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9.5 Magnetoencephalography: A New Window into the Functional Organization of the Cerebral Cortex

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Physiological investigations are not performed as an end in themselves to satisfy the scientist's thirst for knowledge, although many studies may give that impression. Eventually, a new technique is also going to be evaluated in a clinical environment. Electric phenomena are the first physical quantities used for studying physiological processes, and innumerable studies, especially microelectrode studies on the cellular level, have unveiled the function and functional organization of the central nervous system. However sophisticated a technique may be, its applicability to studies in humans is limited by its invasiveness. In contrast to animal experiments, the use of electrical potentials for diagnostic purposes must be restricted — with few exceptions — to potentials recorded from the surface of the body. Their interpretation has for decades been a merely pragmatic attribution of distinct features of the recorded waveforms to specified generator structures.

The development of several imaging techniques — especially magnetic resonance imaging (MRI) and positron emission tomography (PET) — has opened previously unimagined possibilities of visualizing not only structures but also functional processes especially of the brain. The temporal resolution of these techniques, however, is unsatisfactory, creating the need to develop techniques capable of visualizing or more precisely localizing the sources which generate the surface-recorded electrical potentials. Potential differences recordable at the surface are, however, a rather indirect outcome of the underlying processes: intracellular currents of high-density flowing in the excited portions of dendrites, whose spread in the volume conductor body is substantially distorted owing to tissue layers of different conductivity and anisotropy. In contrast to this, an immediate outcome of the intracellular currents are magnetic signals whose spread is undistorted by the body's physical properties. With the advent of the supraconducting quantum interference device (SQUID) these extremely weak biomagnetic signals became detectable.

Fig. 9.5–1. Example of the high spatiotemporal resolution of neuromagnetic source localization. *White dots*, location estimates for successive peaks of the human gamma-band field, forming an arcing trajectory which follows the surface of the transverse temporal gyrus. (From Pantev et al. 1991)

Only true imaging techniques such as computed tomography (CT), MRI, and PET offer the reconstruction of arbitrary slices — tomograms — of the investigated structures. Although often referred to as source imaging, the recording of neuromagnetic — as well as neuroelectric — data from the surface of the head is not sufficient for the spatial imaging of the active generator structures. It is rather the attempt to determine a solution of a set of differential (Maxwell's) equations which, by their nature, is not unique. This "inverse problem", which was first formulated by Helmholtz in the middle of the last century, results from the fact that an infinite number of source configurations within the body can produce exactly the same distribution of electric and magnetic activity on its surface. In many cases, however, it is possible to construct constraints such that only one solution remains which satisfies the equations. Hence, the spatiotemporal distribution of electromagnetic generators becomes unique. The simplest constraint is the assumption of a single focal source which can be modeled with good approximation by a current dipole — regardless of the real shape of neuronal arrays. More sophisticated approaches utilize the knowledge of anatomical structures. It is obvious, for instance, that areas covered by ventricles or white matter do not incorporate active structures. More explicitly, it is reasonable to assume that only current dipoles with an orientation perpendicular to the surface of gray matter contribute to electromagnetic activity on a macroscopic scale. The individual anatomical information is necessary for three different reasons: to construct a realistic body model, to retrieve constraints for a realistic source configuration, and to project the computed source location(s) onto the corresponding anatomical structures. This information is available only from three-dimensional reconstructions of MRI tomograms. Therefore, neuromagnetic (or neuroelectric) source localization must rely on its being combined with a real imaging technique. If the sources can be restricted to cortical structures (which is generally the case for potentials or fields related to cognitive processes), and if both electroencephalogram (EEG) and magnetoencephalogram (MEG), measured simultaneously from many different sites, can be integrated into one unitary model for the solution of Maxwell's equations, then this solution becomes unique. The resulting cortical map, although similar to a PET scan in its appearance, has the unique advantage of not displaying a slowly changing cerebral blood flow but of imaging the neuronal activation changing within a fraction of a second. The image of static activity, averaged across minutes in PET, is replaced by a moving image, unique in respect to temporal and spatial resolution and allowing the detection of the functional sequence in patterns of neural mass activation (Fig. 1).

Neuromagnetic fields are extremely weak. With approximately 1–5 pT (10^{-12} Tesla) for the MEG and some 10 to some 100 fT (10^{-15} Tesla) for cortical evoked magnetic fields, the amplitudes of neuromagnetic signals are not only far below that of the earth magnetic field (seven to nine orders of magnitude) but also considerably below that of environmental noise. This implies that not only an extremely sensitive instrument — as given by the SQUID — is required, but also an effective shielding — a magnetically shielded room — to protect against strong environmental noise.

The distribution pattern, on which even the simplest source localization is based, requires measuring of the magnetic signal from multiple positions. Measurement of both MEG and EEG over the whole neurocranium facilitates arriving at a unique solution. Multi-sensor instruments have been developed during the past decade allowing the measurement of the magnetic field simultaneously from up to 37 different positions (Fig. 2). The latest developments are whole-head systems allowing a simultaneous scanning of the entire neurocranium. These powerful neuromagnetic instruments and the localization techniques associated with them offer the neuroscientist a novel and unique view of cerebral processes and functions in humans.

What other advantages of the MEG justify the use of such an expensive instrument? What are the disadvantages? Distinct advantages are the

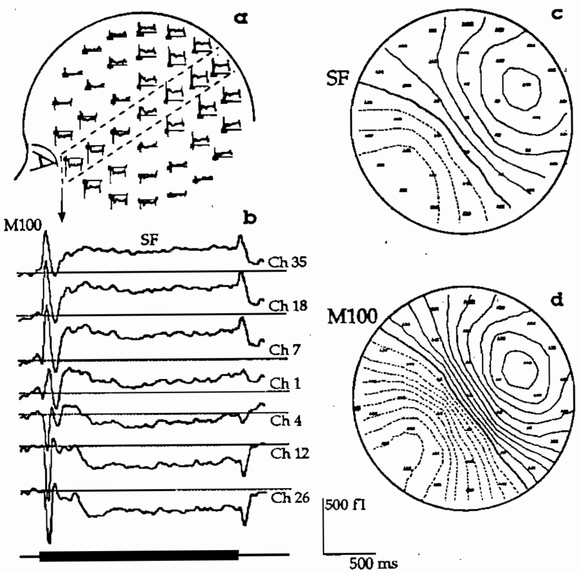

Fig. 9.5–2. **a** Projections onto the outline of the head of a set of 37 averaged waveforms (length 2400 ms), recorded over the left hemisphere in response to a 2s, 1000 Hz tone burst as indicated at the bottom of **b**. **b** Waveforms recorded along a line connecting the minimum and the maximum of the sustained field pattern (enclosed in *dotted lines* in **a**) are represented in magnification, clearly showing polarity reversal (or, more precisely, reversal of field direction) of both the transient on- and off-responses and the sustained field (SF). **c** The surface distribution of the magnetic field is shown in terms of isofield contour maps for selected instants of time (sustained field at a latency of 1300 ms). **d** M100 at a latency of 94 ms. Outwardly going flux marked by *solid lines*, inwardly going flux by *dotted lines*. Spacing between two adjacent isocontour lines is 50 fT. (From Pantev et al. 1993b)

easy modeling for the magnetic signal (the body is transparent for such low-frequency magnetic fields), the higher relative precision of localization, and the faster placement of the neuromagnetometer system without many of the problems of artifact contamination inherent in electrode-based techniques. The major restriction of neuromagnetic measurements is that current dipoles oriented normally to the surface do not produce a magnetic field outside of the body. This restriction is not that crucial, however, in the case of the cerebral cortex. Firstly, approximately two thirds of the cortical tissue is located in sulci. Secondly, the major direction of cortical current flow is, owing to the cortical cytoarchitecture, normal to the cortical surface. Thirdly, the tangential component of an arbitrarily oriented dipole corresponds to the total dipole vector weighted by the sine of the angle by which it is tipped from the normal to the surface. This implies that magnetically detectable cortical sources encompass not only current flows directed tangentially to the surface of the head, but even these sources contribute 50% or more of the total dipole vector whose deviation from the normal to the surface is not less than 30°. Hence, cortical activity is a principal target for tracking functional activation with neuromagnetic measurements.

It goes without saying that MEG measurements cannot compete with microelectrode studies, which certainly provide a main route to the functional organization of cortical structures. However, with microelectrodes it is possible only to monitor a small fraction of actual ongoing activity. Furthermore, knowledge of functional properties of a few single neurons is not sufficient to understand neural nets, and the study of neural nets is insufficient to grasp the dynamics of neural mass action. The magnetic sensors, with a diameter of approximately 20–30 mm, pick up activity from a very large number of active neurons. This activity is not restricted to that of the investigated structures but also incorporates spontaneous activity from surrounding areas. With appropriate experimental paradigms, however, a simultaneous activation of a circumscribed neuronal population can be achieved. The activity of a larger number of similarly oriented, simultaneously active individual neuronal current dipoles can be modeled after the activity of a single equivalent current dipole (ECD), which corresponds to the vectorial integral of all individual dipole vectors. Regarding the complexity of cerebral processes initiated by external stimuli, especially of cognitive processes, it is obvious that a single, or prevailing, source is rather an exception than the rule. Modeling multiple dipoles cannot be a solution unless, as previously mentioned, sufficient restrictions for source configurations, retrieved from individual MRI tomograms and physiological knowledge can be implemented in the model (Lütkenhöner et al. 1992). In addition, the use of distributed source models is another way of treating multiple sources (Grunwald et al. 1992).

Neuromagnetic research originated in the exploration of the spontaneous MEG, followed by the investigation of auditory evoked magnetic fields. Since then magnetic fields elicited by almost all major stimulus modalities have been investigated (visual, somatosensory, olfactory, pain). Magnetic fields preceding and accompanying movements have been studied as well (see Hoke et al. 1992, for a survey of current research).

Where neuroelectric techniques have failed, neuromagnetic measurements have succeeded in demonstrating the cortical representation of specified stimulus features in humans, as well as in separating cortical sources for different components of the evoked fields. These achievements are mainly due to the high precision in relative localization, which is of the order of few millimeters. One of the most impressive examples is the study of the tonotopic organization of the primary auditory cortex. After several futile efforts to reveal tonotopicity in humans by means of neuroelectric measurements or PET (for more information see Pantev et al. 1988), Romani et al. (1982) and Elberling et al. (1982) succeeded with neuromagnetic measurements in demonstrating a tonotopic organization of the human auditory cortex: the depth of the ECD increases with the logarithm of stimulus frequency. A decisive step forward was taken by Pantev et al. (1989a). According to the place principle of the classical hearing theory, the physical entity frequency is encoded in the auditory periphery as place information which is decoded in more central parts of the auditory system to form the perceptual entity pitch. This relation turned out to be true only for pure-tone signals (spectral pitch); it can be quite different in the case of complex auditory stimuli (virtual pitch), thus requiring a multistage process for pitch formation. Neuromagnetic measurements have shown that the tonotopic organization of the primary auditory cortex reflects the pitch rather than the frequency of the stimulus, implying that the pitch formation process takes place in subcortical regions.

Another discovery also concerning functional organization first achieved with neuromagnetic measurements was that of an amplitopic organization of the human primary auditory cortex (Pantev et al. 1989b). In contrast to the place coding of intensity in the auditory periphery, where increasing intensity shifts the place of maximal excitation into the same direction as does increasing frequency, the ECD depth of wave N_1m is shifted for increasing intensity in opposite direction as for increasing frequency. This implies that the unidimensionality of frequency and intensity coding in the auditory periphery is, at cortex, abandoned in favor of a bidimensional representation of the two stimulus features.

Coherent oscillatory brain activity in the 20–90 Hz frequency (gamma) band is now being regarded as a possible fundamental physiological mechanism which may bind features to form objects. An emerging consensus maintains that oscillatory rhythms play an important role in perception and attention and may support the encoding of spatial and temporal order during behavioral adaptation. Such activity was first described for the olfactory (Adrian 1942) and visual (Gray et al. 1989) systems. It was again neuromagnetic measurements which first allowed the noninvasive detection of the transient auditory evoked gamma-band response (Pantev et al. 1991), consisting of four or more cycles phase-locked to stimulus onset in the 20–130 ms poststimulus interval. The source resides in the primary auditory cortex, clearly separated from that of the auditory wave N_1m, and moves in a posterior arcing trajectory 1 cm or more in length. Neuromagnetic source localization demonstrated that the gamma-band response originates from a source location which is also clearly separated from that of the steady-state response of basically the same frequency. The steady-state response, in contrast, originates from the same location as the middle-latency responses, indicating that the former is a mere superimposition of middle-latency responses (Pantev et al. 1993a). A clearly distinct source location has also been demonstrated for the sustained field, which also resides in the primary auditory cortex and also exhibits tonotopicity (Pantev et al. 1993b).

A final example for the localization of spatially distinct sources is the auditory mismatch field in response to minor pitch changes (Csépe et al. 1992). The mismatch field, which corresponds to the so-called mismatch negativity, occurs in response to a deviant stimulus presented with low probability in an otherwise homogeneous sequence of standard stimuli. Results of Csépe et al.'s (1992) neuromagnetic study support Näätänen's (1990) proposal on the basic processing of auditory stimuli. According to his proposal the "task-independent" sensory analysis is composed of a transient detector system, which activates the N_1m generator process and has a permanent feature detector system. Whereas slight deviations in frequency do not activate different N_1m generators, they are obviously sufficient to trigger a spatially distinct mismatch generator.

These few examples of the high precision of relative localization, i.e., the identification of spatially distinct sources in the same experiment, demonstrate that if there is one major source active at a time, i.e., if the requirements for the application of a single moving dipole model are met, neuromagnetic source localization is a powerful, noninvasive tool for the investigation of cerebral organization and cortical processes in humans.

The situation is quite different, however, if the spontaneous MEG is to be investigated. Spontaneously occurring EEG and MEG fluctuations reflect the dynamics of neural mass excitation. Alterations in attention as well as gross changes in cognitive states are related to changes in macroscopic patterns of excitation and hence should result in changes of dynamical attributes such as the largest Lyapunov exponent (LLE) or the Kolmogorov entropy. Together with the fractal dimension (commonly calculated as correlation dimension), such variables characterize the current brain dynamical state, particularly its complexity (Elbert et al. 1993). Mapping the LLE of magnetic activity measured over the auditory regions reveals deviances in specified disorders or during specified symptoms. For instance, the average LLE is larger in tinnitus sufferers than in controls (Kowalik et al. 1993).

Generally these dynamic variables are useful in tracing alterations in the brain's state. Prior to a phase transition, the system exhibits a loss in its global stability, well described by the LLE, a measure of predictability. Consequently, a critical transition can be found by tracing the LLE across time. For instance, an epileptic attack constitutes such a phase transition and can be observed in both the electrocorticogram (ECoG)- and the MEG-derived LLE (Elbert et al. 1993). Distinct local variations in the LLE suggest that under resting conditions the brain dynamics vary considerably between regions, meaning that there is only limited or no coupling among different brain regions. Owing to volume conduction, such a separation is difficult to observe in the EEG. Nearby MEG channels, on the other hand, may often display equal values in their dynamical variables. This cannot be explained solely on the basis of magnetic field propagation but demonstrates how LLE maps indicate the task-dependent coupling among various brain regions.

The closest that we come to an actual clinical application of the MEG is the source localization for the detection of epileptogenic zones. This was previously considered too difficult because, on the one hand, recordings of ictal activity are often contaminated with movement artifacts, and, on the other hand, interictal phenomena seem to be of little validity due to the possible mismatch of the pacemaker zone and the irritative zone. We have explored a unique way of circumventing the necessity of recording ictal activity: the epileptic focus is activated by the administration of methohexital, a short-term anesthetic which provokes epileptic activity while the patient is immobilized (Hufnagel et al. 1992). The results of neuromagnetic localization of epileptic foci (Fig. 3) obtained in patients suffering from temporal lobe epilepsy (Wienbruch et al. 1993) were verified by intracranial recordings. Even at the early stages of development of this technique it has become obvious that — at least in selected cases — such information can provide valuable aid for the presurgical diagnosis and, in addition, is gathered easily by noninvasive measurement.

A final example may highlight perspectives offered through mapping cortical electromagnetic activity. It has been assumed that chronic stimulation leads to changes in the cortical representation of pain, specifically to increased receptive fields for the painful area. Consequently, cortical evoked magnetic activity originates from more extended neural assemblies when evoked from the affected body part of a patient. We have indeed been able to show that pain patients who experience chronic noxious stimulation over extended periods of time produce stronger magnetic fields when phasic somatosensory stimuli are applied to the location of their pain, and that the magnitude of activation is significantly related to the chronicity, i.e., the duration of illness (Flor et al. 1993). These results are in accordance with observations from animal experiments (e.g., Merzenich et al. 1983, Milliken et al. 1992) demonstrating the plasticity of receptive fields subsequent to long-term alterations of afferent input. Magnetoencephalography offers new possibilities of monitoring such alterations in humans.

These examples of ongoing research on spontaneous MEG activity should be sufficient to demonstrate that MEG has indeed opened up a new and unique window into the functional organization and functional processes of the human cerebral cortex.

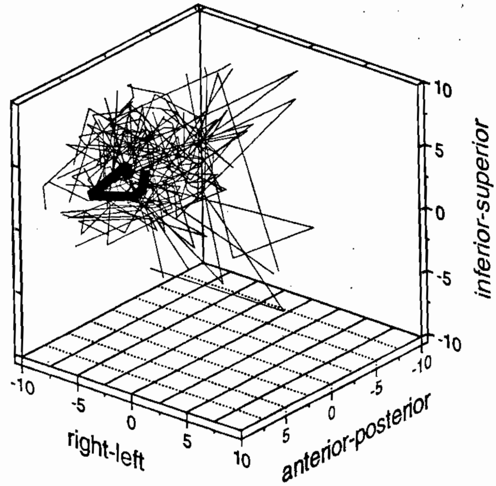

Fig. 9.5–3. Aspects of the spatiotemporal pattern of spontaneous MEG activity as demonstrated by the temporal sequence of ECD locations calculated for every sampling instant (3 ms). *Thin line*, trajectory obtained from the MEG of an epileptic patient measured over the right hemisphere during methohexital induction. To determine whether the trajectory moves in arbitrary directions, or whether it follows at times some main stream, i.e., whether it frequently runs through the same sequence of adjacent voxels, for every volume element the net flow of all trajectories running through it was evaluated (according to Mühlnickel et al. 1993). *Thick*, stereotypic pattern obtained, which in this case corresponds to methohexital-induced epileptic spikes

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