting question raised by the march phenomenon concerns the anatomo-functional relation this suggests between a certain mode of discharge and its trajectory on a cortical map. As such, this can be brought to observation only in sensory and motor areas. In the perisylvian region, for example, sensorimotor seizures or sensorimotor-sensory seizures (with two different sensory phases, the late sensory signs being in a different modality from the initial sensory disturbance) can be recorded, which follow a progressive march-like pattern. A patient might report for example initial tingling in cheek, tongue or throat, then hemifacial twitching or a facial expression of disgust associated with hypersalivation, followed by auditory hallucinations or a language deficit. In such cases, intracerebral recordings confirm the accuracy of 19th-century hypotheses of the march phenomenon, showing local discharges of repetitive spikes slowly moving from one area to the next, with strict anatomo-clinical correlations.

Can the march phenomenon be considered a universal model of emergence of clinical semiology as electrical spread progresses? If this were the case, then it might be expected that the clinical expression due to spread of ictal discharge within associative areas would be

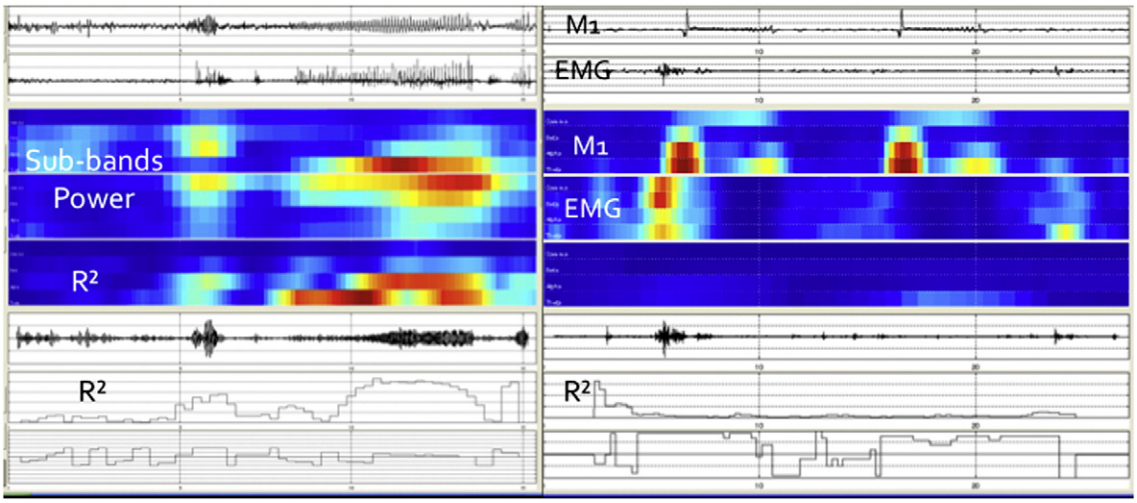

Fig. 2. Correlations between primary motor cortex activity (SEEG) and EMG in central epilepsies. Left: the motor cortex (M1) spike discharge is responsible for a localized muscular activity, with a clear correlation (R2) between both of them in low frequencies. Right: each motor cortex spike is followed by a high-frequency (gamma) burst with no concomitant EMG activity after the background initial voluntary twitch (negative myoclonus). There is no correlation between the central and the peripheral discharge. Below the cortical and EMG traces, sub-band (theta, alpha, beta, gamma) power is represented by a color scale. The bottom graph is the time evolution of correlation (R2).

much less evident than in seizures involving primary cortex, due to less direct connections with the periphery in these associative regions, the more integrative nature of the functions they subserve, or the subtlety of cognitive distortions such seizures generate. On the other hand such progression of seizure discharge might only be characteristic of the primary, secondary and unimodal associative areas through their tight and short inter-connections [63].

Whatever the site of initiation, a single area location of ictal onset seems to be a prerequisite to obtain clinical expression of a march-type spread pattern. It is quite often observed in SEEG practice that long-lasting (up to 1 min.) local discharges, similar in rate and frequency range to the perisylvian sensorimotor seizures described above, may occur in frontal or temporal lobe with no concomitant overt clinical semiology.

This is less true when two or more regions are simultaneously discharging. A usual observation in mesio-temporal epilepsies is the development of rhythmic spiking discharges that remain confined to the hippocampus during tens of seconds. They appear clinically silent until other areas in temporal or extra-temporal neocortex become involved or triggered by the pace of the prolonged abnormal hippocampal activity.

7. Functional coupling between cortical (or cortical-subcortical) areas: the "tuning" effect

Epileptic seizures occur within neural networks that have different possible dynamical states: the (interictal) steady state; and the ictal state of widespread synchronization. The transition between these two states may be more or less abrupt [8,28,64]. A characteristic feature of electrical discharge spread in seizures of temporal lobe origin is low-frequency synchronization between different areas. This could be considered as a form of "tuning" [24] or sympathetic resonance in which an epileptic discharge within a certain brain structure induces activity of the same frequency (or its harmonic) in another structure, presumably in a context of functional connection between the two areas. A whole set of structures within an epileptogenic network may synchronize in this way in the course of a seizure, exemplified by the quite striking and strictly synchronous termination of a temporal seizure across hippocampus, amygdala, parahippocampal gyrus, and diverse neocortical areas of the temporal, frontal or parietal lobes (Fig. 3). Thus in terms of possible mechanisms of production, another aspect to consider in addition to spatial localization and frequency of discharge is the role of synchronization of rhythms between involved structures. A new conception of how clinical semiology might arise in a similar way to normal cognitive functions has arisen from reports from neuroimaging, documenting the necessity of multiple co-activated structures for a cognitive process to occur. In fact, the basis for opening up this new way of thinking of semiology came from theoretical approaches to brain functioning in the visual domain [65–67], relayed by experimental evidence in favor of the "binding-by-synchrony" hypothesis [68]. First demonstrated at the level of cortical intra- and inter-columnar synchronization, phase-locked synchrony of neurons spatially distributed in the visual system in the beta/gamma frequency range proved to be the basic mechanism for constructing percepts, focusing attention, maintaining content in short-term memory, elaborating associative memories, and sensory motor integration (see [69,70]). What had been observed in neural networks at the micro-scale level seemed to be effective at the macroscale level as well.

An indication for the likely role of such functional coupling in the production of semiology in epileptic seizures came from studies of the "dreamy state" arising from the temporal lobe [9,71–74]. Penfield in 1963 had previously highlighted the essential role for the cerebral

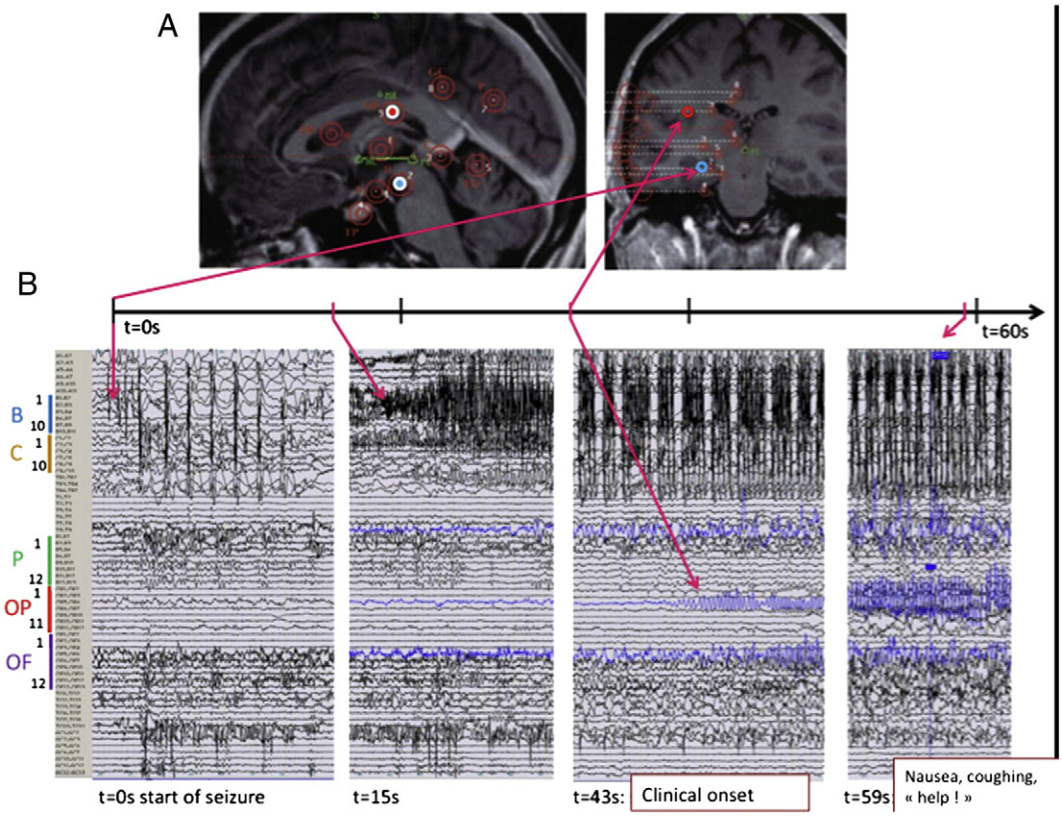

Fig. 3. Temporal seizure recorded in SEEG. After a series of high-amplitude spikes, synchronized in anterior (B) and posterior hippocampus (C) and amygdala (A), a fast discharge is recorded in the same regions, and evolves into rhythmical spike bursts without overt clinical semiology. 43 s after electrical onset, an oscillatory discharge arises from the parietal opercular area (OP) spreading to frontal opercular area (OF), at the time of clinical onset, then develops until the end of the seizure. The discharge frequency at clinical onset in parietal then frontal opercula is in the same range as that of posterior hippocampus and middle temporal gyrus. In terms of the mechanisms of semiology, we can speculate as to whether this is primarily due to pure spatial spread (that is, triggering of local "normal" activity), or oscillatory activity synchronized between all these areas.

cortex of the temporal and occipital convexity, after having obtained experiential illusions and hallucinations by electrical stimulation of numerous sites of this vast region he called "the interpretive cortex"[9]. In the 1990s, Gloor [71] considered the amygdala as a key structure to activate associative areas supporting the recollection content, whereas Bancaud et al. [72] emphasized the fact that memory experiences were simultaneous with ictal co-activation of amygdala/hippocampus and temporal neocortex. The important role of the rhinal cortices was subsequently emphasized by cortical stimulation studies [74,75]. Barbeau et al. [73] used cross-correlation to calculate functional coupling in a case of temporal epilepsy with dreamy state, investigated with depth electrodes, in which stimulation of perirhinal cortex elicited reminiscence of memories. The correlation between after-discharges, recorded simultaneously in multiple areas of the sub-sylvian cortex, increased between rhinal cortices and hippocampus, hippocampus and amygdala, and perirhinal cortex and visual cortex, specifically in the theta band. Non-linear regression analysis of depth-EEG signals in the same areas was subsequently performed in a series of patients who presented déjà vu during their seizures [76]. This confirmed the existence of transient functional coupling between amygdala and hippocampus and between hippocampus and rhinal cortex, particularly in the theta band, when déjà vu was provoked by electrical stimulation [74,76]. Abnormal synchronization in certain frequency bands between two or more cortical (or subcortical) regions of the recognition memory network thus correlated with emergence of déjà vu or recollective experience. Independent theta rhythms in hippocampus and entorhinal cortex in background conditions have been evidenced in humans [77,78]. Synchronization of these theta rhythms by ictal discharge or by stimulation is the mechanism underlying episodic retrieval, as previously demonstrated in rat and humans [78–80]. Since the type of recollection evoked in epileptic patients is mainly in the domain of autobiographical memory [74], such phenomena in epilepsy could be interpreted as an exacerbation of normal retrieval. However sensation of déjà vu may be obtained in the same conditions but at a lower threshold and with a more limited after-discharge. Since rhinal cortices are placed at the intersection between the functional "ventral stream" and hippocampal circuitry, abnormal synchronization of theta waves between hippocampus and neocortex could lead to their misinterpretation as signaling ongoing recollection rather than encoding, hence the "encoding-experienced-as-retrieval" hypothesis [81]. Therefore, déjà vu and paroxysmal recollection both result from increased synchrony between hippocampus and cortex, the network involved in recollection being larger and extending to associative areas. Such a phenomenon appears in the context of disturbing a function in the former situation and exacerbating it in the latter.

Similar observation has been made for the production of humming in temporal lobe seizures. Emission of a low and steady continuous tone with closed lips may occur in temporal seizures, generally delayed after seizure onset. SEEG signal processing demonstrated increased coherence between superior temporal gyrus (secondary and associative auditory cortex), planum temporale, and inferior frontal gyrus (area 44/45) during humming [82]. Interestingly, ictal SPECT performed in another series of patients showed simultaneous hyperperfusion in the same three areas in seizures with the same semiology [83].

Correlation of intracerebral EEG between certain cortical areas in certain frequency bands is therefore an electrophysiological counterpart of the emergence of some clinical signs. The frequency range implied in the works cited above is comprised between theta and beta, so that it rarely occurs in the early stages of a partial seizure, in which the discharge is typically of higher frequency (except for the dreamy state, when an after-discharge can be evoked by stimulation).

Impairment of consciousness is another clinical seizure sign that has been studied in terms of possible underlying neural network changes [84–87]. In the course of temporal seizures, impairment of consciousness is not constant, and may occur at different moments after ictal onset, depending on the rate and extent of spread. A common feature in electrical development of temporal seizures is progressive and rhythmical slowing of cortico-limbic discharges with increasing synchrony across the different areas involved. A quantification study of this phenomenon [88] showed that synchronization indices exploring the extra-temporal interactions during seizures of temporal onset are largely and significantly increased in seizures with loss of consciousness compared with seizures without loss of consciousness. This is actually true only from the middle part of the seizure to its end. This synchronization is effective between posterior supra-sylvian areas, as well as between these structures and posterior thalamus (pulvinar).

Therefore, a temporal relation between increased large-scale network synchrony and emergence of semiology could mean that cell assemblies distributed in the cortex (and possibly in subcortical nuclei) would be constituted by repetition of ictal discharges. By chance, some of these cell assemblies (in their anatomo-functional context) forming elements of cognition or behavior would arise as a consequence of increased inter-structure functional connectivity. Reproducibility, in a given patient, of semiological segments of seizures (like the syntactic structure of words in a sentence) corresponds in fact to the reproducibility of electrical patterns and their functional coupling [89].

8. Functional uncoupling between cortical areas and/or subcortical nuclei: the "release effect"

The Jacksonian concept of hierarchical levels of organization in the central nervous system implies that upper levels controlled lower ones [3]. In the case of disease, i.e. disturbance caused by a cortical lesion, release phenomena would occur as a consequence of a loss of control; in other words, disinhibition of motor signs or behaviors. The possibility that such phenomena might take place in the course of epileptic seizures has long been discussed; for example, in cases where the observed ictal behavior did not readily correspond to the expected functional manifestations of the areas involved.

Seizures in which the electrical signature, correlated in time to clinical semiology, consists of a vast high-frequency discharge could be interpreted according to a release hypothesis. Unlike mesial temporal seizures, which are characterized increased synchrony between hippocampus, amygdala, and parahippocampal areas, most neocortical seizures are initiated by very high-frequency discharges often largely distributed over several regions of the cortex. A spatial decorrelation between these regions has been demonstrated [28]. After transient hypersynchronization during preictal spiking, a marked drop in signal correlation occurs at the onset of extensive fast discharge. Generally, no clinical sign appears at this early stage (which can last more than 5 s), especially in associative cortex, with semiology emerging when rhythmical low frequency subsequently develops, with functional coupling as a consequence (see above). However, clinical signs may also arise during the initial fast discharge, at the time of spatial decorrelation. This is the case in frontal-temporal seizures characterized by apparently fear-related motor behavior (Fig. 4C). Patients characteristically look frightened and show agitated movements with screaming, defensive reactions, and autonomic signs [90–92]. Quasi-naturalistic, integrated fear-like behavior is observed, starting immediately after electrical onset. A massive desynchronization between medio-basal prefrontal cortex and amygdala can be measured during the fast discharge [91]. Although the connections between these two structures and septal nuclei, hypothalamus, and brain stem nuclei (periaqueductal gray) could well explain the resulting behavior through a simple "activation" mechanism, its "organized" pattern would suggest that it is triggered as a whole. Functional disruption in the "anatomic dialogue between prefrontal cortex and amygdala" [93] produced by a high-frequency desynchronizing discharge would liberate amygdala and prefrontal cortex from their mutual gating [94]. Output from these structures could trigger firing in hypothalamic nuclei and periaqueductal gray on the one hand, and ventral tegmental area, nucleus accumbens, then ventral pallidum on the other hand, generating a global fear-like motor behavior.

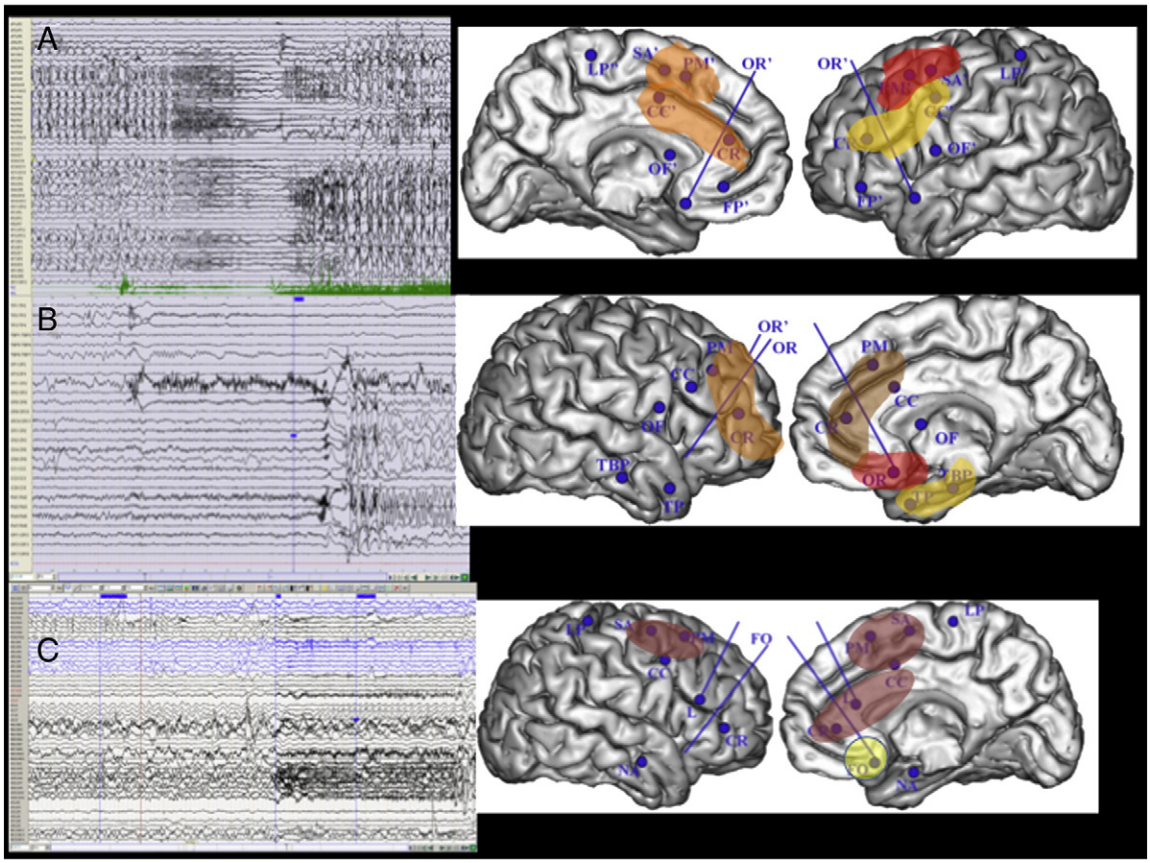

Fig. 4. Frontal seizures (recorded with SEEG) in three patients (A, B, C) involving common areas, but with very different clinical patterns. A: Following rhythmic spike burst activity in premotor medial and lateral areas, without concomitant clinical signs, fast spiking activity in the same areas followed by a fast discharge is associated with an asymmetric posture of the trunk and all four limbs with abduction and raising of arms, head deviation to the right, then clonic jerks of all four limbs; ictal discharge, faster in lateral premotor cortex (in red) spreads simultaneously to medial premotor cortex and anterior and middle cingulate gyrus. B: A fast discharge limited to the medial orbital frontal cortex has no associated clinical manifestation; 10 s later, it spreads to anterior cingulate gyrus and lateral prefrontal cortex which are simultaneously engaged with a spike-and-wave discharge; occurrence of distal stereotypies with utilization behavior is correlated with the second part of ictal discharge. C: Prolonged spiking activity is present in the medial orbital frontal cortex, during which period the patient reports subjective symptoms of fear ("I feel frightened"!); on the other hand when fast activity develops simultaneously in anterior cingulate region and in medial and lateral premotor areas, she briskly stands up straight and screams with a frightened facial expression.

A similar mechanism appears to operate in ictal language disorders. In the majority of seizures involving cortical language areas, clinical semiology is reduced to speech arrest or to diverse types of vocalization, depending on the area involved and their neural distance from the ventral central region. Verbal automatisms are observed in temporal seizures, associated with non-dominant hemisphere for language [95–98]. Abnormal production resembling aphasia resulting from cerebral lesions is less frequent [97,99–101]. Jargonaphasia has been reported in seizures originating from the BTLA (basal temporal language area), with fast discharges simultaneously occurring in BTLA and posterior superior temporal gyrus (Heschl's gyrus and planum temporale) [102–104]. BTLA is connected to language production areas [105] and, furthermore, works as a gate control between perception and production. The desynchronizing effect of the fast discharge could thus functionally disconnect language comprehension from speech production and result in liberation of phonological jargon.

9. Complex gestural motor behaviors and the question of the symptomatogenic zone

A fundamental statement about clinical semiology of epileptic seizures is that it is an emergent property of networks. From focal myoclonus to complex cognitive experience or complex gestural behavior, each seizure engages its proper circuitry in the brains of patients with epilepsy, the plasticity of such circuitry being a trait of the disease. A question behind this would be: if a network, analyzed at the macroscale (as occurs in the context of presurgical investigations), is an assembly of distributed cortical areas (and subcortical nuclei), how does each of these areas express itself? Do signs and symptoms represent functional markers of each area in the network, their temporal succession due to progressive firing in each structure? If so, could functional markers of each area be equivalent to the results of its stimulation? These questions have been addressed in the debate on relationship between epileptogenic and symptomatogenic zones [106,107]. Based on the fact that some ictal discharges initially generated in certain associative areas manifest their "symptomatogenesis" only when propagation reaches "eloquent" areas, such as premotor or motor cortex, the concept of "symptomatogenic zone" existing as an anatomically separate area from the epileptogenic zone arose. This concept implies that the cortical areas invaded by ictal spread manifest clinically as if they were topically stimulated. It is closely akin to the "march" concept (see above), and might seem to account for the observation of delayed signs in anterior temporal or frontal seizures. However, with close examination of some complex motor seizures, such a descriptive view of the relations of spread to the clinical sequence does not appear to hold. The clinical semiology of a given seizure depends upon neither the anatomical origin of ictal discharge nor the target areas of its propagation alone, but the dynamic interaction between them.

This hypothesis stems from observations of functional coupling between cortical areas involved in partial seizures as previously described [76,82,88], as well as on the anatomo-electro-clinical correlations in seizures of prefrontal origin. Prefrontal seizures can manifest with complex gestural motor behavior, which may appear integrated (quasi-naturalistic) and be composed of gestural stereotypies [108].

Their anatomical onset lies in different parts of rostral dorso-lateral or ventro-lateral prefrontal cortex, but their clinical expression is time-related to discharges which, still developing in the seizure onset areas, trigger fast discharges in the anterior cingulate region, pre-SMA, and possibly lateral premotor cortex (Fig. 4B). In these prefrontal seizures, despite the high frequency of the latter spreading discharges within motor cortex, there is no clinical semiology resembling postural, tonic or gestural semiology typical of those regions. The semiology expressed by those regions is therefore strikingly different when they are initially engaged in the pathological discharge from when they are "driven" by a remote area that modulates their activity (Figs. 4A–C).

10. Semiology: which tool for localization?

A long-debated question concerns the localizing value of clinical semiology for presurgical evaluation. Most studies addressing this question have compared symptoms and/or signs, taken either separately or globally, to localization of seizure onset provided by imaging. The question is often ill posed, because the data to be compared cannot be estimated in the same dimension (i.e. the dynamic nature of semiology emergence versus the static and geometric parameters of imaging), and because the conditions of gathering semiological information have progressed relatively little in the last two decades, whereas imaging methods are in constant evolution.

In fact, there are methodological requirements for analyzing the "seizure scene", which are necessary if meaningful analysis is to be made of semiological information. The spatial resolution of the scene depends on the quality of cameras (high-definition) and the framing monitoring during the seizure. The "granularity" of the seizure scene is significantly increased by ictal and post-ictal clinical examination of the patient with appropriate testing of conscious level, language function, and so on depending on the characteristics of the epilepsy. A specific step in analyzing a patient's seizure type is a process of "data aggregation". After recording multiple seizures in a given patient, analyzing each of these can contribute common information, but some seizures might provide clearer data than others on subjective symptoms, gestural behavior, or language alteration. Each seizure may express a more or less complete tableau of the patient's habitual seizure. Data aggregation, in the final analysis of patients' seizures, consists in re-assembling subjective, prodromic, early sensations with objective and observable elements, so as to reconstruct a prototypical seizure (even in comparing video-EEG with video-SEEG data). Such an approach is validated by SEEG [89]. Future development of video quantification utilizing hybrid intelligent systems [109] could help to overcome difficulties in categorization due to the miscellaneous character of semiological data.

The attitude to facing complexity, inherent to the essence of the data, necessarily results in a fuzzy impression about the " localizing value" of clinical semiology. Clinical semiology actually does localize the epileptogenic phenomenon as it is. That the epileptogenic phenomenon is organized as a neural network, and not as an irritative focus, is no longer debatable; even when circumscribed to a small volume, it is ultimately a focal network. As expected from system neurosciences, a single area by itself does not manifest any fixed functionality. Functionality emerges through dynamic patterns of its connectivity [24]. As proposed by McIntosh and colleagues, "cognitive operations emerge from the interactions between brain areas rather than being the sole responsibility of single regions" [110]. Such concepts applied to interpretation of clinical semiology denote that seizures starting in a determined region, such as the fronto-polar region, will bear different clinical expressions according to the set of multiple areas brought into play. In the given example (Fig. 4), area 10 projects anatomically to anterior and posterior cingulate gyrus, to amygdalar and temporo-polar region, and to the superior temporal sulcus. All of these areas, or part of them, can be activated in the course of a seizure and give rise to paroxysmal complex behavior. Depending on the orientation of functional connectivity in the network arborization of its efferent connections, seizure composition will be different. Furthermore, if the epileptogenic zone overlaps adjacent areas (areas 9 or 14 for instance), which is a very common clinical occurrence, the seizure pattern will be strikingly different, with possible combined postural and tonic components in the first case, and emotional and autonomic components in the second one. Despite a wide range of possibilities, the way in which local/regional markers can be spotted is intriguing and merits detailed study [60]. In a given patient, careful mapping of the ictal network in its full spread leads to the conclusion that a given network configuration cannot be generated by a source other than a given area or group of areas. Such extrapolation-based inference method solves the paradox of disentangling a vast ensemble in order to localize its original determinant.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Article 2

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Stereoelectroencephalography in presurgical assessment of MRI-negative epilepsy

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According to most existing literature, the absence of an MRI lesion is generally associated with poorer prognosis in resective epilepsy surgery. Delineation of the epileptogenic zone (EZ) by intracranial recording is usually required but is perceived to be more difficult in 'MRI negative' cases. Most previous studies have used subdural recording and there is relatively less published data on stereoelectroencephalography (SEEG). The objective of this study was to report the experience of our group in using SEEG in presurgical evaluation, comparing its effectiveness in normal and lesional MRI cases. One hundred consecutive patients undergoing SEEG for presurgical assessment were studied. Forty-three patients out of one hundred (43%) had normal MRI and 57 (57%) had lesional MRI. Successful localization was achieved with no difference between these two groups, in 41/43 (95%) normal MRI and in 55/57 (96%) lesional MRI cases ($P = 1.00$). Surgery was proposed in 84/100 patients and contra-indicated in 16/100 with no significant difference between lesional and MRI-negative groups ($P > 0.05$). At 1 year follow-up, 11/20 (55%) of those having undergone cortectomy in the MRI-negative group and 21/40 (53%) in the lesional MRI group were entirely seizure free ($P > 0.05$) and these proportions were maintained at 2 years follow-up. Significant improvement in seizure control (ILAE outcome groups 1–4) was achieved in >90% cases with no difference between groups ($P > 0.05$). Of MRI-negative cases that underwent surgery, 10/23 (43%) had focal cortical dysplasia. This series showed that SEEG was equally effective in the presurgical evaluation of MRI-negative and lesional epilepsies.

Keywords: stereoelectroencephalography (SEEG); depth electrodes; intracranial EEG; epilepsy surgery

Abbreviations: OP = opercular frontal cortex, DLPF9/46 = dorsolateral prefrontal cortex, Brodmann area 9/46; PSMA = preSMA; CG 24 = cingulate cortex Brodmann 24; TP = temporal pole; STG = superior temporal gyrus; Am = amygdala; MTG = middle temporal gyrus

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Introduction

Current practice in epilepsy resective surgery generally relies heavily on the identification of radiologically visible lesions considered likely to be responsible for the epilepsy (Polkey, 2004). The absence of a lesion visualized by MRI has been previously shown to relate to poorer prognosis in resective epilepsy surgery, both for temporal (Berkovich *et al.*, 1995) and extra-temporal cases (Zentner *et al.*, 1996; Smith *et al.*, 1997; Mosewich *et al.*, 2000; Jeha *et al.*, 2007). Despite major advances in neuroimaging, MRI-negative cases still account for up to a quarter of all those presenting for pre-surgical evaluation (Berg *et al.*, 2003). Although some authors previously considered it unhelpful to pursue presurgical assessment in this situation (Scott *et al.*, 1999), it is however increasingly recognized that certain MRI-negative cases, while among the most challenging in terms of presurgical assessment, are indeed surgically

treatable with satisfactory and sometimes excellent outcomes (Alarcon *et al.*, 2006). This has been highlighted in a number of recent series (Cukiert *et al.*, 2001; Siegel *et al.*, 2001; Hong *et al.*, 2002; Chapman *et al.*, 2005; Cohen-Gadol *et al.*, 2005; Lee *et al.*, 2005; Alarcon *et al.*, 2006). The possibility of avoiding invasive monitoring in certain cases of MRI-negative focal epilepsy has been proposed (Wennberg, 2005), particularly in carefully selected cases of temporal lobe epilepsy (Sylaja *et al.*, 2004) and the ultimate goal may indeed be to achieve 'totally non-invasive investigation' in as many patients as possible (Knowlton, 2004). However the need for intracranial recording in the vast majority of MRI-negative cases is generally accepted (Lee *et al.*, 2005). Successful determination of the epileptogenic zone (EZ) is generally considered to be more difficult in MRI negative cases, which is almost certainly a contributing factor to the poorer surgical outcome observed in many (Siegel *et al.*, 2001; Blume *et al.*, 2004). Most recent studies have been based on the majority of patients being investigated with invasive monitoring using subdural grids, subdural strips or a combination of subdural recording and some depth electrodes. The majority of these previous series of MRI-negative cases focus on those patients who were ultimately selected for surgery, that is, those in whom localization by these means of intracranial recording was successful; there is therefore a relative paucity of data on the overall yield of intracranial exploration in such cases.

Stereoelectroencephalography (SEEG) (Bancaud *et al.*, 1965; Talairach *et al.*, 1974; Chauvel *et al.*, 1987) differs in certain respects from other intracranial recording methods such as subdural grids. In particular, deep structures and buried cortex, which are not readily accessible by subdural or cortical methods of recording, can be accessed, and EEG data is obtained simultaneously from superficial and deep brain structures. As the precise position of each electrode contact is determined, a dynamic three-dimensional temporo-spatial picture of epileptic activity may be reconstructed. This aspect makes SEEG ideally suited to the study of the relations between structures involved in seizure production and propagation, and, building on the initial concept proposed by Bancaud *et al.* (1965), has made possible the development of the now widely accepted network model of seizure organization (Chauvel *et al.*, 1987; Wendling *et al.*, 2003; Bartolomei *et al.*, 2005). From this point of view the role of SEEG in presurgical assessment continues to evolve (Bartolomei *et al.*, 2005 [1]). The SEEG exploration is well tolerated by the majority of patients and overall complication rates of SEEG are reported as being of the order of 5% (Guenot *et al.*, 2001; Cossu *et al.*, 2005). This compares similarly to recent studies using predominantly subdural mats or strips (Alarcon *et al.*, 2006), and is somewhat less than studies of subdural grids showing overall complication rates of around 13% even for recent series from a major centre (Hamer *et al.*, 2002). The perception by some authors that depth electrodes are 'more invasive' than subdural methods of recording (Alarcon *et al.*, 2006) (and therefore less desirable than subdural recording) could therefore be questioned.

The SEEG method was developed before the era of magnetic resonance imaging and as such the original cases explored were indeed 'MRI-negative' as often no structural imaging was available. We wish in particular to pose the question of whether SEEG is equally as effective in MRI-negative cases as in cases with lesional MRI. Our aim is to report the experience of our group in using SEEG in the context of pre-surgical evaluation, examining the clinical usefulness of this method in localizing the epileptogenic zone, influencing clinical decision-making regarding surgery, and subsequent surgical outcome.

Patients and methods

From February 2000 to May 2006, 100 consecutive patients underwent SEEG in the Epilepsy Unit, Hôpital de la Timone, Marseille, France. This centre is specialist in surgical assessment and receives tertiary referrals from other epilepsy surgery centres as well as direct referrals from primary and secondary care centres. All of these patients were referred for consideration of surgical treatment for drug-resistant partial epilepsy.

Prior to selection for SEEG, a phase of thorough non-invasive pre-surgical assessment was carried out, including detailed clinical history focussing particularly on seizure semiology, and a period of surface video-electroencephalographic (EEG) recording, to permit analysis of habitual seizures and interictal EEG. All patients underwent MRI that was interpreted by experienced neuroradiologists as well as being reviewed by the epilepsy team.

The MRI specifications evolved during the study period. From 2000 to 2005, the MRI protocol consisted of: transverse diffusion images, transverse T2-weighted images, coronal T1-weighted inversion recovery images, coronal fluid-attenuated inversion recovery (FLAIR) images and a three-dimensional T1-weighted acquisition (Raybaud *et al.*, 2001). Acquisition plans were referred to the bi-hippocampal plane for the transverse acquisitions and to the AC–PC plane for the coronal and axial acquisition. Reconstructions of the 3D T1 images were adapted to the type of epilepsy. MRI examinations were performed on a 1.5-Tesla Symphony machine (Siemens Medical Systems, Erlangen, Germany), with a 4-channel head coil being used from 2000 to 2005; from January 2006 onwards a 12-channel head coil was used. In this latter part of the study period the multi-channel head coil allowed the use of matrix acquisition, isotropic 1 mm 3D T1 images, with reasonable acquisition time especially for inversion-recovery, FLAIR and 3D sequences (overall MRI examination lasting approximately 25 min).

A different neuroradiologist was responsible for overseeing technical parameters and for interpreting the images before and after August 2004.

Functional neuroimaging was also performed in all cases, including single photon emission computerized tomography (SPECT) and/or positron emission tomography (PET). Some patients also underwent magnetic resonance spectroscopy (MRS) (Guye *et al.*, 2005) and/or functional MRI with language activation (fMRI). In 32/43 (74%) of the MRI-negative and 38/57

(66%) of the lesional MRI cases, high-resolution EEG (HR-EEG) with source localization was carried out; some patients also had magnetoencephalography (MEG) within the context of a research protocol. Neuropsychology assessment was routinely performed.

We identified patients as 'MRI negative' from data collected retrospectively and prospectively in a database. This group was defined as those patients in whom standard quality structural cerebral MRI as defined above was considered to be normal by the neuroradiologist and the epilepsy team, at the time of decision to pursue invasive recording. This included re-review of standard MRI and/or repeated imaging in the light of obviously focal abnormalities on functional imaging or after video-EEG recording and the assumption made about the likely EZ location. The obvious limitations of the term 'MRI-negative' are acknowledged and will be discussed later.

Forty-three of the 100 cases were thus considered to have normal MRI and 57/100 to have lesional MRI.

Most cases also underwent additional morphometric analysis of cortical anatomy performed using raw MRI data within a computer model research tool (Mangin *et al.*, 2004), at the time of planning the electrode implantation. In some this data pointed to the possibility of a subtle cortical anomaly, in which cases the planned SEEG implantation took account of this. Research using this as yet unvalidated tool is ongoing and more detailed descriptions of these cases will be reported separately at a later date. In the course of comprehensive presurgical evaluation, non-invasive investigations were therefore directed at obtaining as much information as possible that might help with formulating the eventual hypotheses of seizure organization, including the extensive search for any lesion that might be related to the epileptogenic zone.

Patients were selected for SEEG exploration depending on the conclusion following non-invasive investigations: where the ensemble of non-invasive data led to the formulation of a single hypothesis regarding the likely localization and extent of the EZ, and where no contraindications were present, surgery was carried out directly without invasive recording. Indeed of all cortectomies performed for epilepsy in the same time period, approximately two-thirds were carried out without prior SEEG exploration (the majority of these being 'lesional MRI' cases). However where a surgical decision was not able to be made based purely on non-invasive data (in other words where non-invasive data were unable to distinguish between 2 or more clearly formulated hypotheses), SEEG exploration was proposed, with the planned electrode implantation designed to refute or confirm these hypotheses. SEEG was thus performed on ~20% of all patients undergoing video-EEG recording in the context of possible pre-surgical evaluation during this time period. This step of patient selection for SEEG and planning of electrode position, based on the hypotheses formulated from all available non-invasive data, forms a crucial part of the investigation process and likely determines to a large extent the eventual likelihood of successful exploration.

All patients gave their informed consent prior to exploration. SEEG recordings were performed using intracerebral multiple contact electrodes (10 to 15 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm apart) placed intracranially according to Talairach's stereotactic method (Talairach *et al.*, 1992). The positioning of electrodes was established in each patient based upon available non-invasive information and hypotheses about the localization of the epileptogenic zone. The implantation accuracy was peri-operatively controlled by telemetric X-ray imaging. A post-operative computerized tomography (CT) scan without contrast was used to verify the absence of bleeding and the location of each recording lead. Following the recording period of 3–9 days, intracerebral electrodes were then removed and an MRI performed, permitting visualization of the trajectory of each electrode. Finally, CT-scan/MRI data fusion was performed to anatomically and precisely locate each contact along the electrode trajectory (see Bartolomei *et al.*, 2004 for further description).

Statistical analysis was performed in order to compare the data between the two groups using an analysis of variance (ANOVA) for quantitative data and Chi square (or Fisher's exact test when appropriate) for qualitative data. A P-value <0.05 was considered to be statistically significant.

Follow-up information was determined from out-patient visits, patient telephone calls and telephone calls to referring physicians.

Localization and organization of epileptogenic zone as defined by SEEG

The EZ is defined as the region of primary organization of seizures (Bancaud *et al.*, 1965). Seizure onset recorded using SEEG is often characterized by a high frequency low amplitude rapid discharge (beta and gamma range) (Bancaud *et al.*, 1965; Wendling *et al.*, 2003), often preceded by changes in pre-ictal activity (repetitive spikes and/or slow wave activity in the same region) (Gavaret *et al.*, 2004), and followed or not by more clonic activity. However other patterns of ictal discharge also exist. The temporal relation of the electrical and clinical changes is crucial, in that by definition ictal discharge always occurs prior to the onset of clinical ictal symptoms and signs, in order to be confident that the region of seizure onset has been correctly identified. Where a seizure occurs without clear SEEG evidence of an ictal discharge preceding the first clinical sign, it can thus be concluded that no electrode has been placed within the appropriate structure involved in the EZ. In some such circumstances the EZ cannot fully delineated.

Surgical strategy based on SEEG findings

Identification of the eventual cortical region to be resected may be a complex process, requiring consideration of the whole electroclinical picture (non-invasive and invasive data). This takes account of not only the EZ as defined by SEEG but also the irritative zone (IZ) (characterized by the region of interictal spikes as well as consideration of PET and SPECT data) and the lesional zone (LZ) (characterized by EEG features of interictal slow wave activity, and also reflected in MRI, PET and SPECT abnormalities). Definition by SEEG is clearly dependent upon the position of electrodes, the sampling of particular brain regions and systems having been chosen according to the hypotheses formulated following the non-invasive phase of assessment. The planned resection is informed by the exact position of SEEG electrodes, which are stereotaxically placed and whose location can be reconstructed using the patient's 3D MRI. A zone or region is not defined by a single electrode; estimation must be made of the extent of activity, based on the activity in adjacent electrodes and knowledge of the electrophysiological patterns of activity and propagation in different cerebral systems or structures (Talairach *et al.*, 1974).

The 'MRI-negative' ($n=43$) and 'lesional MRI' ($n=57$) groups were broadly similar in the proportion of males/females, age range, duration of epilepsy and the number of electrodes implanted, with no statistically significant difference (Table 1).

Table 1 Comparison of characteristics of the two groups at the time of implantation, MRI-negative ($n = 43$) and lesional MRI ($n = 57$)

Characteristics	MRI-negative group ($n = 43$)	Lesional MRI group ($n = 57$)	
Age range in years (median)	8–62 (24)	8–56 (31)	ANOVA $P = 0.12$ (NS)
Range of duration of epilepsy in years (mean)	1–50 (17)	6–47 (20)	ANOVA $P = 0.16$ (NS)
Ratio M:F	18:25 (42% male)	26:31 (45% male)	Chi square $P = 0.42$ (NS)
Unilateral: bilateral implantation	15:28	31: 26	Chi square $P = 0.02$
Range of number of electrodes implanted (mean)	5–15 (10)	5–16 (9)	ANOVA $P = 0.07$ (NS)

NS = non-significant.

The MRI-negative group had proportionally more bilateral implantations ($P = 0.02$).

The provisional localizations of epilepsy as determined following non-invasive investigation, and prior to SEEG, are shown in Table 2.

The group was notably heterogeneous. The majority of MRI-negative cases were extra-temporal and frontal lobe epilepsies accounted for 60% of this group (26/43). Conversely, 40% of the lesional group consisted of temporal lobe epilepsies compared with 12% in the normal MRI group. This is likely to partly reflect the various aetiologies implicated in the different groups; for example many of the temporal lobe epilepsy cases showed some radiological evidence of temporal lesion associated with other non-concordant data, necessitating intracranial exploration.

The difference in case-mix also reflects evolution of the referral pattern to our service with more of the extra-temporal and MRI negative cases having been explored in the latter part of the study period. For example in approximately the first half of the series, only 15 of the 56 patients explored from 2000 to 2002 were considered to have normal imaging (27%). In the second half of the series however, 28/44 (64%) patients explored from 2003 to 2006 had normal imaging.

Table 2 Preliminary diagnosis after non-invasive phase of investigation

Likely localization of epilepsy as determined prior to SEEG	MRI-negative group (% of group)	Lesional MRI group (% of group)
Temporal lobe epilepsy	5 (12)	23 (40)
Temporo-perisylvian epilepsy	3 (7)	3 (5)
Temporo-frontal epilepsy	2 (5)	4 (7)
Operculoinsular epilepsy	2 (5)	2 (4)
Frontal lobe epilepsy	26 (60)	14 (25)
Occipital lobe epilepsy	3 (7)	5 (9)
Parietal lobe epilepsy	1 (2)	4 (5)
Temporo-parieto-occipital junction epilepsy	1 (2)	2 (4)
Total	43	57

Table 3 Results of SEEG in determining EZ in each group, MRI-negative ($n = 43$) and lesional MRI ($n = 57$)

	MRI-negative ($n = 43$)	Lesional MRI ($n = 57$)	
Unilateral EZ identified permitting surgical decision	33	52	
Bilateral or multifocal EZ identified	8	3	Fisher's exact test $P = 0.05$
EZ not adequately determined	2	1	Fisher's exact test $P = 1.00$
Failure to record due to complication at time of implantation	0	1	
Total	43	57	

Results

Localization of the epileptogenic zone (EZ) with SEEG

The results show that the vast majority of patients in the present series had successful localisation of the EZ using SEEG. This was not significantly different between the MRI-negative and lesional MRI groups (Table 3).

The type of organization of the EZ varied between cases. Most showed unilateral organization involving several structures that were not necessarily contiguous but known to be closely functionally connected (for example, see Fig. 1). Some cases had bilateral organisation, involving bilateral homotopic regions at seizure onset. Only rarely did we observe very local organization restricted to closely neighbouring structures. By definition, no localization differed greatly from the provisional pre-SEEG diagnosis, as electrode placement had been chosen to confirm or refute the main hypotheses of EZ localization; if these hypotheses had been completely wrong then the SEEG would have been entirely non-conclusive. The localization of the EZ for each patient as determined by SEEG is given in the Tables A1 and A2 of the Appendix.

One patient in the lesional MRI group did not have SEEG recording due to the complication of a haematoma at the time of electrode implantation (discussed later). Only three inconclusive results were obtained following SEEG recording, two in the MRI-negative group and one in the lesional MRI group. In each of these cases, although the EZ was not felt to have been adequately defined in its totality, there was however sufficient indication of

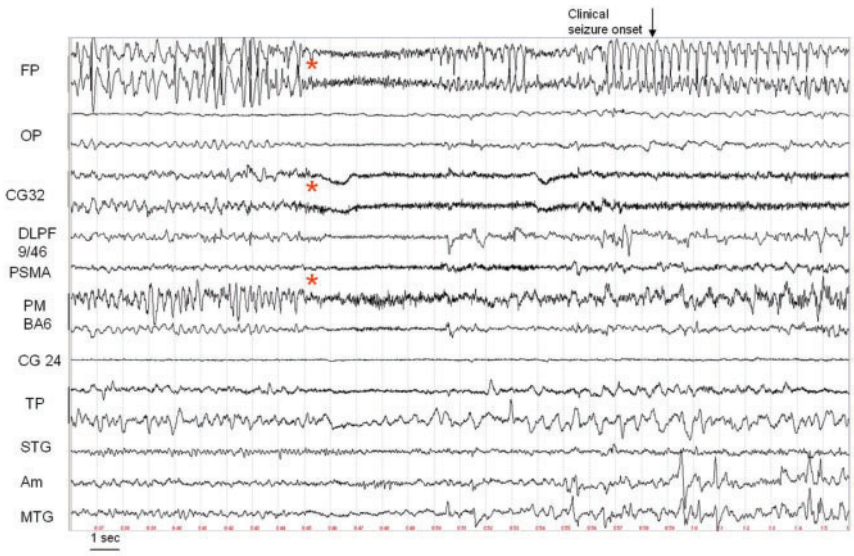

Fig. 1 Seizure recorded with SEEG in a patient with frontal lobe epilepsy (patient 44, Appendix Table A2), showing a representative sample of EEG channels recording within the right frontal and temporal lobes. Following an increase in preictal spike activity (in the first 9 s of the EEG trace shown here), a rapid (gamma range) ictal discharge (marked ∗ on the diagram) is seen simultaneously in certain leads of electrodes exploring the frontopolar (FP) cortex, anterior cingulate region (CG32) and premotor lateral cortex (PMBA6). The electrical seizure onset therefore simultaneously involves areas that are spatially separate but functionally connected. The first clinical sign occurs 13 s after the onset of the fast discharge. OP = opercular frontal cortex; DLPF9/46 = dorsolateral prefrontal cortex, Brodmann area 9/46; PSMA = preSMA; CG 24 = cingulate cortex Brodmann 24; TP = temporal pole; STG = superior temporal gyrus; Am = amygdala; MTG = middle temporal gyrus.

multi-focality to make further attempts at SEEG localization inadvisable as eventual surgical treatment would be contra-indicated. One patient in the series (normal MRI group) underwent two SEEG explorations: the first had partially localised the EZ but showed that some seizures arose outside the structures explored; the second SEEG showed conclusive evidence of a bifocal organization.

Complications of SEEG

Three complications occurred in this series of 100 cases, of which 2 led to a neurological deficit. One patient developed a local haematoma at an electrode site that caused a focal motor upper limb deficit. The deficit partially resolved over several months. One other patient developed an intracranial haematoma at the time of implantation requiring abandonment of the procedure; no further attempt was made and no SEEG recording was carried out in this single case. This patient has a residual moderate hemiparesis. The third patient developed an extradural haemorrhagic collection at the first attempt at implantation, requiring surgical intervention. This particular patient had previously had very mild functional abnormalities of blood clotting attributed to sodium valproate. A second successful implantation was subsequently performed.

Decision following SEEG

As the EZ could be satisfactorily defined in the majority of both MRI-negative and lesional MRI cases, a high yield of either focal localization or clear evidence of multi-focality leading to surgical contraindication was obtained in this series (Table 3). In some cases with a unilateral EZ, surgery was also considered contraindicated due to major involvement of functional cortex. The SEEG was therefore clinically useful in making a definitive treatment decision in the majority of cases in both groups (Table 4), allowing some form of surgical treatment to be offered in 79% of the normal MRI group and 88% of the lesional MRI group, with no statistically significant difference between these (Chi square $P = 0.55$).

The surgical treatment offered depended upon the characteristics of each case. The majority of cases were suitable for tailored cortical resection. In some patients a gamma knife (GK) radiosurgical procedure was proposed (see Tables A1 and A2 for details of these cases, e.g. radiosurgical anterior callostomy; treatment of a surgically inaccessible region such as the insula; patient preference in some TLE cases).

Four patients who were considered suitable for conventional surgery subsequently chose to delay surgical treatment or declined intervention. In two of these this was due to a relative improvement in epilepsy control and in one due to other health problems; one patient no longer wished to pursue surgical treatment.

Surgical outcome

As the time course of post-operative evolution of GK treatment differs markedly from that of cortectomy, and as the numbers with adequate follow-up are small, the results

Table 4 Surgical decision following SEEG

	MRI-negative ($n = 43$)	Lesional MRI ($n = 57$)
Cortectomy already performed	25	42
Gamma knife radiosurgery already performed	4	6
Surgical treatment contra-indicated	9	7
Surgery awaited	2	1
Patient declined or wished to postpone surgery	3	1

of the 10 patients who underwent a GK procedure have been separated from the analysis of outcome. We therefore report outcome data on 60 of the original 100 explored patients, who have undergone resective cortectomy and in whom at least 1 year follow-up is available (20 in the MRI negative group and 40 in the lesional MRI group).

Outcome has been assessed using the International League Against Epilepsy (ILAE) classification (Wieser *et al.*, 2001), with a score assigned at the 1-year and 2-year post-operative assessment based on presence or absence of seizures and their frequency relative to the pre-operative status. Class 1 outcome is defined as complete seizure freedom with no auras [therefore being equivalent to the '1a' outcome of the Engel classification (Engel *et al.*, 1993)]. Range of duration of follow-up was 6–55 months (mean 28 months) in the MRI negative group and 6–67 months (mean 38 months) in the lesional MRI group. The relatively shorter follow-up for the MRI-negative cases reported here relates to the fact that the majority of the MRI negative cases were explored in the latter part of the 6-year study period, many during 2005 and 2006. As this difference in follow-up period is significant between the two groups, we have chosen to compare all patients at the same post-operative time intervals of 1 and 2 years (Tables 5 and 6), accepting that the numbers are obviously smaller in the normal MRI group at the 2-year assessment. The most recent follow-up data for each patient is also listed in Tables A1 and A2 of the Appendix.

The present results indicate that there is no significant difference between the MRI-negative and lesional MRI groups, in the proportion of cases that are seizure free or that have had significant improvement following surgery (Tables 5 and 6), either at 1 or at 2 years post-cortectomy. Seizure freedom rates (Class I ILAE) are 55% in the MRI-negative group and 53% in the lesional MRI group at 1 year, while more than 90% of patients in each group have had significant improvement in seizure control (ILAE outcome groups 1–4). These proportions remain similar at the 2-year follow-up.

Histopathology

Of 67 patients having undergone cortectomy, histopathology results were available in 23/25 MRI negative patients having undergone cortectomy and in 40/42 operated lesional MRI patients. In addition, one patient in the lesional MRI group who underwent GK radiosurgery had had a prior biopsy of the lesion (DNET). In four operated patients, histopathological analysis was not available for technical reasons (for example in cases of temporal lobe resection using aspiration of mesial structures). Histopathology data are therefore provided for a total of 64 patients.

Ten out of 23 patients of the MRI-negative group (43%) proved to have Taylor's type focal cortical dysplasia (FCD) (Table 7). Two MRI-negative patients had pathological evidence of hippocampal sclerosis despite the absence of definite imaging abnormality. Eleven MRI-negative cases showed evidence of gliotic change but no specific evidence of tumour, dysplasia or neuronal migration disorder.

Table 5 Surgical outcome (ILAE class) at 1 year in patients having undergone cortectomy

ILAE class	Normal MRI	Lesional MRI	
Class 1 (seizure free)	11	21	Chi square $P = 0.43$
Class 2 (auras only)	2	3	
Class 3 (1–3 seizures days/year; ± auras	1	9	
Class 4 (4 seizure days/year to 50% reduction from baseline)	5	5	
Class V (<50% reduction)	1	2	
Total	20	40	

Table 6 Surgical outcome (ILAE class) at 2 years in patients having undergone cortectomy

ILAE class	Normal MRI	Lesional MRI	
Class 1 (seizure free)	9	17	Chi square $P = 0.19$
Class 2 (auras only)	1	1	
Class 3 (1–3 seizures days/year; ± auras)	1	12	
Class 4 (4 seizure days/year to 50% reduction from baseline)	1	4	
Class V (<50% reduction)	2	1	
Total	14	35	

Discussion

This study reports our group's experience of using SEEG in a consecutive series of pre-surgical epilepsy patients requiring invasive exploration, comprising a high proportion of MRI-negative cases. The present study illustrates that, combined with thorough non-invasive assessment, SEEG can be equally effective in MRI-negative and lesional

Table 7 Available histopathology results for the 2 groups

	Normal MRI	Lesional MRI
Focal cortical dysplasia (Taylor type)	10	11
DNET and other cortical malformations	0	7
Hippocampal sclerosis	2	2
Gliosis/non-specific findings	11	19
Other	0	2
	23	41

MRI cases. Given the high proportion of clinically useful results obtained following SEEG, particularly the large number in whom some form of surgical treatment could be offered (79% in the normal MRI group and 88% in the lesional MRI group), it seems that patient selection for exploration in this series was satisfactory. This is an important aspect given the risks of invasive exploration as well as issues of cost-effectiveness. The patient population presented here reflects a complete series of consecutively explored patients, representative of our centre's practice as it has evolved over a 6-year period; other aspects of investigation have also necessarily evolved over the same period, notably MRI. The case-mix is therefore heterogeneous and comprises a high proportion of cases that can be considered complex (e.g. presence of extensive lesion; extra-temporal cases with normal MRI) including patients referred from other epilepsy surgery centres. Indeed, surgery had previously been considered contraindicated by other epilepsy surgery teams in 10 of the operated cases presented here. That subsequent resective surgery could be offered to the majority of patients in the present study may seem evident, given that patients were indeed selected with this ultimate goal; however such a rate of subsequent surgical treatment has not automatically been found in some previous series. For example Siegel and colleagues (2001) achieved localization of the EZ in 37/43 patients (86%), using mainly subdural grids, but only 25/43 patients (58%) were deemed to have a 'focal' epilepsy likely to be amenable to surgical treatment. The authors acknowledged that it is important to try to further reduce the failure rate due to 'sampling error' of the exploration.

In terms of surgical outcome in the present study, over 50% of the operated patients in each group became completely seizure free and over 90% of each group had significant improvement in seizure control, with no significant difference between groups. We chose to use the ILAE method of classification in which 'Group 1' patients are strictly seizure-free with no auras. If the Engel method of classification is used to assess outcome in the present study, 13/20 in the MRI-negative group (65%) and 24/40 in the lesional group (60%) have Class I outcome. It is indeed recognized that studies using Engel's classification tend to report higher rates of 'seizure freedom' than those using other forms of classification (Tellez-Zenteno *et al.*, 2005). Comparison with other studies is therefore clearly difficult given the issues of heterogeneous patient groups, different methods of exploration and different surgical outcome measures used. We also acknowledge the importance of longer term follow-up, particularly in view of recent reports of high rates of relapse in patients with normal MRI following frontal lobe surgery (Jeha *et al.*, 2007). Recognizing these limitations of possible comparison, the seizure freedom rate of 55% (or 65% Engel's Class I) obtained in the present MRI-negative group compares well with overall rates of between 40 and 50% patients in Engel Class I found in the majority of other studies of MRI-negative cases comprising mixed temporal and extra-temporal cases (Siegel *et al.*, 2001; Blume *et al.*, 2004; Lee *et al.*, 2005; Tellez-Zenteno *et al.*, 2005). However the high rates of seizure-freedom found in the present study for MRI negative cases are particularly notable considering that three quarters of these were extra-temporal epilepsies, as previous authors have reported poorer outcomes in MRI-negative extra-temporal cases than either 'non-lesional' temporal epilepsies or extra-temporal epilepsies with lesional MRI (Blume *et al.*, 2004; Tellez-Zenteno *et al.*, 2005; Alarcon *et al.*, 2006). In terms of the lesional MRI group, while comparison with other studies remains difficult as mentioned above, outcome is in keeping with previous series of mixed temporal and extra-temporal cases that have undergone intracranial recording (Siegel *et al.*, 2001; Lee *et al.*, 2005; Alarcon *et al.*, 2006). Lesional cases requiring intracranial exploration are a different population from those that can be operated directly. In such cases in the present study the SEEG was performed in order to define the extent of the EZ and its relation to the lesion and to decide whether an absolute surgical contra-indication existed. In some, the results of the exploration were such that a partial resection was proposed with the consideration that, although the chances of obtaining complete seizure freedom were low, the possibility of significantly improving very disabling epilepsy merited surgical intervention.

Earlier SEEG series (Bancaud *et al.*, 1965; Talairach *et al.*, 1974, 1992) demonstrated surgical outcomes comparable with many modern series; in effect these were cases that were correctly localized independently of structural imaging abnormalities. This aspect was also recently illustrated in a study of cerebral dysplastic lesions that were successfully localized using SEEG, with the majority of patients having been investigated before the era of modern brain imaging (Chassoux *et al.*, 2000). An important feature of earlier SEEG series was a relatively high proportion of extra-temporal epilepsy cases, in contrast to the general emphasis on temporal lobe surgery in recent decades. The role of SEEG in the context of modern pre-surgical evaluation has evolved, taking account of the great advances made in non-invasive investigations (particularly MRI), and the method is always used within the context of a full non-invasive work-up leading to clear hypotheses to be tested by intracranial electrode placement. This process of

formulating and testing hypotheses is essentially the same whether or not a visible lesion is present.

The definition of 'MRI negative' is somewhat controversial, as the ability to detect subtle lesions varies according to the techniques used, this being itself an area of extremely rapid current development (Knowlton, 2004; Koepp and Woemann, 2005). Overall, more advanced techniques may show abnormalities in around half of patients in whom conventional MRI is negative, but such abnormalities may not be concordant with other patient data (Koepp and Woermann, 2005). In addition, lack of large series of surgical outcome data means that the clinical implications of advanced imaging techniques, when used to identify potentially operable lesions in epilepsy patients with conventionally normal imaging, are somewhat unclear: ever more sensitive imaging methods carry the risk of increasingly identifying clinically innocuous lesions for which surgery may be unhelpful or even detrimental (Koepp and Woemann, 2005) and results must always be interpreted in the light of the clinical picture and other investigation findings. There are therefore likely to be natural limits to the ability of better imaging techniques alone to improve epilepsy surgical outcome and the need for invasive recording in certain cases is likely to persist. Better knowledge of seizure organisation has been suggested as an essential step to future progress in epilepsy surgery (Bartolomei *et al.*, 2005 [1]; Luders and Schuele, 2006). In addition clearer indications of whether some cases are better suited to certain methods of exploration could help improve patient selection for invasive exploration.

It is of interest that 43% of the MRI-negative cases for whom histopathology results were available showed focal dysplasia, as it is well-known that small dysplastic lesions may be difficult to detect using conventional high-resolution MRI (Duncan, 1997; Lee *et al.*, 2001; Knowlton, 2004; Lüders and Schuele, 2006). Several previous studies have found a high incidence of cortical dysplasia in patients with normal MRI who have subsequently been operated (Hong *et al.*, 2002; Cossu *et al.*, 2005; Lee *et al.*, 2005; Nobili *et al.*, 2006; Jeha *et al.*, 2007). All cases of cortical dysplasia in the present study, whether associated or not with a visible lesion, had significant improvement in seizure frequency following surgery. Indeed of the eight patients with focal cortical dysplasia and adequate follow up in the MRI-negative group, 6/8 were seizure free at 1 year. Of these eight normal MRI cases with FCD, seven had frontal lobe epilepsy and one had occipito-temporal epilepsy. While these numbers are small, these results are in marked contrast to a recent study of operated FLE cases explored using subdural grids (Jeha *et al.*, 2007), in which 11/12 patients with normal MRI plus malformations of cortical development (MCD) relapsed following surgery (the majority relapsing within the first six post-operative months), thus leading to the authors' conclusion that such patients formed the group with the overall worst surgical prognosis. The results of the present study may therefore offer an alternative to this rather pessimistic view. Our findings seem much closer to the findings of an Italian SEEG study (Nobili *et al.*, 2006), which found very good rates of persistent seizure freedom in a group of frontal lobe epilepsy patients: of nine who had normal imaging and evidence of dysplasia on histopathology, six became seizure-free following surgery. It is known that dysplasias are often located in regions that are difficult to satisfactorily record using subdural techniques, such as mesial cerebral structures and the fundus of sulci, and the advantage of SEEG in permitting direct intralesional recording in such cases has been documented (Chassoux *et al.*, 2000). In our cases of focal dysplasia, characteristic interictal surface and depth EEG abnormalities were often present, in keeping with previous observations (Chassoux *et al.*, 2000; Gavaret *et al.*, 2006; Lüders and Schuele, 2006). Finding better ways of identifying the group of likely radiologically 'invisible' cortical dysplasias may therefore represent a reasonable target in terms of future study, and the particular role of SEEG in exploring this group merits further study.

Supplementary material

Supplementary material is available at *Brain* online.

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Appendix

Table A1 Localization of EZ in 43 lesional MRI patients (numbered according to chronological order of SEEG exploration)

Patient number	Sex	Age at time of SEEG (years)	Duration of epilepsy at time of SEEG (years)	Likely diagnosis before SEEG	Laterality of EZ	Structures involved in EZ	Conclusion/clinical decision after SEEG	Histopathology	Duration of follow-up post surgery (months)	Outcome of surgery ILAE class 1 year	Outcome of surgery ILAE class 2 years	Most recent available outcome ILAE class
15	F	42	23	FLE	R	Right temporal pole, right posterior orbitofrontal cortex	Cortectomy	Gliosis	36	1	1	1
17	F	23	16	Occipital epilepsy	R	Lateral occipital cortex (BA 5), posterolateral temporal neocortex	Cortectomy	Dysplasia	49	2	1	1
20	F	20	15	FLE	R	Right dorsolateral premotor region (BA 6)	Cortectomy	Dysplasia	55	1	2	1
21	F	35	5	TLE	Bilateral	Right and left amygdalohippocampic regions	EZ localised but surgery contraindicated	Not operated	–	–	–	–
27	F	13	9	FLE-PM	L	Dorsolateral aspect of left premotor region (BA 6)	Cortectomy	Dysplasia	24	1	1	1
30	F	8	7	FLE-C	R	Right lower prerolandic region (F3, face region)	Cortectomy	Gliosis	28	4	5	5
35	F	18	7	Temporo-perisylvian epilepsy	Bilateral	Implication of right temporal region but some seizures suggestive of occipital onset	EZ incompletely localised by SEEG; no further attempt as evidence of multi-focality	Not operated	–	–	–	–
37	M	37	19	TLE	Bilateral	Right and left amygdalohippocampic region	EZ localised but surgery contraindicated	Not operated	–	–	–	–
39	M	34	19	TLE	L	Left amygdalohippocampic structures	Cortectomy	Hippocampal sclerosis	48	1	1	1
41	M	43	35	Temporo-perisylvian epilepsy	R	Anterior and posterior regions of right superior temporal gyrus	Cortectomy	Gliosis	50	1	1	1
43	F	17	12	FLE-C	L	Left dorsolateral prefrontal and premotor cortex (BA 9/46, BA 8)	Cortectomy	Dysplasia	42	3	4	4
45	M	33	17	FLE-PM	R	Right dorsolateral prefrontal cortex (BA 32 and BA 9/46)	Cortectomy	Dysplasia	36	1	1	1
49	F	15	9	Occipital epilepsy	R	Right supracalcarine and infracalcarine occipital cortex and fusiform gyrus	Cortectomy	Gliosis	38	1	1	5
54	M	31	25	FLE	R	Right mesial prefrontal cortex (BA 24 and BA32), posterior orbitofrontal cortex, temporal pole	Cortectomy	Dysplasia	41	1	3	3
56	F	43	12	TPOJ epilepsy	R	Right lateral temporal cortex, particularly superior temporal gyrus	Cortectomy offered but declined by patient	Not operated	–	–	–	–
58	F	33	30	TLE- mesiolateral	L	Left amygdalohippocampic region and temporal pole	Cortectomy	Hippocampal sclerosis	35	4	5	5
59	F	20	17	FLE-PM	L	Left operculoinsular region and left posterior orbitofrontal region	EZ localised but surgery contraindicated	Not operated	–	1	1	–
62	F	29	18	Temporo-frontal epilepsy	L	Left amygdala, temporal pole and basal temporal regions	Cortectomy offered but the patient wishes to wait	Not operated	–			–
63	M	9	7	FLE-PF	R	Right dorsolateral prefrontal region (intermediate frontal sulcus)	Cortectomy	Dysplasia	40	1	1	1
64	M	29	16	FLE	Bilateral	Right temporal pole and left operculo-insular region	EZ localised but surgery contraindicated	Not operated	–	–	–	–
65	F	18	8	FLE-PM	L	Lateral part of left BA 6, SMA, anterior cingulate gyrus	EZ localised but surgery contraindicated	Not operated	–	–	–	–

66	M	26	16	FLE	L	Left insulo-opercular region, posterior fronto-orbital region and temporal pole	EZ localised but surgery contraindicated	Not operated	–	–	–	–
70	M	13	2	FLE-PF	L	Left supplementary motor area, mesial aspect	Cortectomy offered but the patient wishes to wait	Not operated	–	–	–	–
71	M	28	24	Temporo-perisylvian epilepsy	R	Right superior temporal gyrus and right amygdalohippocampic region	Cortectomy	Not available	24	4	4	4
72	M	42	28	TLE	R	Right mesial temporal structures and basal temporal structures	Cortectomy	Not available	24	2	2	2
73	F	17	14	FLE	L	Left dorsolateral premotor and prefrontal regions (preSMA, 9/46); cingulate cortex	Cortectomy	Dysplasia	24	1	1	1
74	F	62	34	Temporo-frontal epilepsy	R	Right amygdalohippocampic region, entorhinal cortex and temporal pole; posterior part of superior temporal gyrus	Cortectomy	Gliosis	18	4	–	4
75	F	23	16	FLE	Bilateral	Bilateral prefrontal and premotor regions	EZ localised but surgery contraindicated	Not operated	–	–	–	–
76	M	31	16	FLE-PF	L	Prefrontal and premotor regions involving both lateral and medial aspects of left frontal lobe, and left anterior temporal region, with very rapid involvement of right frontal regions	Cortectomy	Gliosis	18	5	–	5
77	F	25	20	FLE	L	Left premotor, dorsolateral prefrontal cortex; anterior cingulate region	Cortectomy	Gliosis	19	4	–	4
79	M	21	4	FLE-PF	Bilateral	bilateral prefrontal regions, particularly mesiobasal aspect	GK (anterior callosotomy)	Not available	21	4	–	4
81	F	16	10	FLE	Bilateral	Dorsolateral aspect of right and left premotor and precentral frontal regions	GK	Not available	18	5	–	5
82	F	26	16	Parieto-central epilepsy	R	Paracentral lobule, mesial aspect	GK	Not available	9	–	–	N/A
84	F	22	20	FLE-PM	R	Extensive involvement of right premotor regions (lateral and mesial)	Cortectomy	Gliosis	8	–	–	3
85	F	32	25	FLE-PF	R	Right paramedian prefrontal region, anterior and posterior regions of superior frontal sulcus	Cortectomy	Gliosis	18	1	–	1
86	M	25	10	Operculoinsular epilepsy	R	Right insular region and posterior part of right superior temporal gyrus	GK	Not available	4	–	–	N/A
90	M	51	50	FLE	R	[Right frontal and right temporal]	EZ localised but surgery contraindicated	Not operated	–	–	–	–
92	F	26	23	Occipital epilepsy	L	Left infra- and supracalcarine occipital regions, lateral parietal cortex	Cortectomy	Gliosis	9	–	–	4
94	M	52	35	FLE-PF	Bilateral	Temporal pole, orbitofrontal cortex	EZ localised but surgery contraindicated	Not operated	–	–	–	–
95	M	8	7	Operculoinsular epilepsy	R	Right insula, perisylvian region	GK	Not yet operated	–	–	–	–
96	F	35	23	FLE	L	Left orbitofrontal cortex, perisylvian region	Cortectomy	Dysplasia	1	–	–	N/A
97	M	18	11	FLE	R	Right prefrontal region	Cortectomy	Gliosis	6	–	–	1
98	F	28	11	FLE	R	Right pre-SMA, medial prefrontal cortex	Cortectomy	Dysplasia	12	–	–	2

BA = Brodmann's area; DNET = dysembryoplastic neuro-epithelial tumour; EZ = epileptogenic zone; FLE = frontal lobe epilepsy; FLE-PF = prefrontal frontal lobe epilepsy; FLE-PM = premotor frontal lobe epilepsy; FLE-C = precentral frontal lobe epilepsy; GK = gamma knife radiosurgery; L = left; MCD = malformation of cortical development; R = right; TLE = temporal lobe epilepsy; TPOJ = temporo-parieto-occipital junction.

Table A2 Localization of EZ in 57 lesional MRI patients (numbered according to chronological order of SEEG exploration)

Patient number	Sex	Age at time of SEEG (years)	Duration of epilepsy at time of SEEG (years)	Likely diagnosis before SEEG	Laterality of EZ	Structures involved in EZ	Conclusion/clinical decision after SEEG	Histopathology	Duration of follow-up post surgery (months)	Outcome of surgery ILAE class 1 year	Outcome of surgery ILAE class 2 years	Most recent available outcome ILAE class
1	F	26	6	TPOJ epilepsy	G	Left mesial temporal and temporobasal regions	GK	Not available	65	4	4	4
2	F	18	10	Temporo-perisylvian epilepsy	G	Extensive involvement of left TPOJ, anterior and basal mesial temporal regions and superior temporal gyrus	EZ localised but surgery contraindicated due to wide involvement of language areas	Not operated	–	–	–	–
3	F	27	11	FLE-PF	G	Mesial aspect of left prefrontal region (BA 32) and mesial orbitofrontal region	Cortectomy	Dysplasia	42	2	1	1
4	M	48	15	FLE	D	Right posterior and mesial orbitofrontal region with rapid widespread propagation to amygdala and posterior frontal regions	EZ localised but surgery contraindicated	Not operated	–	–	–	–
5	M	22	18	TLE	D	Right amygdala, hippocampus and temporobasal regions	GK	Not available	67	2	3	1
6	F	43	7	TLE	D	Right amygdala, anterior and posterior hipocampus	Cortectomy	Gliosis	56	2	3	3
7	F	30	20	TLE	G	Widespread involvement of right mesial temporal and temporobasal structures particularly posterior hippocampus, amygdala, entorhinal cortex; early propagation to TPOJ	Cortectomy	Gliosis	60	1	1	1
8	F	25	20	TLE	D	Perilesional area (right temporal lobe) extending to STG and posterior temporoparietal region (BA 22)	Cortectomy	Ectopic neurones suggestive of MCD	33	1	1	1
9	M	29	15	TLE	G	Left hippocampus, amygdala and entorhinal cortex with early propagation to STG and TPOJ	Cortectomy	Gliosis	66	1	1	3
10	F	44	24	TLE	G	Left hippocampus, temporal pole and STG	Cortectomy	Gliosis	60	1	1	1
11	M	34	6	Mesiolateral TLE	D	Right lateral temporobasal region, mesial temporal and entorhinal structures	Cortectomy offered but declined by patient	Not operated	–	–	–	–
12	M	47	45	FLE-PF	D	Complex EZ with 2 independent "starter zones": right mesial prefrontal region (BA 32 and 24); right frontal operculum (BA 44)	Cortectomy (right mesial prefrontal region)	Dysplasia	60	1	1	1
13	F	30	28	Mesial TLE	G	Left anterior hippocampus; rapid widespread involvement of limbic system	Cortectomy	Gliosis	56	2	1	1
14	F	31	28	TLE	Bilateral	Perilesional area (right parieto-occipital junction); rapid involvement of bilateral posterior cingulate regions	GK	Not available	54	4	4	5

16	F	29	28	Mesial TLE	D	Right amygdala and hippocampus with rapid spread to temporal neocortex	Cortectomy	Gliosis	40	1	1	1	
18	M	8	1	TLE	G	Left mesial temporal limbic structures	Cortectomy	Dysplasia	53	1	1	1	
19	F	40	38	Occipital epilepsy	G	Bilateral parieto-occipital regions, including region anterior to left-sided lesion	Cortectomy	DNET	38	5	5	5	
22	M	20	6	Occipital epilepsy	D	Right mesial occipital structures, particularly supracalcarine cortex	Cortectomy	Gliosis	34	3	3	3	
23	F	38	13	Temporo-perisylvian epilepsy	G	Left mesial temporal structures with secondary spread to left lateral temporal structures	Cortectomy	Not available	56	3	3	1	
24	M	37	11	FLE	G	Left dorsolateral prefrontal region (BA9) as well as mesial prefrontal structures and left frontal opercular region (perilesional)	Cortectomy	Gliosis	42	1	3	3	
25	M	31	26	TLE	D	Right amygdala and hippocamus	Cortectomy	Gliosis	38	1	3	1	
26	F	25	20	FLE	G	Left precentral and premotor regions including BA 6	Cortectomy	Dysplasia	26	4	4	4	
28	M	15	9	Mesial TLE	G	Left posterior hippocampal region with propagation to temporo-occipital region	Cortectomy	DNET	60	1	1	1	
29	M	31	17	Temporo-perisylvian epilepsy	D	Right STG with spread to mesial temporal structures	Cortectomy	Gliosis	42	1	1	1	
31	M	15	12	FLE-C	D	Right mesial perirolandic regions with propagation to premotor regions	GK	Not available	38	4	5	5	
32	M	43	18	Temporo-frontal epilepsy	Multifocale	Onset in several different perilesional areas (nodular hetreotopia) as well as implication of right mesial temporal structures	GK offered but declined by the patient	Not operated	–	–	–	–	
33	M	24	22	Temporo-frontal epilepsy	G	Left anterior temporobasal and mesial temporal structures including perilesional zone; implication of thalamus	Cortectomy	Not available	51	1	3	3	
34	M	33	16	FLE	Bilate	Extensive bilateral involvement of premotor regions (dorsolateral and medial)	EZ localised but surgery contraindicated (bilateral EZ)	Not operated	–	–	–	–	
36	M	31	14	TLE	D	Left amygdala and hippocampus	Cortectomy	Gliosis	36	3	3	4	
38	F	55	1	TLE	G	Onset left mesial temporal region with early propagation to temporal neocortex and insula	GK	Not available	30	3	3	3	
40	F	29	25	FLE-PF	G	Principally perilesional area within left mesial prefrontal region	Cortectomy	Dysplasia	37	1	1	3	
42	M	31	19	FLE-PF	G	Left mesiobasal prefrontal regions, orbitofrontal cortex and temporal pole	Cortectomy	Gliosis	40	1	1	1	

(continued)

Table A2 Continued

Patient number	Sex	Age at time of SEEG (years)	Duration of epilepsy at time of SEEG (years)	Likely diagnosis before SEEG	Laterality of EZ	Structures involved in EZ	Conclusion/clinical decision after SEEG	Histopathology	Duration of follow-up post surgery (months)	Outcome of surgery ILAE class 1 year	Outcome of surgery ILAE class 2 years	Most recent available outcome ILAE class
44	F	41	16	FLE-PF	D	Right, frontopolar, orbitofrontal and dorsolateral premotor region	Cortectomy	Not operated	–	–	–	–
46	M	15	1	TLE	G	Left anterior hippocampus and temporobasal regions	Cortectomy	Hippocampal sclerosis	49	3	3	3
47	M	29	27	Occipital epilepsy	D	Right occipital cortex including perilesional region	Cortectomy	Dysplasia	30	4	4	4
48	F	29	18	Parietal epilepsy	D	Right superior parietal cortex and right perisylvian region	Cortectomy	Rosenthal fibres, gliosis	36	2	4	4
50	M	23	20	Lateral TLE	D	Right STG including perilesional region with spread to perisylvian region and insula	Cortectomy	DNET	42	3	3	1
51	F	36	32	TLE	D	Right mesial temporal structures	Cortectomy	Gliosis	45	3	3	3
52	M	22	21	TLE	D	Widespread involvement of right mesial and lateral temporal structures	Cortectomy	Astrocytoma	28	1	1	1
53	F	39	24	Mesiolateral TLE	D	Right mesial temporal structures with early spread to opercular and insular regions	Cortectomy	Gliosis	36	1	1	1
55	F	35	33	Mesial TLE	D	Right mesial temporobasal structures (entorhinal cortex closely connected to anterior hippocampus)	Cortectomy	Dysplasia	45	3	2	4
57	M	35	32	Mesial TLE	G	Left anterior mesial temporal structures	Cortectomy	Hippocampal sclerosis	29	1	1	1
60	F	17	9	Occipital epilepsy	D	Right perilesional region (V5) and posterior temporal region	Cortectomy	Dysplasia	42	3	3	1
61	F	13	11	TPOJ epilepsy	G	Left mesial temporal structures and temporal pole	Cortectomy	Neuronal migratio disorder	38	1	1	1
67	F	34	25	FLE-C	D	"Bifocal" organisation: right Hesch's gyrus and 2nd independent ZE (different seizure type) involving perisylvian structures and orbitofrontal cortex	Cortectomy	Gliosis	35	4	4	4
68	M	29	28	FLE-C	G	Left frontal opercular and basal central regions	GK	Not available	N/A	N/A	N/A	N/A
69	F	42	1	Mesiolateral TLE	G	No SEEG recording obtained	–	Not operated	–	–	–	–

78	F	26	21	Temporo-frontal epilepsy	D	Onset right amygdala and temporal pole, propagation to ipsilateral prefrontal and mesial occipito-parietal regions	Cortectomy	Dysplasia	15	1	–	1	
80	F	34	22	Parietocentral epilepsy	D	Right perilesional area (parietal cortex)	Cortectomy	Gliosis	15	1	–	1	
83	F	50	36	Parietal epilepsy	D	Right perilesional area (superior interparietal sulcus)	Cortectomy	Dysplasia	14	1	–	1	
87	M	32	16	FLE	G	Left temporal pole with rapid propagation to orbitofrontal cortex, prefrontal anterior cingulate region (BA 32) and SMA	Cortectomy	Gliosis	12	4	–	4	
88	M	16	13	Operculoinsular epilepsy	G	Perilesional region (left parietal operculum) with propagation to lateral frontal opercular region	Cortectomy	Neuroepithelial angiocentric tumour	12	5	–	5	
89	F	36	26	Parietal epilepsy	D	Right mesial parietal region	Cortectomy	Dysplasia	6	–	–	1	
91	M	26	17	Operculoinsular epilepsy	D	Right operculo-insular region	EZ incompletely localised by SEEG	Not operated	–	–	–	–	
93	F	42	26	Occipital epilepsy	D	Right perilesional area (right occipital cortex) with rapid propagation to parietal regions and homotopic contralateral regions	GK	Not available	9	–	–	5	
99	M	56	47	Temporo-frontal epilepsy	D	Right basal temporal cortex and amygdala	Cortectomy	Gliosis	6	–	–	N/A	
100	F	15	12	FLE-PM	G	Left mesial precentral region (hand motor area)	Limited cortectomy	Not yet operated	–	–	–	–	

BA = Brodmann's area; DNET = dysembryoplastic neuro-epithelial tumour; EZ = epileptogenic zone; FLE = frontal lobe epilepsy; FLE-PF = prefrontal frontal lobe epilepsy; FLE-PM = premotor frontal lobe epilepsy; FLE-C = precentral frontal lobe epilepsy; GK = gamma knife radiosurgery; L = left; MCD = malformation of cortical development; R = right; TLE = temporal lobe epilepsy; TPOJ = temporo-parieto-occipital junction.

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**Anatomo-electro-clinical correlations:
the Marseille, France Case Report
Case 02-2008**

MRI-negative prefrontal epilepsy due to cortical dysplasia explored by stereoelectroencephalography (SEEG)

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ABSTRACT – [Case records of *Epileptic Disorders*. Anatomo-electro-clinical correlations. Case 02-2008] We report the case of a young boy presenting with pre-frontal seizures including singing automatisms. There was no visible lesion on MRI, but following localisation using stereoelectroencephalography (SEEG), surgery revealed an underlying dysplastic lesion. *[Published with video sequences]*

Key words: stereoelectroencephalography (SEEG), MRI-negative, pre-frontal, dysplasia

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Epileptic Disorders Case Records, published under the heading "Anatomo-electro-clinical correlations" are expected to provide to the reader a comprehensive approach of pre-surgical evaluation and epilepsy surgery strategies. Authors are expected to provide supplemental data for publication on the DVD to allow further discussion on the surgical approach chosen.
Epileptic Disorders will published all documented comments, critics and suggestions discussing the approach taken by the authors. The readers are invited to submit their eventual comments in the online submission system as « Letter to the Editor » with reference to the Case Records' number.
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Clinical history

The patient first presented to our service at the age of eight years. The product of a normal pregnancy, he had presented a single, uncomplicated febrile seizure at the age of one year in the context of a throat infection. His mother and sister also had a history of febrile convulsions, but there was no family history of epilepsy. His psycho-motor development was entirely normal until the age of 18 months, when he presented with a first diurnal seizure. This was described as an episode of staring with loss of contact lasting several seconds, associated with rubefaction, chewing and bilateral hand tapping movements. Further similar events followed (occurring in the daytime or while falling asleep) and paediatric neurology assessment resulted in a diagnosis of probable frontal lobe epilepsy. Clinical examination was unremarkable and he was right-handed. Initial surface EEG showed rare, right rhythmic anterior spikes (FP2, F4, F8) as well as bilateral polyspike wave discharges (predominant on the right side, activated by sleep). Videotelemetry at the age of two years allowed recording of two frontal seizures, one of which had apparent left-sided and one right-sided onset. Cerebral MRI was normal. Treatment with carbamazepine was commenced, resulting in a one year period of complete remission. However, seizures then recommenced at the age of three years, this time in the form of nocturnal attacks ("night terrors"), characterised by vocalisation and agitation with elevation of both upper limbs; a change in his daytime behaviour was also noted, with a tendency to hyperkinetic activity and attentional difficulty. It was noted that he seemed to remain aware or partially aware, and could ask following a seizure "why am I laughing?" Subsequent trials of various anti-epileptic drug combinations including carbamazepine, valproate, vigabatrin, clonazepam, phenytoin, topiramate and lamotrigine were unsuccessful in controlling the seizures and he was eventually referred to our centre for pre-surgical assessment. At this time, seizures often occurred in clusters of many per day, several times a month with negative consequences for his schooling.

A preliminary phase of comprehensive, non-invasive pre-surgical investigation was performed in our unit, the results of which are summarised below.

Non-invasive investigation

Interictal surface EEG showed bilateral frontal spikes and spike-wave discharges, predominantly right-sided; associated rapid discharges in the same region were also subsequently demonstrated using high resolution EEG (EEG-HR) *(figure 1)*. No independent left-sided abnormality was seen. Three habitual seizures were recorded on video-telemetry, with semiology that can be summarised as follows: sudden onset of bilateral lower limb movements with asymmetric extension and/or flexion; sometimes "beating time" to the tune as he sang; less obvious bilateral upper limb movements sometimes with extension. He also presented humming or frank singing, sometimes preceded by a cry, occurring close to seizure-onset. He would then present verbal automatisms characterised by echolalia (sometimes in a sing-song style), with either comprehensible or incomprehensible words. The duration was around 20 seconds and in the post-ictal period no deficit was noted, but he would often seem euphoric or cheerful. Ictal EEG of these seizures showed a pattern of flattening in right anterior frontal regions and the anterior vertex, followed by a localised, rapid spike discharge 3-5 seconds later, in right frontal electrodes (FP2, F8, FZ) *(see video sequence 1)*. High resolution EEG (EEG-HR) revealed that surface interictal spikes had two separate components, which, when examined sequentially and analysed using source localisation tools (MUSIC), showed antero-posterior propagation from the right medial fronto-polar region to the right superior frontal sulcus (SFS) *(figure 2)*. Cerebral MRI, including careful review following the results of other investigations, was normal. The MR protocol used consisted of transverse diffusion images, transverse T2-weighted images, coronal T1-weighted inversion recovery images, coronal FLAIR (fluid-attenuated inversion recovery) images and a three-dimensional T1-weighted acquisition. Acquisition plans were referred to the bi-hippocampal plane for the transverse acquisitions and to the AC-PC plane for the coronal and axial acquisition. Reconstructions of the 3D T1 images were adapted to the type of epilepsy. MRI examinations were performed on a 1.5-Tesla Symphony machine (Siemens Medical Systems, Erlangen, Germany), with a 4-channel head coil being used. Interictal SPECT on two previous occasions had shown right fronto-temporal hypoperfusion (during initial paediatric assessment); at the time of pre-surgical work-up, bilateral anterior mesial frontal and right anterior temporal hypoperfusion were noted. PET and ictal SPECT were not performed. As part of a research protocol, a computerised analysis of sulcal anatomy was performed using raw MRI data, and this suggested a possibly unusual appearance of the right superior frontal sulcus. This method remains however, an as yet unvalidated research tool (Mangin *et al.* 2004) and the significance of this finding is therefore unclear.

Neuropsychological assessment showed intellectual capacities within the normal range, with no visuo-verbal dissociation. Although a relative preservation of executive functions was demonstrated, a deficit in visuo-spatial programming (deficit in visual exploration strategies) was present as was some mild, verbal dysfunction in terms of impaired narrative ability and difficulty in problem-solving tasks.

Stereroelectroencephalographic (SEEG) exploration

Following this non-invasive assessment, the decision was taken to perform SEEG. The main hypothesis based on electroclinical features was that of a single localised epilep-

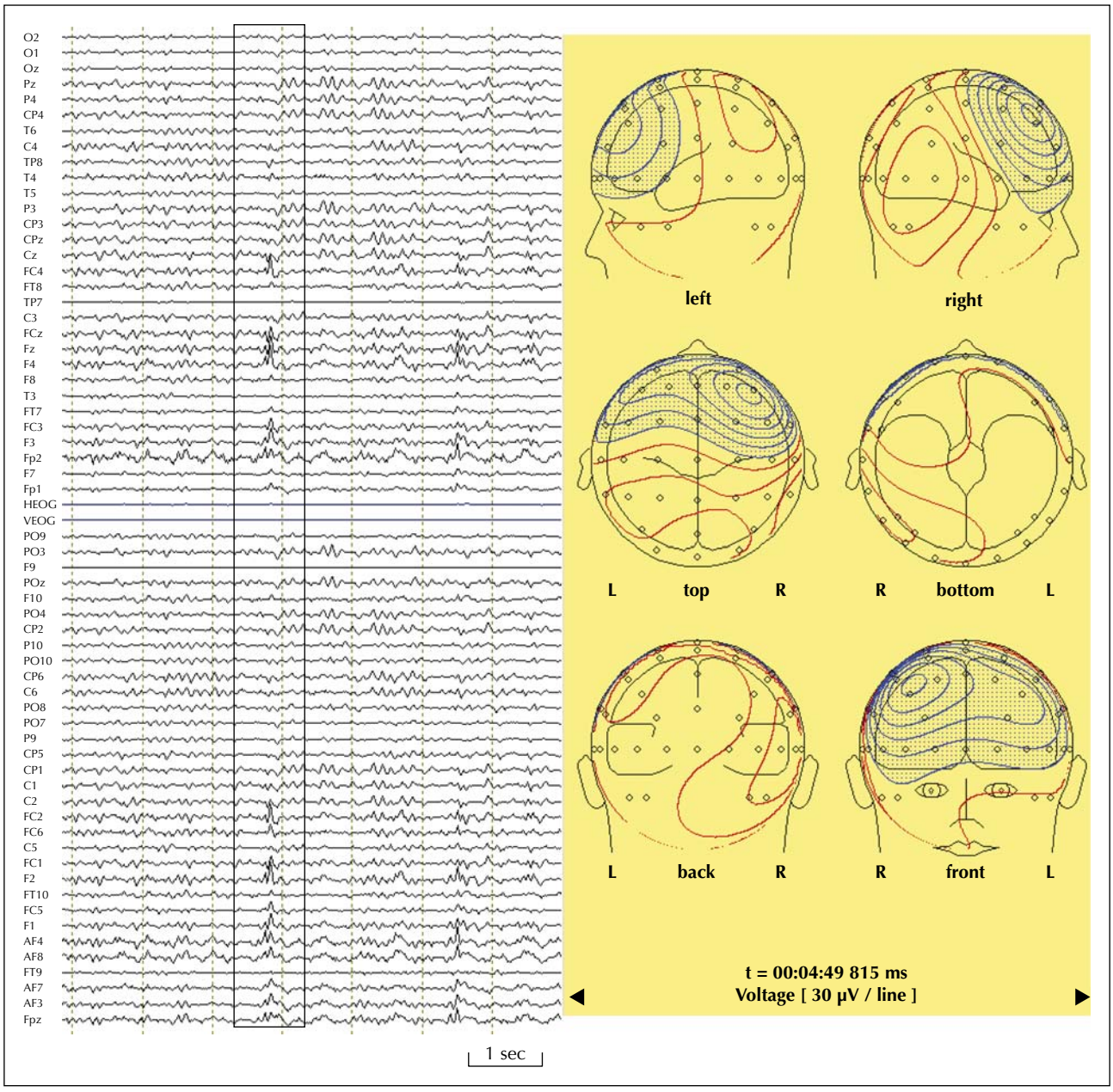

Figure 1. Right frontal interictal spikes on surface EEG. Surface high resolution EEG (HR-EEG) using 64 electrodes; monoplar montage, average reference. Interictal spikes involving bilateral anterior regions, predominantly right-sided (maximum amplitude F4, F2, FC2). Amplitude cartography (using EEGFocus; MEGIS Software, Gräfelfing, Germany) during the scalp-EEG interictal spike shown in the first panel.

togenic zone in the right prefrontal region, with the relative contribution of mesial, dorsolateral and orbitofrontal structures to be determined. The exploration also aimed at excluding a more widespread epileptogenic zone, with electrodes therefore being placed in premotor and temporal lobe structures. The EEG-HR was strongly suggestive of focal right prefrontal interictal activity, and ictal EEG was also in keeping with right prefrontal onset, such that bilateral exploration was not considered necessary.

SEEG recordings were performed using intracerebral multiple contact electrodes (10 to 15 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm apart), placed intracranially according to Talairach's stereotactic method as previously described (Talairach *et al.* 1992). Nine right-sided depth electrodes were placed as follows *(figure 3)*: electrode FP exploring medial and lateral parts of the fronto-polar region with medial and lateral contacts respectively; electrode CR exploring the anterior cingulate region

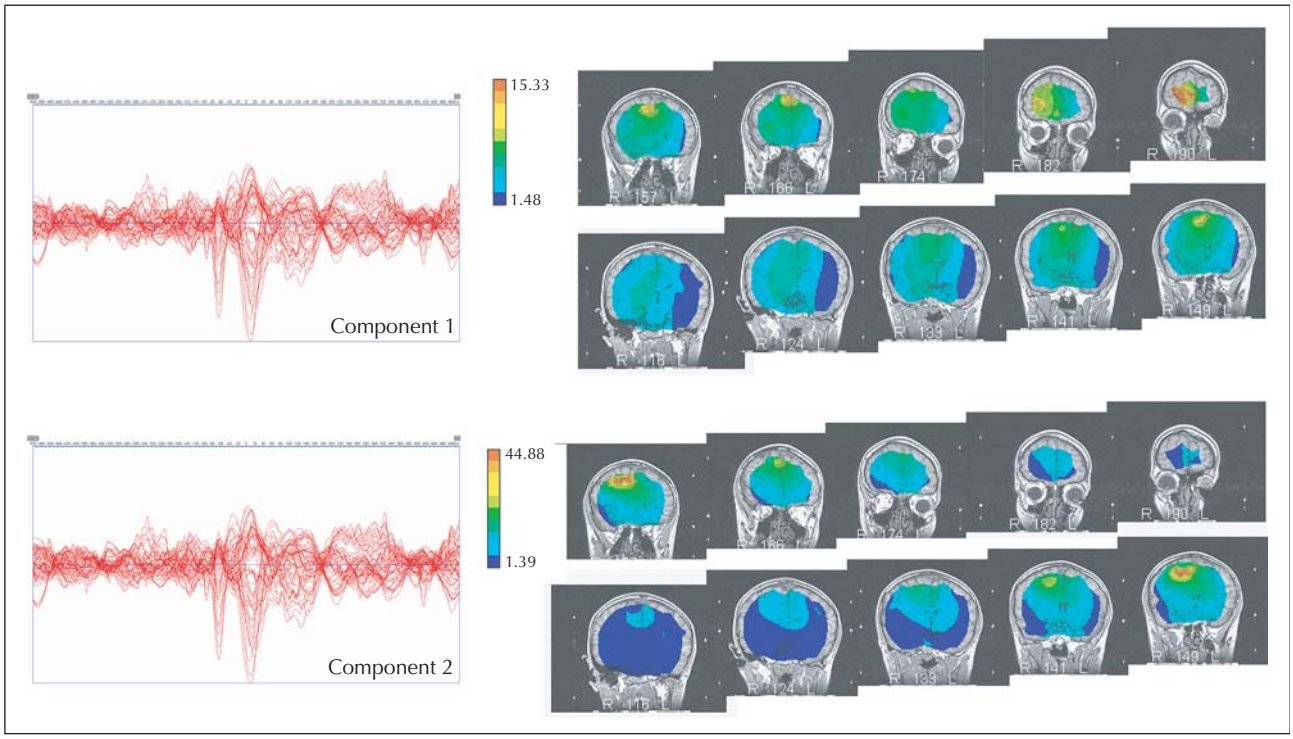

Figure 2. Source localisation with HR-EEG. The same single interictal spike as was shown in *figure 1*, the 64 channels being superimposed in ASA software (ANT software, Enschede, The Netherlands). There were two successive components that were studied sequentially with a source localisation model using a realistic head model and the MUSIC algorithm for solution of the inverse problem (Multiple Signal Classification, Mosher *et al.* 1999). The temporal window of analysis for the first component lies between the two vertical lines. The source of the first spike component was shown by this technique to be the right fronto-polar region. The temporal window of analysis for the second component lies between the two vertical lines. Source localisation was more posterior for this second component, indicating the right superior frontal sulcus area. An antero-posterior interictal spike propagation was therefore demonstrated.

(Brodmann area 32) with medial contacts and the dorsolateral prefrontal cortex (Brodmann area 9/46) with lateral contacts; electrode PS exploring the pre-supplementary motor area (SMA) with medial contacts and frontal eye fields (Brodmann area 8) with lateral contacts; electrode S exploring the SMA with medial electrodes and lateral premotor cortex (Brodmann area 6) with lateral contacts; electrode CC exploring the anterior cingulate gyrus (Brodmann area 24) with medial contacts and lateral premotor cortex (Brodmann area 6) with lateral contacts; electrode OF exploring the caudate nucleus with medial contacts and the frontal operculum with lateral contacts, passing through the insula; electrode O exploring medial and lateral orbitofrontal cortex with medial and lateral contacts respectively; electrode T exploring the medial temporal lobe with medial contacts and the superior temporal gyrus with lateral contacts; electrode TP exploring medial and lateral aspects of the temporal pole with medial and lateral contacts respectively.

Interictal SEEG *(figure 4)* was characterised by continuous spikes, polyspike and spike-wave activity as well as rapid discharges (35 Hz) recorded synchronously from the electrodes exploring the anterior cingulate, dorsolateral prefrontal and fronto-polar regions (contacts CR 2-3 and 3-4, spreading to CR1-2 and CR 5-7) and FP (1-6). These spikes could spread to involve premotor regions (electrodes PS and S). The middle contacts of electrodes O, OF and TP showed interictal slow wave activity.

During SEEG, one spontaneous seizure was recorded and four seizures were provoked by electrical stimulation of selected electrode contracts. The semiology of all five seizures was comparable to those described above.

In terms of ictal SEEG, for the single spontaneous seizure, a modification of background activity was noted 2 min 30 before seizure-onset, in the form of rhythmic spikes in the middle contacts of electrodes CR and FP (dorsolateral prefrontal region). This pre-ictal spiking then stopped abruptly, giving way to a fast tonic discharge (20 Hz) (CR 2-7 and FP 1-7), lasting eight seconds *(figure 5)*. This was followed by a second, faster tonic discharge (80 Hz) in the same region, corresponding to the moment when the first clinical signs occurred. Following this, a clonic spike discharge was seen in the same electrodes, subsequently spreading to more lateral contacts of CR, FP then towards orbital and premotor regions (intermediary contacts of O and S).

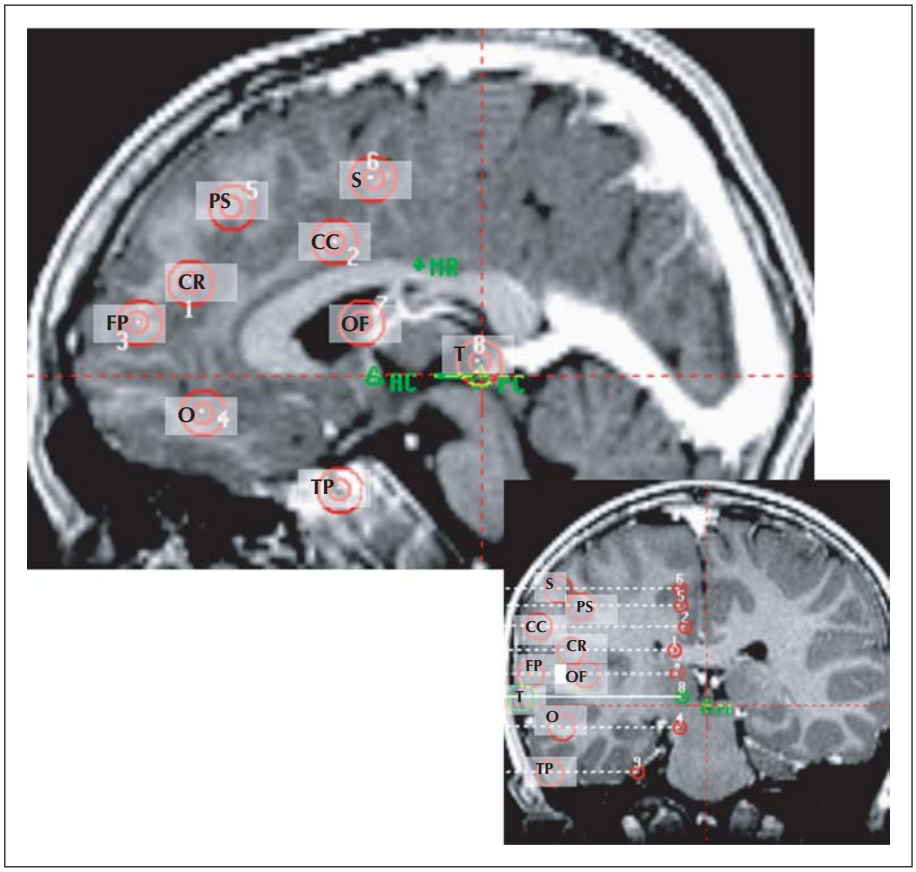

Figure 3. SEEG implantation with nine electrodes. Electrode FP exploring medial and lateral parts of the fronto-polar region with medial and lateral contacts respectively; electrode CR exploring the anterior cingulate region (Brodmann area 32) with medial contacts and the dorsolateral prefrontal cortex (Brodmann area 9/46) with lateral contacts; electrode PS exploring the pre-supplementary motor area (SMA) with medial contacts and frontal eye fields (Brodmann area 8) with lateral contacts; electrode S exploring the SMA with medial electrodes and lateral premotor cortex (Brodmann area 6) with lateral contacts; electrode CC exploring the anterior cingulate gyrus (Brodmann area 24) with medial contacts and lateral premotor cortex (Brodmann area 6) with lateral contacts; electrode FO exploring the caudate nucleus with medial contacts and the frontal operculum with lateral contacts, passing through the insula; electrode O exploring medial and lateral orbitofrontal cortex with medial and lateral contacts respectively; electrode T exploring the medial temporal lobe with medial contacts and the superior temporal gyrus with lateral contacts; electrode TP exploring medial and lateral aspects of the temporal pole with medial and lateral contacts respectively.

The provoked seizures were induced by stimulation of electrodes CR 1-2, CR 5-6 and FP 1-2, 3-4 *(see video sequence 2)*; in other words, in the same contacts as in the initial rapid discharge of the spontaneous seizure.

Conclusion following SEEG and subsequent surgical outcome

From analysis of all available data, including detailed analysis of the exact position of SEEG electrodes using 3D MRI, it was concluded that the irritative zone and epileptogenic zone were practically superimposed, involving a localised region within the right superior frontal sulcus. The preferential propagation pathway involved the orbitofrontal region. The EEG features and the localisation to the base of a sulcus raised the question of underlying dysplasia, despite the lack of any imaging abnormality. The patient subsequently underwent right, prefrontal cortectomy including the right SFS and intermediate frontal sulcus, extending posteriorly to the anterior pre-cingulate region *(figure 6)*. Histopathology of the resected section confirmed focal cortical dysplasia type IIB (Taylor-type with balloon cells). The dysplastic lesion was relatively voluminous, being present in the bases of several adjacent sulci of the superior prefrontal cortex, particularly in their mesial aspect. The patient has been followed up in our service for four years post-operatively and has remained seizure-free since surgery. Neuropsychology assessment shows an improvement in the visuo-spatial and verbal tasks that were slightly abnormal prior to surgery. He has taken no anti-epileptic medication for the past two years and his school progress is entirely normal for his age. He is psycho-socially well-integrated within his family and school activities.

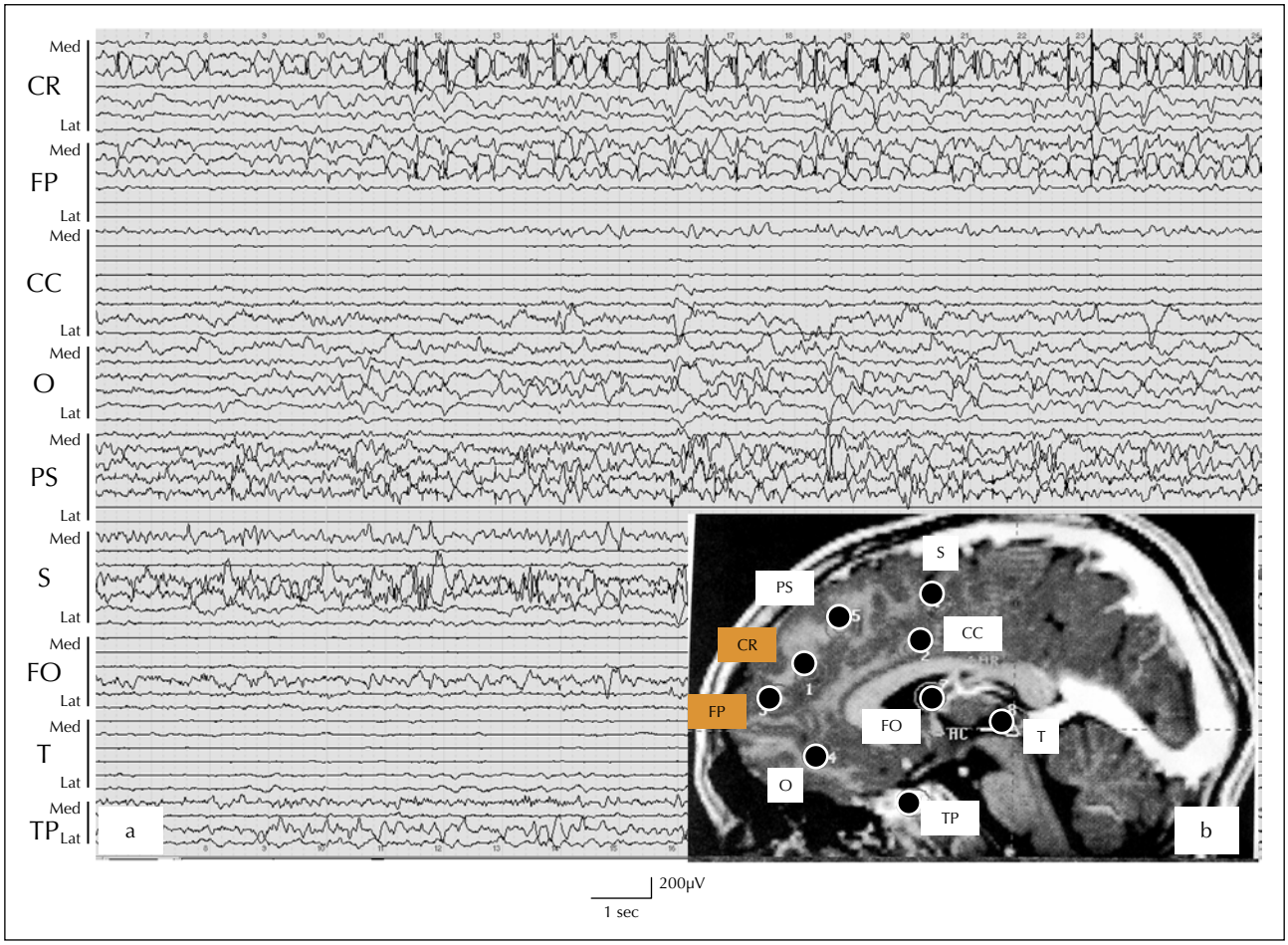

Figure 4. A) SEEG interictal activity. Spikes and spike-wave discharges involving medial and middle contacts of CR and FP (right prefrontal region). **B**) Schema of electrode implantation with main electrode involvement (FP and CR) indicated in orange.

Discussion

This patient falls within the group of those presenting for surgical evaluation with normal structural imaging, but with other features indicating a likely localised region of seizure production. Frontal lobe epilepsy surgery is the second most common resective surgery performed for drug resistant epilepsy after temporal lobe resection, and the group of frontal epilepsies with normal imaging is considered to be one of the most challenging, with relatively poorer surgical outcomes reported in the literature (Jeha *et al.* 2007). While some authors have argued that such patients should be automatically excluded from presurgical assessment because of the low chance of success, it is however, well-recognised that selected patients can have very good surgical outcomes, dependant upon correct localisation, which usually requires intra-cranial recording. The method of SEEG, differing in many key respects from other techniques such as subdural grids, may afford certain advantages as illustrated in the current case. For example, recording from deep as well as superficial structures permits recording from buried cortex or the base of sulci (crucially, in this case, from the base of the SFS where the dysplasia was situated). In addition, simultaneous recordings from both medial and lateral structures allows a temporo-spatial pattern of activity to be characterised (here, confirming the pattern of spike propagation suggested by HR-EEG). Indeed, the current case was previously included in a reported series of 100 SEEG explorations from the Marseille group, which demonstrated no difference in localisation rates or eventual surgical outcome between those with MRI lesions and those with normal imaging (McGonigal *et al.* 2007).

In terms of formulating a set of hypotheses to determine a strategy for intracranial exploration in this case, a number of elements contributed. The semiology was not, in itself, clearly localising or lateralising, other than suggesting frontal and in particular prefrontal involvement. The semiology of prefrontal seizures is complex, variable and certainly remains incompletely characterised (Jobst *et al.* 2000, Chauvel 2003). However, some semiological ele-

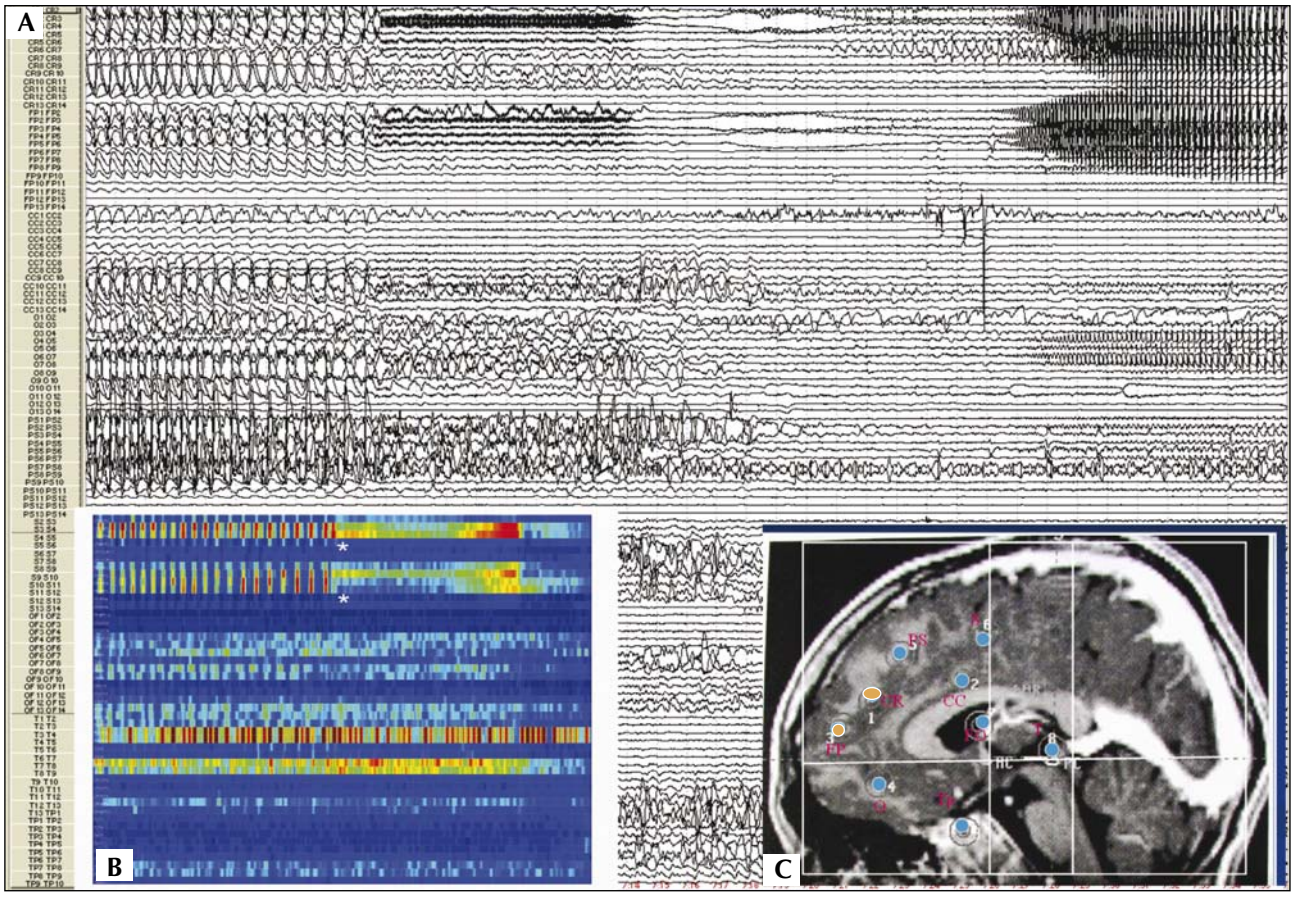

Figure 5. A) Spontaneous seizure recorded on SEEG. A modification of background activity was noted 2 min 30 before the clinical seizure-onset, in the form of rhythmic spikes in the middle contacts of electrodes CR and FP (dorsolateral prefrontal region). This pre-ictal spiking then stopped abruptly, giving way to a fast tonic discharge (20 Hz) (CR 2-7 and FP 1-7), lasting eight seconds. This was followed by a second, faster tonic discharge (80 Hz) in the same region, corresponding to the moment when the first clinical signs occurred. Subsequently, a clonic spike discharge was seen in the same electrodes, subsequently spreading to more lateral contacts of CR, FP, and then intermediary contacts of O and S. **B**) Map of gamma activity (> 25 Hz) showing the detection of tonic rapid discharge (*) in contacts of electrodes CR and FP. Note also the pre-ictal spiking before the appearance of rapid discharge. **C**) Schema of electrode implantation with main electrode involvement (FP and CR) indicated in orange.

ments here, namely the singing, echolalia and distal hand tapping movements, can be viewed as a form of "forced acting" or pseudo-compulsive behaviour, which has previously been described as a feature of dorsolateral prefrontal seizures (Bancaud and Talairach 1992, Chauvel and Bancaud 1994). Indeed, it has been noted that the pattern of distally driven, semi-purposeful movements seen in certain prefrontal seizures is very different from the proximal, purposeless, often violent movements that correspond to what has also been called "hypermotor seizures", this second pattern being rather associated with prefrontal mesio-ventral cortex involvement; the difference in semiological pattern may ultimately present a means of classifying pre-frontal seizures (Chauvel 2003). The association of ictal emotional modification with stereotyped motor behaviours has been identified as a feature of epileptic activity involving the anterior cingulate region (Bancaud and Talairach 1992). Singing during seizures is rare, but in previous series has been associated with involvement of frontal, particularly right prefrontal regions (Bartolomei *et al.* 2007).The retained consciousness during this patient's seizures argued against widespread seizure propagation to bilateral frontal or temporal lobe regions. The absence of significant postural features or forced eye deviation indicated a lack of involvement of frontal pre-motor areas or frontal eye fields, and no secondary generalisation occurred. In addition, there was no ictal language dysfunction or post-ictal deficit, arguing against significant involvement of dominant hemisphere language structures.

Surface EEG showed rhythmic abnormalities associated with fast activity in bilateral anterior regions, predominantly right-sided. The morphology of such abnormalities was quite evocative of underlying dysplasia (Gambardella *et al.* 1996), whilst HR-EEG not only confirmed a clear,

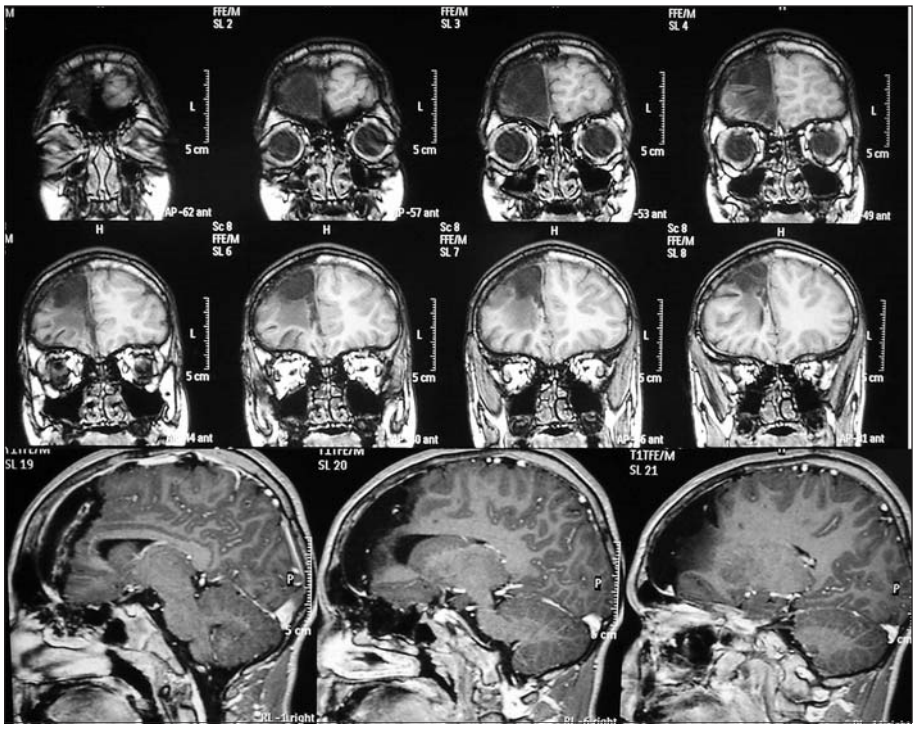

Figure 6. Post-operative MRI showing right frontal cortectomy.

right pre-frontal pattern but also indicated a probable antero-posterior propagation of interictal activity. The HR-EEG was therefore an important argument for proceeding to intracranial exploration, with the main hypothesis being a right, pre-frontal localisation. This technique, when used in association with source localisation tools, has been previously validated in frontal lobe epilepsy by corroboration with depth EEG studies (Gavaret *et al.* 2006), being particularly useful in determining lateral and mesial, but not basal frontal localisations. As has been previously noted in other cases of lateral frontal epilepsy (Foldvary *et al.* 2001), the ictal surface EEG in this case demonstrated a likely localised onset.

In terms of SEEG data, very focal interictal spikes, combined with consistently localised seizure-onsets characterised by a rapid discharge in the same region, were recorded. In addition, stimulation of the middle contacts of the principal electrodes involved reproduced habitual seizures and showed the preferential propagation pathway involving the orbitofrontal region. These data, together with the ensemble of other elements, therefore allowed confident estimation of primary seizure organisation within a limited region centred on the right SFS. The lack of involvement of premotor or temporal regions in seizure production was also confirmed. The recording of seizure-onsets, with a clear temporal relation between rapid discharge and production of clinical signs, indicated that the choice of electrode placement appeared to have been satisfactory. Indeed, the characteristic pattern of SEEG abnormalities (Chassoux *et al.* 2000), including the presence of interictal and preictal rhythmic spike discharges on SEEG and the occurrence of very fast ictal discharge within the same localised region, indicated the probability of an underlying dysplastic lesion despite the normal MRI. These rhythmic discharges recorded with depth electrodes correspond to the rhythmic spiking and fast activities seen on interictal surface EEG.

This patient proved to have a type IIB focal cortical dysplasia (Taylor-type, with balloon cells) in resected tissue. Despite ongoing, rapid advances in MR techniques, an unknown proportion of all dysplasias remain undetected by magnetic resonance imaging, and it is acknowledged that even lesions visible on MRI may only be the "tip of the iceberg" (Luders and Schuele 2006); in addition, the epileptogenic zone is often greater than the lesion itself (Chassoux *et al.* 2000). The usefulness of SEEG in assessing dysplastic lesions has been previously confirmed (Chassoux *et al.* 2000), particularly with regards to permitting direct intra-lesional recording as in the present case. The presence of localised surface EEG interictal abnormalities has been associated with better prognosis in MRI-negative cases, including dysplasias (Lee *et al.* 2005). Despite some studies reporting poor surgical prognosis in malformations of cortical development without visible MRI abnormalities (Jeha *et al.* 2007), excellent outcomes in such patients have been demonstrated by others (Nobili *et al.* 2007), and experience in our own centre is also positive in this respect (McGonigal *et al.* 2007). Outcome in children

appears to be better than that reported for adults and it is argued that improved cerebral plasticity may contribute to this effect (Fauser *et al.* 2008). Early surgical intervention in such cases is therefore desirable. In this case, not only has the patient become and remained seizure-free, but medication has been withdrawn and his educational and neuropsychological progress is entirely normal. □

Legends for video sequences

Video sequence 1

A spontaneous seizure recorded with surface EEG. Note the rapid, rhythmic, anterior right-sided discharge at seizure-onset.

Translation of dialogue
Loic: (he calls out in a sing-song voice, indistinguishable words).
Nurse: "Loic? Loic? What's happening? What's wrong?"
(Commentary on semiology): "We can't understand what he is saying..."
(To Loic): "Turn over... squeeze my hand..."
(Commentary): "There is a loss of contact...He is smiling... There is no mydriasis...He is still smiling..... He's closing his eyes..."
(To Loic): "What's happening Loic? Is that it, is it finished? Do you recognise me?"
Loic: "Yeah."
Nurse: "What were you singing? You don't remember? You were singing, just then. Who is this?" *(She shows him a picture)*
Loic: "Panda" (responds correctly)

Video sequence 2

Seizure recorded during SEEG exploration, provoked by stimulation of intermediate contacts of electrode CR (CR 5-6) exploring prefrontal cortex, corresponding to the region of maximum observed interictal activity and the region involved in the initial organisation of spontaneous seizures. The semiology is identical to that of his spontaneous seizures. Following a stimulation artefact, a fast rhythmic discharge can be seen building up in the middle contacts of CR before spreading to involve FP and then O, PS and the outer contacts of CC.

Translation of dialogue
Loic: *(he reads aloud from a comic then lets out a cry)*
Doctor: What is it Loic? What are saying? Do you want to read that?
(Commentary): "His eyes are looking towards the right... He is kicking out with his legs."
Loic *(imitates)*: "He is kicking out with his legs."
Doctor: "He is kicking his legs up into the air."
Loic *(imitates)*: "He is kicking his legs up into the air."
Doctor: "He was reading the Super Picsou" *(name of comic)*. "What did you read? What did you read for me?"

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Article 4

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FULL-LENGTH ORIGINAL RESEARCH

Frontal lobe seizures: From clinical semiology to localization

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Summary

Objective: Frontal lobe seizures are difficult to characterize according to semiologic and electrical features. We wished to establish whether different semiologic subgroups can be identified and whether these relate to anatomic organization.

Methods: We assessed all seizures from 54 patients with frontal lobe epilepsy that were explored with stereoelectroencephalography (SEEG) during presurgical evaluation. Semiologic features and concomitant intracerebral EEG changes were documented and quantified. These variables were examined using Principal Component Analysis and Cluster Analysis, and semiologic features correlated with anatomic localization.

Results: Four main groups of patients were identified according to semiologic features, and correlated with specific patterns of anatomic seizure localization. Group 1 was characterized clinically by elementary motor signs and involved precentral and premotor regions. Group 2 was characterized by a combination of elementary motor signs and nonintegrated gestural motor behavior, and involved both premotor and prefrontal regions. Group 3 was characterized by integrated gestural motor behavior with distal stereotypies and involved anterior lateral and medial prefrontal regions. Group 4 was characterized by seizures with fearful behavior and involved the paralimbic system (ventromedial prefrontal cortex ± anterior temporal structures). The groups were organized along a rostrocaudal axis, representing bands within a spectrum rather than rigid categories. The more anterior the seizure organization, the more likely was the occurrence of integrated behavior during seizures. Distal stereotypies were associated with the most anterior prefrontal localizations, whereas proximal stereotypies occurred in more posterior prefrontal regions.

Significance: Meaningful categorization of frontal seizures in terms of semiology is possible and correlates with anatomic organization along a rostrocaudal axis, in keeping with current hypotheses of frontal lobe hierarchical organization. The proposed electroclinical categorization offers pointers as to the likely zone of organization of networks underlying semiologic production, thus aiding presurgical localization. Furthermore, analysis of ictal motor behavior in prefrontal seizures, including stereotypies, leads to deciphering the cortico-subcortical networks that produce such behaviors.

KEY WORDS: Frontal lobe, Epileptic seizures, Semiology, Stereoelectroencephalography, Stereotypies.

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It is widely accepted that semiologic and electrical patterns of frontal lobe seizures are difficult to characterize, and liable to be misleading in predicting localization of seizure onset, especially those arising from anterior frontal regions (see O'Muircheartaigh & Richardson, 2012 for review). This current and widely held view reflects lack of substantial arguments to the contrary, despite a long history of investigation of frontal seizures from the end of the 19th century onward. Previous studies have compared semiologic features that could allow differentiation of frontal seizures from temporal lobe seizures (Wieser et al., 1992; Manford et al., 1996), or have looked at patterns that might point to specific frontal regions. However, the relation between semiologic patterns and sublobar localization remains more or less unclear (Laskowitz et al., 1995; So, 1998; Jobst et al., 2000; Kotagal et al., 2003; Bonelli et al., 2007; Bagla & Skidmore, 2011; Beleza & Pinho, 2011; O'Muircheartaigh & Richardson, 2012), leading some authors to comment that "relatively few seizures can be reliably localized on clinical grounds" (Manford et al., 1996). Seizures in a given patient with frontal lobe epilepsy are generally similar, with stable and reproducible electroencephalography (EEG; Schindler et al., 2007) and semiologic patterns (O'Muircheartaigh & Richardson, 2012). However, marked variation exists between patients, making categorization and classification challenging. Frontal seizures are typically brief and often manifest complex motor behavior, sometimes with emotional signs, that may be difficult to accurately observe and describe, in contrast to the relatively well-recognized patterns of temporal lobe seizures (Manford et al., 1996; O'Brien et al., 2008) in which semiologic repertoire is much more limited and seizures unfold more slowly, facilitating electroclinical interpretation. The connectivity of frontal lobe supramodal associative areas supports spread through distant cortico-cortical efferent pathways, which can be both multilobar and multidirectional, typically resulting in rapid, widespread propagation of seizure discharges originating in frontal regions, thus helping to explain both semiologic complexity and difficulties in EEG analysis. In addition, in the frontal lobe (representing 35–40% of total cortical volume in humans [Semendeferi et al., 2002]), accurate delineation of seizure onset is challenging given the large surface of buried cortex and peculiarities of craniocerebral anatomy, the ventromedial prefrontal region in particular being far from EEG electrodes placed on the scalp or on the cortical convexity. Such difficulties in electroclinical localization almost certainly contribute to poorer outcome in surgical treatment of frontal lobe epilepsy compared to other epilepsy types (Téllez-Zenteno et al., 2005).

Descriptions of "pure" samples of frontal epilepsies cured by surgical resection (Rasmussen, 1983; Chauvel et al., 1995; Kotagal et al., 2003) provide an overview of the extent and complexity of semiologic features in a large patient population. However, because ictal semiology appears to be produced via a dynamic discharge that propagates to areas both close to and remote from its origin (Chauvel et al., 1995), it is necessary to investigate the spatiotemporal evolution of this activity and its relation to clinical signs in order to better understand the relevance of different semiologic patterns. Therefore, limiting study to patients cured by surgery, in whom essentially the region of seizure onset has presumably been removed, does not allow conclusions to be drawn regarding the cerebral substrate of semiologic features, since the distributed brain networks involved in producing ictal signs will in many if not all cases involve structures distant from the zone of seizure onset. This fact can help to explain the seemingly incoherent results obtained from such "pure cultures," where semiologic patterns do not seem consistently related to seizure onset in a specific region but presumably reflect patients' individual propagation pathways. On the other hand, it seems likely that seizures with similar semiology involve neuronal activity within the same specific brain networks (O'Muircheartaigh & Richardson, 2012). Stereoelectroencephalography (SEEG), by providing a three-dimensional view of seizure dynamics, is the method of choice to study this question and appears to be equally as useful in magnetic resonance imaging (MRI)–negative cases as in those with radiologically visible lesions (McGonigal et al., 2007).

Although studies of selected populations of frontal epilepsies exist (Bleasel et al., 1996; Kriegel et al., 2012; Lee & Worrell, 2012), to date, a comprehensive overview of frontal seizures is lacking. To this aim we studied a consecutive series of patients with seizures onset in the frontal lobe as determined by SEEG. The two main questions were the following: (1) can patients with frontal lobe epilepsy actually be categorized in terms of semiologic features; and (2) are certain semiologic patterns associated with different sublobar organization of seizures? By performing cluster analysis on electroclinical SEEG data we have been able to differentiate clinical patterns according to anatomic subsystems originating in the frontal lobe.

Patients and Methods

Patients were selected to undergo SEEG exploration in the Clinical Neurophysiology Department of the Timone Hospital (Marseille, France) if clinical features suggested a possible surgical indication and if intracranial studies were necessary to localize the epileptogenic zone (EZ) and/or establish functional constraints. We included only those 54 patients in whom SEEG exploration defined the EZ as being within the frontal lobe, during the period from February 2000 until November 2010, from a total of 180 SEEG explorations during this period. We excluded patients whose eventual intracranial recording was inconclusive (n = 1) or

in whom the EZ did not predominantly involve the frontal regions. Prior to selection for SEEG (Deltamed, Natus Europe, Planegg, Germany), a phase of thorough noninvasive presurgical assessment was carried out, including detailed clinical history and surface video-electroencephalography (VEEG; Deltamed) recording, to permit analysis of habitual seizures and interictal EEG. All patients underwent MRI (1.5-Tesla Symphony, Siemens Medical Systems, Erlangen, Germany), functional imaging, and neuropsychology assessment. All patients gave informed consent prior to exploration. SEEG recordings were performed using intracerebral multiple contact electrodes (manufactured by Dixi Medical [Besançon, France] for patients explored 2000–2005; Alcis [Besançon, France] for patients explored after 2005; 10–15 contacts, length: 2 mm, diameter: 0.8, 1.5 mm apart from edge to edge) placed intracranially according to Talairach's stereotactic method (Bancaud et al., 1970; Talairach et al., 1992). Strategy of electrode positioning was established in each patient based on hypotheses about EZ localization, with the aim of defining subsequent cortectomy. Implantations were unilateral or bilateral depending on individual features of each case. Five to 15 (mean 9) electrodes were implanted per patient. Implantation accuracy was controlled perioperatively by telemetric x-ray imaging. Postoperative computerized tomography (CT) (Siemens Medical Systems) scan verified the absence of bleeding and the location of each recording lead. Following recording, intracerebral electrodes were removed and MRI performed, permitting visualization of each electrode trajectory. Finally, CT-scan/MRI data fusion was performed to locate each contact along the electrode trajectory (for illustration, see Bartolomei et al. (2004)). Patients underwent video-SEEG (128 channels Deltamed system, Natus Europe, Planegg, Germany) following complete or partial withdrawal of antiepileptic drugs during a usual period of 4–10 days (extended up to a maximum of 3 weeks if necessary) in order to record several of the patient's habitual seizures.

To investigate the relationship between semiologic features and involved brain areas, ictal clinical and electrical modifications were analyzed in each patient and a correlation test between ictal signs and brain areas was then performed for the entire series. Subsequently principal component analysis (PCA) was carried out to summarize the semiologic data in a way that would allow meaningful analysis. Based on the resulting PCA data space, a hierarchical cluster of patients was formulated, allowing identification of clinically homogeneous subgroups of patients, in which characteristic symptoms and involved regions were thus identified.

Analysis of anatomic-electroclinical features

VEEG clinical and electrical data were analyzed by three epileptologists independently (FBo, AMcG, PC), using the criteria detailed below.

For each patient, all seizures were examined and the presence or absence of 31 ictal signs noted (listed in Fig. 1). Because frontal seizures, as observed in this series, are characterized by a high reproducibility of the electroclinical pattern for a given patient's seizures, an overall semiologic score was established for each patient, based on review of all seizures, with values ranging from 0 (=absence of that sign), to a maximum of 2 for major features (=constant and early sign present in each seizure), minor features being scored as 1 (=sign not always present).

Description of semiologic features

Because observation of semiology was the essence of this study, it was crucial to choose well-defined terms to describe the different signs, in order to be able to categorize seizures. Motor semiology, characteristic of frontal lobe seizures, was the key factor allowing clinical categorization. Whereas description of elementary motor signs (such as tonic posturing) was straightforward, in order to meaningfully describe subgroups of more complex motor behaviors, it was necessary to define terms other than those proposed by existing semiologic classification (Blume et al., 2001). This issue of definition of semiologic terms has previously been highlighted (Rolnick & Parvizi, 2011).

1. Elementary motor signs. General agreement already exists concerning identification of clonic movements and tonic or dystonic contraction and/or posturing as well as head and/or eye version. Such signs were grouped together here under the generic term *elementary motor signs*.

2. Gestural motor behavior. Accurately describing the complex motor behaviors commonly observed in prefrontal seizures is challenging and many terms commonly used in the literature are less than clearly defined and subject to variable use. A notable example is "automatism," the poor definition of this term in the context of epileptology having recently been highlighted (Rolnick & Parvizi, 2011). The term "hypermotor seizure" or "hyperkinetic seizure" is also problematic, as it does not necessarily distinguish between different types of movement within the seizure or the presence or absence of emotional features. We have referred to the overall (quite heterogeneous) category of complex motor behaviors, readily distinguishable from elementary motor signs, by the term *gestural motor behavior*. This can be further categorized through identifying the presence or absence of certain features of movement within the gestural motor behavior (*stereotypies* and *hyperkinetic movements*, explained below); and overall appearance of the behavior in terms of the syntax or "naturalness" of motor sequence (*integrated* versus *nonintegrated*).

   a. Stereotypies. The stereotypies are defined, according to Ridley (Ridley, 1994), as excessive production of one type of motor act, necessarily resulting in repeti-

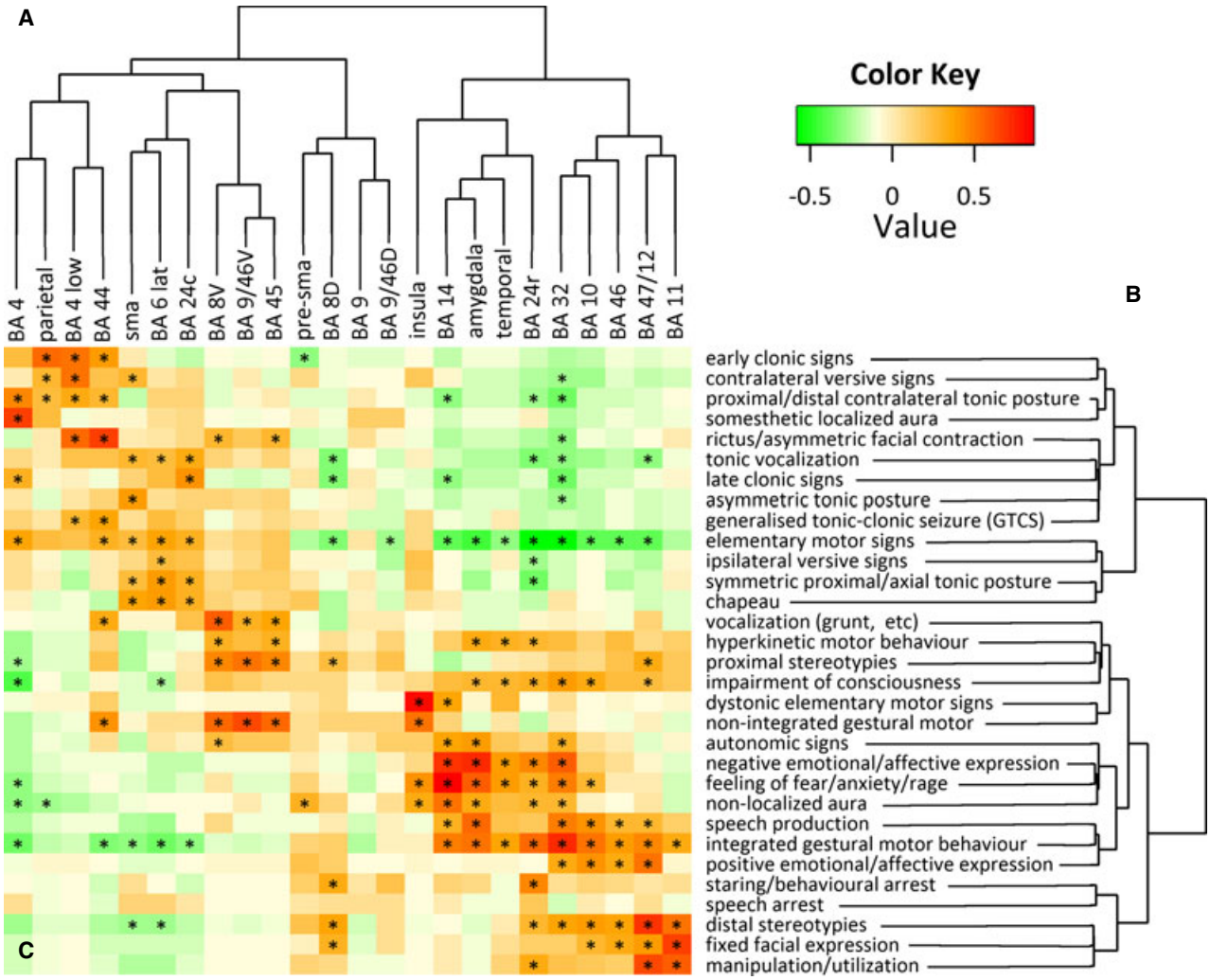

Figure 1.
Correlation matrix between cortical areas and clinical features, as ordered by hierarchical clustering basing on their reciprocal distance. (**A**) Clustering of brain regions is shown on the horizontal axis. (**B**) Clustering of clinical signs is shown on the vertical axis. In these two ordered sequences, neighboring regions as well as neighboring signs occur more frequently together than distant ones. (**C**) Correlation between areas and signs as a function of the color (red, positive correlation; green, negative correlation; starred squares, $p < 0.05$) follows a diagonal pattern of association running from more posterior (top left corner) to more anterior regions (bottom right corner). This pattern, which is conserved for significant correlation ($p < 0.05$ starred squares), indicates the emergence of clinical spectrum developing along a caudorostral axis from primary motor cortex to the frontal pole (BA, Brodmann area; SMA, supplementary motor area; pre-SMA, presupplementary motor area). Architectonic subdivision of lateral and medial prefrontal Brodmann areas according to (Petrides & Pandya, 1994).

tion. We thus included in this category rhythmic repetitive movements of trunk and limbs (*proximal stereotypies*), or of hands/feet (*distal stereotypies*; Chauvel et al., 1995). These could have a nonpurposeful appearance (e.g., whole body rocking) or a semi-purposeful one (e.g., manipulating an object).

b. Hyperkinetic movements. The term *hyperkinetic* was used here not to describe the whole seizure but rather in a quantitative sense to describe excessive amount of movement (hyperactivity) and/or excessive amplitude, speed, and acceleration. This allowed distinction of the character of movement from other clinical features occurring within the same seizure (such as vocalization, autonomic signs, emotional expression, and so on). Motor components of gestural motor behavior could thus be hyperkinetic, or stereotyped; both stereotyped and hyperkinetic; or neither of the two.

c. Integrated and nonintegrated gestural motor behavior. The overall appearance of the sequential pattern of motor action, whether or not including stereotyped and/or hyperkinetic elements, could also be classified

as *integrated* or *nonintegrated*. These terms were chosen to convey the notion of whether or not the sequence of movements appeared to follow a recognizable and somewhat "naturalistic" pattern, even though the overall behavior might appear greatly exaggerated or incongruent in the social context. *Integrated* gestural motor behavior included recognizable, ordered sequences of movement within the seizure such as reaching, grasping, pedalling, kicking, tapping, rocking, or hitting. In addition for integrated behavior, facial appearance was within a "normal range" of human facial expression (Ekman, 1993), whether showing emotion or not, and tended to be congruent with other ictal behavioral features (for example happy facial expression with singing, laughing, and rhythmic tapping). In contrast the motor sequences of *nonintegrated* gestural motor behavior had a disjointed or even anarchic appearance including facial expression.

Definition of early spread network

Concerning analysis of ictal intracerebral EEG, cortical regions involved by ictal discharge were similarly scored according to degree of participation in ictal discharge, by reviewing all seizures from each patient. From an anatomic standpoint, electrode sampling allowed study of 20 cortical

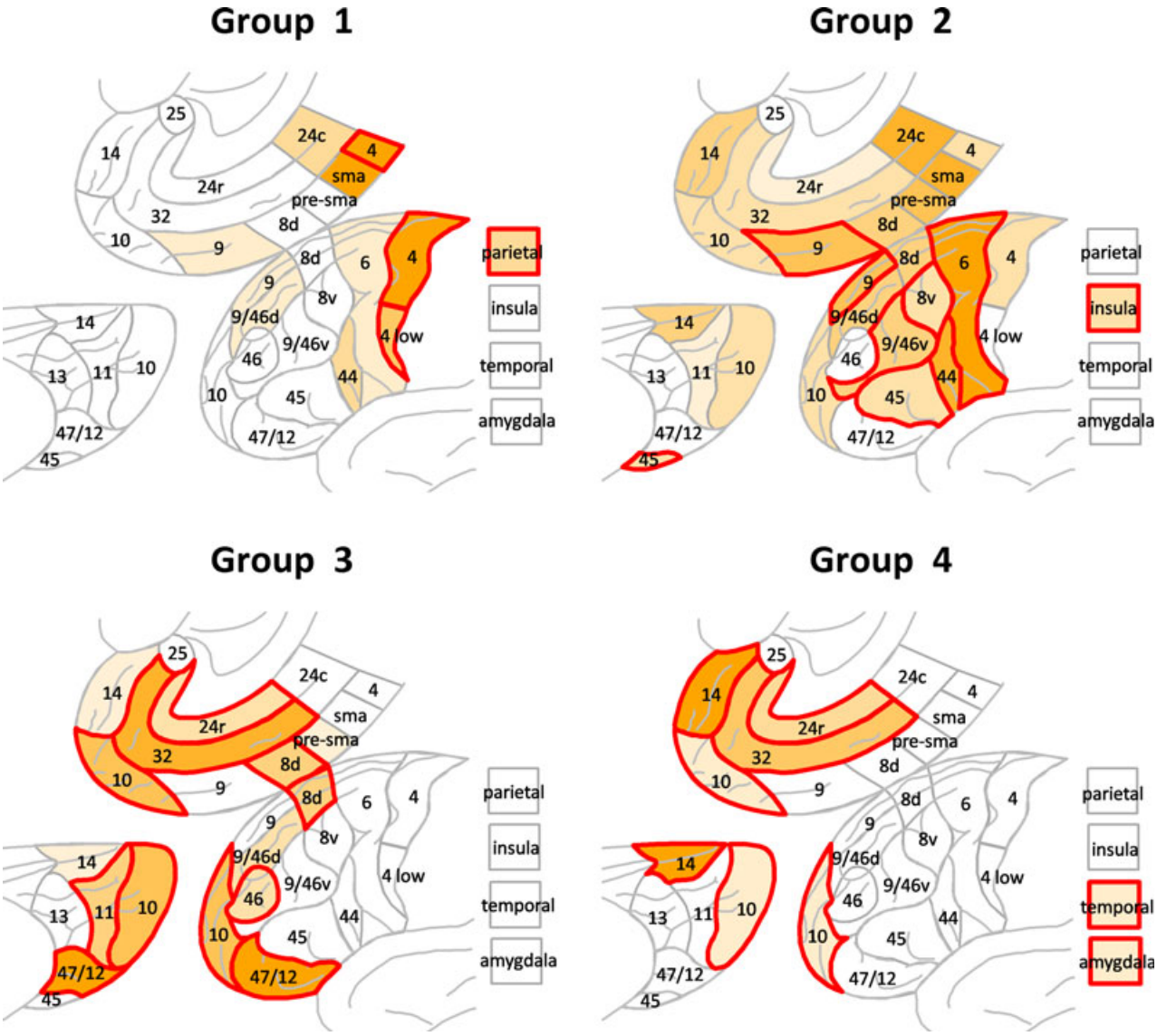

Figure 2.

Cortical regions that characterize the four groups of patients. Brain areas forming part of the early spread network (scored as 2 basing on ictal SEEG) are colored with darker shading, based on the proportion of patients in the group with implication of that area. Brain areas significantly more often involved in one group than the others (value-test > 2) are red bordered. Architectonic subdivision of lateral and medial prefrontal Brodmann areas according to (Petrides & Pandya, 1994).

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regions within the frontal lobe, mostly corresponding to Brodmann's areas (BA; Fig. 2). We analyzed the time-window from electrical onset to full emergence of all semiologic elements (that is until clinical semiology is completed), in order to identify the subset of anatomic structures underlying the period of production of ictal signs. We termed these regions the "early spread network" to distinguish this from the epileptogenic zone (defined as the region of primary organization of ictal discharge; Bancaud et al. (1965)), since in the present study we were interested not only in zone of seizure onset but also early propagation of ictal discharge within the cortical network during appearance of clinical signs.

We thus estimated the level of participation of each region by taking into account the earliness of appearance of ictal activity in that structure as well as degree of change (in frequency, amplitude, or rhythmicity) compared to preictal activity in the same structure. A structure not involved by seizure activity, namely without any EEG modification, was scored as 0, while a structure immediately involved at electrical onset by a low voltage rapid discharge (LVRD) was scored as 2. The intermediate score 1 was used when ictal activity was seen later (after initial electrical onset but within time window of appearance of all clinical features) or when this consisted of lower frequency rhythmic activity, for instance theta or alpha discharge. In the rare case of seizure discharge characterized by slower rhythmic activity (for example spike wave) rather than the usual pattern of LVRD, regions immediately showing EEG change were scored as 2, whereas regions with delayed changes were scored as 1.

In this way two matrices, respectively, encompassing 31 (clinical signs) and 24 (brain areas) variables, scored 0–1–2 for each of the 54 patients, were obtained.

Statistical analysis

Based on these two matrices (signs × patients and areas × patients) two dissimilarity matrices were computed, which were used to perform automatic hierarchical cluster analysis (R software version 2.13.1; R Core Development Team, 2013). Cluster analysis allows ordering of variables such that the proximity of variables within the dendrogram represents their degree of similarity. In other words, signs more commonly occurring together during seizures, or areas more commonly involved together by ictal discharge, appear close to each other. An ordered sequence of ictal signs and another of brain areas were thus obtained, each arranged according to the frequency of their co-occurrence. A correlation matrix between these sequences of signs and areas was then computed in order to demonstrate the relationship between ictal symptoms and involved areas, and to measure the strength of this association. The Kendall correlation test was finally used to assess the significance at $p < 0.05$ for each correlation.

In a second step, given the large number of examined clinical features, principal component analysis (PCA) was performed in order to convert all possibly correlated variables (signs) into a smaller number of linearly uncorrelated variables (principal components). These components account for the largest possible variance, in decreasing order from the first to the last component. As a result the size of the transformed data is reduced and the first components are able to best explain the variance in the data. Because the scores used to represent the degree of presence of signs (0, 1, or 2) are ordinal data, we performed PCA on score ranks in order to better represent the scores and their intrinsic ordinal information.

Lastly, patient position within the new lower-dimensional space supplied by PCA was computed, as defined by ictal signs used as coordinates. Using these new coordinates, hierarchical clustering was performed, aiming to distinguish clinically homogeneous groups of patients.

Semiologic features and involved cortical regions were analyzed with respect to the resulting clusters of patients. For each variable and in each group, the difference was calculated between the mean for patients belonging to that group, and the mean for patients belonging to the other groups. This was expressed in units of standard deviation from the mean (value-test ≥ 2). This enabled identification of the most characteristic clinical features and the most typically involved brain areas.

Results

General characteristics, semiologic features, and SEEG findings

Twenty-two of the 54 patients were male and 32 were female. Mean age at recording was 24.9 ± 9.5 years; mean epilepsy duration was 16.9 ± 8 years. Half of the series (27/54) had normal MRI. Following SEEG exploration, 35 patients (65%) underwent surgical resection. In some patients, due to location of seizure organization (e.g., involving Broca's area or motor cortex), surgery with curative intent was not possible, since resection had to be limited according to functional data; if performed surgical procedures (e.g., gamma knife radiosurgery or callosotomy) were thus not expected to result in seizure freedom but rather in a palliative effect. One patient is awaiting surgery, delayed because of other health problems. Seven had gamma knife radiosurgery. Surgery was contraindicated on the basis of SEEG findings in 8 of 54 patients. Three patients who were considered operable eventually declined surgery, one because of improvement in seizures and two because of other health problems. Of the patients having undergone resection with at least 24 months follow-up (n = 32), 19 are in International League Against Epilepsy (ILAE) class 1 (59%), one in class 2, 2 in class 3, 5 in class 4, and 5 in class 5 (Wieser et al., 2001). In terms of histopathology (n = 33), 19 (58%) had focal dysplasia or dysembryoblastic neuroe-

pithelial tumor and 14 (42%) had gliosis, ectopic neurons, or other nonspecific change. Of those who became seizure free (ILAE class I), two thirds (12/19) had focal cortical dysplasia, whether visible (3/12) or not (9/12) on MRI.

A total of 374 seizures were recorded with SEEG and analyzed. Two to 60 (mean 11, median 7) seizures were recorded per patient, with seizure duration from 2 s to a maximum of 2.5 min (median 29 s) in 52/54 patients. In two patients seizures were longer and lasted a maximum of 10 min.

In all recorded seizures, clinical signs began after appearance of SEEG ictal discharge. Time from electrical onset to completion of clinical semiology was generally short, ranging from 1 to 12 s (median 4 s); shorter values usually occurred with predominantly motor/premotor cortex onset and longer values with prefrontal onset. The interval between electrical and clinical onset varied from 0.5 to 10 s (median 3 s). However, in five patients this delay was particularly long, due either to subtle, gradual onset of clinical symptomatology or to a slow "buildup" of ictal discharge.

We observed as a global tendency in all patients' seizures that ictal discharge with onset in prefrontal or premotor regions, when it did not remain local, propagated toward more caudal regions (respectively, premotor and precentral). Conversely, propagation in the opposite direction, that is from caudal to rostral frontal areas, was not observed in this series.

The occurrence of each ictal sign, and anatomic structures involved in the early spread network, were noted for each patient. For the whole group, elementary motor signs occurred in 72.2% of patients; gestural motor behavior in 46.3%; any form of facial change in 63%. Facial change included the "chapeau de gendarme," a characteristic downturned appearance of the mouth produced by bilateral lip and chin contraction; other facial change included emotional facial expression or fixed neutral facial expression. Impairment of consciousness occurred in 74.1% of cases; autonomic signs (altered cardiac rate/rhythm, pallor, facial flushing, sweating, nausea/vomiting, piloerection, or micturition) in 51.9%; any kind of aura in 39%; and secondary generalization in 16.7%.

Cluster analysis and anatomic-electroclinical correlations

Clinical features and brain areas belonging to the early spread network as classified with hierarchical cluster analysis are shown in Figure 1. Semiologic features are subdivided into two main groups, one comprising exclusively almost all elementary motor signs and the other one including the remaining signs, namely emotional features (objective or subjective), gestural motor behavior, stereotypies, and autonomic changes (Fig. 1B). Smaller clusters at a lower level indicate ictal signs, which are most frequently present together during seizures, such for instance somesthetic localized aura, contralateral versive signs, contralateral tonic posture, and early clonic signs. Cluster analysis of brain regions allows grouping together of motor, premotor and caudal prefrontal regions, separated from rostral prefrontal regions. In addition smaller groups of brain structures grouped together at lower cluster levels also show strong associations; for example SMA, lateral BA6 and caudal cingulate cortex (BA24c); rostral cingulate cortex (BA32), frontal pole (BA10) and other rostrolateral prefrontal regions (Fig. 1A).

Matrix correlation between ictal signs and involved cortical areas, ordered as a function of their reciprocal distance obtained with clustering, shows a diagonal pattern of correlation (Fig. 1C), which follows the posterior-anterior axis of the ordered brain areas. Red-orange squares indicate positive correlation (sign always seen in association with a given brain area) and green squares indicate negative correlation (sign never seen in association with a given brain area). This indicates that certain clinical features occurring together (e.g., early clonic signs, contralateral versive signs, contralateral tonic posture, and somesthetic localized aura) are correlated with certain cortical areas involved together and located in the more caudal regions (namely, primary motor cortex, rolandic operculum). At the opposite corner, other groups of clinical features (e.g., staring, speech arrest, manipulation behavior, and fixed facial expression) are correlated with the more rostral and frontopolar region, thus forming an anatomic rostrocaudal gradient according to the occurrence of ictal clinical signs. Such a diagonal structure is conserved for significant correlation ($p < 0.05$; Fig. 1C, starred squares).

Matrix correlation also shows that certain signs, or groups of signs according to cluster analysis, are associated with different brain regions with varying degrees of specificity: for example, early clonic signs are correlated only with the more posterior regions and manipulation behavior only with the more anterior prefrontal regions. On the other hand, some features, such as hyperkinetic movements or impairment of consciousness, present a weaker association with multiple areas, being correlated with both caudal and rostral prefrontal regions. Therefore, certain semiologic features or patterns seem to be specific to certain systems, whereas others are more "distributed" and thus less valuable indicators of localization along this rostrocaudal axis.

PCA yielded three principal components accounting for 42.36% of variance, thus resuming 31 clinical signs in three groups of signs (which are shown in Table S1). Hierarchical classification of patients according to occurrence of clinical signs, based on the new coordinates obtained by PCA, results in clusters of clinically homogeneous patients (Figs. S1 and S2). The cluster arborization can be cut at progressively lower levels producing ever-smaller subgroups of patients, each sharing specific semiologic features. A cut was chosen that resulted in four main groups, allowing distinction of clusters with sufficient size and clinical homogeneity (Fig. S2). Each group of patients is characterized by a number of

Table 1. Semiologic features for the four groups of patients obtained with hierarchical clustering performed on new PCA coordinates

Group 1		Group 2		Group 3		Group 4	
v-Test	Sign	v-Test	Sign	v-Test	Sign	v-Test	Sign
4.59	Early clonic signs*	4.38	Symmetric proximal/axial tonic posture*	7.16	Distal stereotypies*	5.77	Negative emotional/affective expression*
3.76	Elementary motor signs*	3.76	Nonintegrated gestural motor *	5.33	Fixed facial expression*	4.58	Feeling of fear/anxiety/rage*
3.61	Proximal/distal contralateral tonic posture*	3.75	Chapeau*	4.97	Integrated gestural motor behavior*	4.21	Speech production*
3.56	Somesthetic localized aura*	2.43	Nonlocalized aura*	4.86	Manipulation/utilization*	3.94	Integrated gestural motor behavior*
3.45	Contralateral versive signs*	2.24	Elementary motor signs	3.00	Positive emotional/affective expression*	3.04	Autonomic signs*
3.33	Asymmetric tonic posture*	2.12	Vocalization (grunt, etc.)	2.90	Proximal stereotypies*	2.49	Nonlocalized aura*
3.16	Tonic vocalization*	−2.00	Manipulation/utilization	2.66	Impairment of consciousness*	2.47	Hyperkinetic motor behavior*
2.04	Generalized tonic–clonic seizure (GTCS)	−2.17	Speech production	2.07	Speech production	2.09	Impairment of consciousness
2.01	Rictus/asymmetric facial contraction	−2.19	Fixed facial expression	−2.07	Ipsilateral versive signs	−3.39	Elementary motor signs*
−2.08	Speech production	−2.57	Early clonic signs*	−2.09	Proximal/distal contralateral tonic posture		
−2.09	Negative emotional/affective expression	−2.94	Distal stereotypies*	−2.15	Late clonic signs		
−2.09	Chapeau	−3.34	Integrated gestural motor behavior*	−2.40	Symmetric proximal/axial tonic posture*		
−2.10	Nonintegrated gestural motor			−2.51	Tonic vocalization*		
−2.11	Autonomic signs			−4.73	Elementary motor signs*		
−2.19	Hyperkinetic motor behavior						
−2.21	Distal stereotypies						
−2.36	Proximal stereotypies*						
−2.59	Feeling of fear/anxiety/rage*						
−3.12	Integrated gestural motor behavior*						
−3.78	Impairment of consciousness*						
−3.83	Nonlocalized aura*						

Ictal signs typically present in a group are identified by positive value-test (>2, green colored), whereas typically absent ictal signs are identified by negative value-test (<2, red colored). *p-value < 0.01; p-value < 0.05.

positive and negative signs, a positive sign being a distinctive clinical feature of that group and a negative sign being a clinical feature typically absent (Table 1). Similarly, involved brain areas were analyzed as a function of the resulting homogeneous groups of patients and the characteristics of the early spread networks obtained for each group (Fig. 2).

Value-test > 2 for variables not used to build clustering indicates that the occurrence of variable(s), namely of involved brain area(s), in one group is significantly different to its occurrence in the whole population. For active variables, that is, for ictal signs used to construct the hierarchical cluster, the value-test represents a measure of similarity between specific ictal sign(s) and groups.

Group 1, composed of 16 patients, is characterized by the presence of one or more of the following elementary motor signs: clonic signs, contralateral tonic posture, contralateral versive signs, asymmetric tonic posture, secondary generalization, or asymmetric facial contraction. Somesthetic localized aura and tonic vocalization could also typically occur in these patients. Moreover, this group is characterized by the absence of gestural motor behavior and of emotional features (Table 1, group 1). Significant involvement (value-test > 2) of rolandic cortex (BA 4) and rolandic operculum (low BA4; red bordered in Fig. 2), as well as parietal cortex occurred in this group; involvement of other caudal regions could also be present, particularly lateral and medial premotor cortices (Fig. 2). Ictal discharge could involve both medial and lateral premotor regions at onset, or propagate from lateral to medial aspect, or more rarely in a mesiolateral direction.

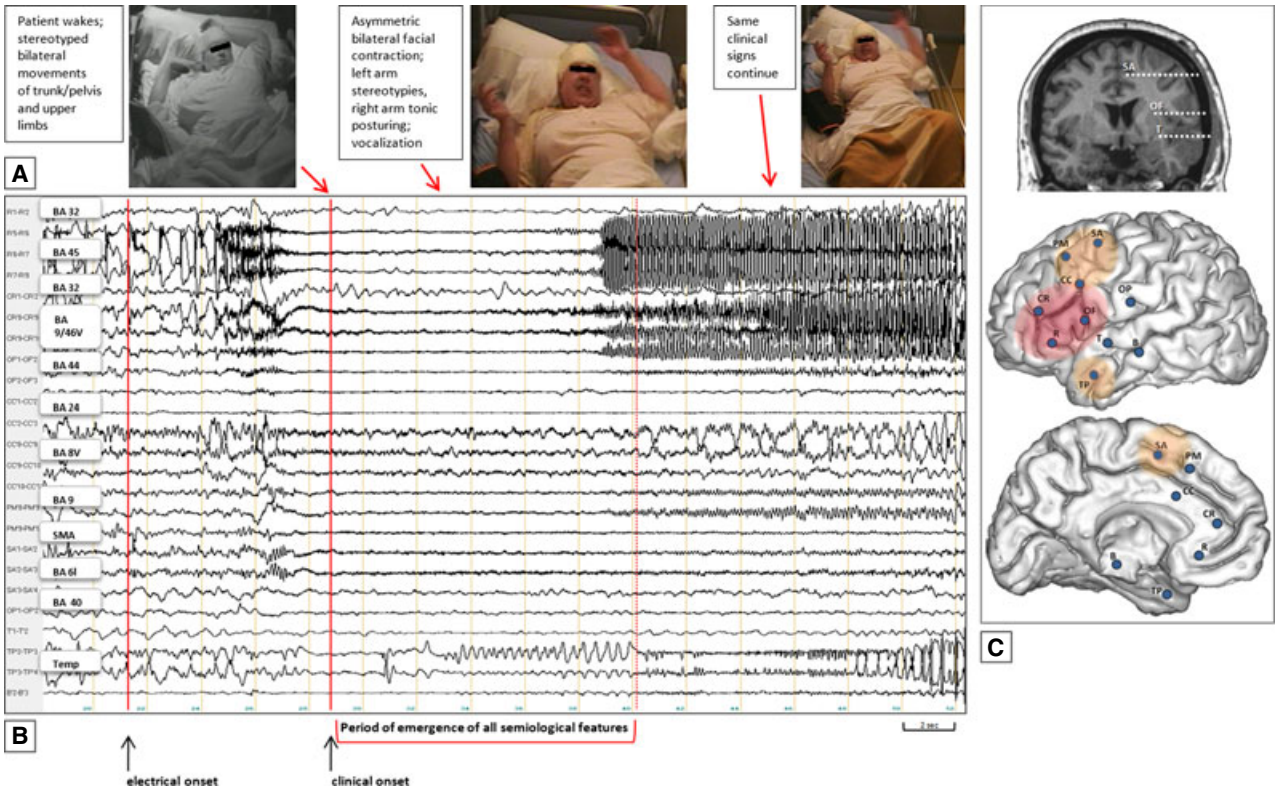

Figure 3.

Anatomic-electroclinical features of a patient from group 2. (**A**) Semiology is characterized by nonintegrated gestural motor behavior with proximal stereotypies of pelvis, trunk, and left upper limb; elementary motor signs (asymmetric bilateral facial contraction, tonic/dystonic posture of right upper limb); and vocalization. (**B**) Ictal SEEG shows increasing synchrony, rhythm, and amplitude of interictal spikes and superposition of a low voltage rapid discharge at electrical onset in the ventrolateral prefrontal cortex (BA 45, BA 9/46V, BA 44; red-colored in box C), followed at clinical onset by a less tonic low voltage fast activity involving premotor and posterior lateral prefrontal areas (BA 8V, BA 9, SMA and lateral BA 6; orange-colored in box C) and by a rhythmic slower activity in the temporopolar region (orange-colored in box C). (**C**) Coronal view of patient's T_1 MRI with three implanted electrodes and lateral and medial view of all implanted depth electrodes on a three-dimensional (3D) reconstruction of the neocortical surface of the brain. Regions showing major involvement in the generation of the ictal discharge are colored in red and regions showing minor involvement in orange. BA, Brodmann area. Electrodes labels: B = Hippocampus; CC = BA 8V (external contacts), BA 24 (internal contacts); CR = BA 9/46V (external contacts), BA 32 (internal contacts); OF = BA 44; OP = BA 40; PM = BA 9 (external contacts), pre-SMA (internal contacts); R = BA 32 (external contacts), BA 45 (internal contacts); SA = lateral BA 6 (external contacts), SMA (internal contacts); TP = temporal pole; T = superior temporal gyrus.

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Group 2 (23 patients) was characterized by the co-occurrence of elementary motor signs (typically symmetric axial tonic posture and facial contraction such as "chapeau de gendarme") and nonintegrated gestural motor behavior. In this more heterogeneous group, nonlocalized aura and more complex nonverbal vocalization were also frequently present, whereas integrated gestural motor behavior, distal stereotypies, early clonic signs, and fixed facial expression never occurred (Table 1). Nonintegrated gestural motor behavior could include proximal stereotypies and could have a hyperkinetic character or not (example illustrated in Fig. 3). Frequent co-involvement of both pre-motor and lateral prefrontal regions occurred. Ictal discharge could involve both medial and lateral aspect at onset. The more frequent propagation pattern was from lateral to medial regions. However, ictal discharge originating in medial premotor areas (SMA and pre-SMA) could propagate to lateral premotor regions (Fig. 2).

Typical semiologic features of group 3 (10 patients) were the following: integrated gestural motor behavior with distal stereotypies, fixed facial expression or, alternatively, positive emotional expression, proximal stereotypies, and speech production. On the other hand, the absence of any elementary motor sign was a significant characteristic of these patients (Table 1). Early spread network underlying these clinical manifestations involved rostral prefrontal ventrolateral regions (BA 47/12, BA 10, BA 11, BA 46) and the rostral cingulate gyrus (BA 32 and rostral BA 24; Fig. 2). A peculiarity of this group was systematic co-involvement of ventrolateral prefrontal cortex and anterior cingulate area, either simultaneously at seizure onset or by propagation in a lateromedial direction.

Group 4 was composed of five patients presenting with integrated gestural behavior of fear, sometimes hyperkinetic, with attempt to fight or to escape, frightened facial expression, sometimes screaming or swearing, and autonomic signs. Elementary motor signs never occurred and underlying involved regions corresponded to the orbital and medial-prefrontal network (BA 14, BA 32 and 24r, BA 10) with propagation to amygdala and anterior temporal regions (Fig. 2), but not propagation to lateral frontal cortex.

The distinctive early spread networks of each semiologically distinct group of patients are shown in Figure 2, with partial overlap between groups of areas as defined by hierarchical clustering (Fig. 1).

Discussion

In this study we report electroclinical characteristics of 54 patients with frontal lobe seizures, looking for characteristic semiologic traits that localize the likely zone of seizure organization. Despite the complex systems involved, and the large number of semiologic variables studied, our results do allow identification of electroclinical patterns, providing a comprehensive overview of this population. Notably two main results were evidenced: the separation of patients into groups according to similarity of semiologic pattern, which correlated with topography of the brain regions involved; and the demonstration that these groups should not be seen as rigid categories but rather bands within a spectrum organized along a rostrocaudal axis. This was possible due to the chosen methodology, in which a large number of consecutive frontal patients were explored using SEEG, with categorization of their semiologic traits, and analysis of not only initial seizure discharge but also propagation pathways during the period of production of ictal signs. Evaluation of this early spread network was indeed crucial in perceiving the relevance of different semiologic patterns to seizure localization, and perhaps helps to explain why certain previous works have not demonstrated a clear relationship between semiologic picture and anatomic substrate across different frontal seizure types (Manford et al., 1996; So, 1998; Rheims et al., 2008).

Categorization of frontal seizures: subgroups or spectrum?

Electroclinical subgroups

Cluster analysis was chosen as the method ideally suited to identify similarities in this a priori heterogeneous population characterized by complex data. Moving anteriorly from the central sulcus results can be summarized as follows: in group 1, seizures were organized within precentral and/or premotor regions, characterized by elementary motor signs with no gestural motor behavior. Within this group distinction can be made between predominantly precentral and premotor patterns. However, "pure" premotor seizures proved to be rare (Ajmone-Marsan & Goldhammer, 1973; Chauvel et al., 1992). The next group moving anteriorly (group 2) is an intermediate one, characterized by nonintegrated gestural motor behavior associated with proximal tonic posturing and facial contraction; the presence of tonic signs that hindered movement magnified the disjointed appearance of motor behavior. Seizures arising from this zone overlapping premotor and posterior prefrontal regions, including the dorsolateral prefrontal convexity, have traditionally remained the most difficult to define (Bancaud & Talairach, 1992). The two anterior prefrontal groups (groups 3 and 4) both manifested integrated gestural motor behavior but no elementary motor signs. As in group 2, both hyperkinetic and normokinetic gestural motor behavior could be observed, not only within the same group of patients, but also in the same patient from one seizure to another, rending this feature per se not a useful indicator of seizure localization. Group 3 seizures primarily involved lateral prefrontal cortex and/or frontal pole, with projection of seizure activity toward anterior cingulate cortex, characterized by gestural motor behavior incorporating distal stereotypies. Grasping or clutching as a semiologic feature occurs more frequently in seizures arising from frontal than

extrafrontal regions (Gardella et al., 2006; Leiguarda et al., 2008), evoking similar phenomena observed outside the context of seizures such as utilization behavior. A previous stimulation study of anterior cingulate gyrus provoked grasping and hand-to-mouth movements (Talairach et al., 1973). In Group 3 behavior, was either apparently devoid of emotional content, or conversely manifested positive emotional expression (joviality, with singing or humming), in which the stereotypies formed part of an overall behavior appropriate to the emotional expression (e.g., rocking and tapping in time to music). In contrast in group 4, seizures arising from ventromedial prefrontal cortex were typified by fearful emotional expression associated with (nonrepetitive, and therefore nonstereotyped) gestural motor behavior evoking a defensive or attacking reaction. The clinical aspect is in keeping with previous descriptions including the original observation of "orbitofrontal seizures" (Tharp, 1972; Ludwig et al., 1975; Williamson et al., 1985). The electroclinical pattern also resembles "type 1 hypermotor seizures (HMS1)" (Rheims et al., 2008), with the important exception that movements were not invariably hyperkinetic in the present study. That the "fearful" seizure pattern was so reproducible between patients likely relates in part to the fact that the paralimbic temporopolar-insular-orbitofrontal network forms a clearly defined and relatively isolated anatomic system (Mesulam & Mufson, 1985), with subcortical outputs but limited connections to other cortical structures (Damasio, 1998; Ghashghaei et al., 2007); its role in seizures involving fearful behavior has been discussed previously (Devinsky et al., 1995; Biraben et al., 2001; Bartolomei et al., 2005; Nobili et al., 2007).

Electroclinical spectrum following a rostrocaudal gradient

Although the present results can therefore readily be expressed as clusters, these should not, however, be regarded as rigidly separated compartments. There is in fact a gradual transition both in terms of ictal semiology and underlying early spread networks, between the four clinical subgroups described, forming a continuum along a rostrocaudal axis. This is illustrated by the matrix correlation between ictal signs and involved brain regions, clearly demonstrating the clinical spectrum developing from rolandic cortex to frontal pole. The most highly integrated behavior was produced by seizure activity arising from rostral prefrontal regions, becoming progressively less integrated in posterior prefrontal regions; in even more posterior motor regions, exclusively elementary motor signs (with no gestural component) occurred. A transition within groups as well as between groups was thus seen. Indeed the most anterior prefrontal seizures, characterized by the most integrated behavior, were immediately striking, since because of their resemblance to normal behavior patterns, for the observer analyzing the semiology, the globally naturalistic appearance of ictal behavior dominated its individual elements, hence our use of the term "integrated." This was quite different from the most posterior prefrontal seizures in which disparate semiologic elements, while complex in their composition, did not allow for instinctive recognition of any fragments of "normal" seeming behavior. However, the most anterior seizure localizations of the intermediate group 2, at the border zone between the premotor-prefrontal and purely prefrontal seizures, could show rhythmic coordinated movement (body rocking) that started to approach the more clearly integrated behaviors of groups 3 and 4. In addition, for group 2 seizures, semiologic differences reflected relative contribution of prefrontal and premotor structures, since seizures arising more anteriorly showed evident (non-integrated) gestural motor behavior relatively unrestricted by tonic posturing, whereas more posterior seizure organization produced prominent tonic posturing that seemed to hinder expression of gestural behavior.

Integrated behavior and the rostrocaudal axis

The concept of integrated behavior is thus fundamental to appreciating this spectrum of frontal seizure patterns. Integrated behavior describes an overall comportment encompassing complex sequences of movement organized in a congruous manner, appropriate to the current state of the organism, its environment, and goals. Observation, description and categorization of such behaviors are clearly difficult (Barlow, 1996). The notion of "syntactic sequence" has previously been used to help characterize motor behavior in neuroethologic and neurobiologic studies (Lashley, 1951; Berridge et al., 2005). Understanding the role of prefrontal cortex in producing integrated behavior remains a great challenge (Goldman-Rakic, 1988).

Our observations regarding the rostrocaudal pattern of semiologic expression in frontal seizures echo current thinking on the rostrocaudal hierarchy of frontal lobe function (Koechlin et al., 2003; Badre & D'Esposito, 2009). Integrated appearance of ictal behavior seems likely related to pathologic activation of established prefrontal circuits that would normally be brought into play in production of specific goal-directed behaviors (Pickenhain, 1988), or in emotional responses such as fear (Damasio, 1998). Although some motor acts are common to many species and programmed such that they may be performed in a largely unconscious manner (for example, the movements of locomotion), more complex behavior necessarily involves more flexibility and variability, being more directly influenced by emotional state or environmental cues as well as by individual experience. It therefore seems logical that prefrontal seizures should involve such diverse and variable ictal manifestations, in contrast to the much narrower repertoire of premotor seizures, for example.

Is medial versus lateral distinction a reliable indicator for localization?

Although the anteroposterior axis thus clearly emerged both in terms of preferential direction of propagation of

individual seizures and discrimination of different anatomic-electroclinical subgroups of semiologic patterns, a similar organization was not observed for the mesiolateral axis. During the time lapse of the early spread, as defined above, characteristics of a semiologic trait could not be attributed only to the lateral or medial origin of the discharge, but also to the medial or lateral pattern of its propagation. For instance, there was a clear tendency for ictal discharge beginning in lateral prefrontal cortex to propagate to medial structures, notably the anterior cingulate region and the pre-SMA, or for ictal discharge beginning in the SMA and pre-SMA to propagate to lateral areas 6 and 8. Primate frontal lobes are characterized by strong cortico-cortical connections from lateral prefrontal cortex to pre-SMA, SMA, and anterior cingulate cortex (Barbas & Pandya, 1989; Bates & Goldman-Rakic, 1993; Devinsky et al., 1995; Morecraft & Tanji, 2009). It seems likely that, even in dorsolateral or ventrolateral prefrontal seizures, projection to medial structures plays an important role in producing the observed motor semiology. Indeed the medial premotor and cingulate regions could be seen as a "final common pathway" for anterior frontal lobe seizure organization.

Stereotypies in frontal seizures

Stereotypy within overall gestural behavior, in its different distal and proximal forms, proved to be an important semiologic category, which allowed distinction between anterior and posterior prefrontal involvement. In addition, stereotypies were predominantly associated with seizures in which lateral prefrontal cortex was involved at onset, projecting to anterior cingulate cortex and/or pre-SMA (Fig 2). The definition of stereotypy has been recently revisited (Edwards et al., 2012). Animal and human models of reduced movement repertoire with abnormal perseveration of one movement pattern have led to identification of physiologic and pathophysiologic roles of specific basal ganglia circuits in producing such movements (see Graybiel, 2008 for review). The developmental role of stereotypies in motor learning has been proposed (Graybiel, 2008; Edwards et al., 2012). In human seizure semiology it has been suggested that "fixed action patterns" such as locomotion are produced via a release mechanism, that is, impairment of higher cortical control over subcortical structures (Tassinari et al., 2005); a possible direct effect of cortical activity on subcortical circuits has also been evoked (Gardella et al., 2008). The findings of the present study, with striking reproducibility of seizure patterns in individual patients, indeed argue in favor of a structured basis of even the most complex ictal behaviors. Considering the pathophysiologic basis of prefrontal seizures within a connectionist context (Fuster, 2001), the recurrence of characteristic ictal motor sequences could indicate a process of "learning" due to seizure activity repeatedly occurring within the cortical compartment of the same cortico-subcortical circuit, becoming progressively more fixed with repetition. Known anatomofunctional separation of specific frontostriatal connections (Alexander & Crutcher, 1990) would seem highly relevant to this hypothesis. Better understanding of the role of subcortical structures in defining seizure networks and their semiologic expression thus offers an intriguing direction for future research.

The clinical utility of such correlations between semiology and anatomy is twofold. In epilepsy surgery, successful operation results from accuracy of presurgical electrode implantation anatomic planning. As this planning cannot exhaustively sample the brain, its strategy hinges upon the localization, beyond a putative lesion, of an epileptogenic network expressing clinical semiology. Because the epileptogenic zone and early spread network are intimately connected, localizing the latter through analysis of its semiologic expression provides access to the region of seizure onset. Furthermore, even in "lesional" cases where surgery can be achieved without invasive presurgical assessment, preoperative surgical planning takes account of anatomic-electroclinical correlations to encompass the same network, in order to augment the chances of postoperative seizure freedom. Because the proposed electroclinical categorization offers pointers as to the likely zone of seizure organization, the present results concern a much wider group of epilepsy patients. The data described here are of interest with regard to guiding imaging postprocessing, particularly where initial MRI appears normal, since localizing a region of interest through electroclinical data facilitates subsequent identification of subtle but detectable lesions. Indeed in one study of surgical outcome of MRI-negative epilepsies, eight of nine patients with initially negative MRI were subsequently found to have visible lesions once the zone involved was known and the MRI restudied (Bien et al., 2009). In the light of the present data, prevailing pessimism regarding the localizing value of semiologic patterns in frontal seizures thus appears to be unjustified; with the caveat that, particularly for seizures not confined to primary areas, clinical expression should be viewed as arising from excessive activation of brain networks at the macroscale level, rather than being symptomatic of outward spread of focal discharges to neighboring normal, passively driven, cerebral cortex.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. First three components issued from PCA performed on score ranks accounting for 44.36% of variance.

Figure S1. Patients' position in PCA space colored as a function of resulting clusters: the first two components are represented in Figure 1A and the first three components are represented in Figure 1B.

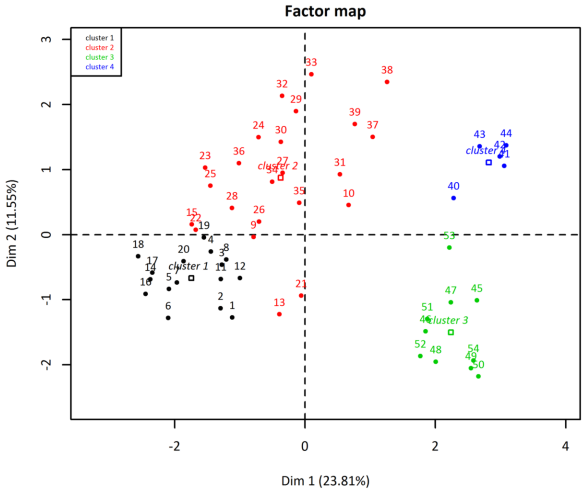
Figure S2. Hierarchical classification of patients based on PCA-resulting space distinguishes four homogeneous groups.

Table S1. First three components issued from PCA performed on score ranks accounting for 44.36% of variance.

Supplementary material Table 1: First three components issued from PCA performed on score ranks accounting for 44.36% of variance

1st Principal Component (23.8 %)		2nd Principal Component (11.55 %)		3d Principal Component (8.94 %)	
correlation	Sign	correlation	sign	correlation	sign
0.89	integrated gestural motor behaviour	0.60	non-localized aura	0.68	rictus/ asymmetric facial contraction
0.61	distal stereotypies	0.56	feeling of fear/anxiety/rage	0.56	proximal stereotypies
0.60	speech production	0.56	autonomic signs	0.56	hyperkinetic motor behaviour
0.58	impairment of consciousness	0.53	non-integrated gestural motor	0.49	tonic vocalization
0.55	feeling of fear/anxiety/rage	0.52	symmetric proximal/axial tonic posture	0.48	vocalization (grunt, etc)
0.53	negative emotional/affective expression	0.43	negative emotional/affective expression	0.43	non-integrated gestural motor
0.48	hyperkinetic motor behaviour	0.41	chapeau	0.38	asymmetric tonic posture
0.46	fixed facial expression	0.37	dystonic elementary motor signs	0.30	autonomic signs
0.45	non-localized aura	0.35	ipsilateral versive signs	0.30	generalised tonic-clonic seizure (GTCS)
0.44	manipulation/utilization	-0.29	early clonic signs (p-value <0.05)	0.27	impairment of consciousness (p-value <0.05)
0.35	autonomic signs	-0.45	manipulation/utilization	-0.33	symmetric proximal/axial tonic posture
0.34	proximal stereotypies	-0.55	fixed facial expression	-0.39	chapeau
0.28	Staring/behavioural arrest (p-value <0.05)	-0.59	distal stereotypies		
-0.34	symmetric proximal/axial tonic posture				
-0.36	somesthetic localized aura				
-0.36	early clonic signs				
-0.40	rictus/ asymmetric facial contraction				
-0.40	asymmetric tonic posture				
-0.41	ipsilateral versive signs				
-0.42	Contralateral versive signs				
-0.43	generalised tonic-clonic seizure (GTCS)				
-0.55	late clonic signs				
-0.55	proximal/distal contralateral tonic posture				
-0.59	tonic vocalization				
-0.92	elementary motor signs				

Figure S1. Patients' position in PCA space colored as a function of resulting clusters: the first two components are represented in Figure 1A and the first three components are represented in Figure 1B.



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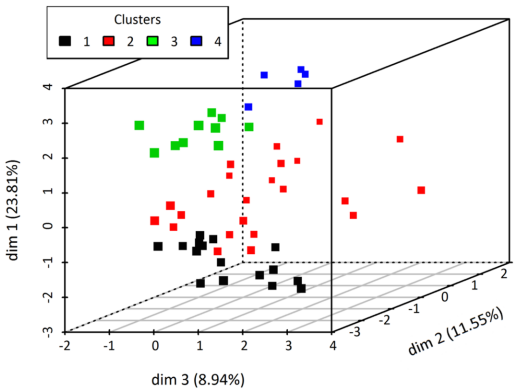
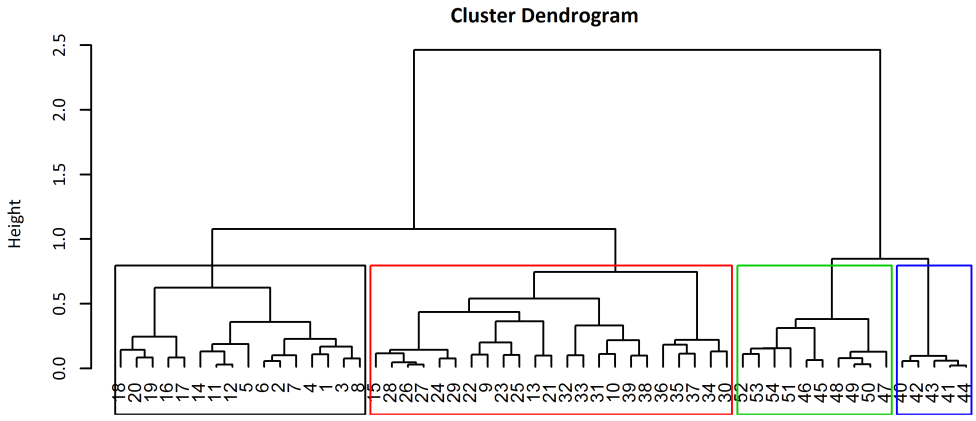


B

Figure S2. Hierarchical classification of patients based on PCA-resulting space distinguishes four homogeneous groups.



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Article 5

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BRIEF REPORT

Prefrontal Seizures Manifesting as Motor Stereotypies

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ABSTRACT

Background: The definition of stereotypies traditionally does not include "epileptic automatisms." However repetitive, sometimes rhythmic behaviors can occur during frontal lobe seizures in a reproducible pattern for a given patient. Thus, the concept of a frontostriatal "motor loop" could be relevant to repetitive ictal behaviors.

Methods: We describe 17 patients with frontal lobe epilepsy who presented with motor and/or verbal stereotypies and who were explored using depth electrodes (stereoelectroencephalography [SEEG]) in the context of epilepsy presurgical evaluation.

Results: Motor patterns were typically reproducible between seizures for a given patient. Distal motor stereotypies were associated with anterior prefrontal localization, and proximal stereotypies were associated with posterior prefrontal localization.

Conclusions: "Stereotypy" is a useful term to describe ictal repetitive behaviors produced by prefrontal seizure discharge. The expression of distal and proximal stereotypies follows a rostrocaudal gradient within the frontal lobes. Exploration of the cortical compartment of frontostriatal networks in epileptic patients offers a unique opportunity to study the mechanisms of stereotypies in vivo. © 2013 International Parkinson and Movement Disorder Society

Key Words: stereotypies; epileptic seizure; frontal lobe; semiology; stereoelectroencephalography

The importance and challenges of achieving a clinically useful definition of stereotypies have recently been highlighted.[1–3] Stereotypies are a common clinical feature of a wide variety of neurological conditions that affect cortical and subcortical function, including autism,[4] Rett syndrome,[5] excessive dopaminergic treatment of Parkinson's disease,[6] and frontotemporal dementia.[7–9] It is increasingly recognized that different clinical behavioral patterns of abnormal repetitive behavior may be associated with different anatomic-pathological entities,[9] such as continuous, complex, midline hand-to-mouth movements in Rett syndrome versus simple, bilateral, intermittent movements in autism disorder.[5]

A recent discussion of the optimal definition of stereotypies[1] lists "automatisms in the context of epileptic seizures" as a differential diagnosis that "may be confused with stereotypies." However, frontal lobe seizures may manifest paroxysmal, reversible, complex behavioral changes due to concomitant cortical seizure activity, including repetitive and sometimes rhythmic movements or vocalizations,[10–13] typically with striking reproducibility of the behavioral pattern in each seizure for a given patient.

Recent debate on the scope and limitations of the definition of stereotypies,[1] as well as evidence of their pathophysiological basis, suggests an interest in revisiting the terminology used to describe repetitive behaviors in seizure semiology. We report a series of patients who presented with repeated episodes of paroxysmal, stereotyped movements and/or vocalizations that reproducibly occurred in a context of localized prefrontal seizure activity, as confirmed by intracerebral electroencephalography (EEG).

Patients and Methods

Patients were selected from a consecutive series of 57 individuals with frontal lobe epilepsy who underwent intracranial exploration with depth electrodes using the stereoelectroencephalography (SEEG) method[14–16] as part of an epilepsy presurgical evaluation. All patients were investigated in the Clinical Neurophysiology Department of Timone Hospital

Additional Supporting Information may be found in the online version of this article.

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TABLE 1. Characteristics of stereotypies in 17 patients with seizures involving the prefrontal cortex as defined by stereoelectroencephalographic exploration

Characteristic	No. of patients (n = 17)	Types of repetitive movement observed	Presence of rhythmic movements	Main zone of frontal cortex involvement
Proximal motor stereotypies alone	6	Bilateral symmetric hip, trunk, or shoulder movements	2	Dorsolateral prefrontal cortex (Brodmann's area 9/46) with or without premotor structures
Distal motor stereotypies alone	4	Bilateral hand movements: grasping, reaching, and fumbling with clothes, bed sheets, or objects in immediate environment (n = 3); tapping hands and feet while singing (n = 1)	1	Lateral orbitofrontal cortex and/or anterior cingulate gyrus; no premotor involvement
Proximal plus distal motor stereotypies	7	Large-amplitude body rocking in anteroposterior plane plus unilateral twirling or grasping hand movements (n = 1); bilateral lateral hip movements while seated or lying with associated grasping or tapping movements of hands (n = 4); bilateral hip/trunk movements and tapping hands and/or feet in time to singing or speech (n = 2)	5	Lateral orbitofrontal and/or anterior cingulate gyrus associated with dorsolateral prefrontal cortex with or without premotor involvement

(Marseille, France) between 2000 and 2012. All patients underwent a full presurgical work-up, including cerebral magnetic resonance imaging, surface video EEG, neuropsychological assessment, and, in most patients, functional imaging with single-photon emission computerized tomography (SPECT) and/or positron emission tomography. In particular, a detailed study was made of the clinical signs that occurred during seizures (semiology), as recorded on video during both surface EEG and SEEG, and their inter-seizure reproducibility for individual patients through an analysis of all recorded seizures. All patients provided written informed consent for use of their clinical data for research purposes.

"Stereotypies" were defined according to Ridley[17] as excessive production of one type of motor act, necessarily resulting in repetition. In the context of the present data, these included repetitive movements or behavior that occurred during seizures, whether simple (such as body rocking) or complex (such as manipulation of an object), and/or vocal stereotypies, such as singing or palilalia.[1,17] The body segment involved was noted (axial, proximal, distal), as were symmetry and the presence of rhythmic movements. Proximal stereotypies consisted of axial body rocking, whether in the anteroposterior or lateral plane, which could be more or less rhythmic. This could involve the whole body or a proximal segment (hips, shoulders) and tended to be symmetric. Distal stereotypies most often involved the hands, whereby the patient would repetitively manipulate the bed sheets, his own clothes, or an object in front of him, usually with both hands but sometimes with an asymmetric involvement. Other distal stereotypies included tapping with the hands on the knees or the bed or tapping rhythmically with the feet. Nonrepetitive movements, including agitated hyperkinetic movements, were not considered to fit the definition of ictal stereotypies.

Results

From 2 to 60 seizures (mean, 11 seizures; median, 7 seizures) were recorded per patient. Of the 57 patients who had frontal lobe epilepsy, 17 presented stereotypies as part of their habitual seizure semiology. All patients also presented other ictal clinical features associated with the stereotypies. These included tonic or dystonic posturing, vocalization, autonomic signs like facial flushing or tachycardia, altered facial expression in some (smiling), or fixed emotionless facial expression in others. No patient manifested stereotypies or obsessive-compulsive behaviors outside of the ictal (seizure) period. All patients were of normal intelligence, as measured by standard IQ tests during a detailed neuropsychological assessment, and had no sensorimotor deficit on neurological examination. No patients had significant psychiatric comorbidity or autistic traits. Stereotypies were associated with prefrontal cortex seizure involvement in all patients but were not observed in patients whose seizures were limited to precentral or premotor structures. Descriptions of ictal stereotypies and the main regions of frontal lobe involvement are listed in Table 1. More detailed SEEG and neuroimaging results are outside the scope of the present paper and will be published separately.

Discussion

Although "epileptic automatisms" have traditionally been grouped as a clinical category more or less distinct from stereotypies,[1,18] the present results highlight the repetitive nature of some movement patterns that

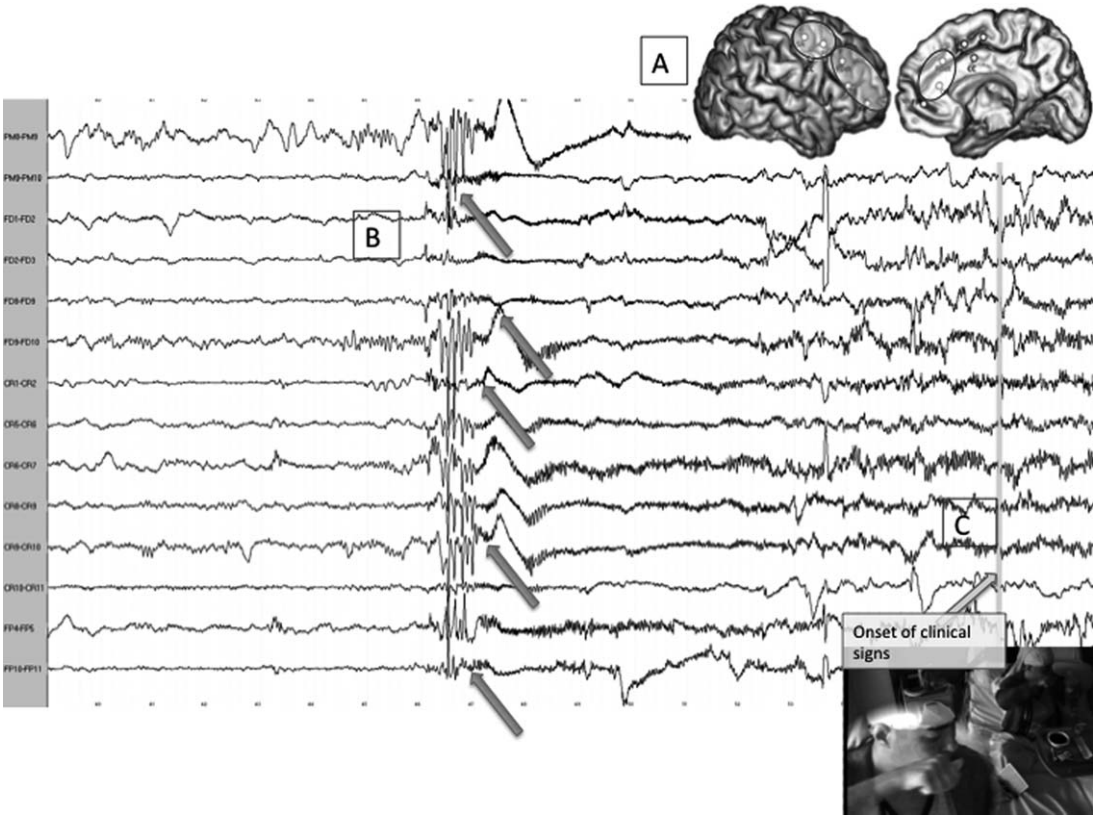

FIG. 1. Stereoelectroencephalography (SEEG) trace, showing seizure onset for the same patient as shown in video clips (Case 1, Segments 1 and 2). Further detail on SEEG methodology can be found in previous works15, 36. (A) Intracranial electrodes placed orthogonally within frontal lobes show high frequency low voltage discharge (B) (left-facing arrows) predominating in right dorsolateral prefrontal cortex and projecting to more posterior lateral premotor cortex as well as medially to anterior cingulate gyrus. Electrical seizure onset precedes the onset of clinical signs (C) (right hand twirling movements and rhythmic axial body rocking in the antero-posterior plane) (right-facing arrow and vertical line, respectively) by around 10 seconds. Shaded areas in (A) show schematically the region involved by initial seizure discharge (anterior dorsolateral prefrontal region) and seizure propagation (posterior dorsolateral frontal cortex and anterior cingulate gyrus).

may be produced because of cortical seizure discharge involving specific regions of the prefrontal cortex. Of course, the observation of automatic behaviors in epileptic seizures, including those with a repetitive nature, is not new. However, in the light of recent debate on the best way to define stereotypies and new evidence on their underlying pathophysiological mechanisms, the presence of repetitive behaviors within seizures merits attention and invites comparison with the stereotypies observed in other neurological conditions. In contrast to other conditions, stereotypies that occur in the course of epileptic seizures tend to be associated with an altered state of consciousness and are not distractible. In addition, because each seizure is limited in time, the expression of stereotypies in the context of epilepsy depends on the time window of transient cerebral dysfunction caused by the ictal discharge.

We could hypothesize that, in frontal seizures, the abnormal electrical activity within specific prefrontal circuits directly influences corresponding striatal structures through their highly topographically organized connections,[19] but whether this occurs through a mechanism of excitation or inhibition remains to be investigated. In our series, a striking observation was that of different topographical organizations of seizure discharge for different clinical patterns of stereotypies, in which predominantly proximal stereotypies were observed when the most posterior prefrontal regions were involved in seizure discharge, whereas distal motor stereotypies (in a context of what could be characterized as ictal integrated behavior[20]) occurred only when seizure activity involved the most anterior prefrontal structures (orbitofrontal cortex, frontal pole, and anterior cingulate gyrus). This anteroposterior distinction might tend to argue in favor of a role for specific cortical-subcortical pathways rather than a more general "release" of cortical control.[21] In addition, the observation that the same motor repertoire of ictal behavior is reproduced with each seizure evokes the notion of "looped motor patterns,"[1] whereby recurrent activation of the same frontostriatal circuit by seizure activity might produce the same clinical phenomena each time through a process of motor learning by "chunked patterns.[22,23]

The notion of a shared pathophysiology across various forms of repetitive behaviors, indicating an overlap

in phenomenology, has previously been proposed.[22,24,25] The pathophysiology of stereotypies within the corticostriatal pathways has been studied extensively in animal and human models[22] and indicates a crucial role for prefrontal structures, especially the orbitofrontal and anterior cingulate cortices. Previous studies of epileptic seizures have identified repetitive hand movements provoked by anterior cingulate gyrus stimulation[26,27] that are evocative of utilization behavior.[28] Although both lateral and medial prefrontal structures certainly play a role in motor control, the relative contribution of different prefrontal structures in producing motor behaviors remains to be fully elucidated.[29,30] In disease processes known to affect the frontal lobes, such as frontotemporal dementia, the presence of motor stereotypies is correlated with the degree of striatal rather than neocortical atrophy[31]; however, there is evidence for altered frontal lobe network connectivity structures in such patients.[32]

Although the concept of "stereotypies" remains somewhat hindered by difficulties of definition,[1] this eventually may offer a more meaningful framework for the study of behavioral frontal seizure semiology compared with "automatism," which is arguably a rather poorly defined category[33] that has no specific pathophysiological basis.[18] Only rare recordings of basal ganglia oscillations in pathological, repetitive behaviors exist.[34] The use of depth electrodes in the course of epilepsy presurgical evaluation offers a potentially useful model with which to explore the cortical component of frontal-striatal pathways.

Legends to the Videos

Video Segment 1: A patient (case 1) presents abnormal, repetitive, rhythmic body rocking in the anteroposterior plane, which is the characteristic manifestation of her habitual epileptic seizures. Seizure discharge reproducibly begins in the same cortical region in each seizure (predominantly the dorsolateral prefrontal cortex) (see Fig. 1). The ictal movements can be characterized as proximal stereotypies. At seizure onset, she presents a twirling movement of her right hand, which also shows a stereotyped character.

Video Segment 2: The same patient (case 1) presents a seizure during stereoelectroencephalographic (SEEG) recording. The reproducible character between seizures of both the anteroposterior body rocking and the right hand movements can be noted. Another patient (case 2) presents predominantly distal movements during a prefrontal seizure that was recorded using SEEG, in which he rapidly flaps both hands while vocalizing and then repetitively taps his leg with his right hand. Two other seizures in the same patient that also demonstrate similar distal stereotypies as well as verbal stereotypies, including echolalia, have been described previously as a case report with video sequences.[35] The epileptogenic zone includes the frontal pole and the lateral orbitofrontal cortex. ■

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Article 6

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Gamma knife radiosurgery of paracentral epilepsy

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ABSTRACT

Background. In pharmacoresistant focal epilepsies involving the central region, risk of motor deficit generally contraindicates cortical resection. Gamma knife radiosurgery (GK) is an established treatment for mesial temporal epilepsy and epilepsy associated with hypothalamic hamartoma.
Objectives. To explore the safety profile and efficacy of GK in motor cortex epilepsies.
Methods. Four patients (18-31 years) with intractable focal sensorimotor epilepsy seizures arising from paracentral lobule, demonstrated by stereoelectro-encephalography (SEEG), in whom conventional surgery was contraindicated because of motor deficit risk, underwent gamma knife radiosurgery. Marginal dose of 24 Gy was delivered to a focal zone involving paracentral lobule.
Results. Volume of treatment ranged from 1.6cm3 to 3.18 cm3 (median 2.34). No motor deficit or other adverse affect occurred. Follow up was available for at least 3 years (range 36-78 months; median 49). No complication of GK, including no motor deficit, occurred. Two patients achieved Engel's Class 1B outcome and two had were unchanged. Both improved patients had gradual disappearance of objective motor ictal semiology (6-12 months post-GK), preceding reduced seizure frequency (12-18 months onwards). Cerebral MRI showed no change.
Conclusions. GK is a potentially useful treatment for focal paracentral epilepsies, where conventional surgery would carry unacceptable risk of motor deficit.

1. INTRODUCTION

Since the development of gamma knife radiosurgery (GK)[1], an increasing body of literature from the late 1980's onwards has described its use in treating focal drug-resistant epilepsy [2-4]. Interest in the potential role of GK in this context arose from observations of improved seizure control in patients treated primarily for vascular malformations [5]. The two main focal epilepsy indications reported to date are mesial temporal lobe epilepsy (MTLE) [6] and hypothalamic hamartoma [7]. The advantage of GK over conventional microsurgery is due to its ability to focus ionizing radiation on small, well-defined zones of tissue, avoiding the risks of craniotomy and brain resection, thus making it a particularly suitable method for treating deep or difficult to reach brain regions. This latter aspect is the main rationale for using GK in hypothalamic hamartoma [7] whereas in MTLE, given the established use of anterior lobectomy as the surgical gold standard [8], the indication for GK is rather related to avoiding risks of conventional surgery, and to patient preference [9]. Reported long-term seizure outcomes following GK in MTLE, when conditions are optimal, are close to results of temporal lobectomy [6]; poorer results are associated with lower doses of radiation (less than 24 Gy) [4], and the presence of a widespread rather than focal epileptogenic zone [10]. The major disadvantage of GK compared with standard surgery is the delay in therapeutic effect [11] with median latencies of 6-18 months reported for obtaining seizure control [4,12]. This latency period is associated in most cases with progressive MRI changes along the same time course [3]; indeed the degree of contrast enhancement and volume of signal change are strongly predictive of good seizure outcome in MTLE [13]. Rare isolated cases of late radiation-induced necrosis have been reported [14,15] but overall GK is well tolerated with low complication rates [16].
To date few cases of GK use in focal extra-temporal epilepsy have been reported. A recent case series described significant seizure reduction in 2 out of 3 patients treated with GK for pharmacoresistant epilepsy involving insular cortex [17]. However use of GK in primary motor cortex has not previously been described. We describe the results of GK in 4 patients presenting epilepsy characterised by focal motor seizures, of which the epileptogenic zone included primary motor cortex, localised to the paracentral lobule in each case using intracranial stereoelectroencephalographic EEG (SEEG) during presurgical evaluation and in whom treatment by GK was chosen to avoid motor deficit.

2. PATIENTS AND METHODS

This observational study of standard patient care was carried out with the accord of the Ethics Committee, Hôpital de la Timone, Marseille. Four patients undergoing gamma knife radiosurgery for intractable focal epilepsy, involving the paracentral lobule, were selected from a total of 217 patients undergoing GK for epilepsy during the period 1993-2010 in the Functional Neuroradiosurgery department, Hôpital de

la Timone, Marseille. Of these 217, 101 were treated for MTLE, 96 for hypothalamic hamartoma, 13 for neocortical epilepsies (including the 4 patients reported here) and 7 for anterior corpus callosotomy. All patients underwent epilepsy presurgical assessment including detailed clinical history and examination, surface video-EEG recording of seizures, cerebral MRI, functional imaging and neuropsychological assessment. SEEG was carried out in each case because of the need to precisely define the epileptogenic zone (EZ) and its relation to cortex subserving motor function [18]. Following presurgical evaluation, resective surgery was contraindicated in all 4 patients because of high risk of producing a motor deficit, and patients were therefore offered GK as an alternative treatment option with the aim of reducing seizure frequency and severity. Details of patients' epilepsy history and results of presurgical evaluation are given in Table 1. Two patients (patients 2 and 4) had undergone prior surgical resection of medial motor structures many years earlier, one because of dysplasia and one because of low-grade astrocytoma (see Table 1); epilepsy presurgical evaluation was performed in these because of persistent seizures.

2.1. SEEG recording

SEEG recordings were performed using intracerebral multiple contact electrodes (manufactured by Alcis; 10 to 15 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm apart from edge to edge) placed intracranially according to Talairach's stereotactic method [19]. Strategy of electrode positioning was established in each patient based upon hypotheses about EZ localization, presence or absence of structural lesion and functional information about involved areas. The accuracy of position of implanted electrodes was peri-operatively controlled using antero-posterior and lateral orthogonal telemetric X-ray imaging. A post-operative computerized tomography (CT) scan without contrast was used to verify the absence of bleeding and the location of each recording lead. Following recording, intracerebral electrodes were removed and MRI performed, permitting visualization of the trajectory of each electrode and relationship with cortical anatomy. Finally, CT-scan/MRI data fusion was performed to locate each contact along the electrode trajectory (for illustration, see [20]). Patients underwent long-term video-SEEG monitoring (128 channels Deltamed system) following complete or partial withdrawal of antiepileptic drugs during a usual period of 4-10 days in order to record several of the patient's habitual seizures.

2.2. Radiosurgical procedure

In each patient, once conventional surgery had been contraindicated on the basis of the extent of the EZ involving functional motor cortex, GK was offered and the potential risks of this treatment fully discussed with patients. All patients signed informed consent and underwent GK. After application of the Leksell Model G stereotactic frame (Elekta Instruments AB, Sweden) under local anaesthesia, all patients underwent stereotactic magnetic resonance imaging (MRI) and computer tomography (CT) for target definition. Stereotactic CT was performed in order to check and correct any potential MRI distortions. Patient-induced susceptibility effect on geometric distortion of clinical brain MRI for radiosurgery is for us a permanent concern[21]. Our quality control procedure therefore includes monitoring of these distortions individually by comparison of stereotactic MR images with stereotactic CT scan.

Preoperative images and previously obtained images of the SEEG electrode positions were co-registered with the images performed on the day of radiosurgery. Thus target definition was based on mapping of cortical anatomy and topography of SEEG electrodes. Model 4C of the Gamma Knife was used (Elekta Instruments AB, Sweden). All patients were treated with a marginal dose of 24 Gy, in a focal zone involving the paracentral lobule, defined in each patient according to SEEG data of maximal involvement in seizure onset (Figure 1 A-D).

Patients were seen at 3 -4 monthly intervals in the first two years and 6 monthly intervals thereafter, with serial MRI (Siemens, 1.5 T) follow up over this period. MRI protocol included transverse diffusion images, transverse T2-weighted images, coronal T1-weighted inversion recovery images, coronal fluid-attenuated inversion recovery (FLAIR) images and a three-dimensional T1-weighted acquisition. Acquisition plans were referred to the bi-hippocampal plane for the transverse acquisitions and to the AC–PC plane for the coronal and axial acquisition.

3. RESULTS

Results are summarised in Table 2.

3.1. SEEG results

The EZ of each of the 4 patients was centered on the paracentral lobule (Fig 1 A-D). The extent of the epileptogenic zone and the type of ictal discharge recorded varied between patients (table 2). In patients 1, 2 and 4 ictal discharge was extremely focal, in the form of a low voltage fast discharge in the gamma band, ranging from 25 to 40 Hz (fig 1 A, B, D), predominantly involving several adjacent contacts of electrodes exploring the paracentral lobule. For each of patients 1, 2 and 4 the predominant clinical sign associated with ictal discharge was tonic contraction, of contralateral foot (patient 1) or arm (patients 2 and 4). Patient 3 on the other hand had seizure semiology consisting of myoclonic jerks of the contralateral foot corresponding temporally to synchronous rhythmic 1-3 Hz spike activity in at least 3 contacts of 3 different electrodes, exploring both paracentral lobule and lateral pre- and post-central cortex (Fig 1C). All

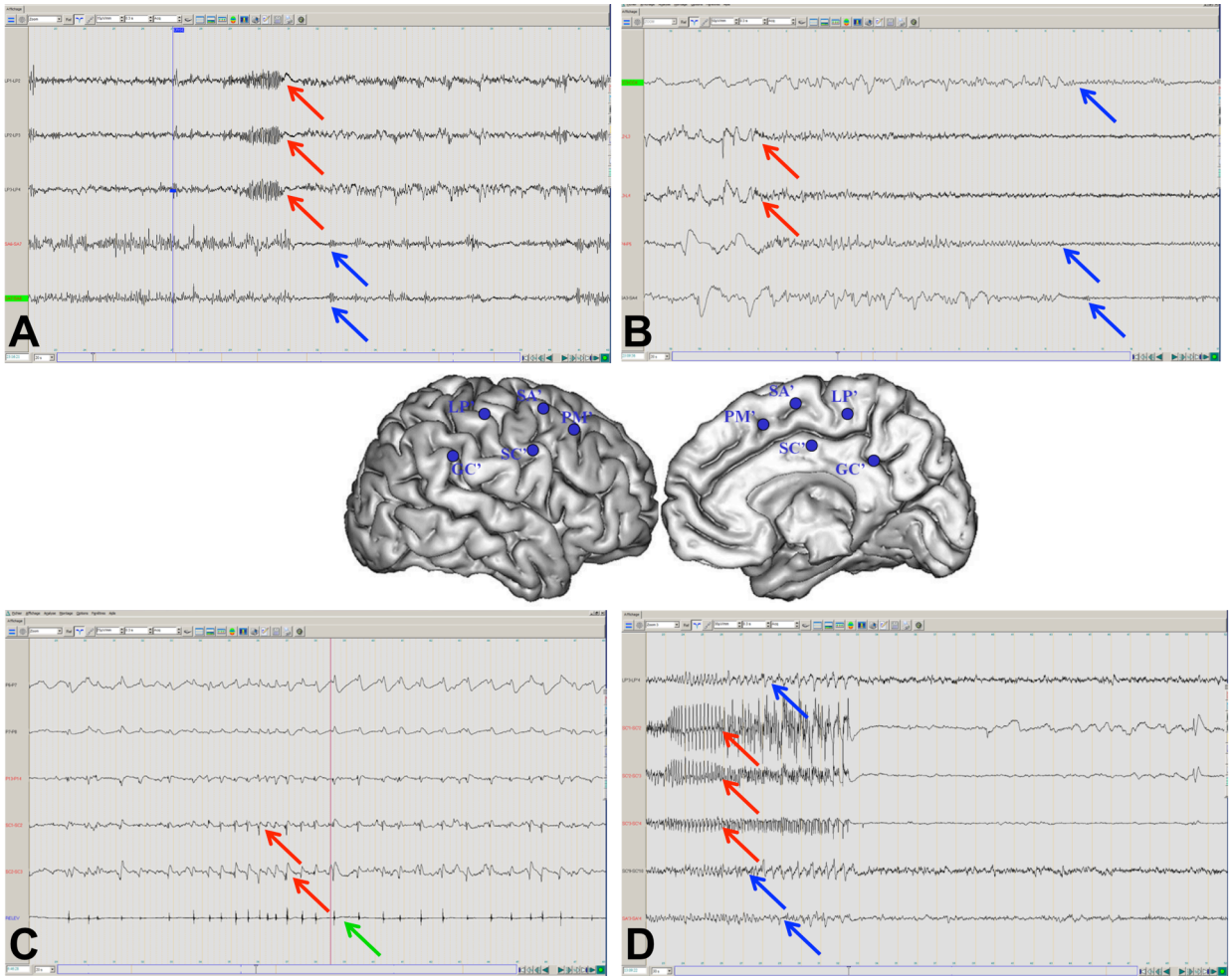

Figure 1. Seizure discharge as recorded by SEEG for each of the 4 patients. For clarity only the electrode contacts maximally involved by ictal activity are shown. A generic 3D SEEG schema is included for illustration with electrode positions in blue dots. **A**. Patient 1: Bursts of high frequency spike activity, maximal in the internal contacts of electrode LP exploring the paracentral lobule, are followed by a brief low voltage fast discharge in the gamma range (red arrow), spreading to lateral precentral cortex (blue arrow). **B**. Patient 2: Low voltage fast discharge in the beta and gamma range, maximal in the internal contacts of electrode L exploring the paracentral lobule (red arrow), spreading to parietal (electrode P) (blue arrow) and anterior cingulate gyrus (electrode CC) regions (blue arrow). **C**. Patient 3:Rhythmic spike and spike wave activity, maximal in the internal contacts of electrode SC (red arrow), time locked with clonic jerks of contralateral foot as shown by EMG (green arrow). **D**. Patient 4: Rhythmic pre-ictal spiking maximal in the internal contacts of electrode SC exploring the paracentral lobule, followed by abrupt disappearance of spikes and appearance of a very fast low voltage (gamma band) discharge (red arrow). A less tonic discharge is also visible in the medial contacts of LP exploring the posterior part of the paracentral lobule (blue arrow) and lateral contacts of SC exploring the precentral convexity (blue arrow).

patients had stimulation studies during intracranial exploration to demonstrate the localisation of primary motor cortex and to confirm the organisation of the EZ; stimulation of the electrode contacts exploring paracentral lobule triggered a typical seizure only for patient 4.

3.2. Radiosurgery results

The anatomical zone treated in each patient is shown in Figure 2 A-D. None of the patients had any complication of gamma knife treatment, notably no motor deficit. Patient 3, who had an existing motor deficit from prior surgery, reported slight difficulty in contralateral hand function over a period of several months immediately following GK, but this was mild with no objective signs of deficit and subsequently

completely resolved. Mild complaints of headache occurred in 2 patients, responsive to simple analgesia. No patient required steroid therapy following GK.

In terms of epilepsy outcome following GK, 2 patients were significantly improved (patients 2 and 4) and 2 patients essentially unchanged (patients 1 and 3), described as follows.

Patient 3 had no discernable change in seizure pattern at any time following GK. Patient 1 had reduced seizure frequency over the first year, with a seizure-free period lasting around 6 months, from the time of treatment, and then a period where seizures recurred with the same semiology and with reduced frequency of about 50% compared to pre-GK, for a period lasting 9 months. However without changes to drug treatment, seizures then recurred, with a return to the pre-GK pattern by the 2nd year after treatment; overall seizure outcome in Patient 1 is thus considered unchanged, like Patient 3. Notably for both these patients, the expected phase of increased seizure frequency, which typically precedes appearance of radiologic change and clinical improvement in MLTLE, was not observed.

On the other hand both patients with good outcome, patients 2 and 4, both had an initial phase of increased seizure frequency, as is typical of successful GK treatment[4,6]. This occurred in patient 4 at 6 months post-GK and in patient 2 much earlier, within 6 weeks of GK; indeed this latter patient presented at this time multiple daily seizures requiring brief hospital admission and temporary increase in anti-epileptic drug treatment to bring seizures under control. The peak of seizure frequency lasted several weeks in both patients, who subsequently showed marked progressive improvement in seizures in terms of both seizure severity and frequency, leading to significant functional improvement over a period of months. Notably the objective motor component of seizure semiology gradually diminished in each case, starting from around 6 months post-GK, until the remaining seizures were subjective sensory ones that did not significantly impair daily function. Rare motor seizures could still arise, especially from sleep, and

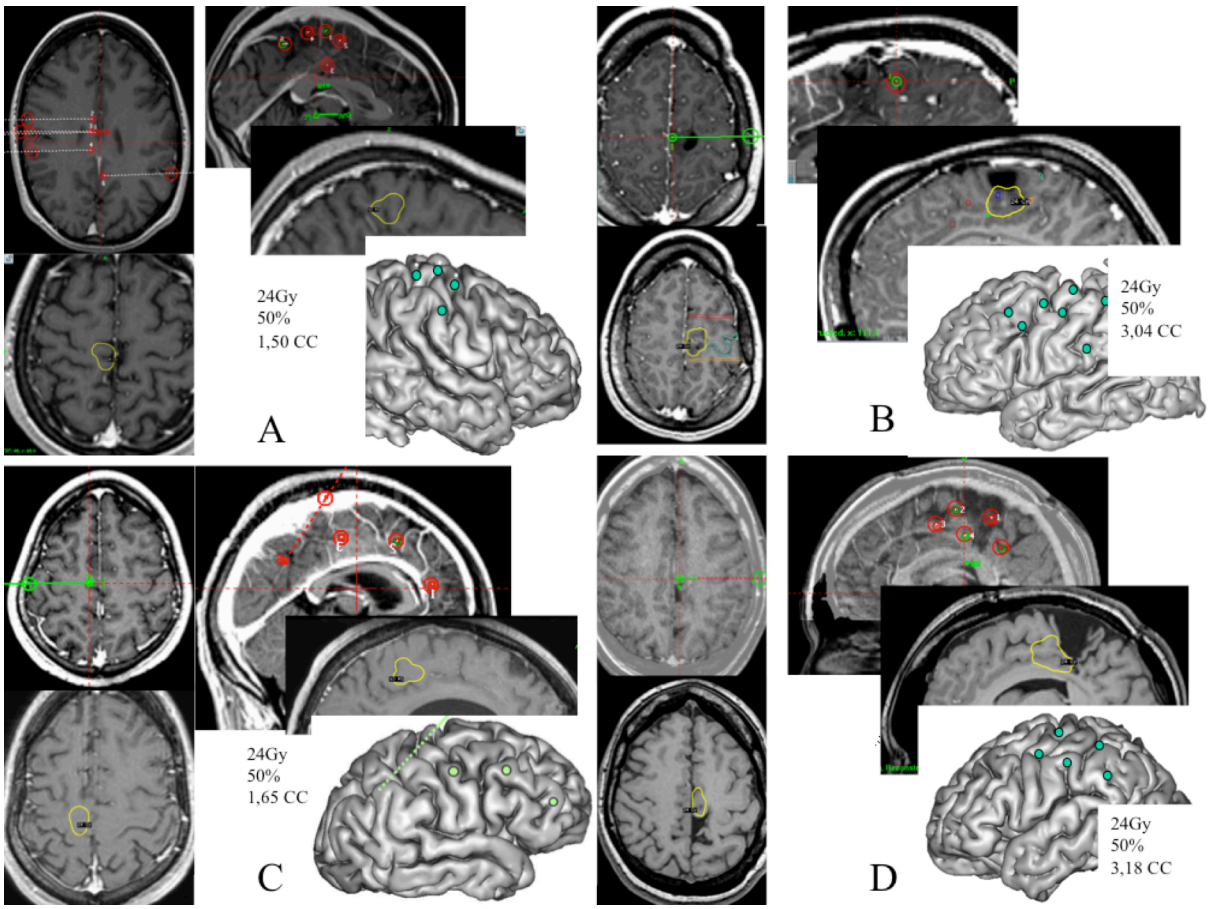

Figure 2. Axial and sagittal MR images for patients 1-4 (**A, B, C, D**) showing SEEG electrode position (red and green markings) as well as the subsequently chosen cortical target for gamma knife treatment (yellow outline). In **B** (patient 2) and **D** (patient 4) the prior surgical resection can be seen. SEEG electrode positions are also shown on the 3D surface rendering diagram (green dots). Gamma knife dose planning parameters are provided for each patient.

patient 4 had periods of transient worsening of sensory seizures during intercurrent illness. Improvement in motor symptoms of seizures (from 6-12 months) preceded reduction in seizure frequency (from 12-18 months). As a result of this improvement in epilepsy patient 4 is now employed as a medical secretary and able to drive an adapted vehicle and patient 2 has obtained her driver's licence. In both patients cautious reduction of their anti-epileptic drug polytherapy was instituted at 2 years post-GK; however the maintenance of a baseline treatment will be continued in both, particularly since rare nocturnal seizures with motor signs still occur in patient 4.

In terms of MRI evolution no significant changes occurred of the whole of the follow up period. In particular neither patient experiencing significant clinical improvement showed any MRI sign of radionecrosis in the follow up period of 2 years, and radiological surveillance continues.

4. DISCUSSION

We report for the first time gamma knife radiosurgical treatment of paracentral epilepsy, in 4 patients for whom conventional surgery carried unacceptable risk of motor deficit. A main result is the absence of any complication of GK, notably absence of motor deficit for these patients treated in the paracentral lobule with 24Gy and a median volume of 2.34cm3. Another main result is the demonstration of marked progressive improvement in 2 of the 4 patients, beginning with a delay of at least 6 months after GK, and showing a characteristic pattern of gradual modification of seizure semiology, with disappearance of objective motor signs thus leading to significant reduction in handicap. This semiological change preceded the eventual reduction in seizure frequency, which finally fell to around 50% of pre-treatment frequency at 2 years post-GK. These 2 patients thus achieved Engel's Class Ib outcomes, through quasi-disappearance of the motor component of their seizure semiology and persistence of less frequent sensory, non-disabling seizures resulting in significant clinical improvement.

The lack of significant MRI change in our patients, including those with successful outcome, is in contrast to the majority of reported MTLE cases, especially given that the doses used in the present study (24 Gy) are similar to those used in MTLE. On the other hand the volume of treatment in the present series (median 2.34cm3) was smaller than for most MTLE cases and thus the total energy delivered to the treated tissue relatively lower. In addition different neuronal systems may have different radiosensitivity [22]. However the GK parameters used the present series (volumes 1.6cm3 to 3.18 cm3, and marginal dose 24Gy) are similar to the series of 3 published cases of insular epilepsy [17], which treated volumes of 1.2 to 3.2 cm3 with a marginal dose of 20Gy.

Whereas technical parameters of GK such as dose and volume of radiation are well known to affect outcome in epilepsy treatment [4,12], the underlying mechanisms of action remain unclear [16]. Based largely on data from animal models, and from human studies of failed GK treatment in which patients have subsequently undergone surgery, there are arguments for both a neuromodulatory mechanism [23] and local neuronal destruction of targeted tissue (see [16] for review). However tissue destruction is by no means essential for seizure control since sub-necrotic gamma irradiation has been shown to have a therapeutic effect in animal models of epilepsy, if appropriate doses are used [24]. In addition there is now a large body of evidence indicating that a wide variety of changes occur following gamma knife treatment at the biochemical and cellular levels, which are independent of any histological necrosis (see [16,23] for review); indeed this aspect may help to explain some of the clinical effects of GK [23]. It has been postulated that a central core of tissue receives a maximal dose of radiation and undergoes neuronal destruction, with a surrounding zone that receives a more moderate dose and manifests functional and biochemical changes producing a neuromodulatory effect [23]. Since seizure semiology is likely produced via a dynamic discharge that propagates to areas both close to and remote from its origin [25], the neuronal modification that takes place in this peripheral region could potentially help to explain semiological changes [16,23], through reduction of seizure propagation [16].

In the present series the gradual evolution of motor semiology was certainly a striking feature in the 2 patients who became free of disabling seizures; such progressive semiological change is in marked contrast to the typical clinical course observed after conventional epilepsy surgery. In addition the absence of neurological deficit or significant MRI change tends to count against a mechanism based on tissue destruction as the main therapeutic effect in the patients reported here, and rather suggests that improvement was due to microscopic changes at the glial/neuronal/white matter cortical levels not visualizable on MRI.

Since these patients all had definition of the EZ through exploration with SEEG, some observations can also be made about the electroclinical pattern of seizures and extent of the EZ, which might have been expected to influence outcome after GK. Focal rather than regional onset, and the presence of a low voltage fast ictal discharge as measured during intracranial recording, have been associated with better outcome in conventional surgical treatment of neocortical epilepsies [26]. Seizure organisation in our patients was of a very focal, limited network, as is quite characteristic of seizures arising within central (primary motor) cortex [27]. If the hypothesis of neuromodulation affecting the extent of epileptogenic network is correct then more focal, rather than widespread networks might be expected to respond better to the "super-selective" nature of GK treatment [16]. This concept clearly requires more investigation in a greater number of patients. As in any analysis of

sub-optimal epilepsy surgical outcome, it is important to distinguish between incorrect localisation of the EZ and inadequate surgical treatment of a correctly defined EZ. In the present series the nature of the SEEG data and its relation to seizure semiology would tend to indicate correct localisation in the paracentral lobule for all 4 patients[28] [29]. The 2 patients achieving Engels class 1B had a larger volume of treatment (around twice the size), and therefore a higher energy radiation dose, than the two with no change in their epilepsy, which could be a factor explaining this difference in outcome. Indeed it seems highly likely that improvement of seizures was related both to optimal target definition (as delineated by maximum zone of epileptic activity on intracranial EEG, when this remains restricted to a readily-defined focal area) and radiosurgery dose delivered. The volume treated, and therefore dose delivered in each case depended upon characteristics of individual patient data. It is noteworthy that even the larger (and more effective) volumes of around 3cm3 used in patients 2 and 4 had no associated MRI change and no neurological deficit, suggesting that this is a safe volume within functional cortex. More experience is of course required before drawing firmer conclusions in this respect.

Another potential contributing factor in outcome is pathological basis of epilepsy, whereby the two who became seizure free had MRI-visible lesions (one an astrocytoma, one a cortical dysplasia) whereas the 2 cases with unsuccessful outcome had "cryptogenic" epilepsy, a factor associated with poorer outcome in conventional epilepsy surgery series [30]. However the other important aspect to consider is that both patients who had sustained seizure improvement had previously undergone cortical resection of the ispilateral paramedian premotor region. Prior reduction in the "critical mass" of epileptogenic cortex in these patients by conventional surgery before receiving GK might well have contributed to successful outcome after GK treatment of residual focal epileptogenic zone. In addition different types of tissue manifest different levels of radiosensitivity [22]; surgical sequellae including gliosis and vascular changes might thus have had a priming effect on the neural tissue to be treated by GK.

5. CONCLUSION

Gamma knife radiosurgery represents a potentially important means of treating focal paracentral pharmacoresistant epilepsy, in which conventional surgery often carries unacceptable functional risks. Our series of 4 cases of focal motor epilepsy treated in the paracentral lobule showed no adverse effects, with 2/4 patients achieving Class 1B seizure outcome and no motor deficit. The observation of progressive modification of seizure semiology in our cases without significant MRI changes lends support to the notion of neuromodulatory mechanisms of gamma knife in treating epilepsy.

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NOTES

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Some of the data for the 4 patients described in this paper were also presented in poster form/as proceedings at the Association of British Neurologists meeting, Glasgow, UK, May 2013.

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Table 1: Patient characteristics

	Age at epilepsy onset (years)	**Seizure semiology**	**Seizure frequency before GK**	**Age of patient at GK (years)**	**Prior resective surgical procedure**	**Neurological examination before GK**	**Initial MRI findings (pre-GK)**
Patient 1	10	Focal sensorimotor seizures L big toe and foot, +/- GTCS	Daily, at least 1 per day	27	No	Normal	Doubtful mild bilateral parietal atrophy, no visible lesion
Patient 2	4	Tingling right hand then R hemibody; speech arrest; breathing difficulty then tonic contraction R hemibody +/- clonic jerks +/- post ictal motor deficit R leg. Never GTCS but 2 episodes of partial status	20-200 seizures per month	31	Left precentral paramedian small cell astrocytoma operated at age 4	Mild motor impairment R hand (dyspraxia?) in childhood causing difficulty in learning to write; however able to play the trumpet	Surgical sequellae left precentral and premotor region (paramedian)
Patient 3	14	Clonic jerks left foot, leg then L arm +/- head version and GTCS	Daily, at least one per day	21	No	Normal	Normal
Patient 4	3	Tonic flexion and clonic jerks R leg, R arm paralysis	2-5 seizures per day	18	L paracentral cortectomy aged 10 for Taylor's cortical dysplasia	Distal sensorimotor deficit R leg since childhood surgery	Surgical sequellae left paramedian precentral region

Table 2: Results of SEEG and outcome after GK

	Volume treated by GK (cm^3)	**SEEG characteristics**	**Previous resective surgery?**	**Duration of follow up (months)**	**MRI change after GK?**	**Outcome after GK**
Patient 1	1.50	Focal tonic discharge involving internal contacts of electrode exploring paracentral lobule	No	78	No	Transient improvement then relapse, overall no improvement at >2 years
Patient 2	3.04	Focal tonic discharge involving mesial contacts of electrode exploring paracentral lobule and adjacent posterior cingulate region	Yes	60	No	Progressive improvement, Engel's 1B at 2 years
Patient 3	1.65	Regional clonic spiking involving paracentral lobule but also neighbouring premotor and parietal cortex	No	36	No	No effect
Patient 4	3.18	Focal tonic discharge involving mesial contacts of electrode exploring paracentral lobule at the level of the central sulcus, inferior and anterior to previous surgical resection	Yes	38	No	Progressive improvement, Engel's 1B at 2 years

McGonigal A, Oto M, Russell A, Greene J and Duncan R. Outpatient video EEG recording in the diagnosis of non-epileptic seizures: a randomised controlled trial of simple suggestion techniques. *Journal of Neurology, Neurosurgery & Psychiatry*. 2002; 72: 549-51

Article 7

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SHORT REPORT

Outpatient video EEG recording in the diagnosis of non-epileptic seizures: a randomised controlled trial of simple suggestion techniques

A McGonigal, M Oto, AJC Russell, J Greene, R Duncan

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Objective: To assess the yield of recorded habitual non-epileptic seizures during outpatient video EEG, using simple suggestion techniques based on hyperventilation and photic stimulation.
Design: Randomised controlled trial of "suggestion" *v* "no suggestion" during outpatient video EEG recording.
Setting: Regional epilepsy service (tertiary care; single centre).
Participants: 30 patients (22 female, 8 male), aged over 16 years, with a probable clinical diagnosis of non-epileptic seizures; 15 were randomised to each group.
Main outcome measures: Yield of habitual non-epileptic seizures recorded, and requirement for additional inpatient video EEG.
Results: 10/15 patients had habitual non-epileptic seizures with suggestion; 5/15 had non-epileptic seizures with no suggestion (p = 0.058; NS); 8/9 patients with a history of previous events in medical settings had non-epileptic seizures recorded during study. Logistic regression analysis with an interaction clause showed a significant effect of suggestion in patients with a history of previous events in medical settings (p = 0.003). An additional inpatient video-EEG was avoided in 14 of the 30 patients (47%).
Conclusions: Habitual non-epileptic seizures can be recorded reliably during short outpatient video EEG in selected patients. Simple (non-invasive) suggestion techniques increase the yield at least in the subgroup with a history of previous events in medical settings. Inpatient video EEG can be avoided in some patients.

Non-epileptic seizures of psychogenic origin (non-epileptic seizures) are often misdiagnosed as epilepsy.[1] A recent estimate suggests the prevalence of non-epileptic seizures may be as high as 33/100 000 of the population.[2] Such patients represent 10–50% of referrals to specialist epilepsy units.[3]

Misdiagnosis of non-epileptic seizures has important implications for patients and health care providers. Not only is there failure to implement appropriate psychological treatment, but the unnecessary use of anti-epileptic drugs and the treatment of "pseudostatus epilepticus"[4] carry significant risks. Correct diagnosis of non-epileptic seizures is associated with a reduction in health care costs.[5]

Video electroencephalographic (video EEG) monitoring is the gold standard investigation, usually during specialist inpatient assessment. Access to this expensive resource is limited in the United Kingdom. Previous non-randomised studies have shown that provocation techniques can produce a useful yield of recorded non-epileptic seizures. Techniques described include injections of saline,[6] the application of a tuning fork or an alcohol soaked pad[7] to the forehead, head up tilt testing,[8] hyperventilation,[9 10] and photic stimulation.[10] The use of provocation techniques, particularly those that are invasive or less honest, remains controversial.[9 11 12] However, some patients have non-epileptic seizures during entirely standard EEG recording, raising the question of whether provocative techniques are necessary.

Our primary aim in carrying out this study was therefore to measure the difference in attack rate between groups of patients randomised to either outpatient video EEG recording plus simple suggestion techniques or to standard outpatient video EEG recording alone. Our secondary aim was to measure the number of patients who, as a result of the diagnostic information gained, did not subsequently require inpatient video EEG.

METHODS

Approval was obtained from the Southern General Hospital NHS Trust ethics committee.

Patient selection

Patients were recruited from a specialist non-epileptic seizures outpatient clinic, between March 2000 and February 2001. Inclusion criteria were: a clinical diagnosis of probable non-epileptic seizures, ability to give informed consent, and age over 16 years. We excluded patients with more than one attack type, those with suspected coexisting epilepsy, and those with only nocturnal attacks, these being considered likely to require inpatient video EEG.

Randomisation and consent

It was explained that video EEG recording of attacks was necessary for diagnosis, and that a psychological cause for the attacks was being considered. After agreeing to take part in the study, patients were randomised to "suggestion" or "no suggestion" groups, using computer generated numbers.

Those in the suggestion group were told that hyperventilation and photic stimulation would be performed during the EEG in an attempt to induce their usual attack. The no suggestion group was told only that outpatient video EEG recording would be carried out. An information sheet reinforcing this was supplied. All patients were asked to attend for the test with a relative or friend who had seen their previous attacks.

Outpatient video EEG

Outpatient video EEG recording was carried out within one to four weeks of initial assessment. Standard EEG and ECG recording equipment was used, with a digital video camera.

For the suggestion group, a doctor (AMcG) was present, as well as the EEG technician, and the history briefly reviewed. It was explained again that hyperventilation ("deep breathing

test") and photic stimulation ("flashing light test") might bring on attacks. The consent form was signed at this stage. Any clinical change occurring during recording (for example, shaking of a limb, apparent unresponsiveness) was commented on by AMcG, for reinforcement. Verbal instructions were given to each patient in as standardised a manner as possible. Any recorded events were discussed with the patient's relative to confirm whether typical or not.

The no suggestion group had a standard EEG recording carried out by a technician, also recorded on digital video. Consent was obtained in the same way as for the suggestion group. A doctor was available should an event occur, in which case it was reviewed with an eyewitness.

RESULTS

Thirty patients were included, 22 female and eight male. Fifteen patients were randomised to each group. There were no significant differences in terms of age, sex, duration of history, previous exposure to EEG recording, or attack frequency.

All patients who fulfilled selection criteria were invited to take part. Four patients failed to attend on more than one occasion and were excluded. Three additional patients were initially randomised (two to the suggestion group and one to the no suggestion group) but were excluded when additional history (at the time of recording) suggested possible coexisting epilepsy.

In the suggestion group, 10 of the 15 patients had events that were electroclinically non-epileptic seizures and were confidently identified as being habitual by eye witnesses. Five of the 15 in the no suggestion group had habitual attacks.

Two of the 15 patients in whom habitual non-epileptic seizures were recorded had events recorded on video without a simultaneous EEG—one (in the suggestion group) had an attack during electrode application, the other (in the no suggestion group) had an attack as she was leaving the room after the test. Both attacks were clinically habitual non-epileptic seizures.

Two other patients (one in each group) had non-habitual non-epileptic seizures.

Nine patients had a history of previous attacks occurring in medical settings; eight of these had habitual non-epileptic seizures recorded during the study. Six of the nine had had similar attacks during previous EEG recordings. Three patients in this group also had attacks in the waiting area either before or after the test.

Statistical analysis

The influence of suggestion and previous history of medically triggered events was analysed by forward stepwise logistic regression, including an interaction term. In univariate analysis, "suggestion" was not independently predictive ($p = 0.058$), but "history of previous events in a medical setting" and the interaction term were both significant. In multivariate analysis, the interaction term remained a significant predictor of attacks ($p = 0.003$), while a history of previous events was not an independent predictor.

Subsequent inpatient video EEG requirement

The 15 patients in whom no habitual event was recorded were offered inpatient videotelemetry, as was one patient with definite non-epileptic seizures, who was subsequently found to have interictal epileptiform abnormalities. Follow up data will be presented at a later stage. Inpatient videotelemetry was therefore avoided in 14 of the 30 patients (47%).

DISCUSSION

Previous studies of inpatient video EEG have shown high yields of non-epileptic seizures with provocation techniques (82–90% of patients[6 10 13]). A non-randomised outpatient study using saline injection[14] induced attacks in 66% of patients, with a spontaneous attack rate of 29%, figures closer to our own.

While we did not find a significant effect of suggestion overall, we did show that the likelihood of producing attacks was increased in patients with previous events in medical settings. These patients may have been particularly suggestible. That as many as one third of the no suggestion group had habitual non-epileptic seizures implies that the EEG procedure itself has a suggestive effect. Video recording and consent of the patient before the recording was done may have exaggerated this. The manner in which a provocative technique is presented appears to be more important than the particular method used.[10 15]

The fact that similar attacks had occurred in six of the 30 patients during previous EEG recordings suggests that a valuable diagnostic opportunity may have been overlooked on those occasions. Routine use of video during standard EEG could help to maximise such opportunities.

Having no good data on which to base a power calculation before starting this study, we chose 15 per group, based on a pragmatic estimate from available data. A post-hoc power calculation indicates that 40 patients would be required in each group to demonstrate a significant difference, assuming that the proportions found in our study were correct.

In agreement with others,[9–11] we consider the use of non-invasive techniques, combined with patient information that is as honest as possible, to be ethically acceptable. The degree of honesty compatible with a positive effect of suggestion is perhaps surprising: we told patients that psychological attacks were being considered, and that recording these was necessary for diagnosis. The fact that 50% went on to produce attacks suggests, as is widely accepted, that the majority of such patients are not malingering, and may not be resistant to a psychological diagnosis.

The technique used in this study is not suitable for all patients with suspected non-epileptic seizures—prolonged inpatient video EEG recording is likely to be necessary where epileptic seizures are also suspected; where there are different types of attack; where events are nocturnal; or where eye witness accounts are insufficient for clinical diagnosis. Expert knowledge of epileptic and non-epileptic seizures, and video EEG recording of events, is required; not all epileptic seizures are accompanied by EEG change, and in both epileptic and non-epileptic seizures the EEG may be obscured by artefact. As hyperventilation and photic stimulation may rarely provoke epileptic seizures in certain circumstances, a simultaneous EEG recording is crucial. Evidence must be obtained that the patient's habitual (and only) type of attack has been recorded.

Non-epileptic seizures are a common problem. Correct and timely diagnosis may improve outcome[16] and saves medical costs,[5] but is limited by relative scarcity of inpatient video EEG resources. A short outpatient video EEG allows prompt diagnosis of non-epileptic seizures in a proportion of patients who would otherwise require inpatient recording, and appears to be particularly useful where there is a history of previous attacks occurring in a medical setting.

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Article 8

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SHORT REPORT

Use of short term video EEG in the diagnosis of attack disorders

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Background: Distinguishing epileptic from psychogenic non-epileptic seizures (PNES) often requires video electroencephalography (EEG) recording. Inpatient recording is a limited resource; some evidence suggests that short term video EEG (SVEEG) is useful, but its role in practice has yet to be evaluated.
Objective: To assess the usefulness of SVEEG in the diagnosis of attack disorders.
Methods: One hundred and forty three SVEEG recordings were performed during an 18 month period.
Results: A diagnostic event was recorded in 72 of 143 (50.3%): PNES (n = 51), epilepsy (n = 7), or other attacks, such as movement disorders (n = 14).
Conclusions: SVEEG is a robust and useful diagnostic technique, which complements existing resources.

The diagnosis of attack disorders can be difficult, and misdiagnosis of epilepsy is common.[1] Distinguishing epileptic seizures from psychogenic non-epileptic seizures (pseudoseizures; PNES) relies on a detailed history from the patient and eyewitness, but recording typical attacks with inpatient video electroencephalography (video EEG) is frequently required. Access to this expensive resource is limited, with waiting lists of many months in some centres.

Short duration outpatient video EEG has been used successfully in paediatric practice.[2] A recent study of adult patients has shown that habitual PNES can be reliably recorded during short outpatient video EEG in 50% of patients, avoiding the need for inpatient video EEG in some.[3] The wider clinical usefulness of this method has yet to be determined.

Early diagnosis of PNES may improve outcome,[4] and avoids inappropriate anti-epileptic drug prescription. A means of diagnosing some patients earlier with a readily available and less costly investigation has important clinical and economic implications.

AIMS

To document the use and diagnostic yield of short term video EEG (SVEEG) as used in our unit over an 18 month period.

BACKGROUND

Our regional epilepsy service has two inpatient video EEG beds, serving a population of approximately 2.4 million in the west of Scotland, with additional referrals from other regions. Eighty to 90 patients are admitted to the unit each year. The mean waiting time for inpatient video EEG is nine to 12 months.

We previously carried out a pilot study of outpatient SVEEG in suspected PNES,[3] since which the technique has been in clinical use. When PNES are suspected, or when an attack of some other type might be recorded (for example, frequent attacks or specific triggers), simultaneous video recording is performed. Therefore, the patients described here have been selected because of a clinical assessment that attacks may occur. SVEEG recordings are performed within four to 12 weeks of referral, or sooner depending on the clinical indication.

METHODS

Clinical neurophysiology medical staff interviewed each patient, to establish the clinical description of the attack, particularly whether one or more types of attack occurred. All patients were asked to bring an eyewitness if possible; if present at the time of recording, their account of the attack was also obtained.

A standard 16 channel EEG with single channel electrocardiogram and simultaneous digital video was recorded, with an average recording duration of 40–50 minutes. If PNES were suspected, simple suggestion techniques were used.[3] If an attack was recorded, it was shown to the eyewitness, to confirm whether typical; if no eyewitness was available at that time, the video was reviewed later. A diagnosis was made only if the recorded attack and EEG findings were unequivocal, and consistent with the available history. If doubt remained, or if not all types of attacks had been recorded, further monitoring was recommended.

RESULTS

SVEEG

One hundred and forty three SVEEG recordings were performed for the investigation of attack disorders during an 18 month period (July 2000 to December 2001). During this period, an additional 15 patients underwent SVEEG as part of a separate randomised controlled trial that has already been reported[3]; these patients were therefore not included in our study. The age range was 14–75 years; 47 patients were male and 96 female.

An attack was recorded in 83 of 143 recordings (table 1). Eleven of these were not clearly confirmed as being typical of the patient's usual event, and were classed as inconclusive.

Table 1 Type of attack recorded in 143 short term video EEG recordings, 2000–2001

Type of attack recorded	Number
PNES	51
Epilepsy	7
Other ''not epilepsy''	14
Inconclusive attack	11
No attack recorded	60
Total	143

EEG, electroencephalography; PNES, psychogenic non-epileptic seizures.

Abbreviations: EEG, electroencephalography; PNES, psychogenic non-epileptic seizures; SVEEG, short term video electroencephalography

Table 2 Diagnostic outcome after inconclusive short term video EEG (n = 60)

	Outcome	Number of patients
Further monitoring (n = 20)	On further monitoring, diagnostic events were recorded*	8
	On further monitoring, no events were recorded but a clinical diagnosis reached	2
	On further monitoring, no events were recorded; the clinical diagnosis remains unclear and the patient is under review	8
	Further monitoring awaited	2
No further monitoring (n = 40)	Clinical diagnosis reached, further monitoring felt to be unnecessary	28
	No further monitoring planned (events too infrequent or patient unsuitable for monitoring); diagnosis unclear, patient under review	5
	Patient declined/did not attend for clinic follow up/further monitoring	7

*Diagnosis after event recorded on further monitoring: 4 patients had epilepsy; 3 had PNES plus epilepsy; 1 had PNES alone.
EEG, electroencephalography; PNES, psychogenic non-epileptic seizures.

Therefore, a diagnostic event was recorded in 72 of 143 (50.3%).

Epileptic events were recorded in seven patients: complex partial seizures in two, myoclonic jerks in four, and one generalised tonic clonic seizure. The ''not epilepsy'' group included movement disorders and hyperventilation related symptoms.

Eleven patients who had no attack recorded had a clinical diagnosis suggested by history and EEG data: in 10 this was epilepsy, and in one probable cough syncope. Appropriate specialist follow up was arranged.

Therefore, the total number of SVEEG recordings providing diagnostic information, either from recorded typical events (n = 72) or history/EEG data (n = 11), was 83 of 143 (58%). The remaining 60 recordings were classed as ''inconclusive''.

Outcome after ''inconclusive'' SVEEG

After inconclusive SVEEG, 38 of 60 patients have since had a diagnosis made (table 2). An appreciable number of patients declined or did not attend for clinic review and/or further monitoring (seven of 60).

Further monitoring (videotelemetry and/or ambulatory EEG) was carried out, or is awaited, in 20 of 60 in the ''inconclusive'' group (table 2); some have had monitoring more than once. The long wait for monitoring in two patients reflects previous failure to attend for the appointment. Further monitoring has also been performed in seven patients with a previous diagnostic SVEEG who have more than one attack type, or who subsequently reported a change in seizure type.

DISCUSSION

SVEEG recording provided a useful yield of recorded attacks in this large series of patients, with habitual diagnostic events positively identified in 50%. Some recordings where no attacks were captured yielded diagnostic information based on history and EEG alone. In these patients, the same information could of course have been gained by clinical consultation and interictal EEG.

Follow up of the original study group[3] at one year indicates that the diagnostic information obtained during SVEEG is robust, with no diagnosis of PNES having been revised (unpublished data, 2002).

It is not possible to calculate accurately the proportion of patients who would otherwise have required inpatient video EEG, or the number of ''bed days'' saved, because not all of the patients who had SVEEG would have required inpatient recording. However, the advantages of SVEEG in terms of earlier diagnosis and lower cost are likely to be considerable.

Although the technique itself is relatively simple and practicable, we would not recommend its use where appropriate clinical and electrophysiological expertise is not available. Expert knowledge of attack disorders and ictal video EEG recording is required. The EEG may be obscured by artefact during attacks, and some types of epileptic seizure may not show changes on surface EEG. It is crucial to obtain evidence that the patient's habitual type of attack has been recorded, and to perform further recording if there is more than one type of event.

The diagnosis of attack disorders is a difficult and common clinical problem. The correct and timely diagnosis of some types of attacks may improve outcome,[4] and saves medical costs.[5] SVEEG is a useful diagnostic tool, particularly for suspected PNES, allowing prompt diagnosis and avoiding the need for inpatient video EEG in some patients. The technique complements existing investigative facilities, and may allow better use of the limited and expensive resource of inpatient video EEG.

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McGonigal A, Oto M, Russell AJ, Greene J, Duncan R and Gates JR. Nonepileptic seizures: An honest approach to provocative testing is feasible. *Archives of Neurology*. 2002; 59: 1491

Article 9

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LETTERS TO THE EDITOR

Nonepileptic Seizures: An Honest Approach to Provocative Testing Is Feasible

We would like to comment on the recent interesting series of articles on the use of provocative testing in the diagnosis of psychogenic nonepileptic seizures.[1-3] As stated by all of the authors, to date there is a lack of evidence for the usefulness of the techniques described.

We have recently completed the first randomized controlled trial of simple suggestion techniques during outpatient videoelectroencephalography in patients with suspected psychogenic nonepileptic seizures.[4] Contrary to many previous studies, we told all patients that a possible psychological cause for the disorder was being considered and that recording a typical attack was necessary to help reach a diagnosis. This approach avoided the ethical problems of nondisclosure. Despite this degree of honesty, we still found a high yield of attacks. In our experience, an honest approach is feasible and less likely to be detrimental to the physician-patient relationship.

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In reply

McGonigal and colleagues refer to their article on a randomized controlled trial of simple suggestion techniques. Apparently they told all of their patients that a possible psychological cause for the disorder was being considered and that recording a typical attack was necessary to help reach a diagnosis. They believe that this approach avoided the ethical problem of nondisclosure, and the study design was approved by their ethics committee.

In their study, they had a yield in the suggestion group of 10 (66.7%) of 15 patients with electroclinically proven nonepileptic seizures that were confidently identified as habitual by eyewitnesses. Only 5 (33.3%) of 15 patients in the no-suggestion group had habitual attacks.

I believe that these authors have come up with an innovative strategy for avoiding some of the ethical issues that complicate a nonepileptic seizure induction: they informed patients that a psychological cause for the disorder was being considered and that photic stimulation or hyperventilation would be performed in an attempt to induce a typical attack. Their study is somewhat limited because it did not describe how many typical events were recorded. Generally, recording several stereotypic events is desirable to be sure that an apparent epileptic event without a clear surface electroencephalographic correlate is not being missed. The selection criteria identified in their study excluded patients with more than 1 type of attack, suspected coexisting epilepsy, or only nocturnal attacks. Also, there was no mention of whether medications were discontinued; from the authors' description of the group, however, I suspect that none of these patients were taking antiepileptic medication. Consequently, although the authors have negotiated the rocky straits of the ethical dilemma of suggestion for nonepileptic seizures, it appears that their technique has limited application by virtue of the rather rigorous exclusion criteria.

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McGonigal A and Bartolomei F. Parietal seizures mimicking psychogenic nonepileptic seizures. *Epilepsia*. 2014; 55.1 196-7.

Article 10

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tor that was imputed from the ratio of depth and other electrodes. However, we had no choice but to extrapolate their raw percentages as being applicable to both depth and cortical electrodes. For regression analysis, we evaluated different adjusted models, but we presented only the best models based on commonly used criteria, as detailed in our paper. We have already mentioned this limitation in our study and cautioned the reader that the estimates are biased and most likely represent conservative figures. Similar argument holds true for the study by Wellmer et al.[3] We agree with Drs. Tandon and Esquenazi that this is an imperfect data synthesis. However, as we have repeatedly pointed out in our paper: there is extensive variability in reporting surgical morbidity associated with invasive epilepsy evaluation and the estimates that we have generated, although biased and likely conservative, represent the currently available data and draw attention to the heterogeneity in practice and data reporting.

Disclosures

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journals position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Parietal seizures mimicking psychogenic nonepileptic seizures

To the Editors:

We would like to comment on the excellent article Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: A staged approach by LaFrance et al.[1] In terms of the difficulty of differential diagnosis between psychogenic nonepileptic seizures (PNES) and epileptic seizures, we note that frontal seizures, especially the so-called hypermotor seizures, have been highlighted several times in this article. However, from our experience working within a tertiary epilepsy center in Marseille, the diagnostic difficulties we have more frequently encountered in recent years tend to arise in differentiating parietal lobe seizures from PNES.

In the past 8 years we have seen five patients considered by us after initial assessment to have a fairly high likelihood of PNES, whose events were subsequently shown to be epileptic seizures of parietal origin. The initial impression of probable PNES was reinforced in two patients by short-term video–electroencephalography (EEG) recording of their habitual events, albeit a mild, mainly sensory version of these, with seemingly atypical clinical features, apparently produced or reinforced by suggestion[2] with no surface EEG change.

However, with subsequent long-term video-EEG monitoring, all five patients proved to have parietal epilepsies with epileptic seizures that involved somatosensory illusions, which were painful or certainly unpleasant, usually involving but not limited to the contralateral hemibody. Vertiginous symptoms or altered body perception could also occur. Motor signs were generally scarce in the early phase of the seizure but subtle dystonic posturing, tremor, or dyspraxic-type movements could be observed in the contralateral upper limb, often in the later part of the seizure. There was also frequently an ictal emotional component of fear or anxiety (with associated distressed behavior) and rather subtle alteration of consciousness. One patient had dysarthria. The early, mainly sensory phase of the seizures seemed to wax and wane (during which period the EEG was noncontributory) with a gradual build-up to more obvious motor signs (at which point the EEG showed changes). This waxing and waning pattern could be particularly observed during the EEG hyperventilation test. In two patients the seizure developed over many minutes before terminating in quite sudden secondary generalization (tonic–clonic seizure). All five patients had interictal anxio-depressive symptoms and a tendency for their seizures to be triggered by emotional events. Three patients had parietal lobe dysplasia that was not visible on initial magnetic resonance imaging (MRI) scans but that became evident with repeated, more detailed imaging, one had cryptogenic epilepsy and one had developed epilepsy following meningitis (MRI normal). Three of the five patients have since undergone presurgical evaluation with stereoelectroencephalography (SEEG), of which two have undergone subsequent parietal cortical resection surgery with good outcome.

The diversity of parietal lobe semiology, including polysensory auras and heterogeneous motor manifestations such as dystonia and hyperkinetic behavior, has been previously highlighted.[3–5] An interesting observation in our own and others cases, which could contribute to giving an initial impression of PNES is the rather frequent occurrence of affective ictal and interictal symptoms.[3,5] Although surface EEG is often nonlocalizing in parietal

seizures,[3] SEEG recordings have allowed description of subgroups of parietal seizure organization.[5]

Over the same time period in our center we have not observed similar diagnostic difficulties in differentiating PNES from frontal seizures. Patients with certain forms of parietal seizures represent an interesting group for further study in the context of differential diagnosis from PNES.

Disclosure

We confirm that we have read the Journals position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflict of interest to disclose.

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In response to comments on Parietal seizures mimicking psychogenic nonepileptic seizures

To the Editors:

We thank Drs. McGonigal and Bartolomei for their remarks on the ILAE nonepileptic seizures (NES) Task Force (TF) Diagnosis paper.[1] We agree with their comments, and we acknowledge that frontal lobe epilepsy (FLE) seizures have been well described in the literature and are in many ways different enough from psychogenic NES (PNES) (with FLEs predominantly nocturnal occurrence, short duration, stereotyped semiology) that diagnostic mistakes involving FLE are becoming less of an issue.[2,3]

Our charge in the TF was to provide a logical and practicable framework for diagnosing PNES and differentiating them from epileptic seizures, one that could be used by a wide range of clinicians, rather than categorizing all potential diagnostic scenarios. We are aware that there are a number of problematic situations in which neurologic and cardiovascular phenomena, such as epileptic seizures and syncope, may appear to have the characteristics of PNES, or may trigger PNES.[4] The letter of Drs. McGonigal and Bartolomei illustrates two important points related to the differential diagnosis for PNES. First, as noted in the epilepsy literature,[5] parietal lobe epileptic seizures can be mistaken for PNES, especially when presenting with some atypical features. Second, a scalp-negative ictal EEG is only one element in establishing the PNES diagnosis, of the three necessary diagnostic components (history, semiology, EEG) in our criteria (Table 2). As noted in the ILAE NES TF paper,[1] The event described should be clinically incompatible with simple partial seizures (whether small motor seizures, or experiential seizures) or hypermotor frontal lobe seizures in which ictal EEG changes may be lacking.

The clinical observations in Drs. McGonigal and Bartolomeis cases are welcome. As many in the field know, no matter how experienced and careful you are, there will sometimes be cases in which your first impression is subsequently proven wrong. The more we know about brain-behavior disorders and the neuropsychiatry of seizures, the better it is for patients and clinicians.

Disclosure

The authors have no conflicts of interest. We confirm that we have read the Journals position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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