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What is Magnetoencephalography and why it is Relevant to Neurosurgery?

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With 3 Figures

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Abstract

Magnetoencephalography (MEG) is a relatively novel technique that allows the study of the dynamic properties of cortical activity. The functional localization of brain sources of MEG signals depends on the models used and it always has a certain degree of uncertainty. Nevertheless, MEG can be very useful in assisting the neurosurgeon in planning and carrying out brain surgery in, or around, eloquent brain areas, and in epilepsy surgery in pharmaco-resistant patients. The following three areas of application of MEG in neurosurgery are reviewed: (i) Presurgical functional localization of somatomotor eloquent cortex; (ii) Presurgical evaluation of epileptic patients. (iii) Functional localization of speech relevant brain areas. The performance of MEG in comparison with EEG and fMRI is discussed.

Keywords: Magnetoencephalography; epilepsy; presurgical planning.

Introduction

Magnetoencephalography (MEG) is the technique of measuring the magnetic fields generated by brain activity. In general, an important asset of MEG/EEG is the ability to record signals generated by the brain in relation to distinct states of activity, whether determined by intrinsic processes, e.g. different states of sleep and alertness, or in relation to motor acts and sensory events. Here we will focus on the core of clinical applications with respect to neurosurgical isssues. In this context three fields of application will be reviewed: (i) Presurgical functional localization of somatomotor eloquent cortex; (ii) Presurgical evaluation of epileptic patients. (iii) Functional localization of speech relevant brain areas.

The implementation of the MEG in clinical settings has had a relatively slow start, after the pioneering studies of Cohen (1968), in comparison with the amazingly rapid development of other brain imaging techniques such as Magnetic Resonance Imaging (MRI). It should be stressed that by no means are MEG and MRI really competitors. Rather, the two techniques are complementary, since MRI provides precise static information about brain anatomy, while MEG allows the study of the dynamic properties of cortical activity. MRI yields unrivalled images of brain structures at all levels, whereas MEG gives information about dynamics of the activities of large populations of neurons of the cerebral cortex. Nevertheless MEG has a more direct competitor in the more recently developed functional MRI (fMRI) technique that is based on measurements of changes of the ratio between oxy- and reduced-haemoglobin, which are related to neuronal activity. Be as it may the time resolution of MEG is unrivalled. Below we analyse more specifically the comparison between MEG and fMRI regarding the problem of localizing cortical areas bordering the central sulcus.

A basic limitation of MEG, as much as of Electroencephalography (EEG), is that the neuronal signals are recorded from the scalp and that there is no unique solution to the question of where, within the brain, are localized the sources of those signals. This means that there is no solution to what is called the inverse problem. The common approach to overcome the non-uniqueness of the inverse problem in MEG/EEG is to introduce constraints in the solutions, in order to exclude all solutions except that one that is most suitable to describe the data. Thus the functional localization of brain sources of MEG/EEG signals depends on the models used and on the corresponding assumptions, and it always has a certain degree of uncertainty. This contrasts with the accuracy of MRI brain scans. It explains partly why the development of clinical applications of MEG has

been slow, since the research on how to optimise the solutions of the inverse problem has been arduous and only recently it is reaching the stage at which consensual strategies may be advanced. These inherent difficulties, along with the fact that MEG needs rather costly facilities, account for the restraint of medical specialists in promoting this new methodology and the hesitation of hospital administrators in supporting the necessary investments in material and human resources.

Some Basic Notions: From Applied Physics to Biophysics

After the pioneer measurement of MEG signals by Cohen (1968) using a simple induction coil magnetometer, this method became practical only after new technologies based on the principle of superconduction became available. In the course of the last decades this led to the construction of whole-head devices that allow measuring simultaneously from more than 150 sensors. In Amsterdam we have a CTF/VSM apparatus, manufactured in Vancouver (Canada). To give a rough idea of the financial aspects, an MEG apparatus costs about 2.5×10^6€, while the yearly running costs, including salaries, are in the order of 6×10^5€. It is most important that a small staff consisting of physicists, software specialists and technicians (at least $1\frac{1}{2}$ positions), will give the necessary support and collaboration in the development of acquisition protocols and signal analysis. I should add that besides the exploration of magnetic signals produced by the brain, the same technique has proved valuable in the study of the heart, both of adults and foetuses. This can be illustrated by two recent studies: it was shown that recordings of the adult heart magnetic field (Magnetocardiogram or MCG) in the depolarization process has the potential to detect subtle myocardial ischemia induced by exercise (Kanzaki *et al.* 2003). The analysis of foetal MCG (FMCG) recordings may also contribute significantly to a better understanding of the heart function of the foetuses, and thus may help improve perinatal morbidity and mortality (Anastasiadis *et al.* 2003).

A few basic notions of applied physics and biophysics may be useful as a short technical introduction into the realm of MEG.

First, we may ponder about some basic notions of applied physics. In general, magnetic fluxes can be measured using induction coils. However, very weak magnetic fields are not measurable using normal wires since the induced currents dissipate as heat by the electrical resistance of the wires. The discovery of the principle of superconduction, i.e. of materials that have essentially no electrical resistance at extremely low temperatures, opened up the possibility of measuring tiny magnetic fields as those produced by the brain. These superconductors are usually known by the abbreviation SQUID (superconducting quantum interference devices). To

assure that SQUIDs work properly they have to be maintained at a very low temperature. This is achieved by immersing the SQUIDs in liquid helium contained in an insulated vessel known as a Dewar (−269 °C). The SQUID may be considered a device for transforming a time-varying magnetic field to a time-varying voltage, since a magnetic flux passing perpendicular to a superconducting coil induces an electrical current in the coil. The latter can be further amplified using appropriate electronics. Thus the field of 'low temperature physics' created new devices that allowed measuring very weak magnetic fields such as those produced by neurons.

Second, we may review some basic principles of biophysics. Neurons generate time-varying electrical currents when activated. Longitudinal intra-cellular currents flowing along dendrites or axons generate magnetic fields around them, just as it happens in a wire, according to the well known right-hand rule of electromagnetism. Pyramidal neurons of the cortex, with their long apical dendrites oriented perpendicular to the cortical surface, if activated with a certain degree of synchrony, generate coherent magnetic fields. In this way we may say that these neurons behave as 'current dipoles', the activity of which can be detected by SQUIDs placed at a small distance from the skull. We should note that the resulting MEG signals depend on the orientation of the neurons with respect to the skull.The MEG 'sees' only those magnetic fields that are perpendicular to the skull. These magnetic fields are generated by neuronal currents that are oriented *tangentially* to the skull. In contrast, those that are oriented *radially* to the skull do not generate a magnetic field outside the head.

Third, we have to note that in order to record MEG signals it is necessary to use specialized recording conditions, since these signals are very weak. Even when thousands of cortical pyramidal neurons are synchronously active the resulting magnetic field at the head surface has a very small magnitude, in the order of 10^{-12} Tesla (1 fT = 10^{-15} Tesla), which is much smaller than the earth magnetic field and urban magnetic noise fields. This poses a hard detection problem, equivalent to that of detecting, at a distance, the voice of one single individual in a large noisy crowd. To accomplish this strenuous task the MEG is generally recorded in a magnetic and radiofrequency shielded room with walls made of mu-metal and aluminium, what adds appreciably to the cost of the system.

Clinical Applications of MEG in a Neurosurgical Setting

In this overview we will examine the evidence available regarding the use of MEG in the clinical settings where the emphasis is on assisting the neurosurgeon in planning and carrying out brain surgery in, or around, eloquent brain areas, and in pharmaco-resistant epileptic patients. The following three areas will be considered, as indicated in the Introduction: (i)

Presurgical functional localization of eloquent cortex; (ii) Presurgical evaluation of epileptic patients. (iii) Functional localization of speech relevant brain areas.

Magnetic Functional Source Imaging of the Sensorimotor Strip

The central sulcus is an important anatomical reference in order to localize the sensorimotor cortical strip. It is important to identify precisely the functional anatomy of these cortical areas with the aim of performing surgical resections in and around these areas without harming the eloquent cortex. In particular space-occupying lesions, as tumours and vascular malformations may deform the cortical anatomy such that pre-operative MRI scans may not be appropriate for the identification of the central sulcus. In these cases a functional method is necessary. The central sulcus (CS) marks the border between the agranular motor cortex in the pre-central gyrus and the granular somatosensory cortex in the post-central gyrus (Zilles, Schlaug *et al.* 1995). The question is whether MEG may provide reliable information regarding the localization of the somatosensory and motor cortical areas.

Functional Localization of Somatosensory Cortex

A number of studies showed that MEG provides a powerful method for the functional mapping of the somatosensory cortex (Hari, Reinikerinen *et al.* 1984), (Wood, Cohen *et al.* 1985), (Sutherling, Crabdall *et al.* 1988), (Buchner, Fuchs *et al.* 1994), (Rezai, Hund *et al.* 1996), (Ossenblok, Luiten *et al.* 2003). This is very relevant to guide the neurosurgeon in interventions where it is necessary to map the somatosensory cortex around the central sulcus. It is well established that the electrical stimulation of the median nerve generates an evoked field in the SI hand area located in the post-central gyrus. Most commonly the component of the cortical electric evoked field that is taken as reference is the negative peak at about 20 ms latency (Okada, Tanenbaum *et al.* 1984; Allison, McCarthy *et al.* 1989).This fits well with the results obtained by way of direct cortical recordings showing (reviewed by Allison (1991)) that the sources of early cortical somatosensory evoked potentials are located in the parietal cortex, more specifically in the primary somatosensory area of the posterior bank of the central sulcus. The source modelling studies of electrical and magnetic fields, along with the cortical recordings, agree that the N20 field is generated by a dipolar source tangential to the cortical surface. This dipolar field is produced by the activity of neurons of area 3b evoked by cutaneous inputs. The localization of this dipolar field is nowadays the standard method to estimate the localization of the central sul-

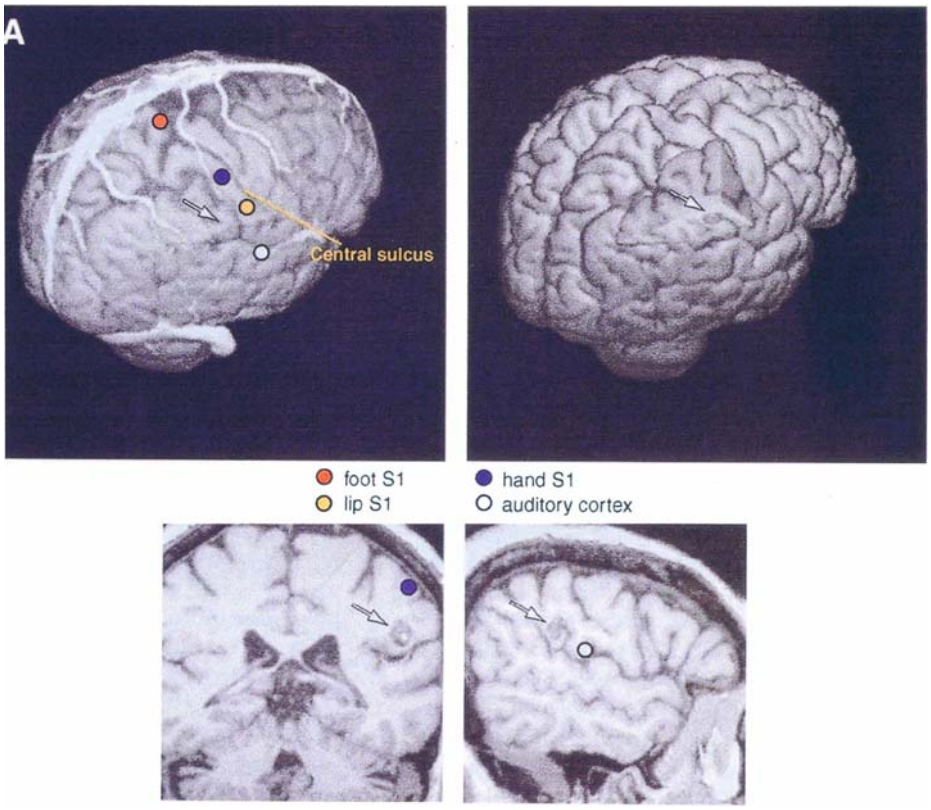

Fig. 1. Three-dimensional surface rendering of the brain of a patient with a subcortical cavernous hemangioma in the right lower parietal lobe. Left, above: Cortical veins and sources of somatosensory MEG fields evoked by electrical stimulation of the median nerve (hand S1), the tibial nerve (foot S1) and lip (lip S1), along with the auditory evoked field (at a latency of 100 ms), are indicated by dots. Right, above: A section of the surface rendering was removed to reveal the subcortical cavernous hemangioma, and the sulcal route (arrow) used for its removal. Below: on the left a coronal MRI section showing the source of the median nerve evoked field (dot) and on the right a sagittal section showing the source of the auditory evoked field (dot); The arrows show the approximate location of the tumour, that is below the median nerve source and posterior to the auditory source. (Adapted with permission from (Mäkelä, Kirveskari *et al.* 2001))

cus (Fig. 1). A thorough analysis of this and other components of the somatosensory cortex evoked potentials is given by Mauguiere (1998) and of the corresponding magnetic fields by Hari and Forss (1999). In this context it is important to note that the MEG is to be preferred to the EEG because the former is less sensitive to the different conductivities of the tissues which, in pathological cases may be even more complex than in

normal cases, due to local changes in conductivity caused by tumour masses, oedema and/or skull defects. In a clinical application (Ganslandt, Fahlbusch *et al.* 1999) during surgery, the pre- and postcentral gyri were identified by neuronavigation and, in addition, the central sulcus was localized using intraoperative recording of somatosensory evoked potentials. In all cases MEG localizations of the sensory or motor cortex were correct. These authors conclude that the method of incorporating functional data into neuronavigation systems is a useful tool that can be used to lessen morbidity around eloquent brain areas.

Functional Localization of Motor Cortex

The studies described above had the aim of localizing the posterior bank of the central sulcus using the evoked responses of the somatosensory cortex. In addition a number of studies have focused on the functional localization of the primary motor cortex on the anterior bank of the central sulcus. This may provide important complementary information. Rezai *et al.* (1996) recorded movement-related magnetic fields to estimate the location of the cortical motor strip. The observation that MEG rhythmic activity of the motor cortex at about 15–30 Hz shows a significant coherence with the EMG of arm muscles during isometric contractions by Salenius and collaborators (Salenius, Portin *et al.* 1997; Hari and Salenius 1999) has yield a new method to estimate the localization of the motor strip. Mäkelä *et al.* (2001) combined information obtained using magnetic fields evoked by median and tibial nerves and by lip stimulation, with that obtained by estimating the maximal coherence of MEG oscillatory cortical activity with the electromyogram of hand and foot muscles in order to estimate the precentral motor and the post-central somatosensory cortices. The neuromagnetic information was displayed on 3D-surface reconstructions of the individual brains. These data were verified using intraoperative corticography. The sources of the somatosensory evoked fields located the posterior bank of the central sulcus correctly in all patients, whereas information about the localization of the motor strip was obtained in 8 of 12 patients. This study shows that this complementary information, obtained pre-operatively, can be useful in guiding the neurosurgeon so that possible damage to eloquent cortical areas of the sensorimotor strip may be substantially reduced.

Comparison Between MEG and fMRI Regarding the Functional Localization of Somatomotor Cortex

Above we noted that fMRI can compete with MEG/EEG to some extent with respect to the functional localization of the cortical areas around the

central sulcus. In this context which of these techniques has the best performance? The fMRI measures changes in magnetic signals related to spatio-temporal haemodynamic events that are associated with neuronal activity evoked by a stimulus. These basic haemodynamic events (Malonek, Dirnagl *et al.* 1997) consist of increased neuronal O2 consumption (latency: 100 ms), and associated increased blood volume (latency: 300–500 ms) and increased blood flow (latency: 500–1500 ms) in surrounding vascular compartments. These haemodynamic changes are reflected in variations of the ratio oxy-/reduced-haemoglobin that can be picked up, to some extent, by fMRI. We should note that there is, however, a time delay between the occurrence of changes of neuronal activity, that in the case considered here is evoked by stimulation of the median nerve, and the associated haemodynamic changes. This implies that there is a physiological dead-time that does not allow to detect the earliest changes of neuronal activity by way of haemodynamic measurements. In addition there are also technical limitations, since the sensitivity of the current MRI apparatuses (1.5 T) is not sufficient to pick up the weak haemodynamic changes occurring at the shortest latencies. This performance may improve with more powerful MRI apparatuses.

What is the correspondence between fMRI signals and neuronal activity evoked by peripheral stimulation in the somatosensory cortex? This question was addressed, in a comprehensive way, by Disbrow *et al.* (2000). Cortical activation maps obtained after somato-sensory stimulation of hand, face and forelimb in monkey, were measured using standard fMRI (1.5 T) and electrocorticography (microelectrode electrophysiology) and compared. In 55% of the maps the centroids of fMRI maps co-localized with those obtained electrophysiologically. In 45%, however, they did not, and the mean distance between the two kinds of centroids was 1 cm. These differences were related to how the cortical maps are oriented in relation to the cortical blood vessels. The cortical maps that are oriented parallel to the blood vessels display a good overlap between fMRI and electrophysiological signals, whereas those that are perpendicular do not overlap, or overlap only partially. This means that in addition to the differences in timing, there are also spatial differences between fMRI and electrical/magnetic signals, determined mainly by the orientation of the surrounding blood vessels that condition the fMRI signals, while they do not affect the MEG.

A direct comparison of fMRI and MEG in their capacity to localize the central sulcus was carried out by Inoue *et al.* (1999) in a neurosurgical setting. They found that fMRI and MEG coincided in defining the central sulcus in all 24 hemispheres of volunteers and all 10 examined non-affected hemispheres of patients. The percentage of concordance, however, decreased to 82% for the affected hemispheres of 11 patients with brain

tumors. All MEG localizations were confirmed by intra-operative recordings of somatosensory evoked potentials from the cortical surface. In those few cases where fMRI was not reliable, this was probably due to venous flow changes by tumor compression. These authors conclude that for precise functional assessment of the brain affected by intracranial tumors, the combination of fMRI and MEG is recommended. The same conclusion was reached by Kober *et al.* (2001) who estimated the distances between MEG and fMRI activation sites in a number of neurosurgical patients. The central sulcus could be identified by MEG and fMRI in 33 of 34 cases. However, MEG and fMRI localization results showed significantly different activation cortical sites for motor and sensory tasks with a distance of 10 and 15 mm, respectively. These authors conclude that both modalities are useful for the estimation of the somatomotor cortex, but a single modality may err in the exact topographical labelling of the somatomotor cortex. In some unclear cases a combination of both methods should be used in order to avoid post-surgical neurological deficits.

In short, the MEG, whether alone or in combination with fMRI, is an important tool for functional localization of the cortical areas surrounding the central sulcus.

MEG in Epilepsy: Identification of Epileptiform Inter-Ictal Foci

With the aim of localizing epileptogenic areas particularly in order to plan surgical resections of these areas it is important to identify where in the brain epileptic seizures start. This cannot be easily done using MEG since it is not practical to monitor epileptic patients during prolonged MEG recordings while waiting for a spontaneous seizure to occur. However, very useful information can also be obtained through the identification of the areas where epileptiform inter-ictal activity, e.g. spikes are present (Sutherling, Levesque *et al.* 1991; Ebersole 1997; Ossenblok, Fuchs *et al.* 1999; Baumgartner, Pataraia *et al.* 2000; Stefan, Hummel *et al.* 2000). Both EEG and MEG can accomplish this task efficiently, but the latter has some advantages since it yields more localized fields and it allows a better differentiation of multiple sources. In our experience this applies particularly to neocortical sources. However, temporal lobe epilepsies tend to yield too few interictal spikes in the MEG, likely due to the distance between the sensors and the hippocampal region. In any case the signal-to-noise ratio of individual spike discharges is usually relatively low. Therefore especial techniques have to be applied to enhance it. Most often the MEG/EEG recordings of inter-ictal epileptiform activity are complex signals, with artefacts and other non-epileptiform transients that have to be avoided using appropriate methods (Gotman and Wang 1991), along with real epileptiform spikes that may arise from multiple brain sources (Engel

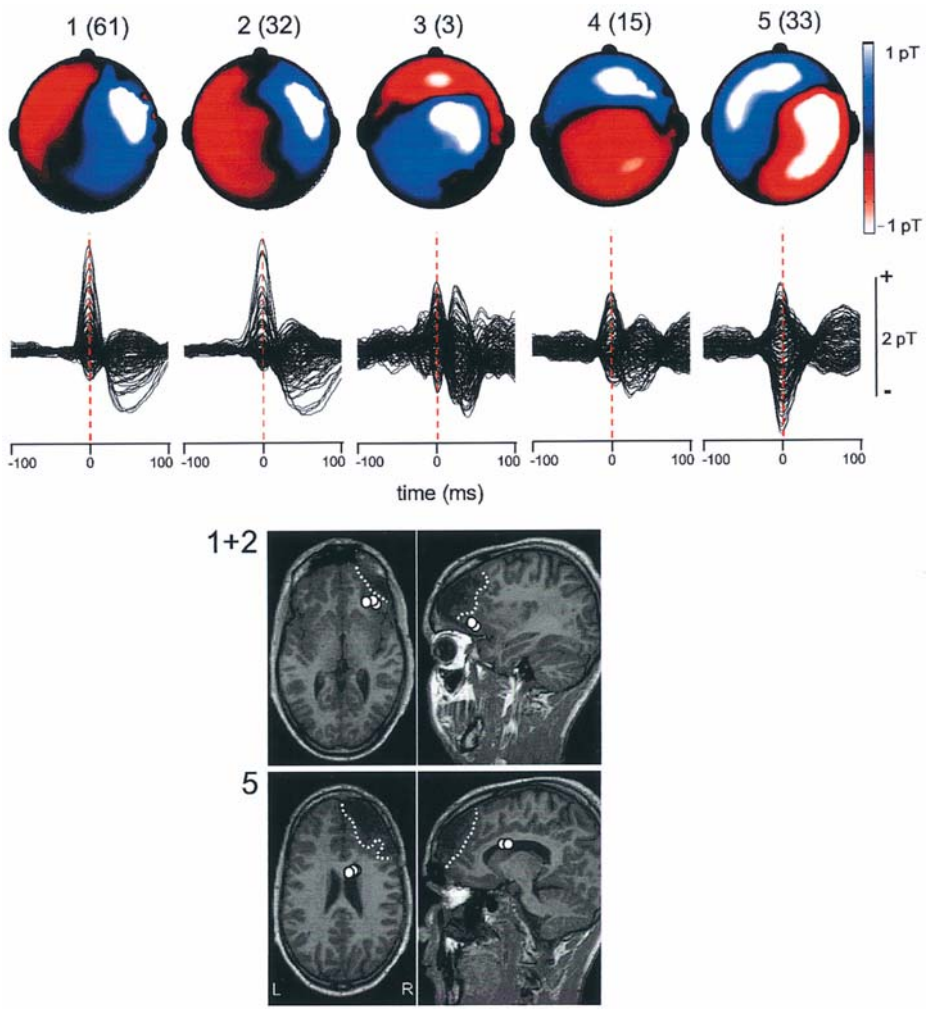

Fig. 2. Above: MEG Topographic maps and overlay of MEG signals recorded from different sensors for 5 epileptiform spike clusters in a patient with a 10-year history of a seizure disorder that became manifest after drainage of an intracerebral abscess in the right frontal lobe. The seizures proved unresponsive to medical treatment so that the patient was evaluated for epilepsy surgery. Above each map the cluster number and the number of spikes it contains (within brackets) is indicated. The field maps represent the magnetic field distribution at the time of the marker indicated by the vertical dashed line, set at time zero. Below: position of equivalent dipoles in MRI slices for clusters 1 and 2 (1st row) and for cluster 5 (2nd row). Clusters 3 and 4 are not indicated because they did not yield residual errors less than 10%. The boundary of the structural lesion in the right frontal lobe is marked by the dotted line. Note that the dipoles of clusters 1 and 2 were located at the posterior border of the lesion in the right frontal lobe. Those of cluster 5 were also located in the same hemisphere but more posterior, likely indicating propagated epileptiform activity from the main more anterior sources. The patient underwent a right frontal lobectomy. Pathology of the

Jr 1993), (Lantz, Wahlberg *et al.* 1998), (Iwasaki, Nakasato *et al.* 2002). This implies that the MEG/EEG epileptiform spikes should be grouped into distinct clusters before estimating the corresponding brain sources. Several methods have been proposed to achieve this objective (Lantz, Wahlberg *et al.* 1998), (Wilson, Turner *et al.* 1999; Wahlberg and Lantz). Recently an automated algorithm for clustering of epilepiform spikes was developed in our group (Van't Ent, Manshanden *et al.* 2003) that was applied to MEG recordings from epileptic patients with localization-related epilepsy. Inverse computations applied to selected averages of spike clusters, in order to identify the corresponding brain sources, yielded source solutions that agreed with the presumed site of seizure initiation and were associated with the structural lesions seen in MRI scans (Fig. 2). Even in patients with no evident brain lesion in the MRI this approach helped to obtain insight in the characteristics of a possible neocortical epileptogenic area.

In conclusion these recent advances indicate that objective cluster analysis of large numbers of MEG epileptiform spikes yields useful clinical information regarding the delineation of an epileptogenic zone. This information can converge with that obtained using classic scalp video/EEG seizure monitoring, even in the absence of a structural lesion in MRI.

Functional Localization of Speech Relevant Brain Areas

In addition to the applications described above, which are directly relevant for neurosurgical applications, the MEG is becoming an important tool for the analysis of dynamical brain activities in relation to neuro-cognitive functions (Momjian, Seghier *et al.* 2003). In this context the functional mapping of speech relevant areas is also clinical useful since in neurosurgery it is of the uttermost importance to avoid damage to these eloquent areas of the brain. This is usually done by way of the invasive Wada test (Wada and Rasmussen 1960). The question is whether the MEG may be an alternative non-invasive method to the Wada test. A number of studies, particularly of the Helsinki school, have shown that MEG signals evoked by speech related tasks can be recorded and localized to speech relevant brain areas (Fig 3). A picture naming task in normal subjects revealed that MEG fields evoked by the visual presentation of pictures to be named appear first in the occipital areas and evolve in time from the posterior to frontal areas (Salmelin, Hari *et al.* 1994). These MEG signals

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excised brain tissue revealed the presence of extensive gliosis secondary to the intracerebral drainage performed earlier. The patient has remained seizure free, on antiepileptic medication, 14 months after surgery. (Adapted with permission from (van't Ent, Manshanden *et al.* 2003))

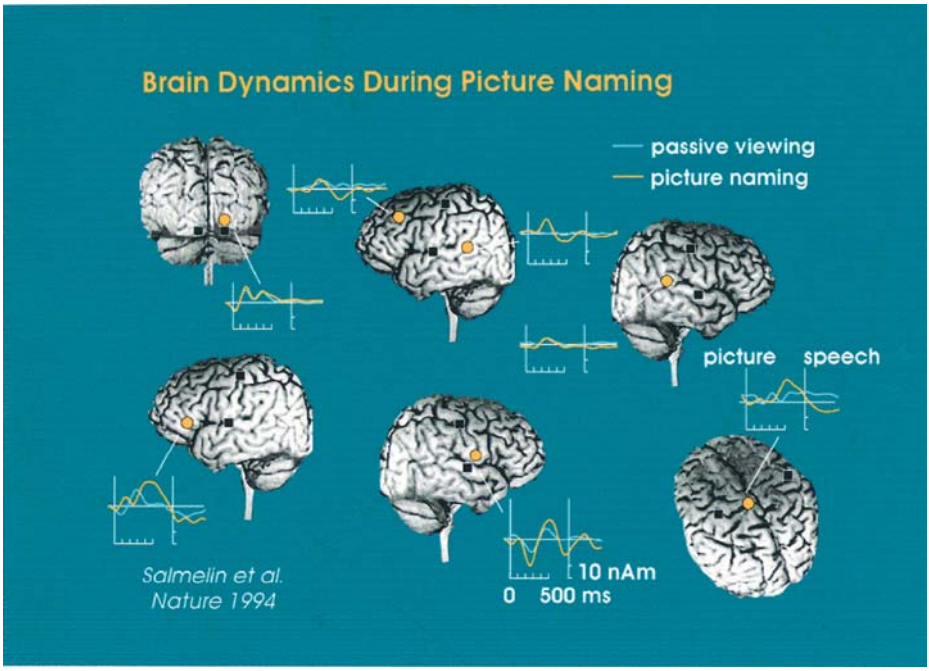

Fig. 3. Brain activation in the course of a naming-aloud experiment (orange traces) of pictures presented on a computer screen once every 5 s. The early visual MEG evoked response (source 1, picture upper left) at the back of the head was followed by more lateral posterior signals in both hemispheres (sources 2 and 3, upper middle and right), suggesting a contribution from Wernicke's area and its right-sided counterpart. Within the same time window (grey rectangles), a left frontal site (4, below left) close to the cortical face representation area showed activation, as in preparation for mouth movements. About 500 ms after the picture had been presented, signals emerged from a site anterior to the face representation area in the motor cortex, reflecting activation of Broca's area (5, below middle) and its counterpart in the right hemisphere. These signals were immediately followed by activity at the top of the brain (6, below right), probably generated in the vicinity of the supplementary motor area. MEG responses during passive viewing (white traces) and quiet naming (green traces) are also shown. The locations of visual (V), auditory (A), and somatosensory (S) projection cortices are marked by yellow squares. (Adapted with permission from (Salmelin, Hari *et al.* 1994))

are bilateral but over the left hemisphere they are usually stronger and leading in time. In a more specific task Gootjes, Raij *et al.* (1999) performed a MEG study in 11 healthy right-handed subjects to estimate individual hemispheric dominance for speech sounds. The auditory stimuli comprised binaurally presented vowels, tones, and piano notes in groups of two or four stimuli. In the left hemisphere, vowels evoked significantly stronger (37–79%) responses than notes and tones, whereas in the right

hemisphere the responses to different stimuli did not differ significantly. Specifically, in the two-stimulus task, all 11 subjects showed left-hemisphere dominance in the vowel vs tone comparison. This simple paradigm may be helpful in non-invasive evaluation of language lateralization. Other MEG studies using different forms of signal analysis are congruent with these findings. Papanicolaou *et al.* (1999) reported that they could identify the dominant hemisphere by inter-hemispheric comparison of the number of dipolar sources, and the same applies to the study of Kober (2001) who used a laterality index calculated from the strength of current density distributions after spatial filtering.

More well controlled studies in larger groups of subjects are, of course, necessary. Nevertheless the results obtained until now allow us to conclude that MEG is a valuable method to investigate the dynamics of speech processing. Furthermore MEG merits being explored as a potential alternative to the Wada test for non-invasive presurgical localization of speech eloquent brain areas and the identification of the language dominant hemisphere.

Discussion and Future Developments

The MEG has been slow in being accepted as a major method of diagnosis due to its high cost relative to the well established EEG. Nevertheless the advantages of MEG over EEG are becoming accepted in a number of applications as indicated above. We discuss here in more general terms the main advantages and disadvantages of MEG versus EEG. Since the MEG is the newcomer we may start by discussing whether it has advantages with respect to the older EEG method. We may distinguish three main advantages of the MEG.

First, the EEG is a relative measurement; it needs a reference electrode, while the MEG does not. This makes the analysis of correlations between signals recorded from different sites over the head, using the MEG, easier to interpret. This is particularly relevant in dynamical investigations of MEG signals during the performance of cognitive tasks, such as in the analysis of speech processing.

Second, the MEG field generated by a given cortical population is more tight than the corresponding EEG field. This is due to the fact that the EEG depends mainly on volume currents that are smeared out by the isolating shell of the skull, whereas the latter do not contribute to the MEG. This implies also that in the case that several generators are simultaneously present in the cortex, the MEG is capable of resolving the corresponding sources more accurately than the EEG.

Third, the MEG is much less affected by the electric properties of the shells that surround the brain, namely the skull and the scalp. This makes

the determination of brain sources of MEG activities more accurate than of EEG sources. There are, of course, also some disadvantages of the MEG. Long recordings such as it may be necessary to be made in sleep research are more difficult to obtain, although not impossible (Simon *et al.* 2000). It is unpractical to record epileptic seizures since the patient may be hurt due to the head confinement in the MEG container. In addition a non-trivial disadvantage is the price of the MEG installation. This is the main reason why there are relatively few MEG facilities around the world, while most of these are still primarily dedicated to fundamental research.

One problem that has hindered the more generalized acceptance of MEG as a clinical tool is the fact that a consensus about how to process MEG signals has not yet emerged. Different methods are being used, which very often are variations of the basic equivalent dipolar source model. Indeed a general approach is to estimate from a given MEG signal, after adequate processing, the equivalent current dipole model for a series of time samples within a time-window of interest. Dipolar solutions should be accepted only when the residual error between measured and computed magnetic fields is below a certain threshold (typically values: 10 or 5%). The dipolar solutions should be presented on the corresponding MRI slices along the three planes (horizontal, sagittal and coronal). Thereafter the dipolar distributions on these MRI slices have to be interpreted as representing reliable sources, either in the form of one single or multiple clusters. Alternative methods have been proposed such as those based on spatial filtering to estimate current distributions (Robinson and Rose 1992). Among other applications this methodology has been used to estimate the dynamics of speech processing both in normal subjects and patients. Be as it may, the field of MEG analysis has entered the phase of maturity such that more comprehensive studies can reasonably be expected.

Besides advances in the creation of comprehensive software for MEG analysis that may be more widely accepted, we may expect, in the near future, also technical developments in hardware, with the implementation of novel high-temperature SQUIDs operating at the temperature of liquid nitrogen, such that the MEG sensors may be brought closer to the scalp improving the signal-to-noise ratio. Accordingly information from brain sources of MEG signals lying deeper under the scalp may become more accessible. New technological improvements may also lead to a decrease of the cost of the MEG installations, what would be most desirable.

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