INTERICTAL AND ICTAL LOCALIZATION DERIVED FROM NEUROELECTRIC DATA

by

Dianne Crisp

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Name: Dianne Crisp

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Examining Committee:

Chair: Dr. R. Blackman

Dr. H. Weinberg,
Senior Supervisor

Dr. W. Krane

Dr. M. D. Low

Dr. A. Diamond

Dr. D. MacDonald

Dr. B. Beyerstein,
Internal-External Examiner

Dr. M. W. Jones,
Clinical Associate Professor,
University of British Columbia,
External Examiner

Date Approved: Aug 18/94

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Interictal and Ictal Localization Derived From Neuroelectric Data

Author:

(signature)

Dianne Crisp

(name)

26 Aug 94

(date)

Abstract

This thesis addresses two major questions. The first concerns the practical issue of whether Electroencepahlographic (EEG) data can be used to effectively locate sources of brain activity. The second addresses the theoretical issue of whether the sources of ictal and interictal epileptiform discharges are congruent or represent different sites of activity. Interictal and ictal EEG data were analyzed for source location using the inverse procedure in four patients with partial epilepsy. For two of these patients interictal Magnetoencephalograph (MEG) data were also analyzed. Results from source location analyses were related to Magnetic Resonance Images (MRI) and clinical impressions of the area of epileptogenesis. In one patient the results showed localized sources for both interictal and ictal data and were consistent with MRI and clinical impressions. In the other three patients the interictal data showed more distributed sources, involving both hemispheres. Of these three patients the ictal EEG was most indicative of epileptogenesis originating in the temporal lobe believed to be the most likely source from MRI and/or clinical data. These results are interpreted as demonstrating that EEG data can be of value in location of sources of brain activity, and that sites of interictal and ictal activity may represent different sites of brain activity.

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DEDICATION

To mum and dad

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I. General Introduction

This thesis addresses two general issues concerning the localization of sources responsible for epileptiform[1] activity. The first is of major theoretical importance: what is the relationship between interictal (between seizure) and ictal (seizure) activity? The second is a more practical matter: what is the relationship between various measures of the localization of epileptiform sources?

For the purposes of addressing these questions, data were derived using multichannel EEG systems that allow the measurement of distributed activities necessary for accurate estimates of sources of interictal and ictal events. In addition, multichannel Magnetoencephalograph (MEG) and Magnetic Resonance Image (MRI) data were examined both for the purpose of validating sources located with EEG and to examine the relationship between source locations derived with the different techniques. Since there is no true method of validating the sources predicted with the techniques used in this thesis, MRI was considered to be the "gold standard", despite recognition that it may not provide the true source location.[2]

The problem of locating sources of brain activity which give rise to seizures[3] in epileptic individuals has been approached in the literature through

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[1] The terms epileptiform discharges or epileptiform events are often used throughout this thesis in place of such terms as spikes or sharp waves. The former terms were selected because they avoid assumptions about the frequency or spatial configuration of the generators of the activity. In addition, they represent less constrained terms than such terms as "spike" which is defined as a transient with a durarion of less than 1/14th of a second (Epilepsia, 1981). In more general terms the event must be clearly distinct from the background activity.

[2] The "gold standard" accepted by epileptologists is cessation of seizures following surgery (Dr. M. Jones, personal communication, August 18th, 1994).

[3] In the majority of studies reported in the present thesis seizures of the complex partial variety have been studied. A seizure recorded with an EEG is represented by the abrupt onset and termination of repetitive EEG discharges in a focal region of the brain. The waveformas vary in

the use of several techniques. These have included structural imaging for abnormal tissue, as obtained with Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI), as well as the functional imaging of pathological activity, as obtained with Positron Emission Tomography (PET), Electroencephalography (EEG) and Magnetoencephalography (MEG) (Crisp, Weinberg & Podrouzek, 1991). For reasons which will be elaborated in the body of the present thesis, the EEG and MEG approaches are presently thought to represent the best methods by which the location problem can be solved. This thesis deals with, most specifically, the application of EEG to the problem of location, and in particular the relative contributions of interictal and ictal EEG data.

The importance of localization of epileptiform sources can be viewed from both theoretical and practical standpoints. Theoretically, it is not yet clear what conditions obtain when brain tissue, which apparently functions normally most of the time, abruptly synchronizes its electrical activity giving rise to either interictal (II) discharges or ictal (Ic) activity which can often be recorded at the surface of the head. In addition, the spatial relationship between interictal and ictal discharges is not entirely clear. Practically, if surgical intervention is being considered, it is usually assumed that the area of brain tissue responsible for the ictal event must be removed to provide seizure relief. It is unclear as to whether interictal and ictal discharges represent the same sources, and thus involve the same areas of brain tissue. Some EEG studies indicate that interictal and ictal activities may arise from different sources (Rossi, 1973), yet many EEG and

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topographic distribution and frequency, but tend to become more widespread and slower in frequency as the episode progresses.

MEG examinations, designed to locate the epileptogenic regions, rely on data from interictal abnormalities rather than ictal activity. However, even the utility of seizure event localization is under debate. Some authors believe that focal ictal epileptiform discharges preceding or simultaneous with the patient's habitual seizures are the most reliable to work with (Quesney & Gloor, 1985). But, controversy over the validity of interictal versus ictal data remains, partly due to the fact that the relationships between II and Ic epileptiform foci are not completely understood (Dichter & Ayala, 1987), and partly because some authors believe that the localizing value of ictal onset EEG is unreliable (Spencer, Williamson, Bridgers et al., 1985). It has even been reported that ictal onset EEG localizations may give falsely lateralizing information (Risinger et al., 1989), although this is not a consistent finding (Leib, Walsh, Babb, Walter & Crandall, 1976). In addition, since the Dipole Localizaton Method (DLM) has not been applied to this problem, application of DLM to II and Ic EEG may improve our understanding of the utility of the two data types.

There is however, recent support for the use of interictal MEG events in the location of epileptogenic activity. Stefan and colleagues (1992), in a study which used MEG localization of interictal and ictal activity in three patients, found that the sources of the two types of activity were in the same region, and that the locations of both types were reasonable in terms of anatomical abnormalities. However, there is, as yet, no direct study of the relative locations of sources derived from interictal and ictal EEG data using more recent modeling techniques than those available up until the early 1970's.

From a practical point of view it remains the case, even in the present day when pharmacotherapies are abundant, that in some percentage of patients,

epilepsy remains intractable to therapeutic drug control (Ward, 1983). For those patients who suffer from frequent, socially disruptive or even physically detrimental seizures, other therapies are sought. In particular, when the seizures appear to be arising from a discrete functionally non-essential brain region (e.g., not the speech area), surgical intervention is a viable alternative.

The task here is to locate and remove the offensive tissue. Surface EEG, for which a phenomenal analysis for location of discharges is customarily performed, is usually utilized as the first step in the location procedure. The second step often involves the application of cortical or subcortical electrodes before or during the resection procedure, which although considered more accurate than surface EEG, still fails to localize seizures in approximately 19% of patients who undergo the procedure (Spencer, 1981). The second step necessarily relies to some extent on the *a priori* location information garnered from surface EEG interpretation. However, the surface EEG analysis, although successful in many cases, provides only a gross estimation of the possible site of involved tissue (Engel, Crandall & Rausch, 1983). This is the result of several problems inherent in the raw EEG data approach: (1) the problem of the reference electrode - EEG is a differential measure between two electrode sites, one of which is often used as a reference electrode but which is rarely, if ever, without influence on the apparent distribution of electrical fields over the head (see Katznelson, 1981, for a detailed discussion); (2) the problem of intervening tissue - the electrical signals generated in the brain must pass through several layers of tissue differing in conductivity, for example Cerebro Spinal Fluid (CSF), dura and skull, which distort and smear the signals observed at the surface (Shaw & Roth, 1955, cited in Henderson, Butler & Glass, 1975); and, (3) the

problem of volume conduction in the EEG - the EEG potentials are the result of electrical currents flowing through the extracellular medium (Petsche, Pockberger & Rapplesberger, 1984) and are thought to represent volume conducted currents over large regions of cortex.

The development of neuromagnetic measurement techniques (known as magnetoencephalography when applied to brain activity) has shown some promise in improvement of non-invasive localization techniques. This is mainly because MEG measurement circumvents the problems ascribed to EEG in the preceding discussion. (1) The MEG is reference free - it measures magnetic flux density at a single point rather than providing a differential recording between two physiologic areas. (2) Intervening tissues are transparent to magnetic fields thus, the fields are not distorted or smeared and show tighter distributions than the EEG (Cohen & Cuffin, 1983). (3) Finally, the magnetic fields recorded at the head surface are due to intracellular current flow and not to volume conducted currents (Cohen & Hosaka, 1976).

Investigations over the past decade have demonstrated that the surface magnetic fields associated with epileptiform discharges can be used in an inverse procedure to locate the sources of abnormal activity in the brain (Barth Sutherling, Engel & Beatty, 1982). The validity of these locations has been supported with convergent evidence from anatomical imaging techniques such as MRI and CT (Barth et al., 1984; Crisp, 1986; Ricci et al., 1987; Stefan et al., 1992), and from depth electrode studies (Sutherling, Crandall, Levesque, Darcey & Barth, 1992).

Along with interest in MEG for source location estimates, a parallel interest in the use of EEG for this purpose has been pursued. Techniques have

been developed which are said to render the EEG reference free, in particular the method of Hjorth which uses a Laplacian transformation of the data (Hjorth, 1975; 1980). The resulting maps are sharper, and reveal areas where volume current emerges and reenters the scalp. Laplacian maps are useful for visual interpretation of the underlying sources (Stefan et al., 1992), but are not utilized for inverse calculations. Furthermore, the problem of head modeling has been investigated, and it is now generally accepted that a 3-sphere head model which incorporates layers of resistive inhomogeneity, is an adequate model for many applications to EEG. Given these developments in EEG and the fact that EEG data mainly represents the activity of radial sources as opposed to the tangential sources detected with MEG (Cuffin & Cohen, 1979), it is of interest in the present thesis to compare location estimates of interictal and ictal EEG to those predicted from interictal MEG.[4]

[4] For ethical reasons, activation of seizures during MEG recording is not possible in the present study, thus, only interictal MEG data will be available.

II. Cellular Models of Epileptiform Activity and its Relationship to Surface-Recorded Activity

One of the questions to be addressed in this thesis concerns the relationship between interictal and ictal epileptiform discharges. As mentioned, there is a great deal of debate in the clinical literature concerning the relationship of the two (Dichter & Ayala, 1987). Data from animal models of epilepsy have provided some insight into the cellular correlates of interictal discharges, and in these models, the development of ictal activity.

Extracellular recordings obtained during seizure activity in the alumina lesion model of epilepsy, demonstrated bursts of high frequency spike activity in extracellular regions (Ward, 1961). Further insights into the activities occurring at the cellular level during epileptiform events were provided initially by Kandel and Spencer (1961) and in more detailed form by Matsumoto and Ajmone Marsan (1964a; 1964b). These included the first intracellular recordings and they demonstrated profound membrane depolarizations with associated spike bursts, which were named Paroxysmal Depolarization Shifts (PDS) (Matsumoto & Ajmone Marsan, 1964 a; 1964b). The PDS was described as being a positive membrane shift of up to 30 mV or more with a duration of approximately 40-400 msec. The burst of spikes usually followed the first action potential to result from the depolarization. Following the PDS a profound hyperpolarization with a duration of 400-600 msec usually occurred (Matsumoto & Ajmone Marsan, 1964 a). Further, these authors noted that recordings from independent cells demonstrated the synchronous occurrence of the PDS, an important observation since synchronization of cellular activity is thought to underlie seizures in humans (Delgado-Escueta, 1986). The relationship between PDS and Surface EEG

spikes was demonstrated by Ayala and colleagues (Ayala, Dichter, Gumnit, Matsumoto & Spencer, 1973) who showed that PDS underlie spike discharges in the surface EEG.

The profound hyperpolarization which follows the PDS has been named the After Hyperpolarization (AHP). The AHP is thought to play a significant role in the prevention of transition from an interictal discharge to an ictal event (Ayala et al., 1973; Matsumoto et al., 1964b). Indeed, Matsumoto and colleagues, in their seminal studies of the intracellular correlates of ictal and interictal surface activity, described the AHP and declared its role as one of limiting the maximal frequency of the PDS, thereby preventing the transition to the ictal event from occurring by inhibition. This phenomenon was predictable to the extent that the breakdown of the AHP was the single electrographic factor by which they could anticipate the onset of seizures. A sequence of events was described which characterized the failure of the AHP to limit epileptogenic activity. The AHP would be the first electrical component to undergo a change; it would decrease in amplitude, shorten in duration, and finally disappear. Concomitant with these changes in the AHP, the PDS increased in frequency, amplitude and duration, until ultimately a seizure event would occur (Matsumoto et al., 1964a; 1964b).

Thus, in animal models, the relationship between interictal and ictal discharges is one in which the same cells for both conditions are directly involved and in which the breakdown of inhibition after hyperpolarization signals the onset of seizure activity. However, these animal models of epilepsy are artificially induced, usually involving a single region of abnormality. Human epilepsy may, and probably often does, involve more than a single area of abnormality in the brain tissue, and the interaction of these abnormal areas may produce a totally

different pattern of interictal-ictal relationship than is produced with animal preparations.

Cellular recordings are not feasible for the present study, and possibly for any investigation of intracranial relationships between epileptiform activities in humans, since the necessary *a priori* assumptions about the location of the sources immediately place the investigator in a situation where they have to already have the answers to the questions they are asking. That is, the investigator must place the intracelluar electrodes in the active sites when the sites are unknown before the investigation begins, and educated guesses are inadequate since the possibility of sampling error is immense. Thus, surface recordings were obtained from patients for the present study.

In order to gain insight into the relationship between interictal and ictal activities in the patients who participated in the present thesis, methods were required which permitted the solution of the inverse problem for the surface data recorded from the patients. These methods included models of the source activity, and the head, and mathematical methods for relating surface activity to the underlying sources.

III. Models of the Generator Sources

For the analysis of EEG and MEG, models of the generator sources and head shape have been developed. The current dipole model has been extensively invoked in both EEG and MEG studies to characterize the underlying generators of electrical and magnetic activity recorded from the head surface. Electric current represents charge flow, which, in biologic tissue, is the result of movement of positively and negatively charged ions across cell membranes. It is now accepted that EEG and MEG activity arises from the activation of three types of source representing the distribution of charged ions: the dipole (positive and negative charge separated in space), the dipole layer, and the action potential (Nunez, 1981). The contribution from action potentials, however, appears to be limited to early components of evoked responses (Picton, Hillyard, Kraus & Galambos, 1974). Thus, the majority of potentials and magnetic fields recorded are the result of activity arising from dendritic post synaptic potentials (PSPs) which can be modeled as dipoles or dipole layers (Goff, Williamson, VanGilder, Allison, & Fisher, 1980; Nunez, 1981; 1986a).

Figure 1 illustrates the basic dipole model at the cellular level. When the selective permeability of a post synaptic membrane is altered in response to reception of a neuroactive substance, ions either enter or leave the membrane producing a local current sink or source respectively. This post synaptic activity produces an electrical dipole by completion of a current loop inside and outside of the cell. For such activity to produce detectable potentials or fields at the head surface, multiple elongated neurons, such as pyramidal cells in parallel organization, must be synchronously active.

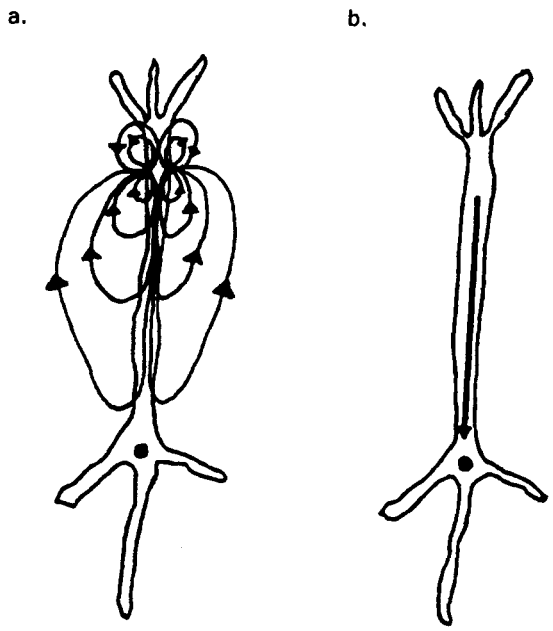

Figure 1. Schematic representation of a pyramidal cell. (a) Intracellular and extracellular current flow following depolarization of the apical dendrites, and, (b) intracellular current flowing away from the dendrite toward the cell body. This current can be represented as a current dipole.

Pyramidal-type cells are considered to be the most likely candidates for generation of this activity because radially configured cells such as stellates form closed fields which produce no externally detectable signals due to self-cancellation effects. In addition, it is highly unlikely that activation of a single cell

will be responsible for the relatively large signals seen at the scalp (Cooper, Winter, Crow & Walter, 1969). Hence a sheet or layer of closely spaced dipoles must be simultaneously active to produce detectable signals. The surface detectable signals produced by this layer will simply be the vector sum of the contributions from each of the individual neurons (Henderson et al., 1975; Nunez, 1981; Vaughan, 1974; Wood, 1982) which may be modeled as an equivalent dipole. The source-sink configuration produced by a dipole layer can be detected by placement of EEG electrodes on different isopotential lines of the field generated by the extracellular current flow, or with the MEG by detecting the extrema of magnetic flux (fields entering the head in one region and leaving in another). On theoretical grounds the EEG detects mainly the volume (extracellular) currents, while the MEG detects mainly magnetic fields produced by the dense intracellular currents (due to cancellation of the flux produced by volume current flowing within the quasi-symmetrical conductor of the brain and head).

There has been some question about the adequacy of the dipole model to describe EEG and MEG generators. However, Barth has shown over several experiments using animal preparations that the dipole approximation is appropriate for modeling magnetic fields generated in neocortex (see Barth, 1991, for a review of this work).

Calculation of the observed activity

Given a physiological model of the underlying sources of EEG and MEG activity, the EEG potentials or MEG fields resulting from such a source in a particular point in space can be derived. Solutions for the numerical calculation

of EEG potentials and MEG fields recorded at the scalp can be used in computer based data fitting routines.

For EEG, a dipole in a homogeneous medium, the potential of a dipolar source at distances greater than 3 or 4 d (where d represents distance between or separation of the positive source and negative sink separation (see Figure 1) can be expressed by the equation :

$$\phi \cong \frac{Id\cos\theta}{4\pi\sigma r^2} \qquad r \rangle\rangle d \tag{1}$$

where ϕ is the potential, I is the current, σ is the conductivity, and r , θ the spherical coordinates (note that the potential falls off as the inverse square of the distance, r , to the source) (Nunez, 1981).

For MEG, when the assumption is made that the measurements are made exactly radial to the sphere, the equation for the radial component of the magnetic field[5] external to a sphere is given by a modification of the Biot-Savart Law:

$$B_r \approx \frac{\left(\frac{\mu_0 Q}{4\pi d^2}\right)\left(\frac{b}{d\cos\varphi\sin\theta}\right)}{\left(\frac{1+2br}{d^2}\right)(1-\cos\theta)^{\frac{3}{2}}} \tag{2}$$

Where Q is the dipole moment in amp-meters, μ_0, the permittivity of free space, d, the distance from the center of the sphere to the dipole in meters, θ, the

5 The radial component is that component of the magnetic field which would be exclusively recorded with present techniques if the head were a perfect sphere.

angle of rotation from the x axis, and ϕ, the angle of declination from the z axis (Grynszpan & Geselowitz, 1973). If, however, non-radial measurements are assumed there are three components, radial, azimuth and declination; then the fields from non radial measurements can be calculated using the following equations derived by Grynszpan and Geselowitz (1973)[6]:

$$B_r = \frac{\mu_{0} \cdot a \cdot q}{4\pi} \cdot \frac{\sin\varphi \cdot \sin\theta}{\sqrt{\left(a^2 + r^2 - 2 \cdot a \cdot r \cdot \cos\theta\right)^3}} \tag{3}$$

$$B\varphi = \frac{\mu_{0} \cdot q \cdot \cos\varphi}{4\pi \cdot a \cdot r \cdot \sin^2\theta} \cdot \left[\frac{r - a \cdot \cos\theta}{\sqrt{a^2 + r^2 - 2 \cdot a \cdot r \cdot \cos\theta}} - 1\right] \tag{4}$$

$$B_\theta = \frac{\mu_0 \cdot q \cdot \sin\varphi}{4\pi \cdot a \cdot r \cdot \sin^2\theta} \cdot \left[\cos\theta + \frac{(a - r \cdot \cos\theta)^3 + r \cdot \left(a^2 - r^2\right) \cdot \cos\theta \cdot \sin^2\theta}{\sqrt{\left(a^2 + r^2 - 2 \cdot a \cdot r \cdot \cos\theta\right)^3}}\right] \tag{5}$$

Where a is the distance of the dipole from the origin, r is the distance of the recording sensor from the origin, q is the dipole strength, and θ and φ are defined as before. The value of the field at the sensor is given by the dot product between the vector sum of these three orthogonal components ($B_r, B_\varphi, and B_\theta$).

Dipole localization of sources

6 Courtesy of CTF Systems Inc.

The calculation of the EEG potentials or MEG fields recorded at the scalp for a dipolar source permit the calculation of an inverse solution. The dipole location method is a technique in which an equivalent dipole is sought such that $B_{i(the)}$, the predicted field a particular dipole would produce at the scalp recording sites, best fits $B_{i(obs)}$, the observed fields at those recording sites [7]. The best fit is defined as a least-squares fit such that the following equation is minimized:

$$SS_{diff} = \sum_{i=1}^{n} \left(B_{i(obs)} - B_{i(the)} \right)^2 \qquad (6)$$

The equivalent dipole is the one for which the predicted fields produce a SUM which is minimum. The SUM for any other dipolar source will be larger than the SUM for the equivalent dipole[8].

Dipole localization using this approach has been common, although it has been widely recognized that epileptogenic tissue probably represents a spatially extended neuronal source rather than a point source (Graf, Niedermeyer, Schiemann, Uematsu, & Long, 1984), and that the single equivalent dipole probably represents the center of the extended source of active tissue (Nunez, 1981).

This relates to another modeling difficulty. Part of the problem with modeling multiple sources has been demonstrated in simulation studies in which it has been shown that a magnetic field distribution generated by multiple dipoles

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7 Although stated here in terms of magnetic fields, this definition can easily be restated in terms of electrical potentials recorded at the scalp with the terms $V(i)_{cal}$ and $V(i)_{obs}$ replacing the terms for the magnetic fields.

8 The calculated field depends on the dipole parameters, the calculated potentials on the dipole parameters, and the head model being used.

can be indistinguishable from those generated by single dipoles (Weinberg et al., 1987). Extensions of the fit for single time points to include multiple dipoles is limited by the number of recording positions since each dipole requires 5 (for MEG) or 6 (for EEG) parameters, and there should be many times more recording positions than parameters (Nunez, 1981).

During the last several years, a spatio-temporal approach to fitting multiple dipoles to data has been developed and applied (Barth, Baumgartner & Sutherling, 1989; Baumgartner, Di, Sutherling & Barth, 1988; Baumgartner, Sutherling, Di & Barth, 1989; Scherg & von Cramon, 1989). In this approach, instead of selecting single time points on which the localization is to be based, the whole epoch over which the epileptiform complex occurs is used in the fitting routine. This increases the number of parameters, and thus dipoles which can be fit, since now there are recording points times the number of data points per epoch. For example, if data from 20 recording points is collected for one second at a digitizing rate of 4 hertz, and the whole epoch is analyzed, then one has 20X4 = 80 data points, and several dipoles can be fit simultaneously. Spatio-temporal source modeling utilizes an approach in which the activities (strengths) of multiple fixed dipoles are described over the epoch of interest. This type of modeling provides position, orientation and current or potential contribution over the span of the electrophysiological event.

As is the case with single-point dipole localization, the dipole starting positions for spatio-temporal modeling can be critical. Indeed, this may be even more crucial in the spatio-temporal case since as the number of parameters to

be fit are increased so are the number of local minima [9]. Procedures for starting locations for the multiple dipoles include peak location (Barth et al., 1989), the DLM (Dipole Localization Method) on single time points, and statistical techniques such as Principal Components Analysis (PCA) with appropriate rotation (Baumgartner et al., 1989). Barth and colleagues (Barth et al., 1989) reported that multivariate statistical techniques (i.e., PCA) resulted in start values equivalent to those obtained with peak location techniques.

For spatio-temporal modeling, once the start values are estimated, a wave shape is associated to each source by linear regression. Sources are moved and the regression repeated in an iterative manner until the minimum residual is found.

Analysis of epileptiform MEG activity using the spatio-temporal modeling approach has been reported by Barth and colleagues (Barth et al., 1989). In this study it was concluded that the technique is useful for estimation of the number, location and temporal activity of cortical sources of interictal events seen in MEG. As yet there are no EEG reports in which spatio-temporal analysis of the data was used. However, as with the MEG, this type of multisource EEG analysis may represent a more realistic view of epilepsy than single source analysis, in that either single or multiple sources may underlie any particular case of epilepsy.

Models of the head

As mentioned, there is an assumption that the dipole sources are in a homogenous medium. The cranium, however, is not a homogeneous medium

9 Both single point and spatio-temporal modeling utilize non-linear optimization procedures for which there can be fits to local minima rather than the absolute minimum error.

and considerable work has been done in the area of head modeling. The inhomogeneity of the head with its layers of differing resistivity has presented a particularly difficult problem for the EEG and the substantial distortion and attenuation of EEG potentials resulting from this has been recognized for many years (Shaw & Roth, 1955). The introduction of three sphere models to correct for conductivity changes in EEG (Kavanagh, Darcey, Lehmann, & Fender, 1978) has gone some way to improving dipole location techniques for EEG data, although there remain some difficulties in analyzing data recorded over clearly non-spherical areas of the head such as the temporal lobe region (Meijs, ten Voorde, Peters, Stok, & Lopes da Silva, 1988).

Magnetic field recordings, in theory, do not suffer from the smearing and attenuation present in EEG because intervening tissues are transparent to magnetic fields, and it has been shown that spherically concentric inhomogeneities have no effect on MEG signals (Grynszpan & Geselowitz, 1973). Nevertheless, as with EEG, there remain some problems applying these solutions to data obtained from head areas which are clearly non-spherical because of induced current at boundaries, and, as with the EEG, these regions include the temporal areas (Sato, Rose & Porter, 1985; Meijs et al., 1988). These areas are most often investigated in intractable epilepsy.

Despite these problems, MEG has met with considerable success when used to locate sources of epileptiform activity. EEG epilepsy data has not yet been sufficiently tested using the models and algorithms discussed above, although results of such tests are beginning to permeate the literature (Wong & Weinberg, 1988), and work done with other forms of EEG data indicate much promise for the application of these techniques (Wood & Wolpaw, 1982).

The application of source modeling to EEG and MEG

Since the introduction of MEG in the late 1960's (Cohen, 1968), much enthusiasm has been generated by the apparent superiority of source localization using MEG compared to EEG. This enthusiasm has been tempered both by the realization that MEG and EEG provide complementary information for electrophysiological investigation, and by the parallel body of research which has arisen in the area of scalp-EEG localization. Unfortunately, the advances in EEG modeling and software - in part driven by MEG research - have not been exploited in the clinical setting, and thus the efficacy of scalp-EEG localizations in such settings is probably underestimated. It is very likely that utilization of these advances would enhance the utility of EEG in source location. This is particularly true for the scalp-EEG, which is, at present, usually analyzed by visual inspection, even in more recent work in which MEG and EEG are compared (Stefan et al., 1992). The analysis of scalp-EEG should include dipole location analyses, with appropriate corrections for non-homogeneous resistivity of different cranial layers such as skull, CSF and scalp. Support for this position and rationales for the use of the various models incorporated in such an approach has come from many sources (e.g. Katznelson, 1981; Meijs et al., 1988). As mentioned, however, very little EEG work has been done in dipole location analysis of epilepsy, and thus the discussion here will be mainly confined to MEG research of this type.

IV. MEG Studies of Epilepsy

Consistent with the law of Ampere, every electrical current has associated magnetic fields. Measurement of the fields associated with the brain's electrical activity, however, did not become possible until the technology for their detection became available. This equipment, known as a Super Conducting Quantum Interference Device (SQUID), is capable of detecting these tiny fields which are of the order of 10^{-13} Tesla (Modena, Ricci, Barbanera, Leoni, Romani & Carelli, 1982)[10]. Like EEG, MEG fields of epileptiform components are frequently distributed in a manner consistent with an underlying dipolar source. The dipole localization approach taken by many researchers has been to generate maps of the magnetic flux distribution across the head in order to assess whether, and at what time points, a dipole source can explain the data. From the maps, an initial estimation of dipole position orientation and strength is made, the predicted fields of which are compared to the observed fields. The position, strength and orientation of one or more current dipoles is then adjusted using standard algorithms for non-linear parameter estimation, until the least squares residual between predicted and observed fields is minimized.

Utilization of the MEG technique has been in both the areas of normal brain activity and in pathological states, but pathological states, particularly epilepsy, provide a unique opportunity for independent verification of the results when structural lesions are identified in CT or MRI scans, or when possible, from intracerebral EEG recordings.

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10 As a comparison, the fields generated by the earth's magnetic field are of the order of 10^{-4}, or 9 orders of magnitude larger than those generated by the brain.

Although there were earlier reports of the use of MEG in detecting epilepsy (Cohen, 1972; Hughes, Cohen, Mayman, Scholl & Hendrix, 1977), a major turning point occurred in 1982 when, almost simultaneously, two papers appeared in the literature, both of which addressed the systematic investigation of partial epilepsy[11] (Barth et al., 1982; Modena et al., 1982). Of particular interest was Barth's adoption of the averaging and contour mapping familiar to EEG practitioners. In order to improve the signal to noise ratio, Barth and colleagues averaged interictal discharges for each recording position, and then used these data to produce contour maps of the flux distribution within the recording matrix. The application of peak location techniques[12] described by Williamson and Kaufman (1981) to these data demonstrated the utility of the current dipole as a first approximation of a source in these patients.

Several reports of the investigation of interictal discharges have appeared since. Many of these have documented the detection of two magnetic field extrema, one where fields leave the head and another where they re-enter, as would be predicted for a source which can be modeled as a current dipole. Applications of dipole localization methods to these data have provided estimates of source location of the epileptiform discharges within the brain (Barth, Sutherling, Engel, & Beatty, 1984; Crisp, 1986; Sato, Sheridan, Smith et al., 1985). In addition to correlating the location derived from MEG data with normal anatomy (Barth, Sutherling, Engel & Beatty, 1984), the spatial relation of

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[11] Partial seizures are those in which EEG and clinical syptoms indicate onset of the seizure in a limited portion of one hemisphere of the brain (Epilepsia, 1981).

12 The peak location technique is a method in which contour maps of the data are constructed and extrema, or peaks, in these maps identified. The bisection of a line connecting these two peaks indicates the position, which is directly obtained by the bisection, and polarity, which is determined from the right hand rule of physics. An estimate of depth is obtained from the angle between the two peaks with respect to the center of the head model.

these sources to abnormal anatomy has been demonstrated by plotting the estimated source on Computerized Tomograms (CT) and Magnetic Resonance (MR) images (Crisp, 1986; Ricci, 1983; Ricci, Leoni, Romani et al., 1985; Weinberg et al., 1987). Sources derived from MEG analysis in these studies are shown to be adjacent to areas of abnormal tissue (see Figure 2).

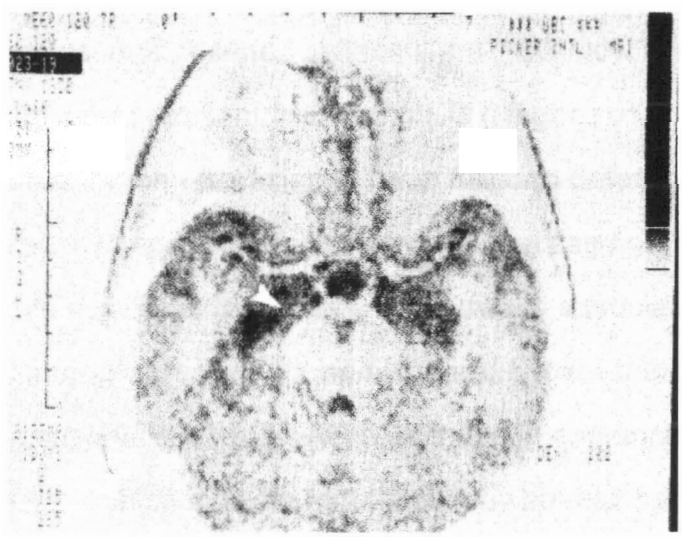

Figure 2. Magnetic resonance image with a dipole estimate from MEG data indicated by the arrow. Note the darkened area adjacent to the arrow which is a region of abnormality on this image.

Although these studies have relied upon structural imaging for validation, the method of choice for validation of MEG is its comparison with intracranial studies and some work, which will discussed later, has been done in this area (Sutherling, Crandall, Engel, Darcey, Cahan, & Barth, 1987; Rose, Sato, Smith, et al., 1987).

MEG and EEG data have been shown to be complementary in terms of the activities they record. MEG may reveal epileptiform abnormalities in the absence of EEG disturbance (Modena et al., 1982; Ricci, 1983), a finding which argues fairly strongly against the exclusive use of the averaging procedure which relies on the EEG abnormality to select the MEG data for analysis. Conversely, signals present in the EEG may not be seen in the MEG. For example in the 3/sec spike and wave of absence epilepsy, the EEG slow wave is either greatly reduced in amplitude or absent from the MEG (Hughes et al., 1977). The MEG has been reported on one occasion to have failed to detect organized magnetic fields associated with epileptiform EEG events in a case of bilateral discharge (Crisp, 1986). In this case, MEG fields were clearly associated with the discharges occurring over the right hemisphere, but not the discharge arising from the left hemisphere. Results such as these in conjunction with results from intracranial studies which indicate that there may be relatively large areas of active tissue, rather than single discrete regions, have led to different approaches to the extraction (preprocessing) of epileptiform activity from the background noise.

The preprocessing of MEG activity

There has been much interest in the literature concerning the optimal method by which abnormal epileptiform MEG signals can be extracted from background activity and noise. Several approaches have been utilized in the preprocessing of epileptiform events in the MEG: Averaging, single discharge mapping, selective averaging, relative covariance, and isospectral mapping.

The use of averaging, as described by Barth et al. (1984) is a technique which has been applied by several of the above-mentioned research groups

(Barth et al., 1982; Crisp, 1986; Sato, Sheridan, Smith et al., 1985). With single channel recording systems, epileptiform activity from each recording position is averaged together without regard for their morphology. As indicated, the purpose of this approach is that it reduces noise, as it does for evoked potentials, but there are problems inherent in this method. The first is the assumption that all epileptiform events arise from the same source. This may not be the case and is a problem confounded by the fact that earlier MEG recording systems were either single sensor systems, or had a limited array of sensors, and thus required sequential recordings over different areas of the head, a problem which can be overcome by multi-channel recording systems as used in the present study.

Techniques which have been developed to avoid the assumption of a single source have included the analysis of single, unaveraged events and the averaging of morphologically and spatially similar discharges. The approaches that have focused on the use of interictal discharges without averaging has been spearheaded by Sato and Rose and colleagues (Sato, Rose & Porter, 1985), and involve single discharge mapping. Based on the assumption that epileptiform events of differing morphology may represent the activity of different generators, Sato and colleagues (Sato, Rose & Porter, 1985), using a single channel collection system, selected single events of similar morphology from each recording position, and used that data to produce maps, and from there localize sources. Thus, Sato et al., were interested in the source of one particular type of discharge, but they did not, at this point, investigate whether more than one source was active during the recording sessions. In 1987 they looked specifically at the issue of whether more than one source was active.

Rose et al. (Rose, Sato & Smith et al., 1987), following an earlier report (Ricci et al., 1985) in which it was concluded that the area of active tissue identified with MEG was considerably smaller than that identified with Electrocorticography (ECoG)[13], investigated the contribution of different sources. Their thesis was that the reason the area identified with MEG was smaller than that identified with ECoG was that averaging MEG discharges led to an estimate of an average of several different sources, rather than reflecting the true situation which involves extended sources. Using morphological criteria for differentiating events, Rose showed that slightly different areas of tissue were active for each event-type. It was concluded that the method of averaging discharges of differing morphology to produce the field distribution for localization caused the solution to represent what is actually a relatively large region as a single three-dimensional "point". Unfortunately, they did not compare the single discharge approach with an averaged discharge approach which would have provided an interesting comparison of source localization. Data from many of the present MEG systems would be, however, too noisy for location analysis of single events.

The third approach, which surmounts the noise problem because averaging is still used, is a refinement of the averaging procedure in which MEG activity associated with discharges of similar morphology is averaged. In this manner interictal discharges can be resolved to reveal several components which can then be located to independent areas in the brain (Barth et al., 1984). Barth used this method to map the temporal and spatial propagation of

[13] Recording of the brain's electrical activity by means of electrodes placed on or implanted in the cortex.

discharges and was successful in spatially and temporally tracking epileptiform discharges (Barth et al., 1984).

The second problem confronted by MEG researchers in epilepsy has been that EEG must be recorded when the techniques described above are used. High voltage EEG discharges must be present to serve as the trigger point around which to select and average the MEG, but, as mentioned, it has been noted that overt EEG abnormalities may not be associated with abnormalities in the MEG (Modena et al., 1982; Ricci, 1983). The next two approaches do not involve the detection of EEG activity at all. Ricci and co-workers (Ricci et al., 1985; Ricci et al, 1987) have avoided the necessity of using high voltage EEG epileptiform events as triggers by using a procedure called the Relative Covariance (RC) technique (Chapman, Ilmoniemi, Barbanera & Romani, 1984). The RC method involves calculation of the covariance between simultaneously acquired EEG and MEG data, filtered for the bandwidth of interest. The covariance coefficient obtained is then divided by the variance of the electrical signal to account for changes in source strength across recordings. Using the RC analysis, Ricci has successfully located sources of MEG activity at the outer edge of anatomical abnormalities detected by tomographic images. Using a different method, Anogianakis and Anninos (1988) have demonstrated that MEG can be used to identify a projection of the epileptiform focus on the scalp without depending on simultaneously collected EEG data. This method of analysis is described as an isospectral synchronized power mapping of scalp distribution (see Anogianakis & Anninos, 1988, for a complete description of the method). In common with the RC method (Ricci et al., 1985; Ricci et al., 1987), this approach maps MEG of a restricted bandwidth, but, unlike averaging and RC, it is not

dependent on the EEG for either a trigger or as a control for variance. In isospectral mapping, the data points in the maps are derived from the inverse of the amplitude variance times the power variance. The maps produced, like those of other methods, reveal distribution of MEG signals across the head and can be used to estimate starting positions for dipole analysis.

Thus, five basic techniques for producing data for MEG contour maps - which represent data suitable for dipole localization - have been used to date in MEG: averaging of all epileptiform events, single epileptiform event mapping and selective averaging, relative covariance and isospectral analysis. Each has its particular advantages and each has its unique or shared disadvantages. For example, a disadvantage of the RC technique is that it is a value derived by temporal integration, thus, the temporal changes in the MEG fields are suppressed (Salustri & Chapman, 1989). Isospectral mapping does share the averaging approach disadvantage of lengthy collection times and in this respect the RC may be of considerable advantage. An additional advantage of the RC shared by isospectral mapping is its non-dependence on overtly abnormal data. Thus, subtle EEG abnormalities, and even abnormalities which cannot be detected with the EEG may be revealed with these approaches. However, for the most part researchers presently active in the field are using single event analysis or selective averaging (e.g., Stefan et al., 1992).

V. MEG versus EEG Localization

An important question to be addressed by MEG/EEG researchers is the relative accuracy of MEG localization compared to EEG localization. There are three major approaches to this kind of comparison in the literature. The first involves the comparison of localization by each technique using interictal MEG and surface EEG data. The second involves comparison of interictal data and intracranial EEG. The third involves comparison of ictal intracranial EEG and MEG[14].

First, comparison of interictal MEG and surface EEG has been reported using data from children with Benign Rolandic Epilepsy of Childhood (BREC) (Cohen, Cuffin, Kennedy, Lombroso, Gumnit, & Schomer, 1988). Using a least squares inverse solution and a four layer spherical model, these authors found that EEG and MEG placed the focus at the same X, Y axes location (right/left, anterior/posterior), but that MEG was more accurate in depth (Z axis) estimation. One difficulty of assessing the accuracy of source localization using EEG data involves the necessity to use a spherical head model and the need to relate source localizations within the sphere to actual 3-dimensional locations in the cranium. Thus, it is not clear from their presentation how Cohen and colleagues assessed the "true" depth of the discharge. In a follow-up study of one patient one year later it was found that the EEG fit no longer accounted for as much of the variance and had shifted several centimeters whereas the MEG fit had remained good and had not shifted (Kennedy, Lombroso, Cuffin, Cohen, Maniewski, & Purcell, 1988).

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14 An omission in the literature is the comparison of interictal data and ictal data. This will be discussed following the present summary.

Second, the use of intracranial recordings has yielded information concerning both the limitations of MEG to detect discharges and its relative localizing power. In terms of its limits to detect epileptiform discharges, the MEG apparently fails to detect epileptiform events arising from parahippocampal locations (Sutherling, Baumgartner, Le Vesque, Crandall, & Barth, 1988). In two cases where the interictal discharges were detected on MEG, Sutherling and colleagues found that the location predicted by MEG differed by 12 millimeters from the center of the cortical spike on intracranial recordings (Sutherling, Crandall, Cahan, Barth, 1988). With data from single subjects, Ricci and colleagues (Ricci et al., 1987) and Salustri and Chapman (1989) found close agreement between ECoG and MEG localizations, as did Rose et al. (Rose, Sato, Smith et al., 1987) with three subjects, although no quantitative estimates of the agreement were reported.

Third, when ictal MEG is compared with simultaneously recorded ictal depth EEG, the MEG is shown to have the same morphology and frequency as the discharges in the EEG, and the MEG localization can be demonstrated to be consistent with the depth EEG (Sutherling et al., 1987). In one case, seizures were mapped with both MEG and surface EEG permitting 3-dimensional localization of seizures which agreed with intracranial depth-EEG studies (Sutherling, Crandall, Engel, Darcey, Cahan, & Barth, 1987; Sutherling et al., 1992). The authors conclude that during seizure, MEG and EEG show simple tangential dipolar patterns on MEG and EEG. Such patterns as these are tractable to dipole localization. In addition, both MEG and EEG localizations for a seizure in one patient agreed with an estimation made with depth electrodes (Sutherling, Crandall, Levesque, Darcey & Barth, 1992). Unfortunately, the

patient had a normal MRI and PET scan and the quantitative values of the estimated co-ordinates for EEG and MEG were not reported. Thus, the relative locations estimated with MEG and EEG cannot be ascertained from either of the published reports on this particular patient, nor can their convergence with anatomical evidence be determined.

Although early studies appear to show that MEG is more accurate than surface EEG in locating foci in complex partial epilepsy (for example, Kennedy. et al., 1988) and comparable with depth EEG in most cases, later reports indicate that surface EEG has considerable potential in this area (Sutherling et al., 1992). Without greater detail in the reported data - for example how Kennedy and his colleagues (Kennedy et al, 1988) estimated the true depth of the discharge when they claimed that MEG was more accurate than EEG in depth location - the exact accuracy of locations obtained through EEG data has not been established.

VI. The Use of Surface EEG in Localizing Epileptiform Discharges

There are several reasons for interest in whether surface EEG can be used as effectively as MEG: EEG is cheap, widely available, easy to use, and well understood in terms of clinical interpretation. MEG on the other hand, in its present generation, is expensive, available only in specialized laboratories, difficult to use and only beginning to be understood for clinical use.

It may be the case that surface EEG can never be quite as accurate as MEG, but that begs the question of what degree of accuracy is necessary for surgical intervention. When one considers work which has compared limited versus extensive resections, the results suggest that limited resections are not as likely to provide seizure relief as are extensive resections (Awad, Katz, Hahn, Kong, Ahl & Luders, 1989). But, it is unclear whether the locations selected for the limited resections performed in these studies were accurate enough, and that by applying new knowledge and techniques to EEG analysis, limited resections of carefully selected tissue may provide good seizure relief and minimal clinical sequela for some patients.

As noted, the general belief in the research community is that because of the smearing due to volume conduction, the extracellular source of EEG signals and the inhomogeneity of the cranium, that the EEG cannot be used to localize sources of brain electrical activity as accurately as MEG. However, for several years some authors have claimed that the comparisons to date have been unfair (Cohen & Cuffin, 1983; Nunez, 1986b). Cohen and Cuffin have pointed out that although the MEG appears to better localize sources than EEG (Brenner, Lipton, Kaufman & Williamson, 1978, cited in Cohen & Cuffin, 1983), this may be the result of measurement of activity in the preferred direction for MEG detection,

"Therefore the MEG localization is not truly much better; it is much better only in that particular situation." (Cohen & Cuffin, 1983 p.47). In addition, Nunez (1986b) has observed that the fairest comparison of MEG with EEG would be one in which a large number of EEG electrodes are used (i.e., a dense array); "Only then can it be claimed that the MEG adds information that would not have been more readily (and cheaply) available from additional EEG channels." (Nunez, 1986b, pp. 76-77).

Empirical studies using implanted dipoles *in vivo* have provided support for the position that the EEG may provide information of comparable quality to that provided by MEG. Using this *in vivo* model, Cohen and colleagues (Cohen et al., 1990) studied MEG and EEG localization errors in three patients. The sources were energized electrodes implanted for the purpose of seizure monitoring. Results showed that the average error for MEG localization of the sources was 8 mm. For EEG, the average error was 10 mm. The authors concluded that MEG offers no significant advantage over the EEG in localizing sources in the brain. This conclusion generated significant scientific debate (Wikswo, Gevins & Williamson, in press), leading to a consensus that more research is needed before the relative merits of the MEG and EEG techniques can be adequately established, and that without additional data, further debate is of no value (Wikswo et al., in press).

The present studies

In the present thesis mulitchannel interictal and ictal EEG data was analyzed using the single discharge approach and spatio-temporal dipole analysis. For two patients, interictal MEG data was also collected and analyzed using the equivalent methods for single discharge spatio-temporal analysis for

MEG data. In addition, MRI studies were obtained for each patient to use in the assessment of the relative accuracy of each procedure (interictal EEG, ictal EEG and interictal MEG) by plotting the source estimates on appropriate slices and evaluating in terms of either the location of a structural abnormality imaged on the MRI or by the location of the estimates with respect to anatomical structures in cases where the MRI was normal.

The rationale for investigating the specific questions of the present thesis is as follows:

The question of whether EEG data from dense electrode arrays produce source estimates which are more accurate than those from loose electrode arrays is derived from the speculations of some researchers (e.g., Nunez, 1986a) who believe that source estimates would be improved with dense electrode placement. Since the seizure data available for study in this thesis is from loose arrays, the issue of loose versus dense is extremely important.

As a method to validate the findings from loose and dense array source estimates, the putative sources will be plotted onto the patient's MRI images.

The question of whether source estimates derived from interictal and ictal data are similar is investigated in order to understand: a) whether the use of interictal data in source location studies is valid in all cases, and; b) to look at the theoretical question of the relationship between interictal and ictal sources.

Objective

As stated, the purpose of the present thesis is to answer the following questions:

1. Empirical - *Are source localizations obtained using interictal (II) EEG data - either loose array or dense array - and MEG data similar. If not, is either*

form of II EEG, loose or dense, consistent with MRI?

Three sets of comparisons will be made to address this question:

a. Sources located with a loose array of electrodes, i.e., standard 10-20 EEG, will be compared to sources located using a dense array (concatenated data from 10-20 and interpolated electrode locations) of active electrodes.

b. For patients for whom MEG was available, sources located with both forms of EEG (loose and dense) will be compared to those obtained with MEG.

c. Sources located with both forms of EEG and MEG will be compared with MRI.

If the EEG and MEG sources are similar - within the error estimated by Cohen et al. (1990) - then one can generalize from the non-physiologic activation used in the modeling studies by Cohen (Cohen et al., 1990), and Cuffin (Cuffin et al., 1990) to the physiologic sources of abnormal as well as normal brain activity.

If source localizations using EEG and MEG differ, in what way do they differ? Further, even if EEG and MEG sources differ is there any consistency with MRI since one cannot necessarily assume a single source of epileptogenic activity. If the sources are different, this would suggest that non-physiologic activation interacts with brain tissue in such a way that it does not represent a good mimetic for true brain activity. One might also suggest from this that a better approach to modeling experiments would be the use of animal preparations in which the neuronal populations involved in the generation of surface fields and potentials can be mapped intracranially.

2. Theoretical - *Are sources of ictal and interictal discharges from epileptic brains similar, and if not is there any systematic relationship which can be revealed?*

Two comparisons will be made:

a. Sources obtained from loose array II data will be compared with sources obtained with loose array Ic data.

Because the ictal data available for the present study is collected in a hospital environment in which loose array electrode placements are used, this comparison depends on one of the following answers to the first empirical question: (i) loose array II EEG = MEG, or (ii) loose array II EEG = MRI. If sources of interictal and ictal activity are similar or one or the other is supported by convergence from MEG and/or MRI, then support is provided for the common practice of the use of interictal discharge in source location studies. If the sources prove to be different in a non-systematic manner, then it will suggest that care is needed in the generalization of findings from interictal to ictal studies, and in the use of interictal data for clinical localization purposes.

b. Sources obtained from loose array Ic EEG will be compared to MEG and MRI. This comparison is worth making even if the II loose EEG studied in the first question does not indicate similar sources as dense EEG, MEG or MRI. This is because, as stated in the introduction, there is neither agreement as to whether the sources of II and Ic discharges are the same or different, nor is there agreement on which is the better measure to use, and it is possible that one or the other is represented more or less accurately at the scalp.

VII. Method

Interictal EEG

Procedure. Interictal EEG events were collected from four patients with complex partial epilepsy. A Bio-logic Systems Corporation Brain Atlas III computer was used for data collection.

Due to a limited number of data collection channels, 10-20 and interpolated data could not be collected simultaneously, thus, data were collected separately using standard 10-20 electrode placement and interpolated electrode placement for construction of dense electrode arrays. Dense electrode arrays were created by concatenating (adding the data) from 10-20 and interpolated arrays during off-line analysis.

For the standard 10-20 data collection gold-plated Grass electrodes were placed in accordance with the International 10-20 system (Jasper, 1958). For the interpolated data collection, electrodes were placed at exact midway points between 10-20 positions, at surface sphenoidal positions bilaterally, and at positions intermediate to the sphenoidal sites and fronto-temporal electrodes. All electrodes were referenced to Cz. Patients sat in a reclined chair and were asked to relax with their eyes closed. Their state varied from alert relaxation to light sleep. The EEG was visually monitored continuously, and upon detection of interictal epileptiform events the computer was triggered by the experimenter to store the two seconds of data prior to the trigger. The amplified EEG signals were digitized at 200Hz with a bandpass at .5-70Hz and stored to disk. Fifty trials were collected for each patient. During the data collection for one patient

(D.P.) intermittent equipment problems made it necessary for the removal of one data channel (P3) prior to analysis.

Analysis. Data collected using10-20 electrode placement, interpolated electrode placement and the concatenation of these placement systems were analyzed. In off-line analysis contour maps of the electric potentials were constructed for equidistant projections on a map of the head. In conjunction with plots of the wave forms, these maps were used to select discharges which were free from eye and other movement artifacts and shifts of the baseline. For each of the 10-20 and interpolated recordings, five to six analyzable events (those free from artifact) were identified for each patient. An initial examination of the data from both 10-20 and interpolated collections suggested that these data could reasonably be combined to form a dense array. For the purposes of producing the equivalent of a dense array, events were visually selected from the 10-20 and interpolated data, aligned around the apex of the spike or sharp wave in each trial, concatenated, and the data saved to a separate file for analysis.

Within the two seconds of data collected for each trial, a discharge represented only a small portion of activity. Thus, windows of time within the data were selected for the estimation of underlying sources. In most cases that window was 130 msec in length surrounding the peak of the spike or sharp wave, but since epileptiform discharges vary in duration some windows were longer (150 msec). Over the course of the window, the data were analyzed with a spatio-temporal dipole analysis (Scherg & von Cramon, 1989). The limits of the windows were selected on the basis of the onset and termination of the discharge. Where these points were unclear in the data, dipole analysis was repeated several times with adjustments of the window limits to earlier and later

portions of the data. Source solutions were stable over up to 50 msec as long as the major components (the onset trough, the peak of the spike or sharp wave, and the following slow wave) remained within the window of analysis.

The sources were modeled as equivalent dipoles that varied over time with respect to current strength (source activity), but were fixed in their locations and orientations. The number of dipoles necessary to best explain the data for each discharge was determined by performing several fits assuming two, three or four sources. Criteria for acceptance of each dipole were its source activity contribution (current strength over the epoch), its contribution to the variance accounted for, and in some cases its compatibility with known anatomy. Those sources which did not meet these criteria were rejected.

Final locations and strengths of the dipoles were determined in an iterative least squares algorithm based on the simplex method (Caceci & Cacheris, 1984). The differences between observed P_{obs} and theoretical P_{the} potentials, $SS_{diff} = \sum_{i=1}^{n} \left(P_{obs} - P_{the}\right)^2$, were calculated following each iteration until convergence was determined by failure to meet a minimum change in a residual variance criterion $\left(SS_{diff} \langle 0.01\% \right)$. The extent to which the theoretical dipoles adequately account for the observed data was expressed as a residual variance, or % error, following the fit.

Following analysis of the single "trials" the discharges for each patient were averaged using the maximum second derivative as the center point for each trial. Once the centre point was identified, and thus the discharge aligned, the averaging was performed by adding data points, for example, time point 1 for trial 1 and time point 2 for trial 2, and then dividing by the number of trials used

for the average. In this way, randomly distributed background activity should be reduced. Sources were then modeled for the average data using the same techniques as described for the single events.

Interictal MEG

Procedure. Magnetic fields accompanying epileptiform interictal EEG events were recorded from two patients with intractable complex partial epilepsy at CTF Systems, Inc., Port Coquitlam, using 64 1st order gradiometers housed within a helmet shaped dewar. The helmet was of a design such that the recording channels covered the scalp surface and extended down 103° from the vertex of the head. In addition to the 64 MEG channels, this system also contained reference channels that allowed a software computation of the 2nd order gradient (Cheyne et al., 1992).[15] While sitting in a non-magnetic chair the patient's head was placed in the dewar and they were asked to relax with their eyes closed. Their state varied from relaxed alertness to spontaneous light sleep. The position and orientation of the patient's head with respect to the gradiometers was determined by affixing coils to three fiduciary points on the scalp, one at the nasion, and one each at the right and left preauricular points. Head location was determined at the beginning of each data collection session by energizing these coils and recording their spatial location. For identification of EEG interictal events, electrodes were applied at standard 10-20 positions at sites considered from previous EEG recordings to be the most likely sites for

[15] At the time these data were collected the MEG recording system was in the last stages of development. With the final system one is able to form the 3rd order gradiometer response. Other experiments using the present system indicated that, in the presence of strong proximal magnetic noise (in this experiment the motion of a strong magnet), formation of the 3rd gradient is necessary for the extraction of signal from noise, but in the presence of low magnetic noise from nearby sources, the 2nd order gradient is sufficient (Cheyne, Vrba, Crisp et al., 1992).

recording epileptiform events. Six channels of EEG were visually monitored on a Nihon Kohden EEG instrument. At the occurrence of an epileptiform discharge, one channel of EEG activity was digitized in response to a manual trigger by the experimenter. Two seconds of MEG and EEG data preceding and two seconds following the button press were digitized to disk as trials. Fifty trials were collected for each patient.

Signals were digitized at a rate of 625Hz and band passed from DC-70Hz for MEG and 0.5-70hz for EEG. The MEG data were low-pass filtered to 35Hz off-line in order to reduce high frequency noise.

Analysis. Analyses of individual discharges and averages of the discharges were performed separately. Individual discharges were selected on the basis of visual inspection of the magnetic field maps of the equidistant projection map. Despite the fifty trials collected, only five discharges for one patient (K.O.) and three for the other patient (D.P.) were considered suitable for modeling. Data collected in the remaining trials was either contaminated by artifact, or the field distribution did not permit dipole analysis because only one extreme was detected (suggesting that the recording coils did not extend far enough around the head).

The localizations were performed using routines which include contributions of non-radial magnetic fields due to volume currents by the method of Grynszpan and Geselowitz (1973). The sources were modeled as equivalent dipoles with fixed locations and strength varying over time. The number of dipoles and adequacy of fit was determined with the same procedures used for the interictal EEG (see pp.34-35).

Following analysis of the single events, averages were formed from the same discharges using the maximum second derivative (apex of the spike or sharp wave) as the center point for each trial. Sources were then modeled using the same technique as for the single events.

Ictal EEG

Procedure. Ictal EEG events were collected from four patients as part of a pre-surgical "work-up" at Vancouver General Hospital (VGH), Vancouver, B.C. *Monitor* software (© Systèms Stellate Enregistré) was used to collect the data on an IBM compatible computer. The data of one or two seizures from each patient were made available to the experimenter by Drs. S. Purves and D. MacDonald for use in the present study. A conversion program was developed at Simon Fraser University by D. Cheyne to read the data into the analysis programs.

As reported by the technologist, the seizure unit at VGH used the following procedures for collection of the original data. Gold plated Grass electrodes were placed in accordance with the International 10-20 system (Jasper, 1958) with the addition of surface sphenoidal electrodes bilaterally, and the exception of Fz and Pz electrodes. All electrodes were referred to Cz. Recording continued for several days until enough seizure events were captured for diagnostic utility. The occurrence of seizures was detected either by the patient "marking" the event for the computer by pressing a button when experiencing warning of a seizure, or by witnesses of the seizure, or by peak detection software. Sixteen channels of EEG band passed between 1.0 and 30hz were digitized at 200Hz and stored to disk.

Analysis. One seizure from each patient was found to be noise-free enough for dipole analysis. Seizure data from two patients (K.O and D.P.) contained continuous artifact in the Fp1 channel. Both Fp1 and Fp2 were consequently excluded from the analysis because it was found in initial analyses that when only Fp1 was removed, unilateral eye-movements led to untenable results. Spatio-temporal dipole fits were obtained for epochs of 120 msec at the onset of the EEG seizure discharge. The fit-routines were as described for the interictal EEG analysis.

MRI dipole plots

Films of MRI scans were obtained from Vancouver General Hospital and were digitized for further analysis. The predicted dipole sources for the interictal EEG and MEG and the ictal EEG were plotted as follows. For each patient those scans were selected in both axial and coronal directions that best summarized fits in the X (anterior-posterior), Y (right-left), and Z (rostral - caudal) directions. Fits required between two and four dipoles. As mentioned, since the number of sources cannot be known *a priori*, several fits of the data were attempted. Following convergence, the solutions were tested for goodness of fit as measured by variance accounted for and the contribution of each dipole to the source activity. In this manner, the solution which best represented the observed data with the minimum number of sources was accepted. In some cases, however, some dipole locations were anatomically unreasonable. In the EEG these anatomically unreasonable fits suggested activity in the optic nerve. The tables presented in the results section, and the sources plotted on the MRIs, include only those dipoles which were consistent with known anatomy.

VIII. Results

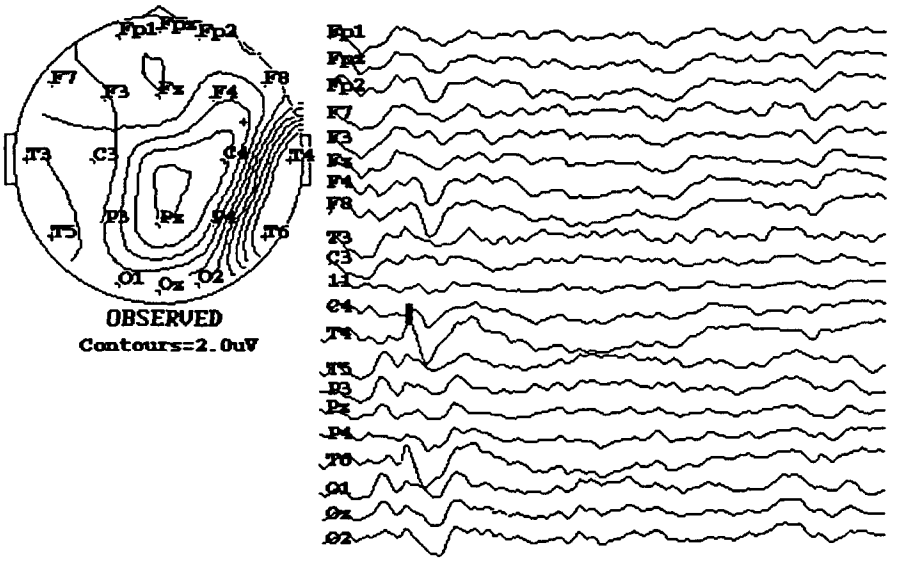
Case 1 (J.S.)

This patient was a 16-year-old female with intractable right temporal lobe epilepsy of lateral origin resulting in complex partial seizures. At three months of age she had experienced a series of atypical febrile convulsions and was placed on Depakene™ until 14 years of age. When the Depakene™ was withdrawn the patient experienced a convulsion and has been pharmaco-resistant ever since, experiencing 3-4 seizure events per week during waking hours. During seizure monitoring at VGH, her interictal EEG was reported to be very abnormal showing frequent high amplitude spike and poly spike discharges with a wide distribution over the right temporal lobe, but phase reversing at the right sphenoidal electrode. Considerably less frequent, independent sharp waves were also recorded from left temporal lobe regions of this patient. Following the monitoring of thirteen seizures, many of which were atypical of her day time seizures, it was concluded by Dr. S. Purves, that her seizures were of right lateral temporal origin. Some left temporal lobe involvement with seizure activity was also reported, however, left temporal seizures were preceded by an electrographic right temporal onset. The patient's MRI indicated "hyperintensity" in the temporo-occipital region of the right hemisphere with "thinned cortex and unusual convolutions" in the same area. Focal cortical dysplasia in the right posterior temporal and temporo-occipital areas was thought to best explain these findings diagnostically (report of Dr. J. Adler and Dr. D. Graeb, March, 1992).

Interictal and ictal EEG events from this patient were analyzed, the MEG equipment being unavailable for use at the time of data collection.

Interictal EEG. All electrodes were referenced to Cz. Twenty-one scalp EEG electrodes, standard 10-20 including Fpz, Oz and an electrode interpolated at the intersection half way between F4-T4 and F8-C4, showed right side discharges of spike and slow wave activity and some polyspike events (see Figure 3a). As shown in Figure 3b similar discharges were represented by recordings from an interpolated montage of twenty electrodes, except the discharges appeared topographically more anterior than those recorded with 10-20 electrodes.

(a)



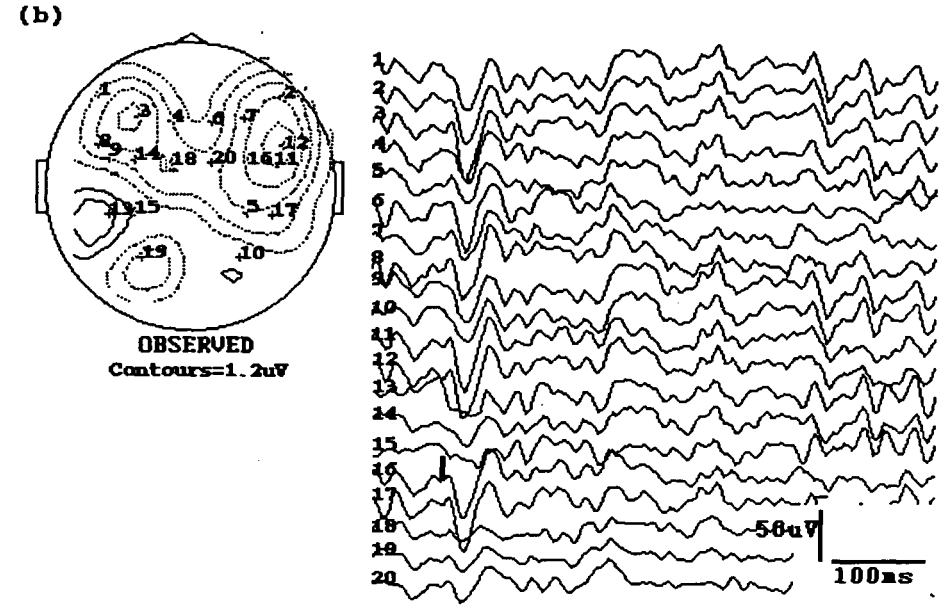


Figure 3. Electrode positions, waveforms and single time point contour maps for subject J.S. (a) for 10-20 electrode positions, and (b) interpolated electrode positions. The cursors indicate the time point at which the maps were constructed.

Out of 50 trials each of 10-20 and interpolated electrode positions, four epileptiform events were found to be analyzable with dipole fitting routines for the 10-20 positions and three for the interpolated positions. The data from 10-20 and interpolated collections were concatenated and dipole locations estimated for the total positions. The topography of the concatenated data, mapped at the peak of the discharge, is shown in Figure 4 where the activity is dipolar at the right anterior central scalp region

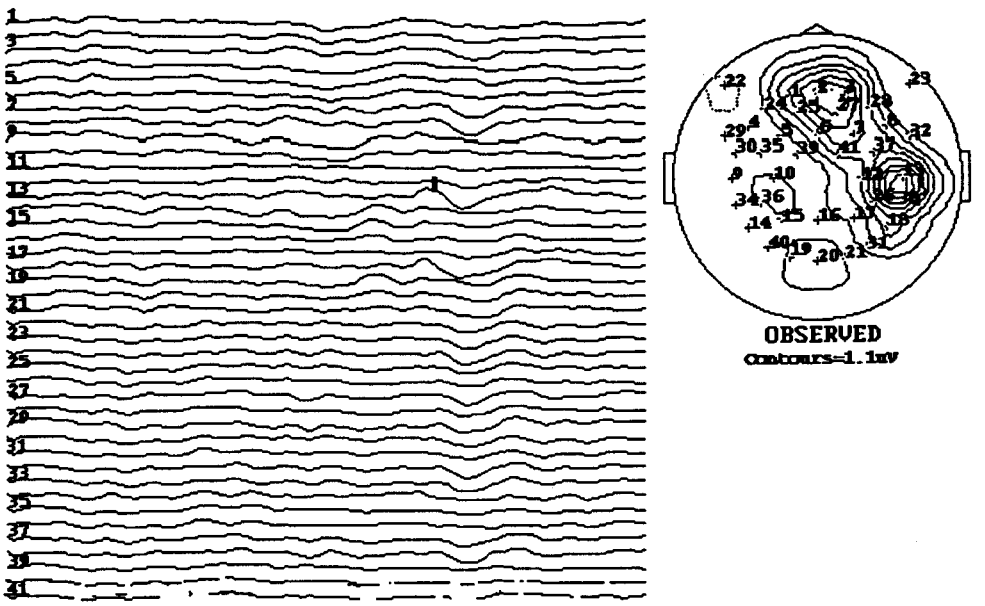


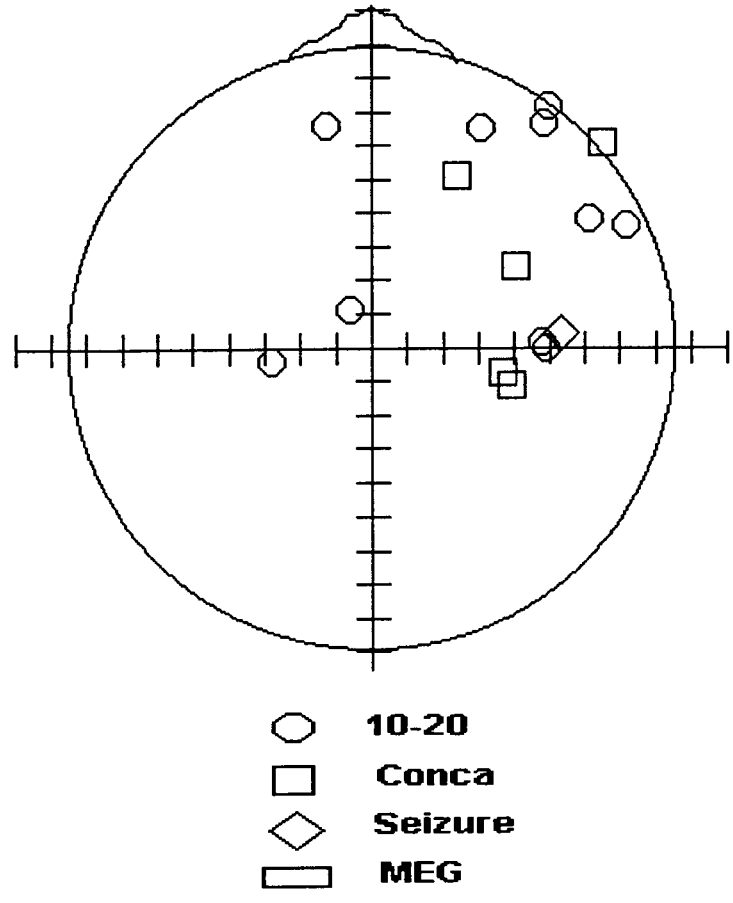
Figure 4. Electrode positions, waveforms and single time point maps for the concatenated data for subject J.S. The cursor indicates the time point at which the map was constructed.

Table 1 indicates the plotted dipole fits (sources) obtained for the 10-20, concatenated and seizure discharges in X,Y,Z co-ordinates. The X dimension represents the anterior-posterior axis with positive X values being anterior to the origin and negative X values posterior to the origin. The Y dimension represents left to right with positive Y values being to the left of the origin and negative values to the right. The Z dimension represents the superior-inferior (top to bottom) dimension with positive values being superior to and negative values being inferior to the origin.

Table1

Fitted dipoles for 10-20, Concatenated (Conca) and Seizure (Seiz) data, Subject J.S.

	Position		
	X	Y	Z
10-20			
1	*7.33*	*-2.31*	*10.02*
	0.99	*-4.01*	*0.42*
2	*7.44*	*-4.09*	*8.60*
	1.92	*1.36*	*9.14*
	0.80	*-4.14*	*-0.06*
3	*7.40*	*2.03*	*1.27*
	4.65	*-5.33*	*9.06*
	4.46	*-6.39*	*3.34*
4	*7.97*	*-4.19*	*8.91*
	0.38	*-3.58*	*-0.45*
Conca			
1	*5.90*	*-1.59*	*8.19*
	-0.34	*-3.15*	*9.94*
2	*6.91*	*-5.74*	*6.17*
	0.09	*-2.88*	*0.12*
3	*3.23*	*-3.29*	*-1.22*
Seiz			
	0.42	*-5.33*	*1.12*



Sources for the 10-20 events were estimated to be occurring in both the right and the left hemispheres and were widespread including mid temporal and anterior temporal regions laterally as well as medially. These sources are illustrated as plots on the appropriate MRI slices in Figure 5a. Despite indications of left hemisphere involvement in the interpolated data in the topographic maps (see Figure 3b), the concatenated (dense) data revealed only right hemisphere involvement, although again, these sources are spread over mid and anterior lateral and medial brain regions. When one considers depth, as illustrated in Figure 5b, the extent of dispersion of computed sources becomes even more striking with discharges appearing to arise from superior and inferior sites.

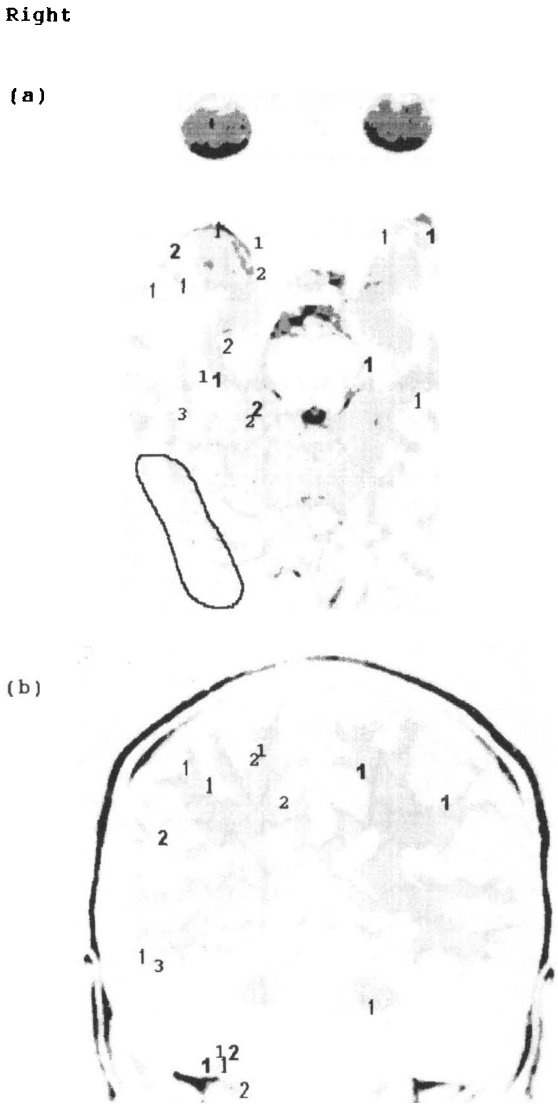


Figure 5. MRI for subject J.S. with dipole positions plotted for (a) axial, and (b) coronal slices. "1" indicates dipoles for 10-20 interictal data, "2" indicates dipoles for concatenated interictal data, and "3" indicates dipoles for seizure data. Text forms within numbers indicate particular epileptiform events. The area of MRI abnormality is outlined in black.

Ictal EEG. Dipole localization of data collected during seizure (see Figure 6) at time points early in the ictal event, places the source of the discharge in the lateral part of the midtemporal lobe (see Figure 5a). As illustrated in Figure 5b, the depth is consistent with what might be expected given her MRI abnormality and the character of her clinical seizures.

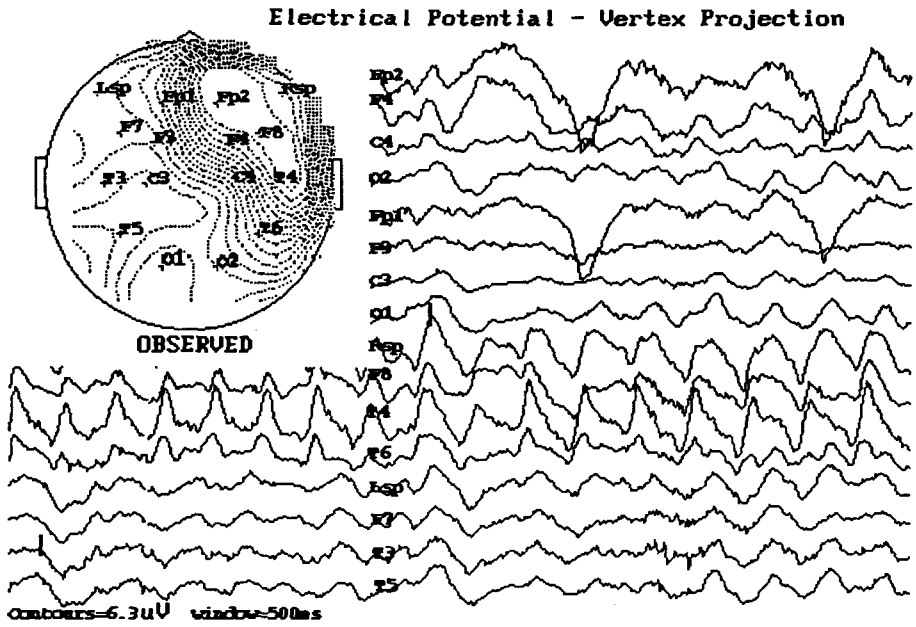


Figure 6. Electrode positions, waveforms and single time point contour map for seizure data from subject J.S. The cursor indicates the time point at which the map was constructed. (Refer to figure 5 for dipole location)

Case 2 (T.B.)

The patient was a 26-year-old female with intractable epilepsy of left temporal lobe origin. A possible history of febrile seizures was reported, however, a more definite history of recurrent seizures since childhood was

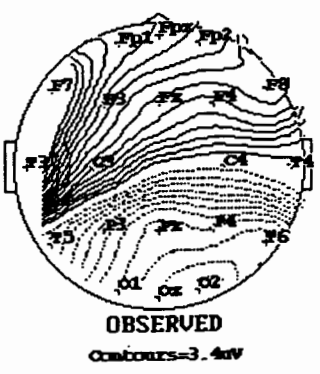
obtained during clinical examination by her neurologist. At that time the patient reported experiencing about 4 seizures per month. Interictal EEGs showed left mid to anterior temporal sharp waves which were accentuated during sleep. During seizure monitoring at VGH, her interictal EEG showed left temporal discharges with frequent polymorphic delta activity from the same region, however, some right temporal sharp waves were also seen during sleep. Following monitoring of 6 seizure events, it was concluded by Dr. D. MacDonald that her seizures were of left temporal origin. An HMPAO (D, L-Hexamethyl, propyleneamine oxime tagged to technicium) scan performed post-ictally revealed decreased perfusion to the left temporal lobe. The MRI scan was reported be within normal limits but to show a mild asymmetry in the size of the temporal horns with a "minimally smaller" left hippocampal complex as compared to the right.

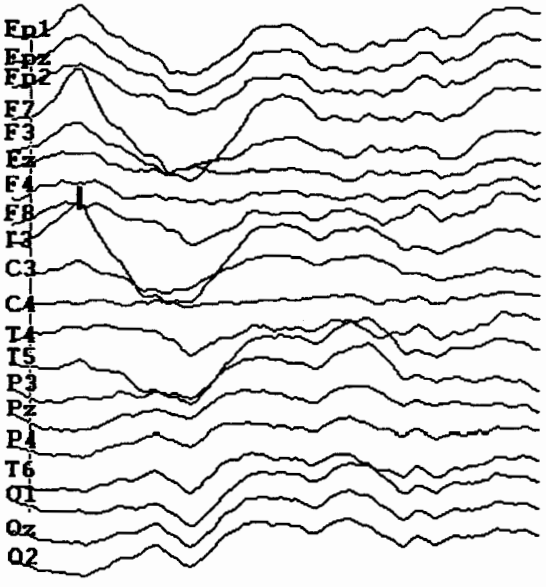
After the EEG data were collected for the present study, the patient underwent a left temporal lobectomy in which 4cm of middle temporal gyrus, 2.5 cm of superior temporal gyrus and 3cm of hippocampus from the tip of the temporal horn were removed. Pathological examination revealed hippocampal sclerosis and ectopic grey matter in the white matter of the temporal lobe. During the surgical procedure itself, pre-excision electrocorticography (ECoG) demonstrated epileptiform activity in the anterior temporal contacts, the superior and middle temporal gyrus and in the subtemporal contacts. Post-excision ECoG demonstrated some small "spikes" at the superior temporal gyrus.

For the purposes of this study interictal and ictal EEG events from this patient were analyzed. The patient underwent temporal lobectomy before the MEG equipment was available.

Interictal EEG. All electrodes were referenced to Cz. Twenty scalp EEG electrodes, standard 10-20 including Fpz and Oz showed left mid to anterior temporal lobe spike and slow wave or sharp and slow wave activity (see Figure 7a). As shown in Figure 7b discharges of similar, although more constrained, topography were recorded with the interpolated electrodes which included surface sphenoidals.

(a)





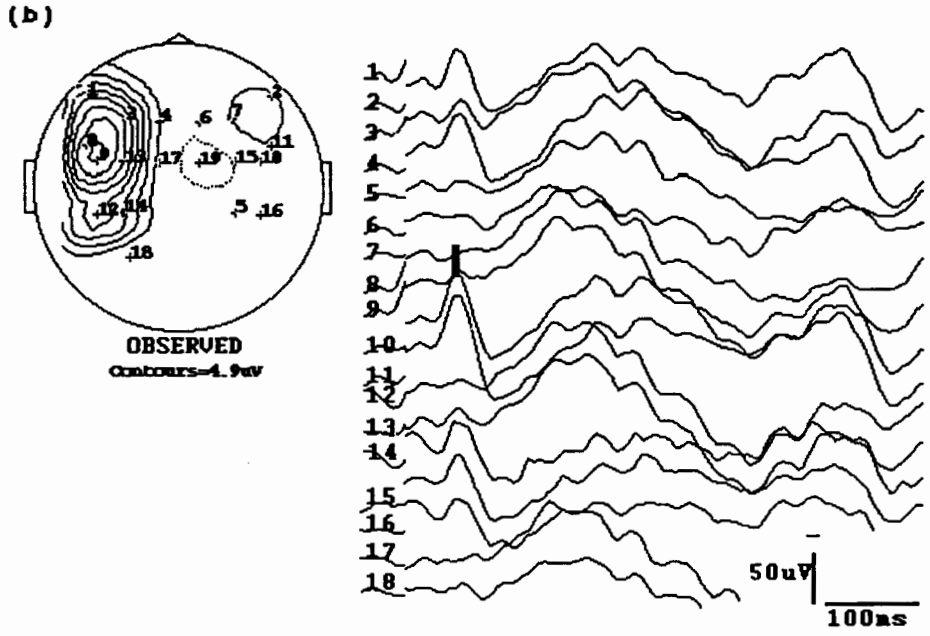


Figure 7. Electrode positions, waveforms and single time point contour maps for subject T.B. (a) for 10-20 electrode positions, and (b) interpolated electrode positions. The cursor indicates the time point at which the maps were constructed.

Out of 50 trials each, 10-20 and interpolated electrode positions, five discharges were found to be analyzable with dipole fitting routines for the 10-20 positions and five for the interpolated positions. The data from 10-20 and interpolated positions were concatenated and showed a similar distribution of activity as seen in the unconcatenated data (Figure 8).

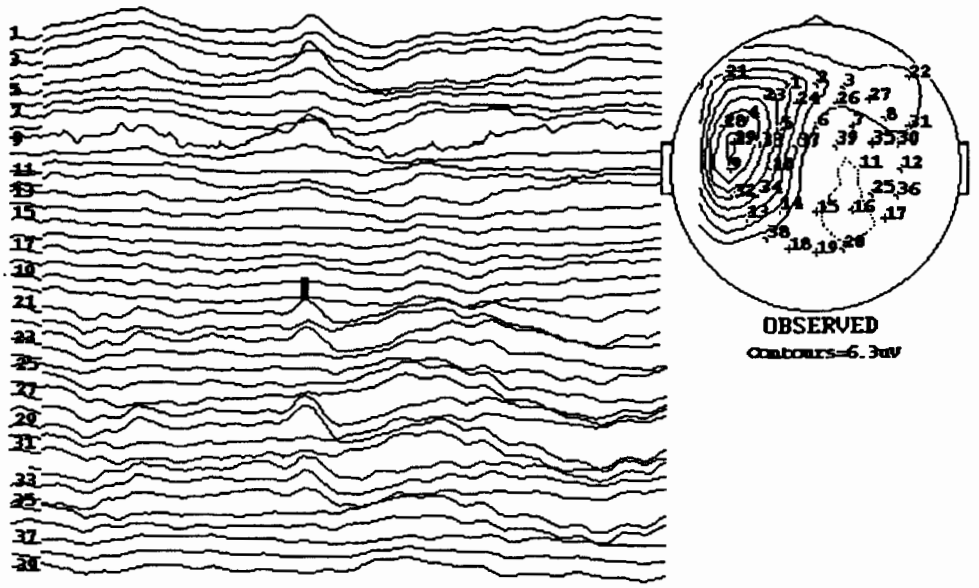


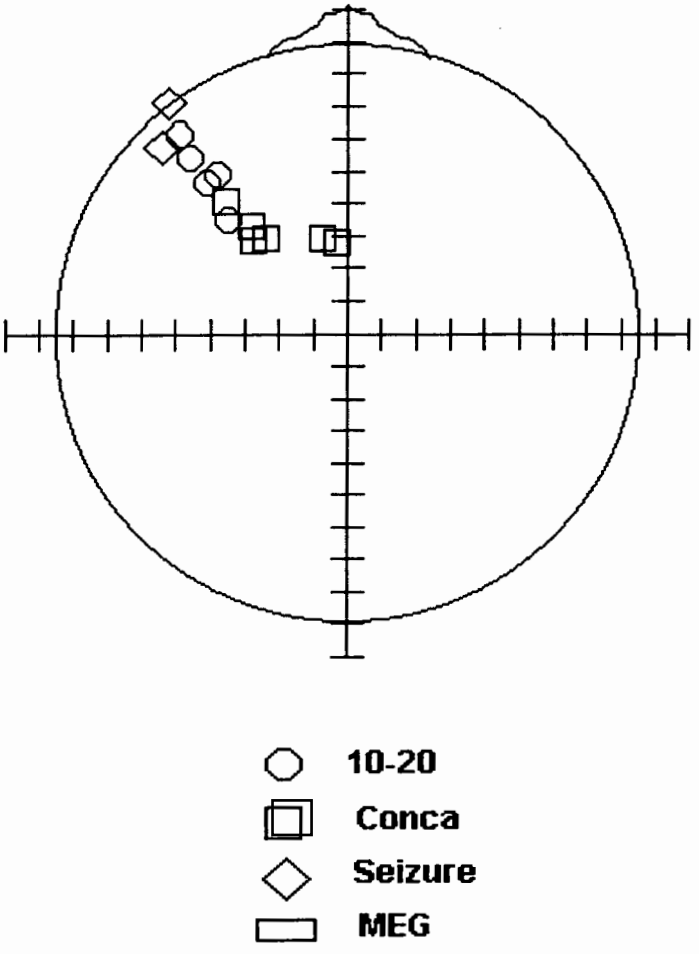
Figure 8. Electrode positions, waveforms and single time point maps for the concatenated data for subject T.B. The cursor indicates the time point at which the map was constructed.

Table 2 indicates the plotted dipole fits (sources) obtained for the unconcatenated, concatenated and seizure discharges in X,Y,Z co-ordinates. The X dimension represents the anterior-posterior axis with positive X values being anterior to the origin and negative X values posterior to the origin. The Y dimension represents left to right with positive Y values being to the left of the origin and negative values to the right. The Z dimension represents the superior-inferior (top to bottom) dimension with positive values being superior to and negative values being inferior to the origin.

Table 2

Fitted dipoles for 10-20, Concatenated (Conca) and Seizure (Seiz) Data, Subject T.B.

	Position		
1	*5.45*	*4.89*	*3.39*
2	*4.30*	*4.27*	*1.12*
3	*6.94*	*5.69*	*2.07*
4	*6.27*	*5.36*	*1.81*
5	*5.74*	*4.56*	*0.39*
Conca			
1	*3.76*	*1.49*	*6.49*
2	*3.68*	*3.50*	*2.79*
3	*3.72*	*3.17*	*1.31*
	4.13	*3.61*	*0.90*
4	*4.93*	*4.31*	*0.23*
5	*3.62*	*1.06*	*3.53*
Seiz.	*5.77*	*5.41*	*1.54*
	7.08	*5.20*	*7.07*



Sources for the 10-20 events were estimated to be occurring in the left anterior temporal lobe (Figure 9a and b). Eight sources were estimated to be arising from areas adjacent to rather than within brain tissue. However, the

estimated error for localization using EEG data is 2cm (Cohen et al., 1990), and, since the calculated sources are 1-2 cm outside the brain tissue, these results fall within measurement error. Sources computed for concatenated data were within the margins of the imaged temporal lobe on the axial section (Figure 9a.) and slightly more widespread in terms of depth (Figure 9b.) than the sources from the 10-20 data. The averaged data for 10-20 recordings shows a source at the left lateral mid-anterior temporal lobe, with the concatenated data showing a more medially placed source in the same region of the lobe.

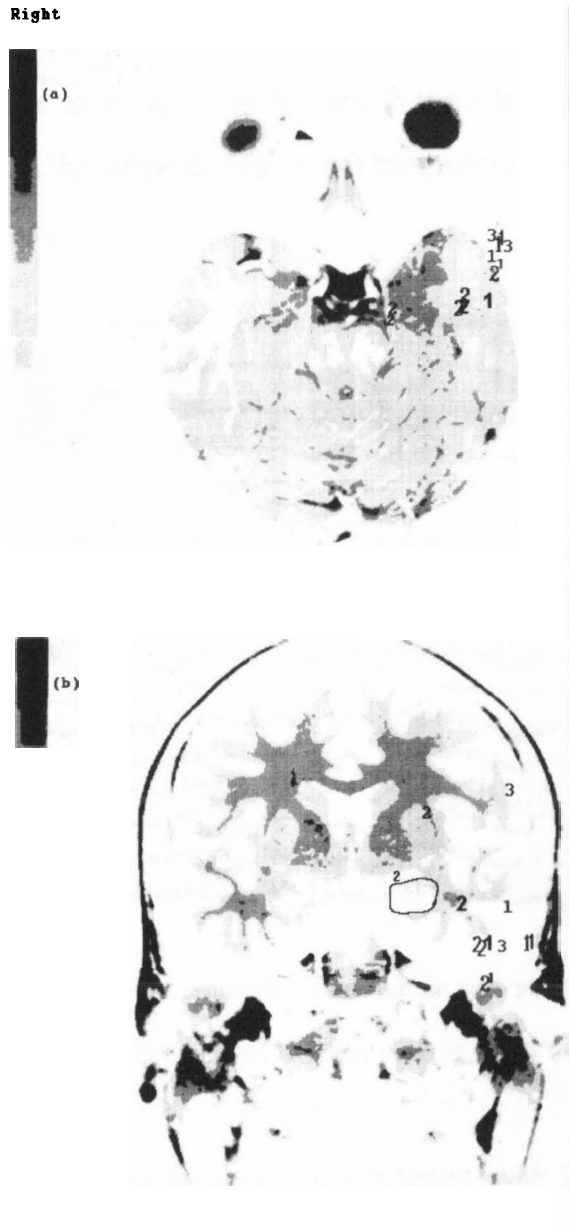


Figure 9. MRI for subject T.B. with dipole positions plotted for (a) axial, and (b) coronal slices. "1" indicates dipoles for 10-20 interictal data, "2" indicates dipoles for concatenated interictal data, and "3" indicates dipoles for seizure data. Text forms within numbers indicate particular epileptiform events. The area of MRI abnormality is outlined in black.

Ictal EEG. Using seizure data recorded from the electrode positions illustrated in Figure 10, dipole localization from early in the ictal event places the sources of the discharge in the anterior-lateral left temporal lobe and in the left supra-sylvian gyrus (see Figure 9).

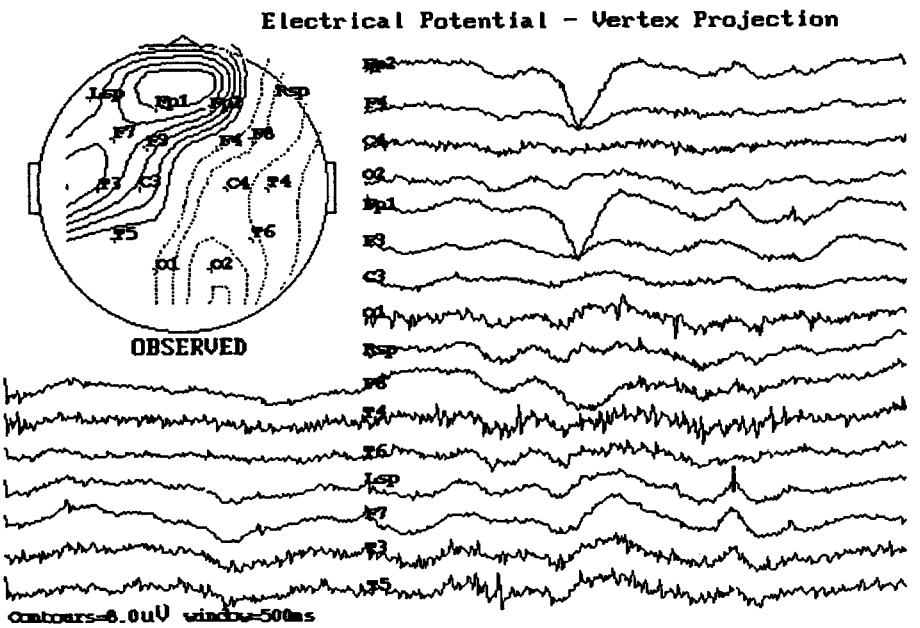


Figure 10. Electrode positions, waveforms and single time point contour map for seizure data from subject T.B. The cursor indicates the time point at which the map was constructed.

In general, these findings are consistent with ECoG tracings at the time of surgical resection in which spike discharges were recorded from the anterior, middle and superior gyri of the left temporal lobe and from the "inferior mesial temporal structures" (Dr. D. MacDonald).

Case 3 (K.O.)

This patient was a 30-year old male with intractable epilepsy of temporal lobe origin. The etiology of his seizures was reported to be unclear, but the first episode was a grand mal seizure in 1987. Since that time the patient has not experienced Grand Mal but does have complex partial episodes which are fairly frequent occurring 5-10 times per month. Clinical interictal EEG recordings showed left anterior-mid temporal epileptiform discharges with some independent right anterior-mid temporal spikes and sharp waves.

Following clinical monitoring of 6 seizures from this patient the hospital records note that bilaterally independent anterior temporal EEG discharges were recorded interictally, but that the right sided events tended to appear during sleep while those from the left side were state independent. The state independent nature of the left sided discharges was believed to favour a left sided epileptogenesis. Ictal EEG recordings were suggestive, but not conclusive of seizures originating in the left temporal lobe.

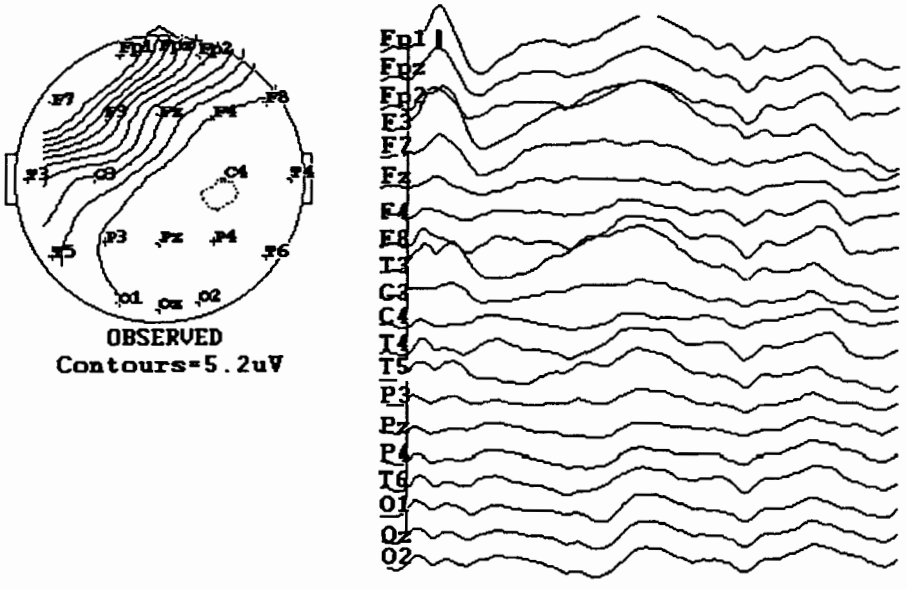
A post-ictal HMPAO scan showed hypoperfusion in the left temporal lobe and right cerebellum. These findings were interpreted as indicating epileptogenesis from the left temporal lobe with right cerebellar and right basal ganglia diaschesis. MRI was within normal limits.

For the purposes of the present study, data were collected with interictal EEG and MEG, and ictal EEG.

Interictal EEG. All electrodes were referenced to Cz. Twenty scalp EEG electrodes, standard 10-20 including Fpz and Oz showed discharges which were at times anterior left temporal (see Figure 11a) and at times mid left temporal (see Table 3). On one occasion a left mid temporal discharge was preceded by

a right sided discharge also from the mid temporal region. It was not possible to tell whether these events were independent or not. As shown in Figure 11b, using the interpolated electrodes, the discharges recorded were more frontal in topography with maximal activity at the sphenoidal positions; these were bilateral on all three occasions. The peak voltage was at a maximum on the right in one discharge, the left in another and was equal for the left and right in the third.

(a)



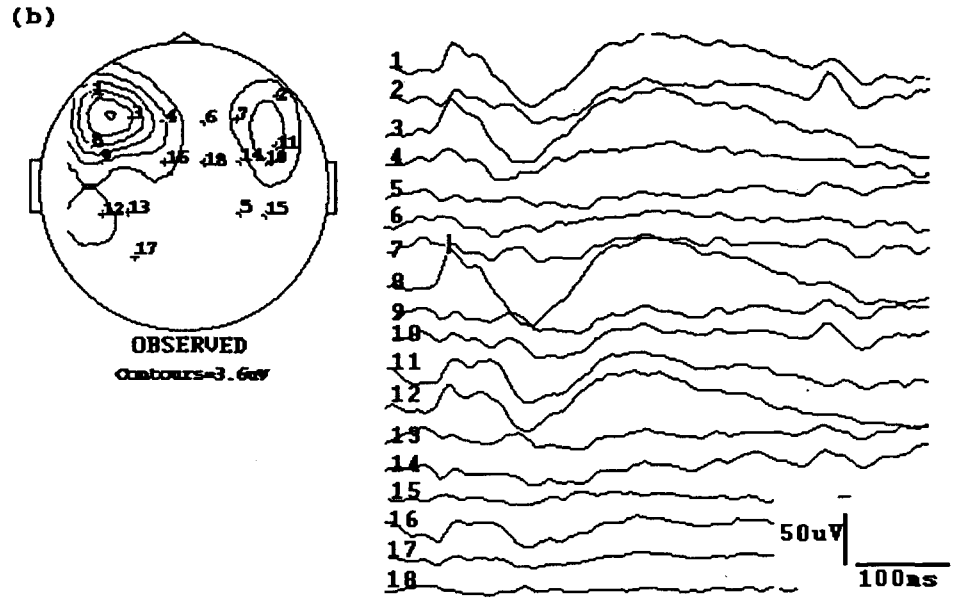


Figure 11. Electrode positions, waveforms and single time point contour maps for subject K.O. (a) for 10-20 electrode positions, and (b) interpolated electrode positions. The cursor indicates the time point at which the maps were constructed.

Of fifty trials each of 10-20 and interpolated electrode positions, six discharges were found to be analyzable with dipole fitting routines for the 10-20 positions, and three for the interpolated positions. One 10-20 discharge was clearly right sided and this was analyzed for sources. The data from the left sided discharge 10-20 and interpolated collections were concatenated and dipole locations estimated for the total positions. The topography of the concatenated data is illustrated in Figure 12 where the activity is left sided and represents a dipolar distribution of activity at the anterior- mid temporal scalp region.

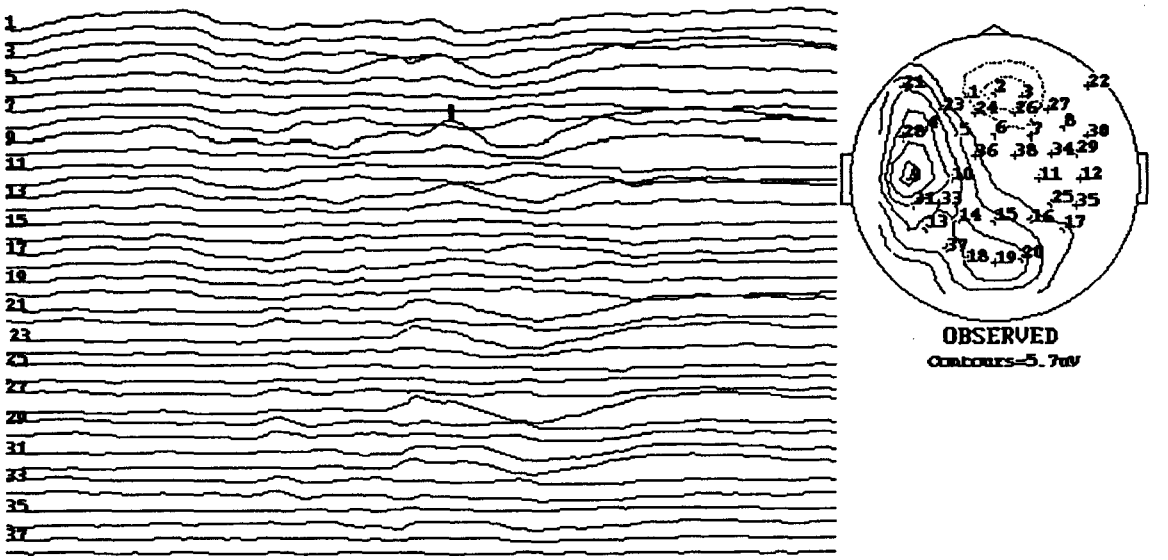


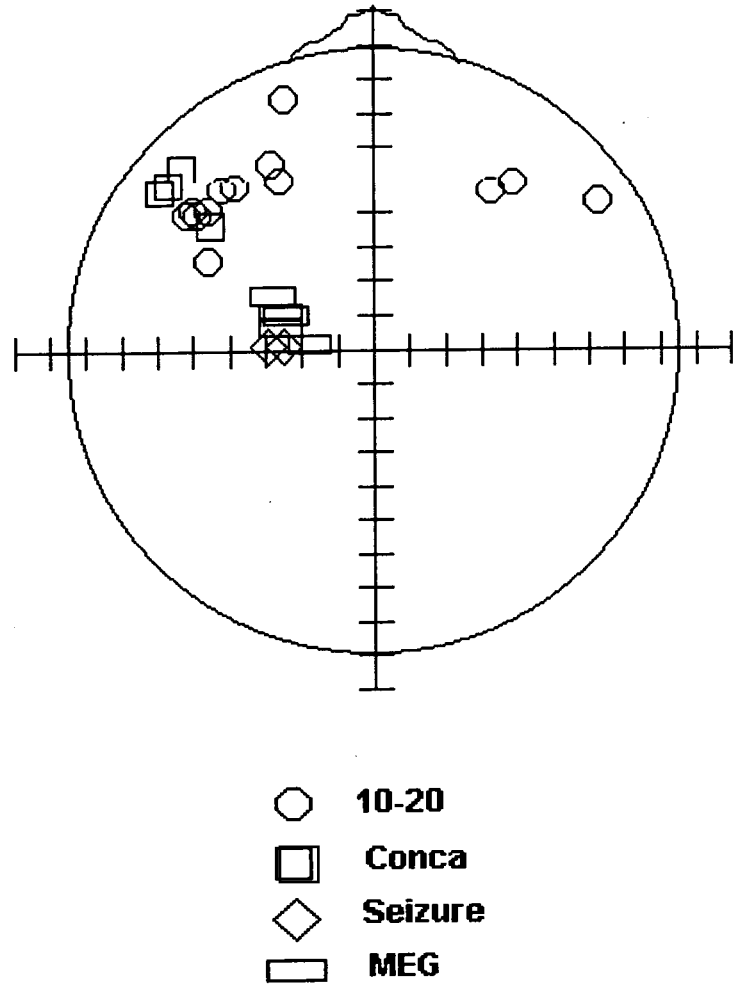
Figure 12. Electrode positions, waveforms and single time point maps for the concatenated data for subject K.O. The cursor indicates the time point at which the map was constructed.

Table 3 indicates the plotted dipole fits obtained for the unconcatenated concatenated and seizure discharges in X, Y, Z co-ordinates. The X dimension represents the anterior-posterior axis with positive X values being anterior to the origin and negative X values posterior to the origin. The Y dimension represents left to right with positive Y values being to the left of the origin and negative values to the right. The Z dimension represents the superior-inferior (top to bottom) dimension with positive values being superior to and negative values being inferior to the origin.

Table 3

Fitted dipoles for 10-20, Concatenated (Conca), Seizure (Seiz) and MEG Data, Subject K.O.

	Position		
	X	Y	Z
10-20			
Left			
1	*5.53*	*4.99*	*2.05*
2	*4.87*	*5.36*	*2.65*
	5.17	*-5.50*	*1.52*
3	*4.92*	*5.81*	*1.53*
	6.31	*3.64*	*1.49*
4	*5.57*	*4.65*	*2.97*
	8.23	*3.26*	*1.92*
5	*4.75*	*5.96*	*1.68*
	5.73	*-3.11*	*0.29*
6	*4.77*	*5.64*	*1.17*
	5.79	*3.40*	*1.61*
Right			
7	*3.38*	*5.34*	*0.70*
	5.45	*-2.51*	*0.33*
Conc			
a.			
1	*5.49*	*6.71*	*5.10*
2	*5.70*	*6.49*	*4.59*
	6.21	*6.10*	*4.97*
3	*4.47*	*5.33*	*9.35*
Seiz.	*0.09*	*2.92*	*7.81*



	0.10	*2.50*	*-0.90*
MEG			
1	*0.66*	*2.60*	*3.70*
2	*1.00*	*2.45*	*2.80*
	0.15	*1.80*	*4.90*
3	*1.60*	*2.80*	*1.80*
4	*1.10*	*2.60*	*2.50*

Sources for the 10-20 events (Figure 13a) were estimated to be predominately occurring in the anterior tip of the left temporal lobe, with three sources located in the right anterior temporal lobe. Similar results were found for the concatenated data except that all sources were predicted to be arising from the left (see Figure 13). Illustration of the depth of all interictal sources in Figure 13 shows them to be confined to regions of the temporal lobe.

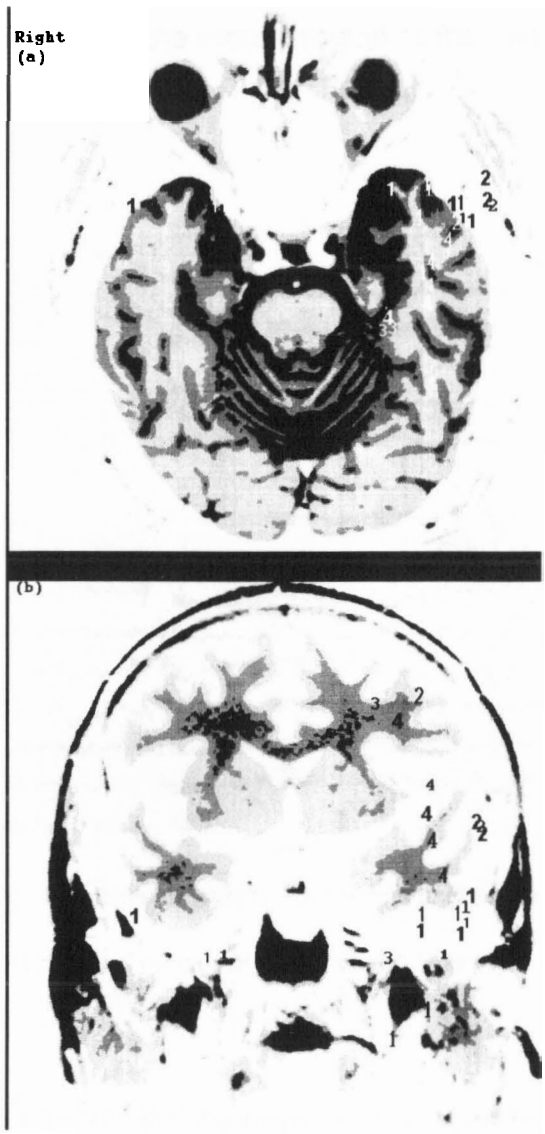


Figure 13. MRI for subject K.O. with dipole positions plotted for (a) axial, and (b) coronal slices. "1" indicates dipoles for 10-20 interictal data, "2" indicates dipoles for concatenated interictal data, "3" indicates dipoles for seizure data, and "4" indicates dipoles for MEG interictal data. Text forms within numbers indicate particular epileptiform events.

Ictal EEG. Using seizure data recorded from the electrode positions illustrated in Figure 14, dipole localization from early in the ictal event places the sources of

the discharge in the medial region of the mid left temporal lobe as shown in Figure 13a and b.

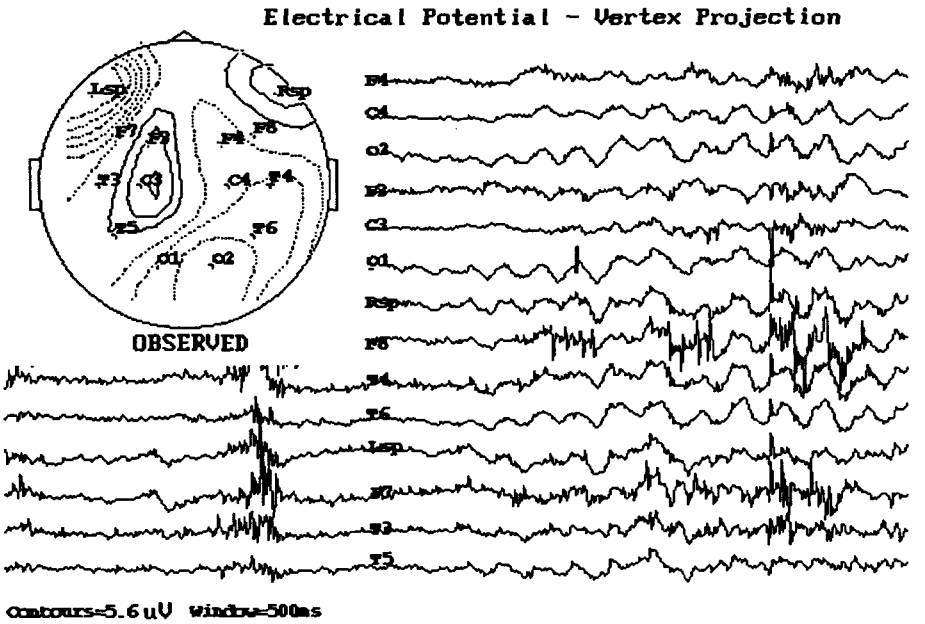


Figure 14. Electrode positions, waveforms and single time point contour map for seizure data from subject K.O. The cursor indicates the time point at which the map was constructed.

Interictal MEG. Of fifty trials of MEG data (discharges detected on EEG recordings), we were able to model four of the discharges with dipole analysis. Some MEG activity associated with EEG discharges was not organized as one would expect for an underlying dipole source, for a few discharges only one peak was recorded, and with the remainder the data were too noisy for analysis. Of the discharges analyzed, Figure 15 shows an example of a typical discharge, mapped at the point of the hard bar marker. The topographic distribution of the map suggests a dipolar source in the left anterior-mid temporal region.

Table 3 shows the estimated MEG source locations in X,Y,Z co-ordinates and these sources are plotted on the appropriate MRI slices in Figure 13. As can be seen (Figure 13a), the discharges appear to be arising from the middle region of the mid left temporal lobe. On the coronal section (Figure 13b) it is apparent that the sources are distributed around the superior region of the left temporal lobe with the exception of one dipole which is more superior.

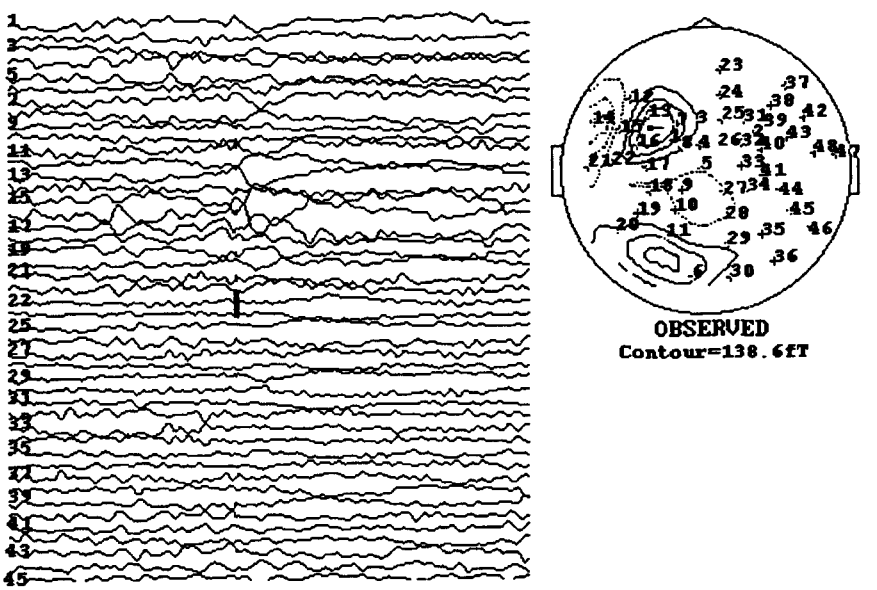


Figure 15. MEG sensor positions, waveforms and a single time point contour map for subject K.O. The cursor indicates the time point at which the map was constructed.

Case 4 (D.P.)

D.P. was a 31-year-old female with intractable complex partial seizures of right temporal onset. The patient experienced a febrile illness which may have been meningitis at age 1½ years. Her seizures apparently began around this time but became characteristic of her adult attacks when she was 18 years.

Around the time of the present study the patient was experiencing 12-16 seizures a month. Interictal EEGs performed during seizure monitoring at VGH showed independent bilateral spike and sharp wave discharges during the sleep and waking state. Temporal Intermittent Rhythmic Delta Activity (TIRDA) was recorded bilaterally but was most organized on the right side. Following recording of seven seizures, it was concluded that although not definitive, the seizures were probably originating from the right temporal lobe.

MRI showed an asymmetry of the hippocampal formations with the right being smaller than the left, as well as a slight increase in the intensity of the signal from the right hippocampus on some images. General atrophic changes were also noted in the cerebella compatible with long-standing anticonvulsant effects. The hippocampal changes were interpreted to indicate mesial temporal sclerosis. An HMPAO scan was "nonlocalizing".

Interictal EEG. All electrodes were referenced to Cz. Nineteen scalp EEG electrodes, standard 10-20 including Fpz and Oz but excluding (due to technical problems) Pz, showed bilateral sharp waves which were at times independent and at times co-occurring. In most cases the left sided activity was more prominent being higher in voltage and more likely to occur independently. The topographic distribution of the sharp waves implicated both mid and anterior temporal lobes. Bilateral discharges were also recorded with interpolated electrodes (Figure 16b), however, they were independent and topographically more anterior (Figure 16a).

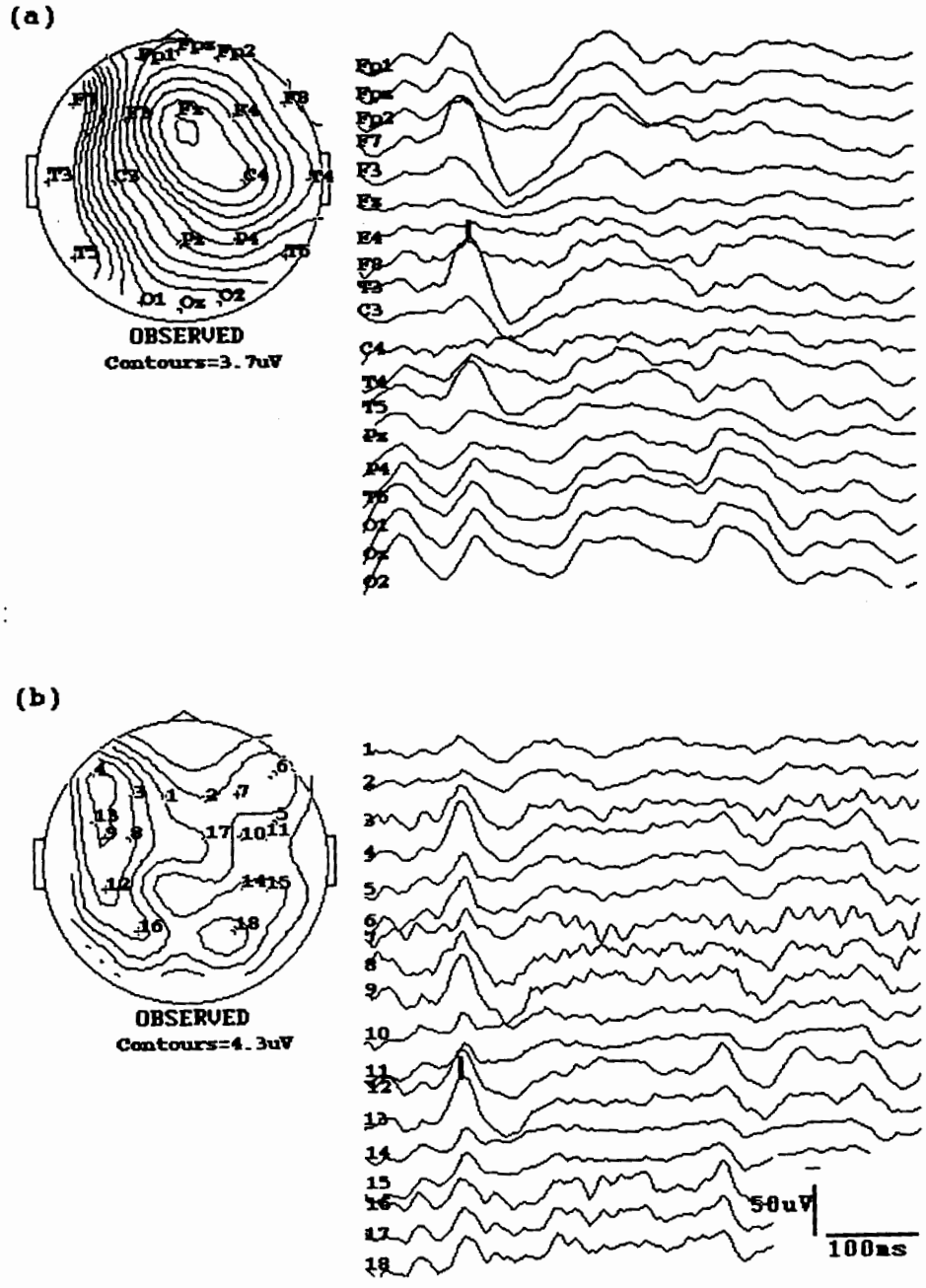


Figure 16. Electrode positions, waveforms and single time point contour maps for subject D.P. (a) for 10-20 electrode positions, and (b) interpolated electrode positions. The cursor indicates the time point at which the maps were constructed.

Of 50 trials each of 10-20 and interpolated electrode positions, five discharges were found to be analyzable with dipole fitting for the 10-20 positions, three for the interpolated positions. The data from 10-20 and interpolated collections were concatenated and dipole locations were estimated for the total positions. The topography of the concatenated data is shown in Figure 17 where a bilateral distribution is seen with maximal activity on the left.

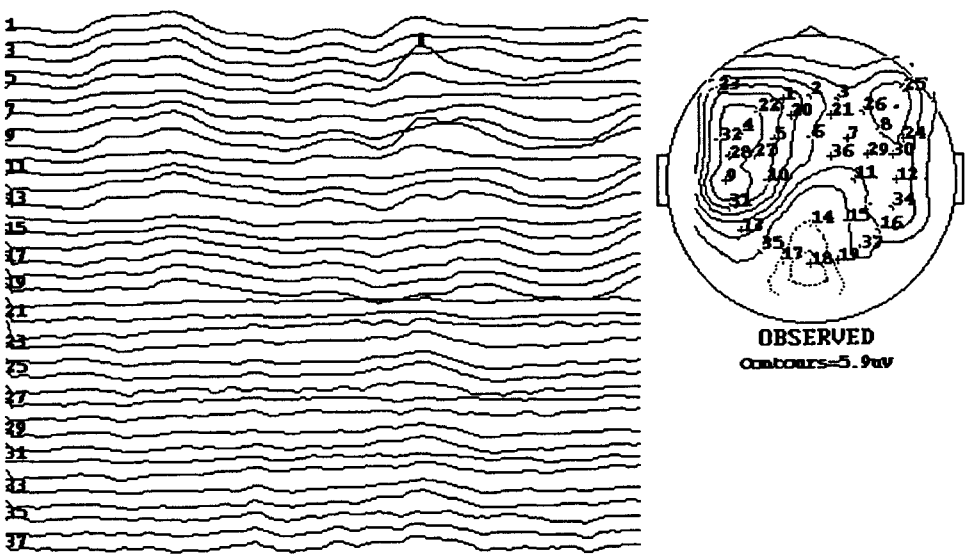


Figure 17. Electrode positions, waveforms and single time point maps for the concatenated data for subject D.P. The hard bar indicates the time point at which the map was constructed.

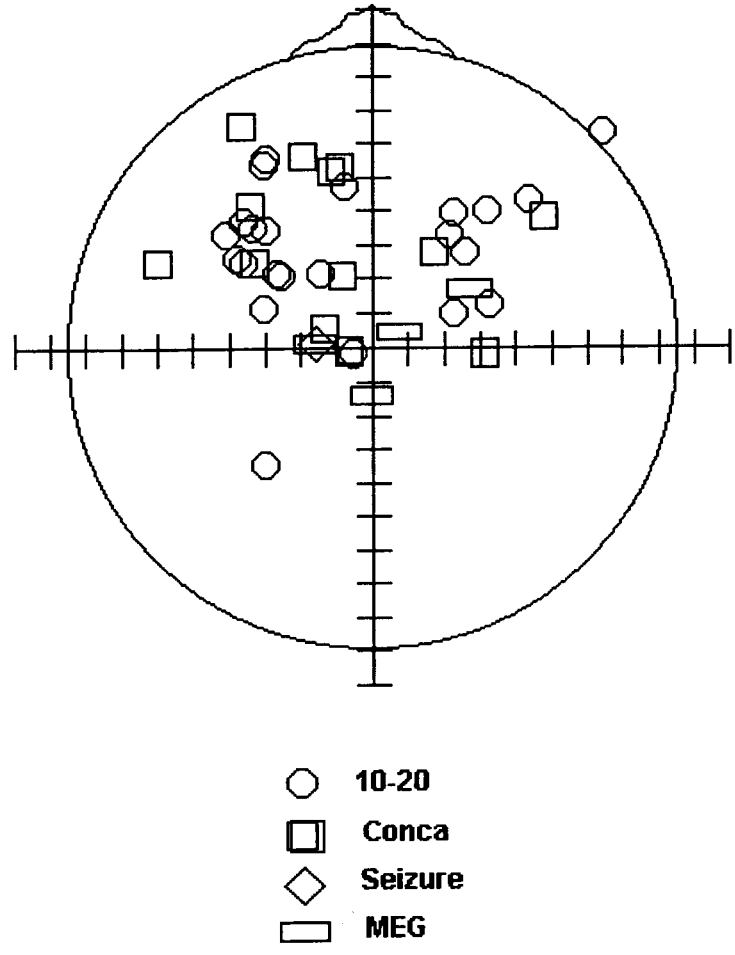
Table 4 indicates the plotted dipole fits obtained for the unconcatenated, concatenated and seizure discharges in X, Y, Z co-ordinates. The X dimension represents the anterior-posterior axis with positive X values being anterior to the origin and negative X values posterior to the origin. The Y dimension represents left to right with positive Y values being to the left of the origin and negative

values to the right. The Z dimension represents the superior-inferior (top to bottom) dimension with positive values being superior to and negative values being inferior to the origin.

Table 4

Fitted dipoles for 10-20, Concatenated (Conca), Seizure (Seiz), and MEG Data, Subject D.P.

	Position		
	X	Y	Z
10-20			
Left			
1	*4.52*	*4.36*	*2.49*
	5.52	*1.54*	*4.67*
2	*4.10*	*4.85*	*2.11*
	1.94	*3.80*	*0.98*
3	*4.34*	*4.14*	*3.54*
	-2.66	*3.76*	*3.15*
	2.93	*2.23*	*6.03*
4	*5.17*	*3.84*	*3.65*
	4.24	*3.74*	*4.10*
5	*6.38*	*3.74*	*2.14*
	2.90	*3.35*	*1.04*
Conca			
Left			
1	*3.31*	*4.10*	*3.09*
	6.02	*1.94*	*1.57*
2	*4.99*	*4.19*	*-0.12*
	6.12	*1.71*	*2.85*
3	*3.30*	*6.79*	*3.47*
	7.37	*4.46*	*-0.10*



10-20 Right			
1	*3.42*	*4.58*	*2.33*
	5.17	*-3.61*	*2.83*
	0.63	*1.33*	*2.58*
2	*2.94*	*3.44*	*5.66*
	4.12	*-1.38*	*6.52*
	4.84	*-2.40*	*1.49*
	3.63	*-1.81*	*0.33*
3	*3.30*	*4.40*	*10.28*
	4.73	*-1.50*	*5.52*
4	*1.77*	*-1.50*	*2.37*
	7.13	*-5.66*	*4.33*
5	*2.09*	*-2.45*	*2.68*
Conca Right			
1	*0.71*	*1.44*	*4.84*
	0.63	*-2.33*	*-2.62*
2	*6.42*	*2.75*	*0.49*
	1.33	*2.13*	*3.95*
	4.66	*-3.99*	*3.20*
3	*3.63*	*-0.95*	*-1.94*
	2.88	*1.65*	*2.55*
Seiz.	*2.95*	*-1.70*	*3.03*
MEG			
1	*0.11*	*-1.60*	*4.22*
2	*0.45*	*-0.74*	*5.99*
3	*-1.40*	*0.03*	*1.01*
	1.70	*-2.70*	*5.34*

Sources for the 10-20 events were estimated to be occurring in both the left and right mid and anterior regions with some predominance on the left side (Figure 18a). In terms of depth most of the sources appear to be temporal lobe in origin (Figure 18b). The concatenated data show very similar findings as indicated in the same Figure (18a and b).

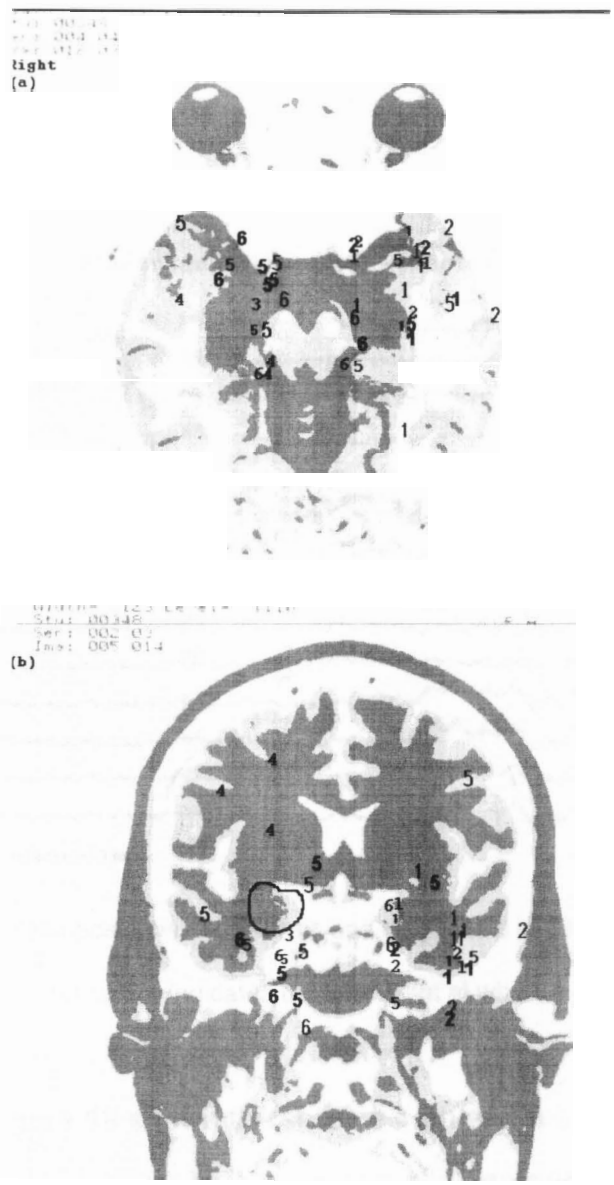


Figure 18. MRI for subject D.P. with dipole positions plotted for (a) axial, and (b) coronal slices. Note that, for purposes of illustrating the right and left sided nature of the discharges, the numbering system in this figure differs from that for previous MRI illustrations. "1" indicates dipoles for left sided 10-20 interictal data, "2" indicates dipoles for concatenated left sided interictal data, "5" for right sided 10-20 interictal data, "6" for right sided concatenated interictal

data, "3" indicates dipoles for seizure data, and "4" indicates dipoles for MEG data. Text forms within numbers indicate particular epileptiform events. The area of MRI abnormality is outlined in black

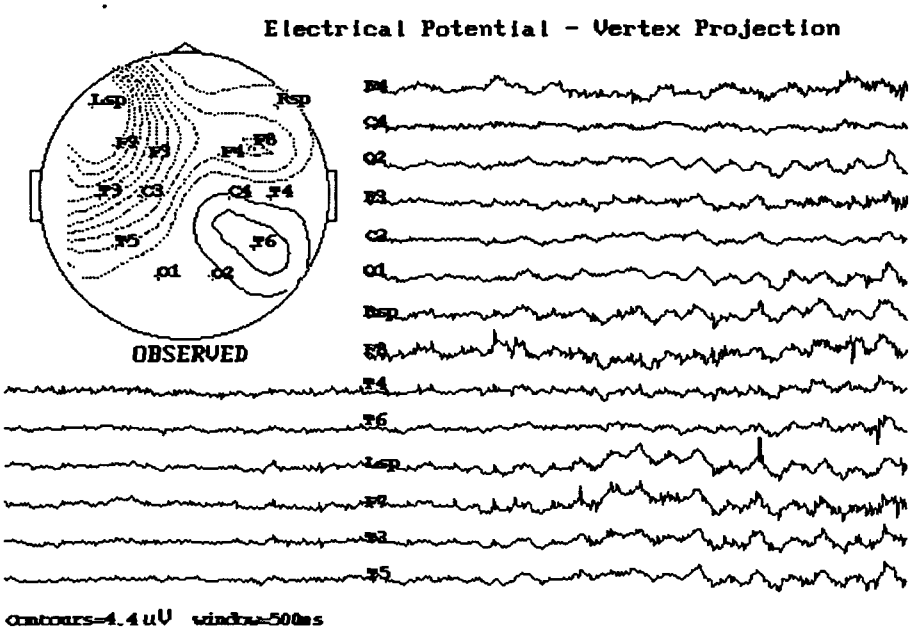


Figure 19. Electrode positions, waveforms and single time point contour map for seizure data from subject D.P. The cursor indicates the time point at which the map was constructed.

Ictal EEG. Figure 19 shows the seizure data and a single time point contour map in which dipolar activity is seen at the left anterior temporal region. Despite the left sided distribution seen in the data at a single time point, when a window of data was used for analysis of source locations, from early in the ictal event the source of the seizure is predicted to be arising from the anterior-mid temporal lobe on the right side at the medial outer edge of the hippocampus (see Figure 18).

Interictal MEG. MEG data were noisy with only three trials being tractable to dipole analysis. Table 4 shows the estimated source locations in X,Y,Z co-ordinates, and these sources are plotted on the appropriate MRI slices in Figure 18. As can be seen from the estimated sources (Figure 18a and b), the discharges appear to be arising from right brain areas superior to the temporal lobe when data from a single time point is plotted. The topographic map of peak of the typical analyzed discharge (Figure 20) suggests 2 dipoles, one in the right anterior region and the other in a more central location.

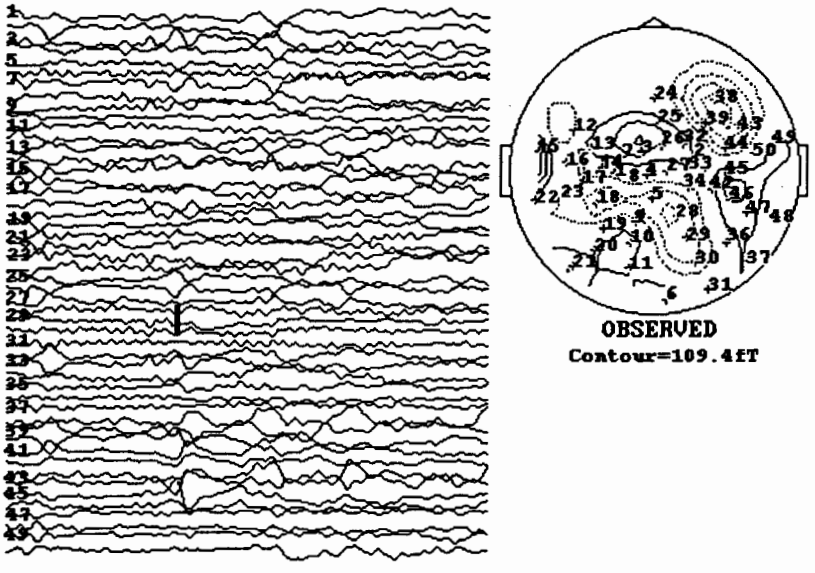


Figure 20. MEG sensor positions, waveforms and a single time point contour map for subject D.P. The cursor indicates the time point at which the map was constructed.

IX. Discussion

The specific questions asked in this thesis were: (a) whether sources located using loose and dense (concatenated) electrode derivations were similar to each other; (b) whether either or both showed spatial congruency with MRI abnormalities; (c) whether locating sources with seizure data yielded similar results to interictal; and (d) whether, in those cases where MEG could be collected, EEG and MEG would show similar sources.

In the following I will discuss the answers to these questions for each patient. Table 5 represents a summary table of the results as discussed in this section.

Generally, the results were somewhat variable, but overall, the data which seemed best for locating sources of epilepsy, assuming that MRI and seizure behaviour pattern are good indicators of areas of epileptogenesis, was the seizure data in three out of four patients. Table 5 summarizes the results for each patient in terms of anatomical distribution of EEG and MRI abnormalities. The column labelled clinical diagnosis indicates the source of the epileptogenesis as determined by seizure monitoring and symptomatology. The columns labelled "10-20", and "Conca" indicate the sources as determined by dipole analysis on interictal data collected respectively with 10-20 and concatenated electrode placement. Ictal data analysis locations are indicated in the column labelled "ictal", and the sources determined by MRI in the "MRI" column.

Table 5

Summary table of results for all patients in terms of anatomical distribution

Pt.	Clinical diagnosis	10-20	Conca	Ictal	MRI
J.S.	R TLE	R + L Wide-spread	R Wide-spread	R lat-mid TL	Hyperintensity R tempor-occipital
T.B.	L TLE	L ant.-mid TL	L ant.-mid TL	L ant. lateral TL	WNL, minimally smaller L hippocampus
K.O.	Probably L TLE	Ant. L TL Few R ant. TL	Ant. L TL	L mid TL	WNL
D.P.	R TLE	L + R mid and ant. TL	L + R mid-ant. TL L>R	R ant. mid TL	smaller R hippocampus

For J.S. who was diagnosed with right temporal lobe epilepsy, showed both right and less frequent left sided EEG discharges, and a right sided temporo-occipital MRI abnormality, the sources located using loose and dense electrode positions, were similar, however, the loose 10-20 sources were both left and right sided, while the dense locations were right sided only. Both show considerable variability in depth with a small cluster of sources in the right temporal lobe. There was no advantage of dense over the loose electrode positions. Using the seizure data a source was located in the mid-posterior temporal lobe which is consistent with her seizure behaviour pattern and possibly

the margin of her MRI abnormality (one would not expect the source to be located within the MRI abnormality as, generally, such abnormalities reflect tissue which is not functionally active).

For subject T.B. who was diagnosed with left temporal epilepsy, showed left and state dependent right sided EEG discharges, whose MRI was within normal limits but indicated that the left hippocampus was slightly smaller than the left, and whose pathology report verified left hippocampal sclerosis, only left sided sources were located for both loose and dense electrode data. The sources were clustered around the left temporal lobe with all but two dense sources being on the lower aspect. There appears to be no advantage to the use of a dense electrode array. For the seizure data, two sources were found to be anatomically reasonable, one was in the lower left temporal lobe the other was located on the edge of the supra sylvian margin. For this subject the results from the three data sets converge and are consistent with the clinical diagnosis and the pathology report of abnormality in the left temporal lobe.

In the case of subject K.O. who was diagnosed with left temporal epilepsy, showed left and state dependent right sided discharges, had a normal MRI, but an abnormal HMPAO scan with left temporal and right cerebella abnormality, loose 10-20 placement indicated left and right sources in the lower aspect of the temporal lobes. Sources derived with concatenated positions were left sided but were in the superior lateral area of the temporal lobe with one exception which was a few centimeters superior to the sylvian gyrus. Sources derived from 10-20 positions appeared to be more accurate with respect to clinical data than those derived from concatenated positions. Two sources were located for seizure data: one was in the medial inferior temporal lobe, the other was considerably

more superior. MEG sources were fairly widespread with two being located in the left temporal lobe and three in more superior areas of the brain. MEG does not appear to add any diagnostic information for this subject.

D.P. who was diagnosed with right temporal lobe epilepsy with bilateral EEG spiking and a right hippocampal abnormality on MRI, showed both right and left sided sources for 10-20 and concatenated positions. The sources were for the most part clustered around the temporal lobes with those on the left being medial and lateral, while those on the right were mainly medial. There was no advantage of concatenated versus loose electrode positions for this patient. Seizure data was used to locate a source on the medial aspect of the right anterior mid-temporal lobe in the region of the hippocampus which is consistent with the MRI findings. Of the three MEG sources, one was in the superior region of the right temporal lobe, another was superior to the right sylvian fissure and the third was at the horn right lateral ventricle. The MEG did not add any diagnostic information for this subject.

A qualitative comparison of the results for each data type, Il, loose and dense, Ic EEG and Il MEG, with respect to anatomical findings in MRI is shown in Table 6.

Table 6

Qualitative comparison of 10-20, Concatenated, ictal and MEG dipole fits with anatomical findings in MRIs

Pt.	10-20	Conca.	Ictal	MEG
J.S.	Poor	Poor	Fair	N/A
T.B.	Good	Good	Good	N/A
K.O.	Good	Good	V. Good	Good
D.P.	Good	Good	V. Good	Poor

Again, it can be seen that dense (concatenated) electrode arrays do not lead to an improvement in the localization of sources with respect to normal and abnormal anatomy imaged on the MRI scans. The ictal EEG data most consistently localizes the sources to brain areas which are most likely responsible for epileptogenesis in these patients. The MEG performed in two patients, did not add any diagnostic information beyond that available with the EEG data in one patient (K.O.), for whom four MEG discharges were analyzed. In the other patient (D.P.) for whom 3 MEG discharges were analyzed, the dipole analysis produced source predictions which seem unlikely, and thus, in this case, the EEG data led to better estimates than MEG when MRI criteria were used.

While some theoreticians have suggested that increased electrode density would improve the spatial location of sources underlying EEG activity (Nunez, 1986b), that is not what was found in the present study. There are three conclusions which may be drawn here: (1) localizations with dense electrode montages resulted in somewhat different dipole locations. One explanation for the different locations is that in the interpolated , and thus the dense arrays,

electrodes were place over the sphenoidal region, a recording area frequently employed by epileptologists as being particularly sensitive, but not part of the standard 10-20 montage. The surface sphenoidal area overlies part of the skull which has openings, such irregularities have been suggested to lead to distortions in MEG potentials at the surface (Sato et al., 1985) and may well have similar effects on EEG potentials (Meijs et al., 1988); (2) there was no systematic relationship in the differences found between loose and dense montages, and; (3) most importantly, neither loose nor dense electrode montages were more consistent with MRI abnormalities in those cases where they were present, or anatomy corresponding to seizure type.

The results of this portion of the study are very suggestive but not conclusive that there is no advantage to increasing electrode density. The conclusions drawn here are based on an assumption that data collected from two different montages (10-20 and interpolated) can be concatenated. There are actually two issues here. The first and most important is whether one can visually choose discharges from the same sources based on morphology as suggested by Sato et al. (Sato, Rose & Porter, 1985) and Barth et al. (1984). It may not be possible to choose with the degree of accuracy necessary to ensure that the discharges arise from the same source. The second reason is that there may actually be differences between measurements from a single source taken with a full set of dense electrodes recorded simultaneously, and with two half-sets concatenated in off-line processing. Those differences may include such things as noise in the data, and background activity arising from other sources. Both may alter the final source location derived through DLM techniques, and would be expected to do so in non-systematic ways. To be certain that the

density of electrode placement is not important in source localization, it would be beneficial to repeat this study using equipment which permits the simultaneous collection of data from dense montages.

Having demonstrated that loose electrode arrays are not at a localization disadvantage with respect to dense arrays, it is possible to comment with some confidence on the findings of the primary theoretical portion of this study which investigated whether localizations using loose montage interictal EEG and ictal EEG would yield similar results. As mentioned there is debate in the literature on the issue of whether interictal discharge localization is adequate as a predictor of seizure epileptogenesis site (Quesney & Gloor, 1985; Stefan et al., 1992), and indeed whether seizure data itself is reliable in this regard (Spencer et al., 1985). The conclusions which can be drawn from the present study are as follows: (1) interictal EEG discharges appear to be the product of several sources, some of which may be consistent with ictal sources, but others of which are independent of the area of epileptogenesis. (2) source locations derived by the DLM using ictal EEG data appear to be more consistent with MRI abnormal and normal anatomy than those derived from interictal data.

The results of this portion of the study suggest that multiple sources are responsible for the discharges present in EEG between seizures, and that these sources are not necessarily the same as those which produce behavioral seizures since they occur in different brain regions. The patient whose data least support this conclusion (T.B.) in that her seizure and interictal sources are often similar, is the one in whom clinicians had the most confidence in terms of their localization. In addition, her interictal data required the fewest sources to fit of all patients, and those sources were more consistent with her ictal sources than

those derived in other patients supporting the view that her abnormalities were more highly focal. In general, three of the patients who participated in the present study had been found difficult to localize by clinical studies. The data obtained here suggest that distributed sources are involved for these three patients (J. S., K. O., and D.P.).

As discussed previously (pp. 7-8), investigations in animal models of epilepsy have led to the suggestion that the relationship between interictal and ictal activity at the cellular level is one in which a single cell or group of cells is involved for both conditions. Breakdown of the inhibitory AHP has been described as being the electrographic signal for the onset of seizures in these animal preparations. The result of the breakdown of the AHP is that the frequency, duration and amplitude of the PDS increases until a seizure event occurs. Although this situation describes the sequence of cellular events in animal models, it may well be inadequate as a description of the events that occur in many human epileptic patients. Despite the fact that the epilepsies investigated in this thesis are diagnostically focal, the data collected from EEG and MEG suggest that several areas of brain tissue are involved in the production of interictal and ictal discharges. This is not surprising considering the nature of the pathogenesis of the disorders. The question is, how many of these areas are involved in the development of ictus? The results suggest that sources involved in ictus are more limited than those involved in interictal activity. In addition, the ictal sources are more closely related to the sites suggested by MRI and /or clinical seizure reports. Although the present results only speak directly to the spatial location of the sources of the two different types of activity,

one may speculate on the physiological relationship - if indeed there is one - between interictal and ictal discharges.

Interictal discharges may represent the activity of abnormal tissue, but may not be directly related to epileptogenesis, at least in some patients. The epileptogenic area may be either completely independent of the interictal discharge area, or related in such a way that abnormal activity in the interictal regions converges in influence on the ictal area, gradually releasing it from inhibition. This seems unlikely since in a study of surface EEG discharges, no temporal relationship could be established between the frequency of interictal activity and the onset of seizures in humans and if there were a mechanism involving gradual release one would expect a temporal relationship to exist.

Alternatively, abnormal activity in the epileptogenic area - which even during seizure may not cause surface spiking - may, without generating either a surface discharge from its own location or a seizure, influence the activity in the interictal regions, causing them to produce PDS and thus surface discharges (perhaps by causing some disinhibition in areas for which the threshold for inhibitory release has been lowered by the original pathology) . It may be that the abnormal neuronal activity at the epileptogenic site which does <u>not</u> influence the production of interictal activity, may be precisely that activity which entrains a sufficient number of neurons in its surrounding tissue to produce a behavioral seizure event.

In summary, several sites are involved in the generation of interictal and ictal discharges. The physiological relationship between them can only be speculated upon, but it appears to be clear that it is not the same relationship as is described in the animal models of epilepsy.

The final portion of this study was directed at investigating the relationship between spatial locations predicted with EEG and those predicted with MEG. MEG data were collected from two subjects since it is possible that although ictal EEG is superior to interictal EEG data for these purposes, interictal MEG is sufficient.

The MEG in one subject predicted sources that were consistent with those predicted with EEG seizure data and were, with the exception of one source, of temporal lobe origin on the left side. For the other subject the MEG sources were found to be less reasonable in terms of anatomy and clinical findings than the EEG sources. Since there were a limited number of subjects used here, it is not possible to draw any firm conclusions regarding these findings. In both cases the MEG data were compromised by noise and by the inability to detect both extrema of the magnetic fields for some discharges due to the design of the equipment. Thus, it is possible that those discharges which would have arisen from different sources (indicated by the differing topography) would have contributed to the accuracy of the MEG findings.

In general, the present study supports the use of loose electrode EEG data in the localization of epileptiform sources using the Dipole Localization Method. However, only in cases where there is little clinical doubt of the general location of the abnormal sources, is the interictal data likely to be as effective in this regard as the ictal data. In cases where the general location is less clear clinically, EEG seizure data appears to be superior in terms of the predictions of source location. In terms of MEG, the data are less clear, in one patient suggesting that interictal source locations are reasonable, yet in another

suggesting they are not. However, as was pointed out, technical limitations in the collection of the MEG data for these patients may have distorted the findings.

Finally, this study represents a series of four case studies rather than an experimental study. As such, as in all clinical studies, whether the results would be repeatable in other patients is not clear.

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