Functional localization of brain sources using EEG and/or MEG data: volume conductor and source models

Fernando Lopes da Silva
Center Neurosciences, Swammerdam Institute for Life Sciences, University of Amsterdam, 1098SM Amsterdam, the Netherlands
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Abstract

In this overview we examine the basic principles of properties of electroencephalogram and magnetoencephalogram and the corresponding models of sources and of the volume conductor. In particular we show how the dipolar model is anchored in neurophysiological findings and how the different conductivities of the brain and the tissue surrounding it can be estimated. Using these basic models as tools we show how the functional localization of the neural sources of rhythmic activities (alpha and mu rhythms and sleep spindles) and of epileptiform activities can be estimated and integrated with structural data of the brain obtained with MRI.

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1. Introduction

The electrical activity of the brain, that is, the electroencephalogram (EEG), either the ongoing activity or the changes of activity related to a given sensory or motor event — the event-related potentials — gives us the possibility of studying brain functions with a high time resolution, although with a relatively modest spatial resolution. The latter, however, has been improved more recently with the development of the magnetoencephalogram, or MEG, and of more sophisticated source imaging techniques. These new methods allow an analysis of the dynamics of brain activities not only of global brain functions, such as sleep and arousal, but also of cognitive processes, such as perception, motor preparation and higher cognitive functions. Furthermore, these methods are essential for the characterization of pathophysiological processes, particularly with a paroxysmal character, such as epilepsy.

The EEG consists essentially of the summed electrical activity of populations of neurons, with a contribution of glial cells. Considering that the neurons are excitable cells with characteristic intrinsic electrical properties and that the inter-neuronal communication is essentially mediated by electrochemical processes at synapses, it follows that these cells can produce electrical and magnetic fields that may be recorded at a distance from the sources. Thus, these fields may be recorded at short distance from the sources, called the local EEG or local field potentials, or from the cortical surface (the electrocorticogram) or even from the scalp, that is, the EEG in the most common sense. The associated MEG is recorded usually by way of sensors placed at a short distance around the scalp [1].

In order to understand how the electrical and magnetic signals of the brain are generated, it is necessary to examine how the activity of assemblies of neurons is organized both in time and in space, and which biophysical laws govern the generation of extracellular field potentials or magnetic fields.

2. The generation of extracellular fields: the importance of spatial and temporal properties. Models of neural sources and dynamics

It is generally assumed that the neuronal events that cause the generation of electric and/or magnetic fields in a neural mass consist of ionic currents that have mainly postsynaptic sources. For these fields to be measurable at a distance from the sources, it is important that the underlying neuronal currents are well organized both in space and time. The ionic currents in the brain obey Maxwell’s and Ohm’s laws. More extensive treatments of the basic biophysical issues can be found in the list of selected references (e.g., [2,3]).
The most important ionic current sources in the brain result from changes in membrane conductances caused by intrinsic membrane processes and/or by synaptic actions. The net membrane current that results from changes in membrane conductances, either synaptic or intrinsic, can be either a positive or a negative ionic current directed to the inside of the neuron. These currents are compensated by currents flowing in the surrounding medium since there is no accumulation of electrical charge. Let us consider as the simplest case that of synaptic activity caused by excitatory (EPSC) or inhibitory (IPSC) postsynaptic currents. Because the direction of the current is defined by the direction along which positive charges are transported, we may state that at the level of the synapse there is a net positive inward current in the case of an EPSC and a negative one in the case of an IPSC. Therefore, extracellularly, an active current sink is caused by an EPSC and an active current source by an IPSC. Most neurons are elongated cells and thus along the passive parts of the membrane, that is, at a distance from the active synapses, a distributed passive source is created in the case of an EPSC and a distributed passive sink in the case of an IPSC. In this way a dipole configuration is created (Fig. 1). At the macroscopic level, the activation of a set of neurons organized in parallel is capable of creating dipole layers. Important conditions that have to be satisfied for this to occur are the following:

- the neurons should be spatially organized with the dendrites aligned in parallel, forming palissades, and
- the synaptic activation of the neuronal population should occur in synchrony.

Lorente de Nó named the type of electric field created in this way an “open field” in contrast to the field generated by neurons with dendrites radially distributed around the soma which form a “closed field.”

The importance of the spatial organization of neuronal current sources for the generation of electric and/or magnetic fields measurable at a distance can be put forward in a paradigmatic way for the cortex. Indeed, the pyramidal neurons of the cortex are lined up perpendicular to the cortical surface, forming layers of neurons in palissade. Their synaptic activation can occur within well-defined layers and in a synchronized way. The resulting electric fields may be quite large if the activity within a population of cells forms a coherent domain, that is, if the activity of the neuronal sources is phase-locked. In general, we may state that the electric potential generated by a population of neurons represents a spatial and temporal average.

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**Model of the neural sources:**

*the equivalent dipole model*

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Fig. 1. Model cortical pyramidal cell showing the patterns of current flow caused by two modes of synaptic activation at an excitatory (EPSP) synapse localized at the level of the distal apical dendrite and an inhibitory (IPSP) synapse localized at the level of the soma, respectively. Typically, the apical dendrites of these cells are oriented toward the cortical surface. (Left) Current flow caused by the activation of an excitatory synapse causes a depolarization of the postsynaptic membrane, that is, an excitatory postsynaptic potential or EPSP, and the flow of a net positive current, that is, an EPSC. This current flow creates a current sink in the extracellular medium next to the synapse. The extracellularly recorded EPSP drawn at the top left has a negative polarity at the level of the synapse. At the proximal part of the apical dendrite exists a distributed passive current source resulting in an extracellular potential of positive polarity. (Right) Activation of an inhibitory synapse at the soma creates extracellularly at this level an active source and passive sinks at the level of the distal dendrites. Note that both cases show a dipolar source-sink configuration, with opposite polarities. This illustrates the fact that not only the nature of the synaptic potential determines the polarity of the potentials at the cortical surface, but that the position of the synaptic sources within the cortex is also important (adapted from Niedermeyer et al. [4]).
of the potentials generated by the single neurons within a macrocolumn.

A fundamental property of a neuronal network is the capacity of the neurons to work in synchrony. This depends essentially on the way the inputs are organized and on the network interconnectivity. Thus, groups of neurons may work synchronously as a population due to mutual connections.

These connections range over distances in the order of magnitude of hundreds of micrometers, and this determines the characteristic length of intracortical interactions. It is not simple to relate directly the dynamic behavior of a neuronal network to the basic parameters of neurons and synapses. In order to construct such relationships, basic physiological and histological data have to be put together very much as the pieces of a puzzle. However, the available knowledge of most neuronal networks in terms of detailed physiological and even histological information is still rather incomplete. To supplement this lack of specific knowledge a synthetic approach can be useful. This implies the construction of connectionist models of neuronal networks using all available and relevant data. Such models can be of practical use to obtain a better understanding of the main properties of a network. Indeed, a model offers the possibility of studying the influence of different parameters on the dynamic behavior of the network and of making predictions of as yet unexplored properties of the system, which may lead to new experiments. In this way, EEG signals, particularly local field potentials, can also be modeled. Thus, hypotheses concerning the relevance of given neuronal properties to the generation of special EEG features may be tested.

In general terms we have to consider that neurons, as integrative units, interact with other neurons through local circuits, as well excitatory as inhibitory. In a neuronal circuit, feedforward and feedback elements have to be distinguished. In particular, the existence of feedback loops can shape the dynamics of a neuronal network affecting its frequency response and even create the conditions for the occurrence of resonance phenomena and other forms of oscillatory behavior. Furthermore, we should note that the transfer of signals in a neuronal network involves time delays and essential nonlinearities. This may lead to the appearance of nonlinear oscillations and, possibly even to what is, in mathematical terms, called chaotic behavior.

In recent years we have learned a lot about these issues with the advent of the theory of nonlinear dynamics. This has resulted in the application of nonlinear time series analysis to EEG signals with the aim of estimating several nonlinear measures to characterize different kinds of EEG signals. This matter is the object of recent interesting studies reported in specialized publications where the question “chaos in brain?” is discussed. We stress here only that a theoretical framework based on the mathematical notions of complex nonlinear dynamics can be most useful to understand the dynamics of EEG phenomena. In this context we may obtain an insight into how different types of oscillations may be generated within the same neuronal population and how such a system may switch from one type of oscillatory behavior to another one. This occurs, for example, when an EEG/MEG characterized by alpha rhythmic activity suddenly changes into a 3-Hz spike-and-wave pattern during an absence seizure in epileptic patients. Based on the use of mathematical nonlinear models of neuronal networks it is possible to formulate hypotheses concerning the mechanisms by means of which a given neuronal network can switch between these qualitatively different types of oscillations. This switching behavior depends on input conditions and on modulating parameters. Accordingly, such a switch can take place depending on subtle changes in only one, or more, parameters. In this respect the most sensitive parameter is the neuronal membrane potential that in the intact brain is modulated by various synaptic inputs. This is what is called a bifurcation in the theory of complex nonlinear dynamics. Typically, the change of oscillation mode may be spectacular whereas the initial change of a parameter may be minimal. These issues are treated in more detail in: Lopes da Silva et al. [5] and Suffczynski et al. [6].

3. Models of the volume conductor with layers of different conductivities

A basic problem in EEG/MEG is how to estimate the neuronal sources corresponding to a certain distribution of electrical potentials or of magnetic fields recorded at the scalp. This is called the inverse problem of EEG/MEG. It is an ill-posed problem that has no unique solution. Therefore, one must assume specific models of the sources and of the volume conductor in order to estimate approximate solutions. The simplest source model is the equivalent current dipole. However, it should not be considered that such a model means that somewhere in the brain there exists a discrete dipolar source. It just means that the best representation of the EEG/MEG scalp distribution is by way of an equivalent dipolar source. The latter describes in the sense of a best statistical fit the centroid of the dipole layers that are active at a certain moment. In any case the estimation of equivalent dipole models is only meaningful if the scalp field has a focal character and the number of possible active areas can be anticipated with reasonable accuracy. An increase of the number of dipoles can easily lead to rather complex and ambiguous interpretations. Nevertheless, methods have been developed in order to obtain estimates of multiple dipoles with only the a priori information that they must be located at the surface of the cortex. An algorithm that performs such an analysis is multiple signal classification. An alternative approach is to use linear estimation methods applying the minimum norm constraint to estimate the sources within a given surface or volume of the brain. Currently, new approaches are being explored using combined fMRI and EEG/MEG recordings.
in order to create more specific spatial constraints to reduce the solution space for the estimation of the underlying neuronal sources.

In general, the problems put by the complexity of the volume conductor, including scalp, skull, layer of cerebrospinal fluid and brain, are easier to solve in the case of the MEG than of the EEG since these different media have different conductivities that affects the EEG much more than the MEG. In a recent study the conductivities of the skull and the brain were estimated “in vivo” using two different methods based on spherical head models [7]. The first method uses the principles of electrical impedance tomography to estimate the equivalent electrical resistivities of brain ($r_{\text{brain}}$), skull ($r_{\text{skull}}$) and skin ($r_{\text{skin}}$). The second one estimates the same parameters through a combined analysis of the evoked somatosensory cortical response, recorded simultaneously using MEG and EEG.

The electrical impedance tomography results show a wide variation of the ratio $r_{\text{skull}}/r_{\text{brain}}$ among subjects (average=72, S.D.=48%). However, the $r_{\text{skull}}/r_{\text{brain}}$ ratios of the individual subjects are well reproduced by combined analysis of somatosensory evoked fields (SEF) and somatosensory evoked potentials. These results indicate that the $r_{\text{skull}}/r_{\text{brain}}$ variations over subjects cannot be disregarded in solving EEG inverse problem when a spherical model is used. One can say that the major advantage of MEG over EEG is the relative ease of source localization with the former. This means that when a dipole source algorithm is used on the basis of MEG recordings, a simple homogeneous sphere model of the volume conductor is usually sufficient to obtain a satisfactory solution. The position of the sources can be integrated in MRI scans of the brain using appropriate algorithms.

4. Functional localization of brain oscillatory activities: EEG/MEG and functional MRI

A basic question in EEG/MEG studies is whether the main rhythmic activities, alpha and mu rhythms on the one hand, and sleep spindles on the other, are generated in distinct or overlapping cortical areas. In order to solve this question, advanced spatiotemporal analysis methods are necessary. The recent development of a new algorithm [8] with the aim of estimating sources of large data sets, as is the case with this kind of signals, led us to investigate this issue, namely, whether generators of spontaneous MEG/EEG alpha and mu rhythms and sleep spindles are distributed over distinct or overlapping cortical areas.

The basic approach consists in finding good fitting dipoles using a dipole model applied to each time sample. First, the data are band-pass-filtered to select the rhythm of interest. Then a global search algorithm is applied, based on

![MEG: distribution of sources per voxel](image)

Fig. 2. Dipole density plots of EEG sleep spindles, visual alpha and mu rhythms of subject 4. Voxel containing a relative high number of dipoles are represented in red. Blue voxels contain relatively few dipoles. Voxel containing less than 10% of the maximal number of dipoles are omitted. These plots show that there is no overlap between alpha and mu dipoles. Furthermore, the “hot spot” of the alpha rhythm was located more superficially than that of sleep spindles, whereas the spindle cluster was more widespread than that of the alpha rhythm and involved the frontal cortex (adapted from Manshanden et al. [9]).
precomputed lead fields on a fixed grid, to obtain a good initial guess for the nonlinear dipole search. Finally, the dipole search is applied on those samples that have a low initial guess error. The equivalent dipoles encountered are then plotted on the corresponding MRI slice of the brain as shown in Fig. 2.

It is important to emphasize what equivalent dipolar sources of ongoing brain activity mean. Sleep spindles, alpha rhythms and mu rhythms are spontaneously occurring brain rhythms that can be recorded from the scalp. This indicates that extended cortical areas are involved in the generation of these signals. The use of equivalent dipoles as source models for these distributed brain activities yields an oversimplified solution of the problem of determining the underlying sources of these signals. The equivalent dipoles should be viewed just as descriptors of the ‘center of gravity’ that best describe, in a statistical sense, the spatial distribution of the corresponding active cortical area at a given time. The position of the dipoles with respect to the cortical surface depends on the extent and geometry of the activated cortical area: superficially positioned dipoles (i.e., near to the cortical surface) like those of the mu rhythm, correspond to more localized cortical activity, while deep-lying dipoles, like those of sleep spindles, represent rather the activity of extended cortical surfaces. Thus, dipole locations give only an approximation of the localization of the active brain area and the extension of the area.

When comparing the results of the alpha rhythms and of the sleep spindles (Fig. 2) we should emphasize that there is no overlap of the centers of gravity of these two kinds of rhythms. This indicates that different regions of the cortex are involved in the generation of these brain rhythms. The same applies to the mu rhythm that appeared to be generated in a distinct brain region than the alpha rhythm and the sleep spindles. The superficial location of the mu rhythm dipoles (especially in MEG) suggests that the mu rhythm is generated in a relatively well-localized cortical area. Thus, the equivalent dipole model appears to be a reliable model for the estimation of the mu sources. The close spatial relation of the MEG mu rhythm dipoles with the dipoles of the N20 component of the medial nerve somatosensory evoked fields demonstrates that the mu rhythm arises from the cortex around the central sulcus. Currently, the correlations between dipolar sources of the alpha rhythm
EEG and the blood oxygen level-dependent signal of fMRI, recorded simultaneously, are being studied systematically in order to better understand the functional relations between both kinds of physiological signals and their respective spatial distributions [11]. Preliminary results show a good correspondence between the spatial distribution of the EEG alpha dipolar sources and the fMRI voxels, which display a significant negative correlation between alpha power and the magnitude of the blood oxygen level-dependent signal (Gonçalves et al., in preparation).

5. Functional localization of epileptiform transients: contrast between EEG and MEG

Source localization of spontaneously occurring interictal epileptiform transients often becomes a tedious exercise, involving tens or hundreds of individual source solutions of an equal number of paroxysms per data set. Moreover, the daily practice in source localization of individual paroxysms frequently yields solutions too dispersed within the brain to be plausible. In addition, solutions may be identified to arise from plainly impossible sources, for example, bone tissue, ventricles, or white matter. Thus, when the number of recorded discharges is large it is feasible to apply data reduction. For this purpose we used the cluster analysis methodology [10] to whole-head MEG recordings. The cluster analysis classified the paroxysms into groups with similar magnetic field characteristics (Fig. 3). This in turn warrants the use of averaging the data in each group to improve the signal resolution and the quality of equivalent source estimates. In our study cluster analysis and subsequent dipole modeling yielded clinically plausible equivalent sources for the patients that showed a structural lesion on neuroimaging. In addition, these results suggest that objective cluster analysis of large numbers of spontaneously occurring epileptiform paroxysms on MEG records obtained from well-documented cases of lesional and nonlesional neocortical localization epilepsy shows a high degree of convergence with the purported zone of ictal onset as identified on scalp video/EEG seizure monitoring, even in the absence of a structural lesion on neuroimaging. The method is automated and therefore saves a lot of analysis time compared with the laborious work of manual spike classification. Our procedure of spike grouping combined with averaging of similar spikes and subsequent dipole modeling also provides insight in the spatiotemporal spreading behavior of spikes which in turn gives information about the cortical networks involved during the interictal discharges and presumably also the epilepsy of the patient. A prospective study for the evaluation of the specificity and sensitivity of our approach in such patients is therefore now in order.

References