INTRODUCTION TO MEG AS A TOOL FOR FUNCTIONAL IMAGING: SOURCES, MEASUREMENTS, AND ANALYSIS

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INTRODUCTION

Timing is essential for proper brain functioning. Magnetoencephalography (MEG) and electroencephalography (EEG) are at present the only noninvasive human brain imaging tools that provide submillisecond temporal accuracy and thus help to unravel dynamics of cortical function. MEG (and EEG) reflects the electrical currents in neurons directly, rather than the associated hemodynamic or metabolic effects. MEG well suited for investigation of brain regions embedded within cortical sulci. These cortical areas are poorly accessible even with intracranial recordings but produce an extracranial magnetic field, which can be detected with MEG. State-of-the-art neuromagnetometers contain more than 300 SQUID sensors in helmet-shaped arrays so that signals can be recoded simultaneously over the neocortex and the cerebellum. The principal advantage of MEG over EEG is that skull and scalp, which affect the electric potential distributions, do not smear the magnetic signals and MEG is thus able to see cortical events 'directly through the skull'.

SOURCES AND FIELDS

Neuronal currents generate magnetic and electric fields according to Maxwell's equations. The neural current distribution can be described as the primary current, the "battery" in a resistive circuit comprising the head. The postsynaptic currents in the cortical pyramidal cells are the main primary currents giving rise to measurable MEG signals. In many calculations the head can be approximated with a spherically symmetric conductor but more realistic head models for field calculations can be constructed with help of anatomical MR or CT images.

If we approximate the head with a layered spherically symmetric conductor, the magnetic field of a dipole can be derived from a simple analytic expression [1]. An important feature of the sphere model is that the result is independent of the conductivities and thicknesses of the layers; it is sufficient to know the center of symmetry whereas calculation of the electric potential is more complicated and requires full information on conductivity. Because radial currents do not produce any magnetic field outside a spherically symmetric conductor, MEG is even in realistic conditions to a great extent selectively sensitive to tangential sources. EEG data are thus required for recovering all components of the current distribution. Since the resultant current orientation on the cortex is normal to the cortical mantle, MEG is selectively sensitive to fissural activity.

The analytic sphere model provides accurate enough estimates for many practical purposes but when the source areas are located deep within the brain or in frontal areas it is necessary to use more accurate approaches [2]. Within a realistic geometry of the head, the Maxwell's equations cannot be solved without numerical techniques. In the boundary-element method (BEM), the electrical conductivity of the head is assumed to be piecewise homogeneous and isotropic. Under these conditions electric potential and magnetic field can be calculated numerically starting from integral equations that are discretized to linear matrix equations [2, 3].

The conductivity of the skull is low. Therefore, most of the current associated with brain activity is limited to the intracranial space and a highly accurate model for MEG is obtained by considering only one homogeneous compartment bounded by the skull's inner surface [2, 4]. The boundary-element model for EEG is more complex because at least three compartments need to be considered: the scalp, the skull, and the brain.

It is also possible to employ the finite-element method (FEM) or the finite difference method (FDM) in the solution of the forward problem. The solution is then based directly on the discretization of the Poisson's equation governing the electric potential. In this case any three-dimensional conductivity distribution and even anisotropic conductivity can be incorporated [5]. However, the solution is more time consuming than with the boundary-element method. Therefore FEM or FDM have not yet been used in routine source modelling algorithms that require repeated calculation of the magnetic field from different source distributions.

THE INVERSE PROBLEM

The goal of the neuromagnetic inverse problem is to estimate the source current density underlying the MEG signals measured outside the head. Unfortunately, the primary current distribution cannot be recovered uniquely, even if the magnetic field (or the electric potential) were precisely known everywhere outside the head [6].

However, it is often possible to use additional physiological information to constrain the problem and to facilitate the solution.

The Current-Dipole Model

The simplest physiologically sound model for the neural current distribution consists of one or more point sources, current dipoles. In the simplest case the field distribution measured at one time instant is modelled by that produced by one current dipole [7]. The best-fitting current dipole, commonly called the equivalent current dipole (ECD), can be found reliably by using standard non-linear least-squares optimization methods.

In the time-varying dipole model, first introduced to the analysis of EEG data [8], an epoch of data is modeled with a set of current dipoles whose orientations and locations are fixed but the amplitudes are allowed to vary with time. This approach corresponds to the idea of small patches of the cerebral cortex or other structures activated simultaneously or in a sequence. The precise details of the current distribution within each patch cannot be revealed by the measurements, performed at a distance in excess of 3 cm from the sources.

From a mathematical point of view, finding the best-fitting parameters for the time-varying multidipole model is a challenging task. Since the measured fields depend nonlinearly on the dipole position parameters, standard least-squares minimization routines may not yield the globally optimal estimates for these parameters. Therefore, more complex optimization algorithms [9-11] and special fitting strategies [12] have been suggested to take into account the physiological characteristics related to particular experiments.

Current Distribution Models

An alternative approach in source modelling is to assume that the sources are distributed within a volume or surface, often called the source space, and then to use various estimation techniques to find out the most plausible source distribution. The source space may be a volume defined by the brain or restricted to the cerebral cortex, determined from MR images. Distributed source-modelling techniques may provide reasonable estimates of complex source configurations without having to resort to complicated dipole fitting strategies. However, the size of an activated region in the source images does not necessarily relate to the actual dimensions of the source but rather reflects an intrinsic limitation of the imaging method. In fact, without an extremely high signal-to-noise ratio it is unrealistic to claim that it would be possible to determine the extent of a source giving rise to the MEG signals [13].

The first current-distribution model applied in MEG analysis was the (unweighted) minimum-norm estimate [14, 15], one in a group of linear approaches which can be described in a common framework. Here linearity means that the amplitudes of the currents are obtained by multiplying the data with a (time-independent) matrix. This kind of estimates have been employed by several authors [see, e.g. 16, 17, 18].

It is also possible to enter into the source imaging method the assumption that the activated areas have a small spatial extent. For example, the MFT (Magnetic Field Tomography) algorithm obtains the solution as a result of an iteration in which the probability weighting is based on the previous current estimate [19]. Another possibility is to use a probability weighting derived from the MUSIC algorithm, combined with cortical constraints [16].

The l1-norm approach employs the sum of the absolute values of the current over the source space as the criterion to select the best current distribution among those compatible with the measurement [20, 21]. The resulting Minimum-Current Estimates (MCE) are focal and may resemble the time-varying dipole model solution. However, an important difference is that the source constellation is allowed to change as a function of time. Consequently, closeby sequentially activated sources can be identified without the cross-talk problems inherent to the current dipole model.

DISCUSSION

With the advent of whole-head neuromagnetometers it has become evident that MEG is a valuable tool for studying both healthy and diseased human brain. The method is totally noninvasive and the measurements can be repeated as desired without risk. In contrast to PET and fMRI, MEG and EEG reflect the neural activation directly instead of indirect measures of blood flow or metabolism. Thus MEG is not hampered by haemodynamic delays, and it can track brain events at submillisecond time scale. In contrast to the EEG, the tissues outside the brain do not significantly modify the distribution of the MEG signals outside the head. Therefore, it is often easier to interpret MEG than EEG data. At best, a source having small spatial extent can be located with an accuracy of about 0.5 centimeters. In addition to source locations and orientations, MEG also provides quantitative information about activation strengths.

The main contribution to MEG signals derives from tangential and relatively superficial currents in the fissural cortex; these areas are difficult to study with other means, including even intracranial recordings. EEG is the natural companion of MEG because it provides information about radial currents as well. However, the problems in this combination arising from, *e.g.,* larger systematic errors in EEG than MEG forward modelling is still unsolved.

The signals from deep structures are attenuated both due the larger distance from the sensors to the sources and due to the effects of symmetry in the almost spherical head. Furthermore, signals from deeper structures are often masked by simultaneous activity of the cortex. Identification of deep sources reported in some MEG studies relies on accurate forward calculations and on the use of the information obtained with whole-head sensor arrays [22].

In constrast to the EEG electrodes, the MEG sensor array is not fixed to the subject's head. Therefore, a head position measurement is necessary to determine the relative location and orientation of the sensor array and the subject. Even if continuous position measurements of head position were available, it may be extremely difficult to study awake young children and recordings cannot be performed during major epileptic seizures.

It is important to note that MEG signals are typically evident without resorting to complicated statistical analysis apart from signal averaging. Thus it is possible to evaluate the signal quality during the data acquisition. Also, conclusions can be made on the basis of single subject data, which allows studies of individual processing strategies. Furthermore, subtractions between conditions are not needed, although possible – again an important difference compared with PET and fMRI studies.

The ambiguity of the inverse problem has been often cited as a major drawback of both EEG and MEG. Both methods thus have to rely on a restrictive source model and the analysis is rather difficult for a beginner. It is also perhaps confusing to find that several competing source models are available and sometimes the authors introducing them are not clear enough in stating the underlying assumptions and their consequences for data interpretation. Constraints for the inverse problem can be obtained from other imaging modalities, for example fMRI. However, the combination fMRI–MEG is non-trivial because the two methods do not necessarily reflect directly the same brain events.

We expect major future progress in the development of efficient and automated MEG analysis methods, novel experimental paradigms to fully utilize the benefits of MEG, and reliable routines to combine MEG with other imaging modalities. We anticipate such approaches to significantly increase our understanding of human brain functions, especially their temporal dynamics.

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