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MAGNETIC SOURCE IMAGING OF VISUALLY EVOKED AND OSCILLATORY ELECTRICAL ACTIVITY OF THE HUMAN BRAIN

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Dissertation for the degree of Doctor of Technology to be presented with due permission for public examination and debate in Auditorium F1 at the Helsinki University of Technology, on the 6th of June, 1994, at 12 noon.

Espoo 1994
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1 Introduction

Magnetic source imaging (MSI) is a method by which the distribution of electrical activity in the brain is estimated on the basis of magnetoencephalographic (MEG) recordings, i.e., measurements of the magnetic field outside the head [196, 71, 60, 69] (Fig. 1). MSI is a promising technique for detecting sequences of activation in the human cerebral cortex during processing of visual information, as well as for studying organization, for example, the representation of the visual field, within individual functional areas.

Apart from observations of behavior, there are only a few experimental methods that allow functional studies of the intact human brain. Measurements of electric potentials on the scalp (electroencephalography, EEG [145]) provide information about the same electrical events in the brain as MEG does. The temporal resolution of better than one millisecond for both EEG and MEG is excellent for studies of the transmission of signals in the nervous system. With the magnetic method, the spatial accuracy of locating an active area in the cerebral cortex is a few millimeters [105, 64, 204, 177, 176]. Images of brain activity with a good spatial resolution, a few millimeters everywhere in the head, can be obtained by means of positron-emission tomography (PET), single-photon-emission tomography (SPECT), and functional magnetic resonance imaging (fMRI) [125, 111, 135, 46]; the temporal resolution of these methods, however, is only moderate, ranging from seconds to minutes. Improvements in the overall spatio-temporal resolution of functional brain studies are to be expected from the combination of information provided by different imaging methods; in this development MEG will have an important role to play.

The aim of this thesis work was to develop biomagnetic recording and analysis techniques and to apply them to studies of visually-evoked and spontaneous electrical activity in the human brain.

The forward problem of MEG, i.e., calculating the electromagnetic field generated by known sources, is reviewed in Section 2; the effect of the conductivity distribution on biomagnetic signals is discussed and the possibility of determining the conductivity experimentally using a neuromagnetometer is examined (Publications II and III). Biomagnetic instrumentation is described in Section 3, with special attention devoted to registration of biomagnetic data with anatomical images; a head position indicator for MEG measurements is reported in Publication I. Section 4 is concerned with the determination of cerebral sources of MEG signals by the means of equivalent current dipoles (ECDs) and minimum-norm estimates (MNEs). The use of MNEs for standard representation of biomagnetic data is demonstrated with magnetocardiographic measurements in Publication IV.
An overview of the human visual system is presented in Section 5. Visual evoked responses and their cortical generators are discussed in Section 6 and in Publications VI-IX; the emphasis is on cortical activity related to simple pattern stimuli, the understanding of which is essential for studies of more complex higher-level visual processing. Spontaneous rhythm in the auditory cortex (Publication V) and visually evoked oscillations (Publication VII) are discussed in Section 7.

**Figure 1.** An example of neuromagnetic field generated by currents in the human cerebral cortex, measured with 122 SQUID sensors outside the head. The curves at left show the magnetic field as a function of time in two sensors over the occipital lobe. The isocontour map depicts the extrapolated normal component of the field 90 ms after the appearance of the checkerboard stimulus; the squares indicate locations of double-sensor units. The estimated distribution of primary currents in the brain, the minimum-norm estimate, is depicted by the small arrows on a brain surface reconstructed from magnetic resonance images.
2 Origin of bioelectromagnetic fields

2.1 Primary current

In the brain, there are about $10^{11}$ neurons, connected by means of $10^{14}$ synapses [180]. Signals are mediated by action potentials, which propagate along axons and ultimately trigger the release of neurotransmitters in synapses. The transmitter molecules open selective ion channels in the dendritic membrane of the postsynaptic cell, thus generating excitatory or inhibitory postsynaptic potentials and current flow in the dendrite. The current pattern associated with action potentials is quadrupolar [195]; therefore, the magnetic and electric fields produced by action potentials decrease faster as a function of distance than those generated by dipolar postsynaptic currents. In addition, the longer duration, tens of milliseconds, of the postsynaptic potentials favors temporal summation of fields generated by postsynaptic currents, compared with the one-millisecond action potentials. In the cerebral cortex, apical dendrites of the pyramidal cells tend to be oriented perpendicularly to the surface of the cortex; the net effect of dendritic currents in an ensemble of pyramidal cells is believed to be the origin of the macroscopically detected MEG and EEG signals (see, e.g., Ref. [60]).

The total current distribution in the head can be written as [182]

$$\mathbf{J}(\mathbf{r}) = \mathbf{J}^p(\mathbf{r}) + \mathbf{J}^v(\mathbf{r}).$$

(1)

The primary current $\mathbf{J}^p$ represents ionic currents related to active processes in the neurons, whereas the volume current $\mathbf{J}^v(\mathbf{r}) = \sigma(\mathbf{r})\mathbf{E}(\mathbf{r}) = -\sigma(\mathbf{r})\nabla V(\mathbf{r})$ is a passive ohmic return current; $\sigma$ is the conductivity, $\mathbf{E}$ the electric field, and $V$ is the electric potential.

Both the volume current and the electromagnetic field are determined by the primary current $\mathbf{J}^p(\mathbf{r})$ and by the conductivity distribution $\sigma(\mathbf{r})$ of the head. The forward problem of bioelectromagnetism refers to the calculation of the magnetic field and the electric potential outside a volume conductor for a known source distribution. In the quasistatic approximation, the magnetic field is given by the Biot-Savart law

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_G [\mathbf{J}^p(\mathbf{r}') - \sigma(\mathbf{r}')\nabla V(\mathbf{r}')] \times \frac{\mathbf{R}}{R^3} d\mathbf{v}',$$

(2)

where $G$ is the conducting region and $\mathbf{R} = \mathbf{r} - \mathbf{r}'$ is the vector from the source point $\mathbf{r}'$ to the point $\mathbf{r}$ where the field is calculated. Equation (2) can be transformed into [83]

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_G [\mathbf{J}^p(\mathbf{r}') + \nabla V(\mathbf{r}')\sigma(\mathbf{r}')] \times \frac{\mathbf{R}}{R^3} d\mathbf{v}'$$

(3)
A similar equation can be derived for the electric potential [83], viz.

\[ V(r) = \frac{1}{4\pi \sigma(r)} \int_G [J^p(r') + V(r') \nabla \sigma(r')] \cdot \frac{R}{R^5} dv'. \]  

(4)

The primary current, when it is spatially confined to a small volume of the brain, is often modeled as a current dipole \( Q \delta(r - r_Q) \), where \( Q \) is the dipole moment and \( \delta(r) \) is the Dirac delta function. The magnetic field generated by a current dipole at location \( r_Q \) in a spherically symmetric conductor is [86, 158]

\[ \mathbf{B}(r) = \frac{\mu_0}{4\pi} \frac{F(r, r_Q) \mathbf{Q} \times r_Q - (\mathbf{Q} \times r_Q \cdot r) \nabla F(r, r_Q)}{(r, r_Q)^2}, \]  

(5)

where \( F(r, r_Q) = a(r^2 + r - r_Q \cdot r) \) and \( \nabla F(r, r_Q) = (r^{-1}a^2 + a^{-1}a \cdot r + 2a + 2r)r - (a + 2r + a^{-1}a \cdot r)r_Q \), with \( a = (r - r_Q) \). It is of great practical importance that radial primary currents produce no magnetic field outside a spherically symmetric conductor [56]. Because the magnetic field decreases rapidly as a function of the distance from the source to the measurement point, MEG is most sensitive to cerebral sources near the surface of the head. At the center of a spherically symmetric conductor, all current dipoles are radial, thus producing no magnetic field outside.

Both \( \mathbf{B} \) and \( V \) depend linearly on \( \mathbf{J}^p \). Therefore, the signals recorded with magnetic sensors (indexed with \( i \)) and scalp electrodes (\( j \)) can be expressed in the form

\[ B_i = \int_G \mathbf{L}_i^M(r') \cdot \mathbf{J}^p(r') dv', \]  

(6)

\[ V_j = \int_G \mathbf{L}_j^E(r') \cdot \mathbf{J}^p(r') dv', \]  

(7)

where \( \mathbf{L}_i^M \) and \( \mathbf{L}_j^E \) are, by definition, the lead fields of the magnetic and electric sensors, respectively. The lead field \( \mathbf{L}(r') \) describes the sensitivity of a detector to primary current at \( r' \). It is evident that, by approximating these integrals with a sum of discrete point sources, the MEG and EEG signals generated by any primary current distribution can be decomposed into a superposition of signals produced by current dipoles.

It is possible to construct a current multipole expansion for a chosen point in the source volume which generates exactly all externally observed field patterns [100]. The primary interest in MEG, however, is to determine the spatial distribution of the physiological activity in the brain; for this purpose the primary current distribution is more suitable. In fact, higher order moments, quadrupoles and octupoles, can be represented as a set of dipoles located close to each other.
2.2 Conductivity distribution

The bioelectric and biomagnetic fields are determined by the distributions of the primary current $J^p(r)$ and the conductivity $\sigma(r)$ (cf. Eqs. 2–4). In principle, the conductivity distribution of the head can be estimated indirectly by combining morphological MRI and CT images with the specific resistance of tissues [49]. This has, however, proven difficult in practice. In electrical impedance tomography (EIT), current is fed into the head via scalp electrodes generating a potential which is recorded with the same or another set of electrodes. The conductivity distribution $\sigma(r)$ can be estimated from these measurements [7, 192]. The resolution of present-day techniques, however, is inadequate for the purposes of EEG and MEG analyses. The poor conductivity of the skull poses a severe problem for EIT: most of the injected current flows in the scalp, and little information is obtained about the skull and brain.

The concept of using magnetometers for impedance tomography is presented and examined in Publications II and III. The superior accuracy in locating cerebral sources with MEG than with EEG suggests that magnetic measurements and source-localization techniques might help to improve the results of EIT. Figure 2 illustrates the principles of electric and magnetic imaging of conductivity and their relationship to EEG and MEG. For practical measurements, the elimination of the strong fields produced by the leads of the current-feeding electrodes will require special techniques, for example, difference recordings and new electrode designs.

The term $V \nabla \sigma$ is in the same position as the primary current $J^p$ in Eqs. (3) and (4). Therefore, $V \nabla \sigma$ is sometimes called "secondary current" or "equivalent source current." Variations in conductivity modify the electromagnetic field in the same way as if there were additional primary currents in a homogeneous space at locations where $\nabla \sigma \neq 0$. In the case of small perturbations $\Delta \sigma$ from a known conductivity distribution, the equivalent source current is $J^e = \Delta \sigma \mathbf{E}^0$, where $\mathbf{E}^0$ is the electric field in the absence of the perturbation. The equivalent-source-current formulation allows direct application of the source-estimation techniques of MEG (Section 4) to conductivity imaging.

For magnetic source imaging, the head is often approximated by a spherically symmetric volume, in which the conductivity depends only on the distance from the origin. In this model, $\sigma$ disappears from Eqs. (2) and (3) [60] and, therefore, no quantitative values for $\sigma$ are needed. The sphere origin should be determined from the local curvature of the inner surface of the skull near the assumed site of the primary current [86]. MEG is rather insensitive to small variations in the thickness of the skull, because radial anisotropy in a spherically symmetric conductor does not affect the magnetic field outside [89].
Figure 2. Principles of electric and magnetic imaging of source currents and conductivity. In electroencephalography (a) and magnetoencephalography (b) the primary current $J^p$, generated by neuronal activity, produces a scalp potential $V$ and a magnetic field $B$ outside the head. By measuring $V$ or $B$ or both, the distribution of $J^p$ can be estimated; the conductivity $\sigma$ is assumed known. In electrical and magnetic impedance tomography (c,d), current is fed via surface electrodes and, from the measured signals $V$ or $B$, the distribution of conductivity is estimated.

The effect of the skull has been found to be small in MEG experimentally as well. Somatosensory evoked magnetic fields of a swine were almost identical before and after removing a part of the skin and the skull overlapping the active brain area [139], and gross changes in the conductivity properties of a human cranium had little effect on the magnetic field generated by an implanted artificial current dipole [8]. The conductivity boundaries between the gray matter and the cerebrospinal fluid in normal sulci can be ignored because effects due to adjacent sulcal walls tend to cancel each other [82]. If the realistic shape of the head is taken into account in MEG analysis, it is reasonable to assume that the conductivity is homogeneous in the brain and zero outside [63]. This approximation is independent of the actual magnitude of $\sigma$.

Imaging conductivity perturbations could be applied to determination of cerebral conductivity anomalies, which modify the EEG and MEG signals [184]. Equivalent source currents have been manifested, for example, in simulations on the effect of a tumor or
an edema on the magnetic field. A radial current dipole, which would be magnetically silent in a spherically symmetric conductor, generates a field pattern resembling that of a tangential dipole at the site of the conductivity anomaly [92]. Determination of small deviations from spherical symmetry is one potential application of magnetic conductivity imaging.

3 Detection of biomagnetic signals

3.1 SQUID magnetometers

The superconducting quantum interference device (SQUID) is the only practical sensor for detecting neuromagnetic signals. The first measurements of the magnetic field generated by the human heart and the brain were, however, made with induction-coil magnetometers [10, 29]; Cohen was the first to record the alpha rhythm, unaveraged, with a SQUID magnetometer [30].

The SQUID consists of a superconducting loop with either one (rf SQUID) or two (dc SQUID) Josephson junctions (see, e.g., Refs. [116, 154]). The device is a demonstration of macroscopic quantum coherence; the current through the junction is a function of the phase difference in the quantum mechanical wave function. When a current is fed through the SQUID junctions, the voltage across the loop varies periodically with the external magnetic flux. Thus, the SQUID transforms changes in magnetic flux to a change in the voltage across the junction. In contemporary MEG instruments, the dc SQUIDs are made of niobium-based superconductors and kept at the temperature of 4.2 K in liquid-helium dewars.

Neuromagnetic fields are only on the order of $0.01 - 10$ pT in the frequency range of 0–200 Hz; therefore, MEG recordings are usually made in magnetically shielded rooms. In the Otaniemi facility [104], a $90 - 110$ dB attenuation of external magnetic noise above 1 Hz is achieved with ferromagnetic and eddy-current shielding.

Neuromagnetic measurements described in this thesis were performed partly with a 24-channel magnetometer [99, 2] and partly with a 122-channel whole-head instrument (Neuromag Ltd) [1] (Fig. 3), both constructed in the Low Temperature Laboratory. The gradient noise level of the IBM-made dc SQUIDs [178] is $5 \text{ fT}/(\text{cm} \sqrt{\text{Hz}})$ or less. The sensors are arranged in units of two SQUIDs, with planar first-order gradiometric flux transformers, measuring the two orthogonal components $\partial B_z/\partial x$ and $\partial B_z/\partial y$, where $x$, $y$, and $z$ refer to the local coordinate system of the sensor unit; $z$ is approximately normal to the surface of the head. Planar gradiometers are somewhat less sensitive than axial
gradiometers to deep sources. The more focused lead fields of these detectors, however, together with the property that the maximum signal is sensed just above the source, facilitate the interpretation of signals originating from multiple simultaneous generators (see Section 4.2).

Our 24-channel instrument and other devices of 19 – 37 channels (reviewed in [60]) were a considerable improvement over the previous systems with 4 – 7 channels (see, e.g., [84]), because, for the first time, a dipolar source could be located with a single placement of the magnetometer over the scalp. This shortened the measurement time, reduced errors due to uncertainties in the relative locations of the sensors, and allowed the detection of non-repeatable brain signals that cannot be synchronized for averaging.

The recent development of multichannel neuromagnetometers covering the whole scalp [1, 25] makes it possible to monitor simultaneously cortical activity from all lobes and from both hemispheres of the brain. The Neuromag-122 system has the largest number of channels of currently operating MEG instruments. CTF has developed a 64-channel helmet-like magnetometer [25], and Biomagnetic Technologies Inc. (BTI) has introduced a system of two 37-channel instruments [19].

The SQUID sensors are calibrated by means of an accurately known magnetic field. Currents flowing in coils that are large compared with the dimensions of the flux transformers, can generate a magnetic field or field gradient that is uniform within the region occupied by the sensors [32, 16]. Large coils, however, may be problematic inside a magnetically shielded room where the high-permeability walls distort the field pattern; in addition, the orientation of the flux transformers with respect to the coil may be difficult to determine. In our laboratory, a calibration method based on an array of 25 small precision-made coils on a printed-circuit board has been developed. This method was first used with a movable coil in New York University [88, 18]. The position and orientation of the flux transformers, with respect to the array of coils, are determined together with the calibration coefficients. Prior information about the relative locations of the gradiometers can be used either to constrain the least-squares minimization procedure or to check the results.
Figure 3. Neuromag-122 SQUID magnetometer during a visual experiment. The 122 planar gradiometers lie on the helmet-shaped bottom of a liquid-helium dewar. Each unit of two sensors consists of orthogonal figure-of-eight-shaped thin-film flux transformers and integrated dc SQUIDs. The average separation of neighboring two-channel units is 44 mm. The distance from the flux transformers to the room-temperature outer surface of the dewar is 16 mm. The computer monitor and the mirrors are used for presenting visual stimuli to the subject. The gray area indicates part of the wall of the magnetically shielded room.
3.2 Registration of functional and anatomical data

The objective of most MEG studies is to locate brain activity. Unfortunately, neither the sources nor the sensors are directly accessible to the experimenter: the brain is inside the skull and the flux transformers are inside the dewar. To correlate brain functions to anatomy, either individual structures or a brain atlas, the relative position of the magnetometer and the head must be known.

Mainly two kinds of approaches have been used. One possibility is to align the subject consistently, for example, with individually constructed head holders (plastic helmets) [54] or tooth moulds [160]. Care has to be taken that the helmet does not significantly increase the distance between the head and the measuring instrument. Alternatively, the location of fiducial points on the scalp are determined in each imaging modality. Suitable points are the nasion, the inion, and the preauricular points [42, 204, 200, 59]. Extended three-dimensional markers may facilitate the identification of these points in anatomical images [201, 185]. Here, only methods based on fiducial points will be discussed.

In Publication I, a procedure was developed in which the position of the magnetometer is found with respect to magnetic markers on the head. By measuring the field produced by the marker coils, their position is obtained directly with respect to the flux transformers [105, 42]. If the markers are not placed directly on the fiducial points, their locations must be measured separately, for example, by means of a three-dimensional digitizer. The markers can also be attached on EEG electrodes (Publication I, [200, 11]).

The magnetic field of a current loop is well approximated by the field of a magnetic dipole \( \mathbf{M} \) at \( \mathbf{r} \) when measured at a distance large compared with the diameter of the loop, viz.

\[
\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi R^3} \left( \frac{3}{R^2} \mathbf{M} \cdot \frac{\mathbf{R}}{R^2} \mathbf{R} - \mathbf{M} \right),
\]

where \( \mathbf{R} = \mathbf{r} - \mathbf{r}' \); \( \mathbf{r}' \) is the position of the dipole. The relative error caused by the finite diameter \( l \) of the loop is less than 1% when the distance \( r \) to the sensor is more than 6\( l \). The locations and orientations of the dipoles can be obtained with the method of least squares, in the same way as the equivalent current dipoles for MEG signals (see Section 4.2). Six independent measurements (five if the magnetic moment is known) are needed to determine one dipole, but for an accurate and stable solution the number of measurements should exceed the number of unknown parameters. Three positions are enough to define a coordinate system, but with a larger number of markers, the total error caused by uncertainty in the location of a single marker is reduced. The price to be paid, however, is the increased technical complexity and longer recording time.
All available information, for example, the distances of separate coils or the shape of the head extracted from MRI, should be used to maximize the accuracy when locations of the coils are determined. Special coil configurations can improve the accuracy and make the convergence faster and more stable. Sets of three unidirectional \[106\] or orthogonal (Publication I, \[187, 78, 11, 90, 48\]) current loops have been reported. The orientation of a set of three orthogonal dipoles at the same position can be eliminated (Publication I). If all components of the field or its derivatives are measured at a single point, the relative position and orientation of the orthogonal dipoles can be obtained analytically \[203\] and realized with analog electronics \[103\].

A plate containing three unidirectional coils \[106\] was used with our 24-channel magnetometer. Since the coils are tangential to the surface of the head, they define a local coordinate system that is useful for combining signals from several magnetometer positions, especially when registration with MRI is not attempted. The fixed relative locations of the coils make the calculations more robust because a larger number of independent recordings are obtained for determining a single position. This was crucial for our instrument with only 7 channels \[106\]. For the 122-channel device, three to four single coils attached on the scalp have been found to be practical.

Although random noise can usually be made negligible by increasing the input current, the calibration error of the magnetometer typically causes an uncertainty of 1–5\% in the signals. Therefore, the signal-to-noise ratio of $10^4$, assumed in some simulations \[42\], is too optimistic for practical systems. The accuracy in locating one magnetic marker depends on its distance from the magnetometer and on the number of sensor channels. The standard deviation of the estimated position of an orthogonal-coil marker at 80 mm from the 7-channel magnetometer was about 3 mm. Comparable results have been reported by other groups as well \[48, 11, 90\]. The accuracy of locating a marker coil (and a current dipole in the brain) improves when more measurement channels are available.

Another set of sensors can be used for detecting the field of the markers instead of the biomagnetometer. BTi has modified a 3D digitizer to be suitable for biomagnetic measurements. Their probe-position-indication system contains sets of three orthogonal transmitters and receivers, attached on the head and on the magnetometer. The location of the coils with respect to the flux transformers has to be determined separately, for example, with X-ray imaging. The superconducting flux transformers must be far enough from the coils so as not to distort the field pattern generated by the transmitters. In an extensive set of repeated measurements with two 7-channel SQUID magnetometers and an artificial source in a head phantom, the equivalent current dipoles obtained with this
method lay within 3 mm from the right location. The precision in the position of the dipole for an auditory evoked cortical response was the same [204].

The criterion for the required accuracy of the position indicator system is the same as for the calibration of the magnetometer: it should not limit the overall accuracy of the source analysis. The location error of single-channel devices can be considered as additional noise in the measurements [101], whereas with large-array magnetometers, the error results in a systematic shift of the estimated source images. In simulations with various types of multi-channel magnetometers, the typical error in the location of a dipolar source has been of the same order as the error in sensor location (a few millimeters) [152, 35, 17, 126].

4 Determination of signal sources: the inverse problem

The biomagnetic inverse problem, i.e., determining the primary current distribution \( \mathbf{J}^p(r) \) in the brain on the basis of measurements of the magnetic field outside, does not have a unique solution. Helmholtz [77] already proved that an infinite number of source distributions within a volume conductor can produce the same potential on the surface. The non-uniqueness is equivalent to the existence of "silent" sources: if \( \mathbf{J}^1 \) and \( \mathbf{J}^2 \) generate the same signal \( B_i = \int \mathbf{L}_i(r') \cdot \mathbf{J}^1(r') dv' = \int \mathbf{L}_i(r') \cdot \mathbf{J}^2(r') dv' \) in an arbitrary sensor \( i \), then it follows from linearity that the difference current does not produce a signal. An example of a magnetically silent source is a radially oriented dipole in a spherically symmetric conductor [56] (cf. Section 2.1).

To make the solution unique, constraints based on anatomical and physiological knowledge must be taken into account. An obvious anatomical constraint is to restrict the sources within the brain. The dimensions of the problem can be reduced remarkably by allowing the primary current to be confined into the gray matter and oriented perpendicularly to the surface of the cerebral cortex [61, 190, 47]: sources then lie on a two-dimensional surface, with only one degree of freedom (instead of three) for the current dipole moment density at each location. Even this rather complex constraint, however, does not prevent distributed source estimates (to be discussed in Section 4.1) from being too superficial [51]. The typical sulcal width may be too small, compared with the distance from sources to sensors, to make the cortical-surface constraint significantly different from the unrestricted case.
The physiological constraint set by the maximum allowed amplitude of $J^p(r)$ eliminates inverse solutions that have pairs of strong nearby sources with opposite polarities and, therefore, field patterns that mostly cancel out. Typically, the current dipole moment density, both for evoked responses [68, 118] and for spontaneous activity [119] is about 50 pAm/mm². A possible constraint is to select the current distribution that has the least energy [61] or maximal entropy [97] among all possible solutions.

Prior knowledge about the spatial or temporal characteristics of the activity can also be used as a constraint. The most common assumption in MEG studies is that of spatially localized sources that can be modeled by a few current dipoles. The area of the cortex that is needed to produce a strong biomagnetic signal is estimated to be about 100 – 400 mm² [24, 68, 118]; activity that is spread on an area of this size cannot be distinguished from a point-like dipolar source [140].

### 4.1 Linear methods

The constraints determine the nature of the algorithms that are used for solving the inverse problem. If a set of current dipoles is assumed to be in fixed locations, their amplitudes as a function of time can be found by solving the linear problem of minimizing the sum of squared differences between the measured signals and those obtained from the model

$$S = (b - Gq)^T(b - Gq).$$

(9)

The vector $b$ contains the measured signals at a single instant of time, $q$ the amplitudes of the source elements, and $G$ is a matrix whose elements are the lead field components of the sensors at the locations of the dipoles; $T$ indicates the transpose. The problem of determining the dipole locations is discussed in Section 4.2.

When the number of dipole moments to be solved is smaller than the number of measured signals, an exact solution does not, in general, exist. $S$ is then minimized by

$$q = G^T b = (G^T G)^{-1} G^T b,$$

(10)

where $G^T = (G^T G)^{-1} G^T$ is the pseudo-inverse of $G$, which depends only on the measurement geometry. This approach has been applied for obtaining the temporal activation pattern of a few localized sources for auditory [159], somatosensory [66], or visual [163, 3] evoked responses, and of epileptic spikes [9].

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If there are more components for the fixed-position dipoles than there are measurement points, the problem is under-determined. Among all the possible solutions that explain the measurements, the pseudo-inverse

$$\hat{q} = G^T b = G^T (G G^T)^{-1} b$$  \hspace{1cm} (11)$$

has the smallest norm $\sqrt{\hat{q}^T \hat{q}}$ [61]. This type of solutions have been applied mainly for obtaining a distributed source estimate for data measured at a single instant of time [61, 164]. Linear estimates can also be calculated by means of the spatial Fourier transformation [36, 110].

If second-order statistics for the noise $n$ and the sources $q$, i.e., the correlation matrices $R_n = E\{nn^T\}$ and $R_q = E\{qq^T\}$ are known, the optimal inverse solution that minimizes the expected error is the Wiener estimate [166, 165]

$$\hat{q} = (G^T R_n^{-1} G + R_q^{-1})^{-1} G^T R_n^{-1} b \hspace{1cm} (12)$$

or

$$\hat{q} = R_q G^T (G R_q G^T + R_n)^{-1} b \hspace{1cm} (13)$$

where $E\{.\}$ denotes the expectation value.

In the continuous case [61, 27, 91], in the limit of an infinite number of discrete dipoles, the estimate $\hat{J}^p(r)$ is a linear combination of the lead fields $L_i(r)$ of the sensors, viz.

$$\hat{J}^p(r) = \sum_i w_i L_i(r) \hspace{1cm} (14)$$

This formulation automatically excludes all source configurations that cannot be detected with the particular set of sensors. A unique solution is obtained by selecting the coefficients $w_i$ so that the measured data are explained exactly:

$$b_i = \int_G L_i(r') \cdot \sum_j w_j L_j(r') dv' = \sum_j w_j \int_G L_i(r') \cdot L_j(r') dv' \hspace{1cm} (15)$$

or in matrix notation

$$b = \Gamma w \hspace{1cm} (16)$$

where $\Gamma_{ij} = \int_G L_i \cdot L_j dv'$. Solving for $w = \Gamma^{-1} b$ and inserting into Eq. 14 one obtains

$$\hat{J}^p = L^T w = L^T \Gamma^{-1} b \hspace{1cm} (17)$$

where $L = (L_1, \ldots, L_M)$. The solution given by Eq. (17) is called the minimum-norm estimate (MNE) [61]. Its formal similarity with the discrete solution (Eq. 11) is obvious.

An example of the MNE for the sources of visual evoked magnetic fields is shown in Fig. 1.
Figure 4. The effect of regularization on the MNE. The magnetic field was evoked by a visual pattern stimulus in the upper-right visual field. The arrows illustrate sampled values of the estimated continuous current distribution. The cut-off parameter \(d\) indicates how many eigenvalues (out of 24) were taken into account in calculating the inverse of the inner-product matrix \(\Gamma\). The profile of the head shows the spherical surface on which the MNEs were computed; the dotted sphere matches the local curvature of the head. The pattern that is stable for a wide range of the regularization parameter \((d = 12 - 19)\) becomes distorted at \(d = 20\). In this example, it is evident that the eigencurrents corresponding to \(d \geq 20\) are dominated by noise. (Modified from Publication VI.)

The 3-dimensional MNE, without additional constraints, will always display maximum primary current density at the boundary of the source volume [76]. Therefore, it is reasonable to construct the MNE on simple horizontal [61, 164] or vertical [190] surfaces, or some weight function emphasizing deep sources is applied to the three-dimensional reconstruction [91, 147]. Source images can be enhanced by including additional constraints with the help of iterative projections on convex sets [136]. The results of simulations, although obtained with a rather unphysiological (and not even convex) constraint favoring continuous, line-like primary currents, suggest that the method could be applied to other types of constraints as well. In general, it is important to realize that the solutions are strongly affected by the choice of the source space and the constraints.

In practice, the lead fields of a multi-channel magnetometer are often almost linearly dependent and, therefore, regularization is needed when inverting the nearly-singular inner-product matrix \(\Gamma\) [62]. This can be accomplished by setting, in the singular-value
decomposition of $\Gamma^{-1}$, the smallest singular values equal to zero; these correspond to the combination of lead fields that are most sensitive to noise. In the study reported in Publication VI, we found that the regularization cut-off parameter has a noise-dependent critical value above which the 2D MNE of visual evoked responses abruptly becomes completely distorted (Fig. 4). In Publication IV, MNEs were regularized with a continuous-source-distribution analogue to Eq. (13) [134].

The minimum-norm approach can be applied to conductivity imaging as well (Section 2.2). In Publication III, a formalism analogous to Eqs. (14 – 17) is presented. The basis functions $\Lambda_{ij} = L_{ij}^M \cdot L_{ij}^E$ (cf. Eqs. 6–7) are scalar products of the magnetic and electric lead fields.

### 4.2 Non-linear methods

The locations of dipolar sources can be found with non-linear least-squares methods. Three parameters are needed to describe the location $r_i$ of each dipole, in addition to the three linear parameters (only two, if the radial component is ignored) of its moment vector $\mathbf{q}_i$ at each instant of time. The linear parameters for a given set of the non-linear ones are obtained from the pseudo-inverse solution: $\hat{\mathbf{q}} = \mathbf{G}^\dagger \mathbf{b}$ (cf. Eqs. 10 and 11). The cost function

$$S(r_1, \ldots, r_n) = \| \mathbf{b} - \mathbf{G}(r_1, \ldots, r_n)\mathbf{q} \|^2 = \| (\mathbf{I} - \mathbf{G}(r_1, \ldots, r_n))\mathbf{G}^\dagger (r_1, \ldots, r_n)\mathbf{b} \|^2$$

is, in general, not concave in the parameter space; therefore, search algorithms may converge to a local minimum instead of the global one. The problem of finding the global minimum becomes more difficult when the number of non-linear parameters increases; in practice, it is already quite difficult to find the locations of only two dipoles when their field patterns overlap.

For the multi-dipole fit, a lower limit for the number of sources can be estimated with the principal component analysis (PCA): it tells how many independent source components are needed to account for the variance, up to the noise level, in the spatiotemporal distribution of the signals [102, 60]. The principal components as such do not necessarily correspond to any dipolar or other physiologically meaningful sources [188]. Underestimating the number of dipoles may result in erroneous temporal waveforms for the dipole moments; on the other hand, if the chosen order of the model is too high, a multi-dipole fit will give arbitrary sources whose locations are determined by noise [176].

There are several approaches for finding initial guesses for the locations of dipoles: visual inspection of the field distribution, a single-dipole fit using only a small subset
of the channels, the multiple signal classification method (MUSIC), and the maxima of MNE.

Approximate sites of underlying sources can be deduced directly from characteristic features in the field pattern. As an example, consider a current dipole in a homogeneously-conducting half-space. The normal component \( B_z \) (here \( x, y, \), and \( z \) again refer to the local coordinate system of the sensor) has two extremes of opposite polarity. The location of the dipole is beneath the midpoint of the line connecting these extremes, the direction is perpendicular to this line, and the depth is proportional to the distance between the extremes [196, 182]. The maximum change in \( B_z \) also occurs just above the dipole; in fact, the maximum of \((\partial B_z / \partial y)e_x - (\partial B_z / \partial x)e_y\) indicates both the location and direction of the underlying dipole. Therefore, this is a useful way to visualize the field distribution measured with planar first-order gradiometers [31, 58]. The extreme of a pair of tangential components of the magnetic field, \(-B_y e_x + B_x e_y\), possesses a similar property. These types of features have been applied in a rule-based expert system that automatically estimates locations of dipoles [142]. The usefulness of characteristic field patterns demonstrates the importance of proper visualization of the measured signals; the MNE-based standard form of biomagnetic data (Section 4.3) is an attempt to unify the presentation of results obtained with different types of instruments.

For practical spatio-temporal source analyses, it may be useful to fit a single dipole for time instants at which only one source appears to be active, for example, in the early part of an evoked response, taking only a subset of the measurement channels into account. The linear moments for that dipole are then calculated in the whole time interval of interest. From the difference between the measured and modeled signals, the presence of other sources is examined, these are then added to the model one by one. Finally, the locations are refined with a non-linear multi-dipole fit.

In the MUSIC method the locations of multiple dipoles are estimated by scanning the source space with only a single dipole [129, 114]. This approach has been successfully applied to detect locations of two separate sources in somatosensory evoked-response experiments [129, 66].

Initial guesses for the dipole locations can be obtained with MNE as well: spatial filtering with optimized dipole detectors [149, 150] or templates derived from the MNE corresponding to a dipole [72] have been suggested. For the visual evoked responses reported in Publication VI, the extremes in 2D minimum-norm estimates often coincided with the lateral location of the equivalent current dipole (cf. Fig. 7). Even though the depth of the source plane affected the shape of the MNE, the site of the extremum was
stable. Our results suggest that the combined use of MNE and equivalent dipoles is beneficial when several simultaneous generators are present. The MNE can both indicate initial dipole locations for iterative refinement and verify that the dipole positions have converged to a reasonable solution.

### 4.3 Standard representation of data

The minimum-norm estimate provides a natural and convenient way to extrapolate magnetic field values [87] because the important constraint about the allowed source space is directly taken into account [62]. Therefore, MNE can be applied to visualization and standard representation of data. Let \( \mathbf{L}_i \) denote the imagined lead field of a "virtual" magnetometer; then, from Eq. (17), the extrapolated signal is

\[
B^*_i = \int_G \mathbf{L}_i \cdot \mathbf{J} dv' = \sum_j w_j \int_G \mathbf{L}_i \cdot \mathbf{L}_j dv',
\]

or in matrix form

\[
\mathbf{b}^* = \Gamma' \mathbf{w} = \Gamma' \Gamma^{-1} \mathbf{b},
\]

where \( \Gamma' = \int_G \mathbf{L}_i \cdot \mathbf{L}_j dv' \).

In Publication IV, magnetocardiographic recordings performed with the 24-channel brain magnetometer were successfully transformed to the standard-grid presentation [155] designed for single-channel instruments. No extrapolation of the magnetic field is needed for the determination of the primary current distribution in the heart, but the standard representation, which is independent of the sensor type and its placement, may be of help in suggesting an appropriate approach for source estimation.
5 Processing of visual information in the human brain

More than 30 cortical areas associated with visual processing, in both hemispheres, and over 300 interconnecting pathways between them have been described in monkeys [43]. Humans and macaque monkeys have comparable visual capabilities according to psychophysical experiments, which suggest similarities in the structure and organization of their brains [34]. Recent advances in non-invasive functional brain imaging have indicated several distinct visual areas in humans as well [209]. In this section, an overview of the anatomy and physiology of the human visual system is presented; in the next section, visual evoked magnetic fields will be discussed as a tool to study the locations and temporal sequences of cortical activity.

5.1 From light to neural impulses

The visual sensory system receives a huge amount of information from the surrounding world. In the retina, about $10^8$ photoreceptors transform the intensity of light into electrochemical impulses in neurons. Rods are sensitive to low levels of intensity, whereas cones take over at brighter illumination. The signal is transmitted from the retinas of both eyes via the axons of about one million ganglion cells, to the lateral geniculate nucleus (LGN) of thalamus. The LGN, in turn, is connected to the primary visual cortex. Other visual pathways to the cortex proceed through the superior colliculus and the pulvinar.

In primates, two functionally segregated afferent geniculocortical pathways are anatomically separated all the way from the retinal ganglion cells, proceeding through the magnocellular and parvocellular layers of the LGN, respectively, to different laminae of the primary visual cortex [115, 206, 109]. Different aspects of visual input are transmitted along these pathways. The ganglion and geniculate cells of the magnocellular system have fast transient responses to changes in light intensity, large receptive fields, and a high sensitivity to contrast. Cells in the parvocellular pathway are wavelength-selective and their response is slow and sustained. In visual evoked-response recordings, the relative amount of activation of the two pathways can be selectively controlled by the choice of the spatial and temporal properties of the stimuli [131].

The anatomical segregation of functional pathways continues beyond the primary visual cortex [115, 206]. The magnocellular pathway leads to visual areas V2, V3, and V5 and is involved in handling of information about the movement and depth of objects. The parvocellular pathway, which continues to areas V2 and V4, contributes to perception of
color and detailed forms.

5.2 Visual areas in the occipital lobe

The primary visual cortex V1 (also called striate cortex or Brodmann area 17) lies, in both hemispheres, in the calcarine sulcus and the medial surface of the occipital lobe (Fig. 5). A characteristic anatomical feature of V1 is the stria of Gennari, a heavily myelinated layer, which can be seen with MRI as well [26]. Individual variations in the shape of V1 are large [14]. It is of special interest in visual evoked response studies to know how much of V1 extends to the convexity (outer surface) of the brain in the occipital lobe. In one study, maximally 13% of the striate cortex was at the convexity, and in more than half of the 20 hemispheres examined, V1 did not extend to the convexial part at all [144]; in another report V1 extended 0 – 30 mm laterally from the longitudinal fissure [133].

![Visual Areas Diagram](image)

**Figure 5.** Schematic sites of visual areas V1, V2, V3, V4, and V5 in the human occipital cortex. a) Lateral surface of the left hemisphere. b) Medial surface of the right hemisphere. (Adapted from Refs. [98] and [80]).

Topographic representation of the retina in V1 has been deduced by correlating brain lesions with defects in the visual field [79, 167, 81]. The fovea is represented posteriorly in the occipital lobe, the peripheral visual field more anteriorly in the calcarine sulcus and the medial walls of cerebral hemispheres; this has been confirmed also in PET studies [45]. All parts of the visual field are not equally represented in V1. The magnification factor, *i.e.*, the ratio of the cortical surface area and the corresponding extent of the visual field is largest for the fovea, and diminishes for more peripheral fields [33, 153, 45]. For example, the central 30° of the visual field occupies more than 80% of V1 [81]. The
left and right visual hemifields project to the contralateral occipital lobe. The upper and lower hemifields project into the lower and upper parts of the primary visual cortex, respectively. The horizontal meridian is represented in the depth of the calcarine sulcus. This topographic mapping has been found in the distribution of phosphenes as well; phosphenes are sensations of small light spots in the visual field, generated by invasive electric stimulation of the cortex [44, 15].

The cytoarchitectonically defined Brodmann areas 18 and 19, surrounding V1, contain in monkeys several regions, each having a separate topographic map of the visual field [43]. In post-mortem human brains, borders of regions have been defined by mapping inter-hemispheric connections between representations of the vertical meridian of the visual field, especially, the border between V1 and V2 [28]. The topographic map of the visual field in V2 is believed to be inverted compared with V1. The upper and lower parts of the vertical meridian are projected next to the ventral and dorsal borders of V1, respectively, and the visual field near the horizontal meridian is represented in the parts of V2 that are furthest from V1. The separation of the upper and lower visual field in the ventral and dorsal parts of V2 explains why some patients with occipital lesions have a defect limited into exactly one quadrant of the visual field [80]. Based on the anatomical connections between V1 and V2, it has been proposed that V2 performs higher level visual processing than V1 [20].

A third visual area, V3, surrounds V2. The dorsal (sometimes called dV3) and ventral (VP) part of V3 have the representations of the lower and upper visual fields, respectively. These two parts of V3 differ cytoarchitectonically [28]. Callosal connections indicate that dV3 as well as the ventral part of V2 lie mainly in the lingual gyrus, not extending to the fusiform gyrus [28]. In monkeys, V3 is part of the magnocellular pathway, but its function is poorly understood [113].

Visual area V4 of monkeys receives afferent input from the parvocellular pathway and it participates in the processing of color and form [205]. In human PET studies, an area in the fusiform and, possibly, lingual gyri in the ventro-medial part of the occipital cortex has been found to be active when the subject views a color-contrast stimulus [121, 208, 57]. Electrophysiological evidence of an area participating in color processing, human homologue of V4, has been obtained, as well, with subdural recordings in epileptic patients [5]. With functional MRI, four different areas in a cortical ribbon have been identified [161], probably corresponding to visual areas V1, V2, V3, and V4.

A human homologue of the monkey visual area V5 has been suggested to lie in the lateral part of the occipital cortex, in the lateral occipital gyri. In PET studies, a change in
regional cerebral blood flow (CBF) has been found during visual motion stimulation [208, 191]. Anatomically, this area is heavily myelinated [28]. Another area closely related to V5, called V5A, has been found with PET to be active when the subject is looking at a stationary figure that produces a subjective perception of motion [207].

5.3 Visual cortical areas outside the occipital lobe

A further division in the visual system has been proposed between temporal and parietal pathways, sometimes called the ventral and dorsal visual streams: lesions in the inferotemporal area impair the ability of a monkey to recognize objects, and postero-parietal lesions affect their localization [127]. Instead of the distinction between object and spatial vision, studies on patients with visual agnosia have suggested that the ventral and dorsal pathways could better be characterized by visual perception and visual control of actions, respectively [52].

Dissociation of object and spatial visual processing has been found in humans with PET [75, 39]. A face-matching task activated a region of occipito-temporal cortex that is anterior and inferior to the area that is activated by both face and dot-location discrimination, whereas the dot-location task alone activated a region of lateral superior parietal cortex [75]. In another PET study, a large number of visual task-dependent active spots were found with physically identical stimuli; with a task requiring temporal comparison, activity was detected in area 19 which, although being rather posterior, might be a human homologue of the monkey inferotemporal area [39]. This area contains cells that respond selectively to faces and other complex visual patterns (see, e.g., [55, 143]). Both PET [162] and electrophysiological [6] recordings have indicated an area related to processing of faces in the ventral surface of the human occipito-temporal cortex. Even during simple checkerboard reversal stimulation, regional cerebral blood flow (CBF) is increased in the lateral temporal region, in addition to the occipital lobe [22].

Single-cell recordings in monkeys suggest that segregated areas involving object and spatial vision exist in the prefrontal cortex as well [202]. During a memory task involving recognition of faces, as compared with a perceptual face matching task, increased CBF was found, besides in the occipital and occipito-temporal cortex (posterior and mid fusiform gyrus), also in the right prefrontal cortex (inferior frontal gyrus); CBF decreased in bilateral anterior temporal cortex [74]. Another frontal area involved in vision is the frontal eye field, which participates in the control of eye movements.
6 Visual evoked magnetic fields

Visual evoked magnetic fields (VEFs) were first recorded two decades ago by Brenner et al. [13], Teyler et al. [179], and Reite et al. [146]. Visual evoked potentials (VEPs) have a longer history, and VEPs are widely used clinically to assess the function of visual pathways [23]. Because both VEPs and VEFs are generated by the evoked primary current distribution $\mathbf{J}^p(\mathbf{r})$ in the brain, they are expected to depend similarly on the properties of the stimuli. Different current distributions, however, may have a different relative contribution to VEPs and VEFs. Therefore, VEPs and VEFs give complementary information. The selective sensitivity of MEG to the tangential component of $\mathbf{J}^p(\mathbf{r})$ does not seriously limit VEF studies because a large part of the visual cortex lies in the longitudinal and calcarine fissures. Also the ventral surface of the occipital lobe is largely perpendicular to the skull. The lateral outer surface of the occipital lobe is mostly convex and, therefore, not optimal for MEG. There are, however, several small sulci and, in addition, the region is close to the sensors.

I shall first review the effect of the stimulus parameters on VEFs and then consider the generators of contrast-onset evoked responses, based on previous VEP and VEF measurements, as well as recordings described in Publications VI and IX.

6.1 Choice of the visual stimulus

The retinal image is defined by the intensity of the incoming light as a function of wavelength, retinal position, and time. In vision research, the basic attributes of visual images have been listed as form, color, motion, and stereopsis [115, 206]. My work concentrates on form vision: in Publications VI – IX, high-contrast small-area checkerboard-onset stimuli were presented at several locations in the central visual field. They consisted of patterns formed by luminance differences (achromatic contrast). The images were stationary during the period between the onset and offset (no motion); and the same image was viewed binocularly. In the literature, some effects of motion [117, 183], color [108, 73], and stereopsis [193, 194] on VEFs have been reported.

Both transient and steady-state stimuli are common in visual evoked-response studies (see, e.g., Ref. [145]). In the transient presentation, the background pattern changes abruptly to the stimulus pattern. Ideally, no other changes in the image should take place. In practice, however, both the background and the stimulus can be presented for a finite period of time only. The duration of the stimulus should be sufficiently long so that the response evoked by the next change in the image does not overlap with the previous
response. Other non-idealities in transient stimulation include the finite rise time of the visual pattern. A cathode-ray tube may also produce a flickering display, and the time of its appearance is different for the upper and lower parts of the screen. Movements of the eyes or the head may produce unwanted changes in the retinal image.

In Publication VIII, the optimal choice of the interstimulus interval was considered. Typically, 20 – 200 responses to repeated transient stimuli must be averaged to obtain an adequate signal-to-noise ratio (SNR). The optimum is a trade-off between a fast stimulation rate, which shortens the measurement time needed to obtain a predefined number of epochs, and a slow rate, for which the amplitude of the response is often enhanced [64]. The period between the stimulus onsets \( \Delta \) that maximizes the SNR within a given time or, equivalently, minimizes the time needed to obtain a given SNR, satisfies the relation \( dA/d\Delta = A/2\Delta \), where \( A \) is the stimulus-rate-dependent response amplitude.

The stimulation rate, however, has an effect on other response properties besides SNR. For example, source components of auditory evoked magnetic fields generally have a different stimulation-rate dependence [65, 120]. Therefore, there is no universally optimal stimulation rate. The optimum always depends on the purpose of the study. Because determination of the best stimulation rate requires that the \( \Delta \)-dependence of the responses of interest is known, the estimation of the optimal \( \Delta \) will pay off only when the amount of stimuli to be given is large. This could be the case, for example, in an extensive mapping of the visual field [85]. However, if stimuli are presented in sequence at different locations of the visual field, a high stimulation rate may lead to the perception of apparent motion. To obtain an optimal stimulation rate for clinical VEPs and VEFs, \( A(\Delta) \) that is valid across subjects must be found.

When the stimulation rate is high (\( \geq 5 \) Hz), the response resembles a sinusoidal wave with the same frequency as the stimulus. This so called steady-state response, which is completely characterized by its amplitude and phase, provides a good signal-to-noise ratio, but interpretation of data is more problematic than in the transient case because all source components merge together. The apparent latency of VEFs (deduced from the phase of the steady-state response) as a function of spatial frequency has been found to resemble closely the corresponding reaction times, with a constant time difference that has been explained by the delay caused by the motor system [197]. The apparent latency may reflect, however, not only the delay in the signal transmission, but also the complex summation of transient waveforms [70]. In this thesis research (Publications VI – IX), only transient stimuli were used.

The most common transient stimuli in the VEP and VEF literature have been flash,
contrast onset, contrast offset, and contrast reversal [145]. In flash stimuli, the luminance either increases or decreases transiently. In contrast onset, a spatial pattern appears in a uniform-luminance region of the visual field; in contrast offset, the pattern changes to a uniform field; and in contrast reversal, the dark regions turn to bright and vice versa. Different responses, probably generated by partly separate neuronal populations, are evoked by these stimulus-presentation modes [169, 107]. Reversal responses have been suggested to reflect motion onset rather than contrast onset [168]. In this thesis, contrast-onset responses were studied.

The number of available stimulus patterns is enormous (one may think about the set of all images that can be shown on a television screen). Grating and checkerboard stimuli are characterized by mean luminance, contrast, spatial-frequency content, and the location and extent of the pattern in the visual field. To avoid difficulties in interpretation caused by changes in the level of light adaptation, the mean luminance of patterned stimuli is usually kept constant. This is easily achieved with contrast-reversal stimulation. Local adaptation effects are reduced when the stimulus duration is short compared with the interstimulus interval [95]. For brief stimulus pulses, however, onset and offset components overlap.

The amplitude of steady-state grating-onset VEFs is invariant with changes of the mean luminance, but increases approximately with the logarithm of the stimulus contrast, with saturation at high contrast levels [138, 137]. The phase lag, or apparent latency, of steady-state responses is shorter for high contrasts [138]. For a given contrast, the amplitude of the steady-state VEF is largest at intermediate spatial frequencies [138]; the apparent latency increases with the spatial frequency [197]. The locations of equivalent dipoles for pattern-appearance VEFs depend on the spatial frequency. In addition, high-frequency stimuli produce larger amplitudes when presented in the central visual field whereas maximum signals for low frequencies have been obtained with more peripheral stimuli [50]. The effect of spatial and temporal frequencies on VEFs can be attributed partially to different relative contributions of the magno- and parvocellular pathways.

Checkerboard stimuli were used in this thesis (see, e.g., Fig. 1). The pattern contains contrast edges of many different orientations and spatial frequencies: the local edges between the neighboring checks, stripes oriented diagonally to the checks, and the outer boarders of the stimulus pattern. The check size of the stimuli in the study of Publication IX was 10° – 20° of visual angle, corresponding to the dominant (diagonal) spatial frequency of 2 – 5 cycles per degree (cpd). Because of the intermediate spatial frequency range and the high contrast of the stimuli, probably both magno- and parvocellular
streams were activated (cf. [131, 130]).

The rationale for the commonly-used large-area stimuli has been to activate wide regions of the cortex and, thereby, to obtain a good SNR. Some canceling may, however, occur when nearby sources point to opposite directions. Small stimuli would facilitate a detailed retinotopic mapping, and also the sources are expected to agree better with the assumptions made when the sources are modeled with equivalent dipoles. Stimuli in which the checkerboard pattern extended only 2° evoked strong VEFs that could be measured with low-noise SQUID sensors with a reasonable SNR even with only 20 averaged epochs (Publication VI). In the study reported in Publication IX, the diameter of the stimuli was 1°.

The evoked responses depend strongly on the visual field location of the stimulus. In many VEF studies, the stimuli have been presented in one hemifield or a quadrant of the visual field at a time. The most prominent magnetic response is usually obtained from the hemisphere contralateral to the stimulus [198, 12, 148]. For peripheral stimuli, the ECD for steady-state VEFs lay deeper (more anterior) than the dipole for central-visual-field responses [122, 85]. These findings agree with the general features of the retinotopic map in V1 (and V2 as well, see Section 5.2). For studies of areas V1 – V3, stimuli in the central visual field are suitable because the representation of fovea is in the posterior tip of the occipital lobe and VEFs are most sensitive to shallow sources. On the other hand, the orientation of the tangential component depends on the individual folding of the occipital pole.

The retinotopic variation of the VEFs can also be of help in the estimation of the sources of evoked responses. Jeffreys and Axford [96, 95] assumed a simple model for the functional anatomy of the visual cortex and deduced the generator areas of contrast-onset VEPs from the retinotopic dependence of potential distributions on the scalp. In Publication IX, the retinotopic dependence of VEFs facilitated the analysis of multiple sources. VEFs were decomposed into two parts, one being specific to the position of the stimulus and the other independent of it (see Section 6.2).
6.2 Generators of contrast-onset evoked responses

The waveform of the contrast onset VEPs has been characterized with three components (C1, C2, and C3), originating from different generators [93]. C1 peaks at 65 – 80 ms, C2 at 90 – 110 ms, and C3 at about 150 ms [95, 145]. The locations of the sources of these components have not been unequivocally solved. Jeffreys and Axford [95, 96] suggested that C1 and C2 have surface-negative sources in the striate and extrastriate cortices, respectively. However, subsequent source-determination attempts with equivalent current dipoles [37, 21, 123, 186, 175] or scalp current source densities [171, 172] have given controversial results about the relative contribution of striate and extra-striate sources (see, e.g., Ref. [38]). The combined principal-component and ECD analysis of VEPs has given evidence that C1 originates in the extrastriate areas and that both striate and extrastriate sources contribute to C2 [123]. Equivalent dipoles for C1 lay in the convex lateral surface of the extrastriate Brodmann area 18, whereas the invariance with stimulus location has suggested that C3 is generated in area 19 [141].

One aim of the studies reported in Publications VI and IX was to examine using MSI the spatial and temporal distribution of the sources of contrast-onset responses. Previously, Aine et al. [4] have reported VEF evidence that supports the proposition of Jeffreys and Axford: the equivalent dipole at 90-ms latency for a sinusoidal grating stimulus lay medially, near the calcarine sulcus, but at 120 ms more laterally (or more anteriorly and superiorly) agreeing with an extrastriate source. The 2-dipole analysis of VEFs indicated retinotopically organized sources in V1 and V2 [3].

Figure 6 shows averaged magnetic responses over the occipital lobe, evoked by the appearance of a checkerboard pattern. The most prominent deflections peak at the latencies of 80, 100, 130, and 200 ms. The peak amplitudes in Fig. 6a do not occur simultaneously in all channels: e.g., the two gradient components circled with a dashed oval peak at different times, 80 and 100 ms. This indicates that one source of varying amplitude cannot explain the time development of the responses; at least two sources must be active. The location and orientation of the extreme of the minimum-norm estimate change as a function of time (Fig. 6b).
Figure 6. a) Visual evoked magnetic fields measured with a 24-channel magnetometer, whose location over the occipital lobe is shown in the inset at lower left. The pairs of curves show the vertical and horizontal derivatives of the radial magnetic field component as a function of time, measured at 12 different locations. The averaged responses were lowpass filtered at 0 – 40 Hz. The stimulus appeared for 250 ms in the lower right quadrant of the visual field; the time between stimulus onsets was 0.85 – 1.25 s. b) Minimum-norm estimates of the primary current distribution at 4 latencies. The estimate was calculated on a spherical surface 30 mm below the scalp over the occipital lobe. (Modified from Publication VI.)
The earliest deflection that was reliably detected in our contrast-onset VEFs started at about 50 ms and peaked at 80 ms. The deflection was typically 60 – 80 fT/cm in amplitude and occurred in channels over the longitudinal fissure at the occipital pole. This component may correspond to C1: the small amplitude is in accordance with the moderately large check size in the stimuli (10' – 40'), checks smaller than 10 – 15' have been reported to be necessary to evoke C1 foveally [93]. The equivalent current dipoles for this early component are at or near the calcarine sulci, suggesting a generator in V1 (Fig. 7). Retinotopic distribution of the equivalent sources for the responses to the octant stimuli was not, however, as systematic as could have been expected on the basis of the gross anatomical features of the retinotopic map in V1. The dipole moment of the ECDs (about 5 nAm) agrees with the moment obtained by multiplying the typical value (50 pAm/mm²) for the current dipole moment density in the cortex [118] and the area (30 mm², corresponding to 1° × 1° stimulus at the eccentricity of 1 – 2°) calculated with the cortical magnification factor for V1 [153].

In the VEF experiment described in Publication VI, systematic differences were not found among pattern-appearance VEFs for stimuli at two eccentricities. It is possible that the sources were laterally distributed around the occipital pole, instead of lying deep inside the longitudinal sulcus. Another explanation could be that the single-dipole model does not adequately represent the underlying source configuration.

The whole-scalp distribution of VEFs is shown in Fig. 8a. Occipital deflections depend strongly on the location of the stimulus (Fig. 8b, channel 4). Around 200 ms, there are signals that are invariant of the stimulus in many extra-occipital channels (1 – 3 in Fig. 8b). To facilitate the analysis of multiple simultaneous sources, the responses were divided into two components. The average signal over the responses to the eight octants represents the non-retinotopic part, whereas the retinotopic parts were obtained by subtracting the mean signal from the original responses. The standard deviation of the responses, calculated over the octants, provides a measure of the retinotopic variation. In this context, a non-retinotopic area means simply that the possible topographic order cannot be resolved using MEG. The decomposition reduces the number of generators that have to be determined at a time. Even when the complex source distribution in the occipital cortex can not be resolved, it may be possible to deduce the extra-occipital sources that are spatially more separated.
Figure 7. Retinotopic dependence of the minimum-norm estimate (MNE) at 80-ms latency, measured with the 24-channel instrument. Each MNE is normalized individually; the amplitudes of the currents are, therefore, not directly comparable. Large shaded arrows show the equivalent current dipoles, which are situated close to the maxima in the MNEs. (Modified from Publication VI.)
Figure 8. a) Visual evoked magnetic fields recorded with the 122-channel helmet-like magnetometer. The contrast-onset stimuli appeared in the lower-right visual field. The shading indicates the channels that are directly above the occipital lobe. The vertical electrooculogram is shown at top right. b) Superimposed responses to stimuli in eight different octant sectors of the visual field. The selected channels are indicated as numbered circles in a). The retinotopic dependence is prominent in channel 4, whereas the signals in channels 1 – 3 are the same for different stimulus locations. (Modified from Publication IX)
Figure 9 illustrates MNEs for the non-retinotopic component. For this subject, there is a strong source at 210 ms in the region between the parieto-occipital and calcarine sulci (denoted by b), another more lateral in the left hemisphere (a), and a third one in the right occipital cortex (c). In addition, four local maxima in the MNE at 210 ms occur in the parietal lobe (d – g), two in each hemisphere.

The VEF measurements reported in this thesis provide evidence that passively-viewed contrast-onset stimuli activate several spatially distinct cortical areas, both occipital and non-occipital. Our results, obtained with a large array of low-noise sensors, suggest that the three-component model deduced from VEP measurements [93, 123] is an oversimplification of the spatiotemporal distribution of visual evoked cortical activity. Evidence of extra-occipital visual areas in the temporal and parietal lobes has been obtained previously with EEG and MEG [171, 173, 151], especially in response to the presentation of faces [170, 94, 157]. The sources of VEPs to local flash stimuli in the upper central visual field have been explained with seven dipoles with time-varying amplitudes: the primary visual cortex was first activated, followed by bilateral prestriate areas, then by the inferior parietal regions, and finally by the inferior temporal cortex [163]. After voluntary blinks, activation of the posterior parietal cortex, close to the parieto-occipital sulcus, has been found in neuromagnetic recordings [67]. The checkerboard pattern is expected to evoke activity in the ventral extra-striate pathway involved in the perception of objects. The occipitotemporal sources in Fig. 9 could correspond to the areas that have been found with PET to be related to object vision [75]. The sources near the parieto-occipital sulcus may be part of the dorsal pathway involved in the processing of information about spatial locations of objects.
Figure 9. Minimum-norm estimate of cerebral generators of the non-retinotopic VEF component at four latencies. MNEs were calculated on a spherical surface about 10 mm below the scalp over the posterior parts of the brain, but drawn on images of the cortical surface reconstructed from MRI slices. The arrows indicate the estimated amplitude and direction of the cortical source currents; arrows smaller than a threshold value are not displayed. The activity pattern has several distinct maxima (a – h) in both occipital and extra-occipital regions. (From Publication IX)
7 Cortical alpha-frequency oscillations

Different behavioral states are accompanied with characteristic rhythmic electrical activity in the brain. For example, alpha oscillations in the frequency band 8 – 13 Hz are prominent in awake subjects when their eyes are closed. Slow waves at 0.5 – 4 Hz occur during natural sleep [174]. In the visual cortex of cat and monkey, 40 – 60 Hz and 70 – 80 Hz oscillations, respectively, have been recorded in response to moving stimuli [40, 53, 41]. It has been proposed that these oscillations provide a mechanism for feature linking in the cortex. MEG recordings have suggested a thalamocortical origin of coherent 40-Hz oscillations in humans [147].

The spontaneous alpha rhythm usually appears when the subject's eyes are closed and disappears at eye opening. The provocation of alpha, however, has been reported to be almost as common in response to photic stimuli as is the blocking reaction [128]. Alpha rhythm is increased also when the eyes are open but the subject is viewing a uniform visual field [112]. Equivalent dipoles for magnetic alpha rhythm lay near the parieto-occipital and calcarine fissures [189, 199, 156, 124].

Previous MEG studies have provided evidence that the somatosensory projection cortex has its own local spontaneous rhythm, as well [181]. This mu rhythm, which contains both 10- and 20-Hz components, is generated near the primary somatosensory hand projection area and is blocked by movement and tactile stimuli. In the study of Publication V, a spontaneous rhythm generated in the auditory cortex was found. The ECDs for this magnetic tau rhythm were within 2 cm from the source of the 100-ms auditory evoked response in the supratemporal cortex. The tau rhythm was occasionally dampened by an auditory stimulus, but not by opening of the eyes.

In addition to the alpha rhythm, 10-Hz rhythmic activity appears in several types of vision-related recordings of electrical brain activity. It has been suggested that steady-state VEPs to unpatterned flicker stimuli are generated by three functional subsystems, one of which shows a peak response at 10 Hz (Ref. [145], pp. 380-384). In magnetic measurements, the strongest responses were obtained when the repetition rate of the visual stimulus was 10 Hz [132]. These oscillations continued for several cycles after the stimulation was ended. A visual flash stimulus may evoke an after-discharge oscillating at about 10 Hz, which can be seen in averaged responses (Ref. [145], p. 379).

In the study reported in Publication VII, an oscillatory 10-Hz waveform was found in the averaged grating- or checkerboard-onset responses (Fig. 10a). The oscillations were found in 3 out of the 7 subjects studied. A change in the stimulus contrast caused a shift in the latency of both the transient components and the oscillation, indicating
that the latter is, indeed, triggered by the stimulus, and not due to random-phase alpha rhythm that had remained in the averaged data. The estimated source locations for the oscillations were 2 – 5 cm superior to the 100-ms VEF components (Fig. 10b), close to the parieto-occipital sulcus.

The various manifestations of the alpha-frequency signals suggest that the neural circuitry in the brain has properties that favor the system being in an oscillatory state.

\[ \frac{\partial B_r}{\partial y}, \frac{\partial B_r}{\partial x} \]

100 ms 200 ms 100 fT/cm 1 s

\[ \text{Inion} \]

Figure 10. a) Average of 54 grating-appearance evoked magnetic responses. A 10-Hz oscillation is seen in several channels over the occipital lobe. The location of the 24-channel magnetometer is indicated at bottom left; the stimulus is shown at top right. Passband 0.05 – 40 Hz. b) Equivalent current dipoles for the 100- and 200-ms deflections and for the oscillations (480-ms latency). (Modified from Publication VII.)
8 Summary

In this thesis, the magnetoencephalographic method was applied to studies of the human visual cortex and oscillatory brain activity. Cerebral source currents evoked by simple, passively viewed checkerboard stimuli were found to be distributed over large regions of the cortex, showing complex variations as a function of time. The usefulness of minimum-norm estimates was evident in cases in which a multitude of sources overlap, both when giving a 2D estimate of the primary current distribution and when providing a standard representation of the measured magnetic field. With retinotopically organized stimuli, some of the difficulties inherent in the biomagnetic inverse problem could be overcome. Similar differentiation of the underlying source patterns should be possible in future studies by varying other stimulus properties as well.

For an interpretation of detected sources, registration of MEG data with anatomical images is essential. In the future, further progress in mapping brain function is expected from more intimate integration of different imaging modalities, such as MEG, EEG, PET, and MRI. One part of my work considered the possibility of improving the conductivity models in MEG and EEG by measuring the conductivity distribution with the help of a SQUID magnetometer. Although this method has not yet been applied to the human head or body, it may prove to be useful in complementing electrical impedance tomography techniques, thereby also helping to improve the source-locating accuracy of MEG and EEG.
9 Publications

The publications included in my thesis are the result of joint efforts with several members of the brain research group in the Low Temperature Laboratory. I have participated in many aspects of the group’s work, including in the development of a visual stimulation system, together with Risto Ilmoniemi, and in measurement and analysis of the visual evoked responses described in Publications VI, VII, and IX, mainly using the MEG software developed by Matti Hämäläinen. I participated in all aspects of the work discussed in Publications I, II, and III, including the development of both hardware and software. In Publication V, my contribution concerned the determination of the magnetometer position with respect to the head. Publications I, II, VI, VII, VIII, and IX were written mostly by me. I actively participated in the writing of Publications III and IV.

I Magnetometer position indicator for multichannel MEG

A method for determining the relative positions of the head and the SQUID magnetometer was developed. Small coils are attached on the head and current is fed to each of them. The magnetic field thus generated is measured by the magnetometer, and from the recorded signal the positions of the coils and, thereby, the position and orientation of the head with respect to the magnetometer array is calculated. The standard deviation of the position of coils was 3 mm at 80-mm distance from the 7-channel magnetometer.

II Magnetic imaging of conductivity

A novel method for measuring the conductivity distribution of an object was suggested. Current is injected into the object via surface electrodes and, simultaneously, the magnetic field, instead of or in addition to the electric surface potential, is measured outside. From the measured field distribution the current pattern inside the object and, thereby, the conductivity can be determined. In the case of small variations from a known conductivity geometry, common source estimation techniques of biomagnetism can be applied directly. The conductivity distribution of the head is of importance for the interpretation of neuromagnetic measurements. It would be useful if the conductivity geometry could be estimated with the same SQUID magnetometer that is used in biomagnetic experiments.

III Equivalent source current formulation in impedance tomography

Changes in the conductivity distribution were shown to modify the electromagnetic field due to an injected current in the same way as an equivalent primary current
distribution does. The equivalent-source-current formulation allows the direct use of biomagnetic and bioelectric source-determination methods for impedance imaging. The minimum-norm estimate of the equivalent source currents was applied to detect the location of conductivity anomalies in a model experiment.

IV Transformation of multichannel magnetocardiographic signals to standard grid form

A method based on the minimum-norm estimate was introduced for presenting multi-channel recordings in a standard-grid format. This is useful for visualization of biomagnetic data and for an easy comparison of results obtained with different types of instruments. The desired field components in the standard grid points were computed from the MNE of the primary current distribution in the torso. Magnetocardiographic signals were recorded for 3 subjects, both with a single-channel magnetometer and with a 24-channel, curved-bottom neuromagnetometer. The signals extrapolated from the multi-channel measurements corresponded quite well to the single-channel recordings in the standard grid locations. The effect of errors in the location and orientation of the multichannel magnetometer was studied by simulations.

V Magnetoencephalographic 10-Hz rhythm from the human auditory cortex

Spontaneous magnetic oscillatory activity was recorded with the 24-channel magnetometer over lateral aspects of the head. The observed 8–10 Hz rhythm was occasionally dampened by auditory stimuli but not affected by opening of the eyes. The equivalent sources for this tau rhythm were in the supratemporal cortex, within 2 cm from the source of the 100-ms auditory evoked response. The result suggests that each sensory modality, including the auditory one, has its own local rhythm, which appears in awake subjects in the absence of sensory input.

VI Estimates of visually evoked cortical currents

The distribution and retinotopic dependence of visual evoked cortical currents was studied with the 24-channel magnetometer. Small-area checkerboard stimuli were presented in octant sectors of the visual field. The sources of the measured magnetic field were estimated by means of equivalent current dipoles (ECDs) and minimum-norm estimates (MNEs). The extreme of the MNE was in many cases close to the location of the ECD. The behavior of the 2-dimensional MNE as a function of the
chosen depth or the regularization parameter was examined. Reliable detection of single responses by spatial averaging with the help of MNEs was demonstrated.

VII Cortical alpha-frequency oscillations evoked by visual pattern stimuli

A magnetic field oscillating at 10 Hz was found to be synchronized to visual contrast-onset stimuli in 3 of the 7 subjects studied. The oscillations lasted in some cases more than a second, and they were not affected by the duration of the stimulus. Lowering the stimulus contrast increased the latency of both the transient deflections and the oscillatory response, but the waveform remained the same. The locations of the estimated sources for the oscillations were superior to the transient 100-ms responses.

VIII The effect of stimulation rate on the signal-to-noise ratio of evoked responses

It was shown that the stimulation rate can be chosen so that the signal-to-noise ratio of a specified feature in the evoked responses can be maximized when the dependence of the signal amplitude on the stimulation frequency is known. The same stimulation rate also minimizes the data acquisition time for obtaining a required SNR.

IX Whole-head distribution of visual evoked magnetic fields

Visual contrast-onset-evoked magnetic fields were measured with a 122-channel magnetometer covering the whole scalp. To facilitate the estimation of the spatial and temporal distribution of cortical generators, the responses were decomposed in two parts according to the dependence on the visual-field location of the stimulus. Minimum-norm estimates suggested that the generators for the part that was independent of the stimulus position were located in several occipital and extra-occipital regions, whereas the visual-field-dependent generators were predominantly in the occipital cortex. Our results support the view that information about the retinal image, even during passive viewing, is routed to several cortical areas.
Acknowledgments

I am deeply grateful to Professor Olli V. Lounasmaa, Director of the Low Temperature Laboratory, for continuous support for my work, comments and criticism on the manuscript of this thesis, and for providing excellent facilities for research. I also owe my sincere thanks to Professor Riitta Hari, Leader of the AIVO group, for guidance and constructive criticism of the manuscript. The enthusiastic international atmosphere in the laboratory is unique and unforgettable.

I am greatly indebted to my supervisor Dr. Risto Ilmoniemi for teaching me theoretical, practical, and philosophical aspects of scientific work. His own innovative example has shown me the way to research in electromagnetism.

I am obliged to my coauthors, Dr. Matti Hämäläinen, Mr. Matti Kajola, Dr. Jari Karhu, Dr. Jukka Knuutila, Mr. Juha Montonen, Dr. Jukka Nenonen, Mr. Jussi Numminen, Ms. Karin Portin, Dr. Juha Simola, Dr. Jari Tiihonen, and Ms. Satu Tissari for their inspiring collaboration.

I want to express my gratitude to the members of the AIVO group. Working with Dr. Antti Ahonen, Ms. Nina Forss, Dr. Juha Huttunen, Mr. Veikko Jousmäki, Mr. Petteri Laine, Ms. Sari Levänen, Prof. Norman Loveless, Dr. Singh-teh Lu, Dr. Linda McEvoy, Dr. Jyrki Mäkelä, Prof. Yoshio Okada, Dr. Ritva Paetau, Dr. Patricia Pardo, Mr. Lauri Parkkonen, Mr. Stephan Salenius, Dr. Riitta Salmelin, Dr. Mikko Sams, Mr. Mikko Uusitalo, Mr. Juha-Pekka Vasama, and Mr. Visa Vilkman (†), has really been a pleasure. Special thanks are due to Prof. Claudia Tesche, for kindly reading and giving comments on the manuscript. Sincere thanks are also due to Ms. Maria Helle, Mr. Markku Penttilä, Mr. Tommi Raji, Mr. Raimo Ramstad, Mr. Mika Seppä, Mr. Kimmo Uutela, and many others who have participated in the research activities during this period.

I have benefited from discussions with Dr. Kimmo Alho, Ms. Minna Huotilainen, Mr. Juha Lavikainen, Prof. Risto Näätänen, Ms. Mari Tervaniemi, and Mr. Hannu Tiitinen.

I am indebted to Prof. Toivo Katila for support and advice.

I thank Dr. Pekka Karp and Prof. Göte Nyman for reviewing the manuscript.
I want to thank the whole personnel of the Low Temperature Laboratory for the fine environment for research work. I am especially grateful to Ms. Teija Halme, Ms. Marja Holmström, Ms. Tuire Koivisto, and Ms. Liisi Pasanen, who have always been willing to help.

Financial support from the Academy of Finland and the Jenny and Antti Wihuri Foundation is gratefully acknowledged.

I wish to express my gratitude to my parents and to Outi for continuous support, care, and patience.

Otaniemi, May 1994

Seppo Ahlfors
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