Section 1

The method

Contributors

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1

Basic concepts

Magnetoencephalography (MEG) is the noninvasive method of recording from the head surface the magnetic flux associated with intracranial electrical currents. An MEG recording resembles the familiar electroencephalogram (EEG) and is used in two ways. The first use, similar to that of conventional EEG and evoked potentials (EPs), is for detecting the presence of signs of abnormality in spontaneous brain "activity" (e.g., epileptiform spike-and-wave patterns) or in evoked-response activity (e.g., delayed or low-amplitude somatosensory activity averaged in response to multiple median-nerve stimulations). The second use of MEG recording is for estimating the locations and time courses of sources of either spontaneous or evoked events of interest, a process called magnetic source imaging (MSI). This second use renders MEG a unique supplement to – and, in some cases, a substitute for – EEG and EPs. Although MEG denotes processes involving the recording of signals and their evaluation as they appear on the head surface (sensor space) and MSI refers to processes involving the localization of the sources of those signals and the construction of "maps" or "images" of brain activity and activation, in practice – and even in formal discourse – these two terms (MEG and MSI) are often used interchangeably.

The source of the activities recorded by MEG originates from an electrochemical process called neural signaling. Of the three main processes that occur in the brain, neural signaling is the most basic and direct. The other two processes, metabolism and blood flow, have rates that *depend* on neuronal activity and thus are imaged indirectly through methods such as positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI). The specific events that constitute signaling among neurons include the release of neurotransmitters into synapses and the flow or movement of ions within and outside of cells, i.e., electrical currents.

These electrical currents are associated with magnetic signals that, much like the light reflected from an object, radiate from their point of origin inside

the brain to the outer brain surface where, during MEG, they are captured by special sensors (magnetometers or gradiometers). These magnetic signals do not interact causally with the biological events with which they are associated (i.e., the signaling or communication among neurons) and, therefore, do not affect the neuronal-signaling events, any more than light reflected from an object changes the nature of the object. Because MEG/MSI records these causally noninteractive magnetic signals as they naturally occur, without the mediation of any additional form of energy – as is necessary for PET and fMRI, with radiopharmaceuticals, strong static magnetic fields, and radiofrequency pulses – testing is completely noninvasive.

The events of neuronal signaling are continuous, but the rates at which they occur vary from time to time and from one brain region to the next so that each brain structure displays a characteristic baseline activity. Capturing a baseline–activity profile is the most basic step in functional imaging.

Almost as basic is the recording of noticeable spontaneous deviations from the expected baselines in particular areas of the brain – indicative of either hypoactive or hyperactive signaling. These deviations are of two kinds. The first is chronic and constant over time; the second is phasic, appearing intermittently. An example of the former is focal slow-wave activity, where a particular brain area, usually bordering a lesion, is constantly producing low-frequency, high-amplitude signals. One example of the latter type of deviation is the epileptiform spike-and-wave discharge, which will be dealt with extensively in a later part of this book.

In addition to recording baseline activity of the brain and the spontaneous chronic or phasic deviations from baseline, capturing activities that are specific to the execution of particular behavioral or psychological functions – whether simple sensory and motor or "higher" cognitive functions – is of special interest. Such activities are evoked either by environmental events (e.g., sensory stimuli) or by internal processes (e.g., decisions or thoughts). To facilitate discussion, we will refer to all function-specific activities as **activation**.

Moreover, two types of activation can be distinguished: those that are stimulus and motor-act specific, corresponding to simple sensory and motor functions; and those that are task specific, corresponding to higher functions, such as language, that may or may not be occasioned by environmental events.

Describing sources of activity or of activation accurately – or, alternatively, constructing functional images of high fidelity – constitutes a very serious challenge for MEG/MSI. Fidelity depends on both reliability and validity. Determining *reliability* logically comes before determining validity and is usually easier to solve. The question can be stated as follows. Provided we image the same brain circuitry or brain mechanism several times and use the same instruments and procedures, how consistently do we obtain the same image? Clearly, if images of the same mechanism – or maps of the same activation

pattern – differ, our method of imaging is not trustworthy. How trustworthy or reliable the particular procedures of MEG/MSI imaging are can be readily ascertained by replication, and in many cases they have been (please see the following chapters).

The question of determining *validity*, on the other hand, is much more difficult to answer. Suppose we intend to capture the pattern of brain activation that corresponds to the function of perception of speech. Does our image represent the pattern specific to that function only, or **also** to, say, the function of attention, or **instead** to the function of memory? Or, how accurately and to what degree of completeness and detail does the image represent the brain-activation pattern we intended to capture?

The first requirement for answering such questions is to know what constitutes the requisite degree of detail. If all we require is an outline of regions of the brain most activated, a rather coarsely grained map of the activation pattern would be satisfactory. However, if we wish to image the entire brain circuitry that mediates some particular function, the picture must have a much greater degree of detail and must show not only which structures are activated but also how much they are activated relative to one another, for what duration, and in what order. The image in this case must possess the greatest possible temporal and spatial resolution.

Spatial resolution may be conceived in two alternative ways. First, the term may be used – and most often is – to refer to the minimum size of an area of brain activation that can be differentiated from adjacent areas of activation, i.e., the minimum size of pixels, two-dimensional (2-D) picture elements, or of voxels, three-dimensional (3-D) volume elements, in which different degrees of activation can be distinguished. Second – and less commonly used – spatial resolution may refer to how many areas (pixels or voxels) of a given size can be simultaneously assigned different degrees of activation, i.e., what is the maximum number of activated areas that can be monitored and differentiated simultaneously. The two definitions of spatial resolution are clearly different; therefore, if the meaning of the term is not explicit, misunderstandings may occur. For example, according to the first definition, one can claim that the method of MEG/MSI, when the single dipole model is used to represent brain sources (see below), may provide images of much higher resolution than those of PET or fMRI. But, according to the second definition, precisely the opposite is true: MEG/MSI, again when utilizing discrete source models (see below), has the poorest spatial resolution among the imaging methods. MEG/MSI cannot detect all areas of the brain that are simultaneously active, especially those most distant from the head surface, a feat that can be accomplished easily with the other functional neuroimaging methods.

The *temporal resolution* of MEG/MSI is very high, in the millisecond (ms) or submillisecond range. The magnetic flux that MEG/MSI records varies continuously over time, is coincident with the rise and evolution of the intracranial

currents that produce the flux, and may be sampled in the kilohertz (kHz) range. In contrast, the temporal resolution of PET and fMRI is in the order of minutes or seconds, rendering them incapable of imaging rapidly changing patterns of brain activity or activation like those produced by epileptiform events or normal responses to sensory or language stimuli.

2

The nature and origin of magnetic signals

Signaling among neurons constitutes the most basic form of brain activity and activation imaged today and consists of electrochemical events that take place at synapses and in the axons and dendrites of neurons. Although neurotransmitter release and uptake at synapses are caused by electrical activity (i.e., action potentials), these events do not involve electrical activity directly. Dendritic and axonal currents are produced by the movement or flow of electrically charged particles, or ions, either between "electrical synapses" or within the axons or the dendrites of neurons, resulting in a physical, potentially measurable quantity, namely, an electrical current.

Were we to view directly the variation of the electrical currents at each and every cell or set of cells in the brain, referred to as current sources, and were we to plot these variations as a function of time as they sum on the scalp surface, we would obtain the familiar picture of activity we obtain with multichannel EEG. We would find that the amount of signaling the brain is producing changes from moment to moment in an apparently random manner but within certain limits.

We consider that variation is apparently random because we simply do not know what the purpose of each ripple or surge of activity is or to what end each of the intracranial sources that contribute to the signals is signaling at each point in time. We assume, however, that signaling always serves some purpose, is always the necessary condition of some function that the brain is engaged in. For example, temporal variations in signaling could be associated with external stimulation, initiation of movement, regulation of temperature, thinking, attending, memorizing, or any other activity or combination of activities that may transpire at any given time. The pattern of activity or signaling throughout the brain that corresponds to each of the many functions that is taking place simultaneously is contained in this apparently random variation, and special procedures are necessary to isolate it, extract it, and image it.

At times, however, abnormal deviations in activity take place that clearly exceed the normal range of variation; these deviations do not require any special procedures for their identification, isolation, or extraction.

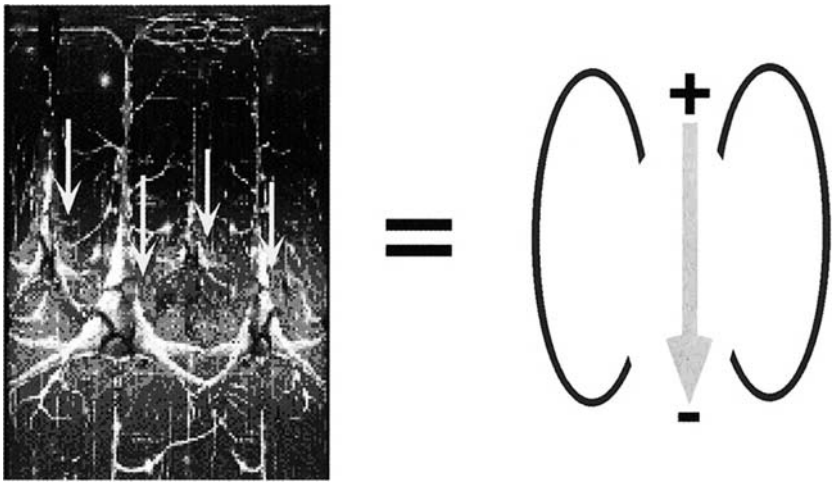

Fig. 2.1. A schematic representation of a set of neurons whose apical dendrites have a parallel orientation. Ion flow within these dendrites renders the set equivalent to a current dipole shown on the right.

Let us then consider what might be the nature of such signs of deviant signaling and how they may be captured in an MEG record. Assume that a large set of cells that typically are not synchronized begin to signal in unison. Their combined electrical currents will create a large deviation, much beyond the typical range. Such a phasic deviation could well be an epileptiform event: a spike-and-wave discharge.

The questions that can be addressed through the use of MEG in such a case are the following. Where is the source of the deviation, is more than one source responsible, what is the pattern of this abnormal activity of the brain? Needless to say, the pattern of activity of the brain itself is hidden from our view. We have no direct access to the source currents themselves; we have only indirect access that is defined by the degree that these currents are associated with other forms of energy that can travel outside the head where they can be captured and recorded. In this case, the two forms that act as echoes or shadows of the actual but hidden source currents are the secondary, or volume, currents and magnetic flux. Volume currents are recorded through the familiar method of EEG; magnetic flux, through MEG.

When cells in a set are activated in unison, they create current that has a particular direction: from the dendrites to the axon terminals. If the cells in the set have an approximately parallel orientation (as is the case with cells forming cortical columns), their combined current can be viewed as a single current dipole, as shown in Fig. 2.1.

Primary currents give rise to volume currents. Volume currents are extracellular and propagate outside the nerve cells throughout the brain volume. They

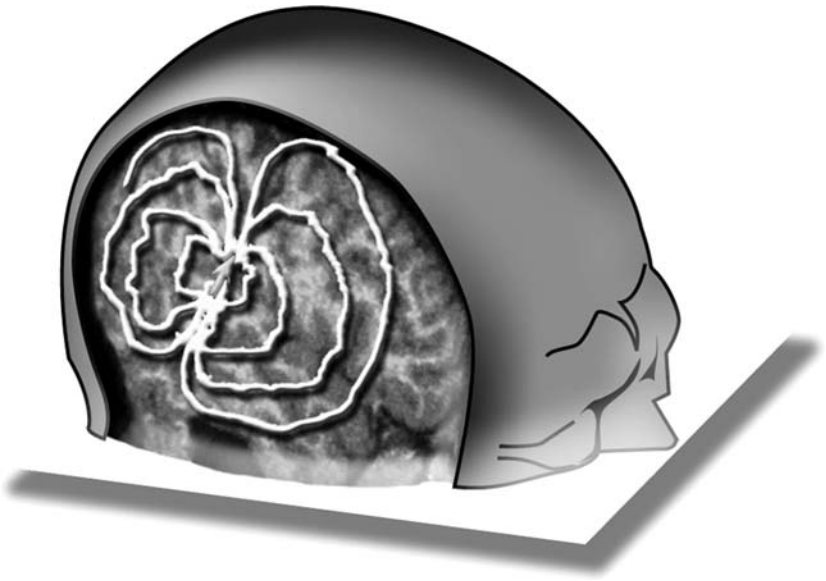

Fig. 2.2. A schematic representation of source (arrow) and volume currents inside the head.

form irregular patterns because they follow lines of least electrical resistance as they spread away from the source and encounter the irregularly arranged layers of various tissues (white matter, gray matter, meninges, cerebrospinal fluid) that offer different degrees of resistance (see Fig. 2.2).

As the volume currents spread, they encounter the much more resistive barrier of the skull bones. There, they are distorted further because the skull is not uniformly resistive, is least resistive in the apertures and most resistive in the thickest regions. As these currents emerge on the head surface, greatly distorted and attenuated, they may be recorded as voltage differences among the electrodes of the conventional EEG method.

The shape of the voltage distribution of these volume currents, recorded by multiple EEG electrodes, imperfectly mirrors the shape of the primary currents from which the distribution arises. This imperfect relation between the surface voltage distribution and the primary, or source, currents makes obtaining functional images of high fidelity technically challenging. Reducing this difficulty is the main contribution of the MEG method. With MEG we aim to capture the surface distribution of the magnetic flux.

As shown in Fig. 2.3, a current is always associated with a magnetic field perpendicular to its direction. The relative direction of the current and the magnetic flux are described by the right-hand rule, which states that, if the direction of the thumb of the right hand represents the direction of the current,

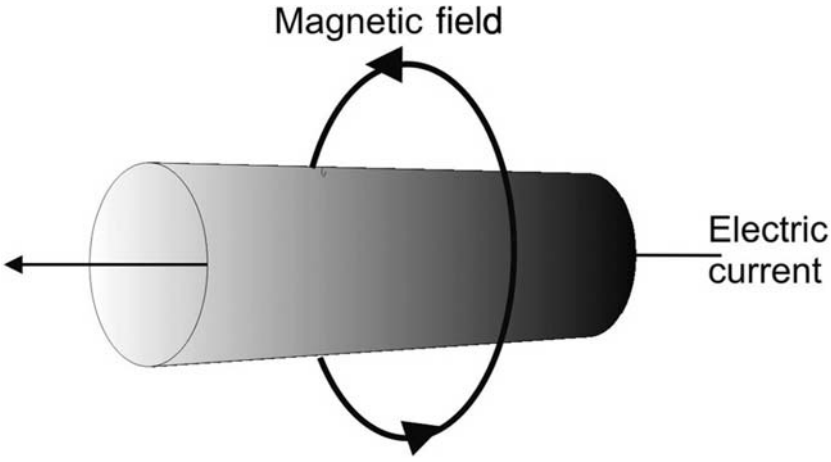

Fig. 2.3. A moving charge (i.e., electric current) induces a magnetic field.

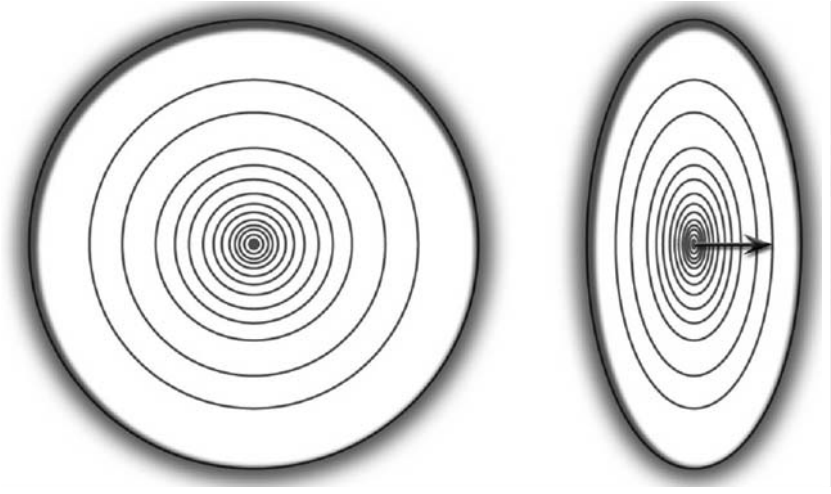

Fig. 2.4. The source current (arrow) and the magnetic flux density lines it produces.

the direction of the curled fingers indicates the direction of the associated flux.

The magnetic flux density – or, equivalently, the magnetic field strength – is proportional to the strength of the source current measured in ampère meters (A m) and dissipates as a function of the square of the distance from the current source, as shown (arrow) in Fig. 2.4 where the source strength is pictorially represented by the density of flux lines (circles).

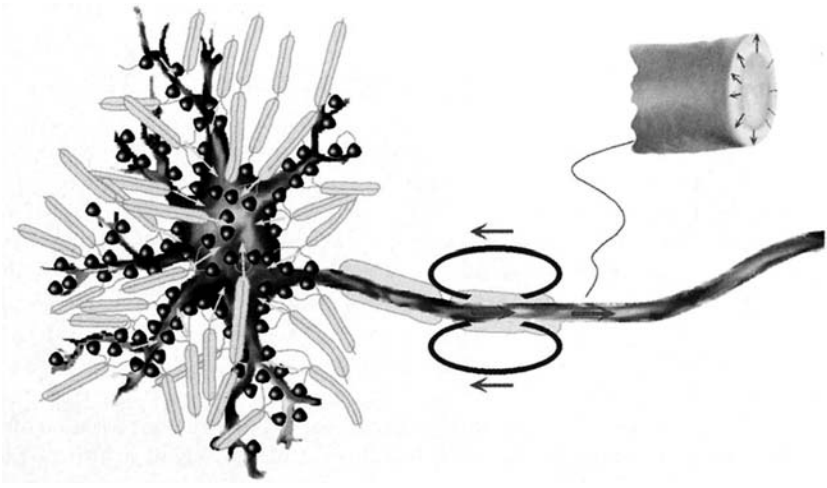

Fig. 2.5. A schematic representation of a neuron showing the axial symmetry of currents moving down its axon.

The property of proportional dissipation of magnetic fields is very important because the constituent flux lines are not distorted as they emerge from the brain source to the head surface. Flux lines could – and often do – result in geometrically regular surface distributions from which we can construct fairly accurate functional images.

The reason flux lines are not distorted as they pass through the various tissue layers is that all biological tissues offer practically zero resistance to them. The magnetic permeability of tissues is practically the same as that of empty space.

Both source and volume currents produce magnetic fields. However, the fields that emerge on the head surface are due mostly to source currents, although volume currents may contribute appreciably. The contribution of volume currents to the magnetic field depends on the shape of the head. Volume currents, unlike source currents, have a high degree of symmetry in the approximately spherical shape of the conductor (i.e., the head) within which they pass; therefore, the magnetic fields they produce tend to be relatively simple. Consequently, the greater the deviation of a particular head from a spherical shape, the greater the contribution of volume currents to the recorded magnetic fields. For more details on this issue, see the report by Hämäläinen and coworkers [1].

Of the three component currents – dendritic, synaptic, and axonal – that constitute source activity, the dendritic current contributes most to the flux that exits the head. Synaptic and axon-terminal currents are not reflected in the surface flux mainly because they are randomly oriented with respect to each other, their associated magnetic fields cancel out, as shown in Fig. 2.5.