Functional Imaging and Localization of Electromagnetic Brain Activity

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Summary: Functional imaging of electric brain activity requires specific models to transform the signals recorded at the surface of the human head into an image. Two categories of model are available: single-time-point and spatio-temporal methods. The instantaneous methods rely only on the few voltage differences measured at one sampling point. To create a spatial image from this limited information, they require strict assumptions that rarely conform with the underlying physiology. Spatio-temporal models create two kinds of images: first, a spatial image of discrete equivalent multiple dipoles or regional sources, and second, an image of source current waveforms that reflect the temporal dynamics of the brain activity in circumscribed areas. The accuracy of the spatial image is model dependent and limited, but it can be validated from the spatio-temporal data by the "regional source imaging" technique, introduced here. The source waveforms are linear combinations of scalp waveforms, and thus, specific derivatives which image local brain activities at a macroscopic level. Brain source imaging of somatosensory evoked potentials revealed temporally overlapping activities from the brainstem, thalamus and from multiple sources in the region of the contralateral somatosensory projection areas.

Keywords: Brain source imaging; Regional source imaging; Spatio-temporal dipole model; Dipole localization; Functional imaging.

Introduction

The main purpose of brain imaging is to map the internal structure of the brain and to localize areas of dysfunction using non-invasive measuring techniques. Over the last decade structural imaging techniques, magnetic resonance imaging (MRI) and X-ray computed tomography (CT), have become precise enough to delineate cortical fissures and gyri. Positron emission tomography (PET) has been able to demonstrate highly localized functional areas of increased metabolism during specific sensory or mental processes (Petersen et al. 1988; Zatorre et al. 1992).

These imaging methods use densely spaced sensors in a circular array around a planar slice of the head. The information collected is sufficient to reconstruct a discrete scalar density image in the plane of measurement. The resolution is given by the voxel size which depends only on the number of voxels that can be calculated uniquely, i.e., this number cannot exceed the number of outside measurement locations. In contrast, electroencephalography (EEG) and magnetoencephalography (MEG) are recorded at relatively few (21 - 128) locations spaced in 3 dimensions around the surface of the head. The quantity to be imaged from the surface EEG or MEG, the density of the source current in a brain voxel, is a vector having 3 magnitudes represented, for example, by the current densities in the x, y and z-direction (figure 1c). Hence, if we attempt to reconstruct the currents in discrete voxels uniquely, we cannot assume more than 7 voxels for 21 recording channels, or 42 voxels for 128 channels. Unless we impose further constraints, the model brain has to be divided up into not more than this number of voxels to solve the "inverse problem" of estimating a brain source image (BSI).

In contrast to the limited spatial information, EEG and MEG have a much higher resolution in time than MRI or PET. Changes in the distribution of the current flow in the brain occur within milliseconds, whereas the PET-images evaluate brain activity over many seconds. This unique capability of the EEG and MEG to measure rapid changes of brain activity allows for the imaging of source current or source potential waveforms (Scherg and von Cramon 1986). Each source waveform represents the macroscopic sum of the source currents in a certain brain region and reflects the continuity of the underlying physiological neural mass action (Freeman 1975; Scherg and von Cramon 1985). The repeated measurements at different time instances also provide additional information which can be used to decrease the voxel size or to localize discrete active voxels. Accordingly, a distinction should be made in the methods to solve the inverse...
problem of EEG and MEG between instantaneous (single-time-point) methods and spatio-temporal methods.

Instantaneous methods, for example single or moving dipole localization methods (Schneider 1972; Wood 1982; Fender 1987) and minimum norm current density imaging (Hämäläinen and Ilmoniemi 1984; Ioannides et al. 1990), use only the spatial information at one point in time, regardless of the source current configuration at the previous sampling point. Spatio-temporal methods (Scherg and von Cramon 1985, 1986; Achim et al. 1988, 1991; Baumgartner et al. 1989; Scherg et al. 1989; Scherg 1990; de Munck 1991; Scherg and Picton 1991; Mosher et al. 1992) use a model with discrete sources to decompose the signal matrix into a reduced number of basic or source waveforms. This provides an image of brain function in terms of the magnitude and timing of the source currents in the activated brain areas. In patients with circumscribed vascular lesions, significant abnormalities could be detected from the source waveform images even when the scalp waveforms appeared normal (Scherg and von Cramon 1986, 1990).

This paper discusses various single-time-point and spatio-temporal methods to solve the inverse problem of EEG and MEG as well as their assumptions and limitations. This paper also introduces regional source imaging (RSI). This new method, based on multiple dipoles with specific local constraints, can be used to scan the brain, to focus on those brain areas which contribute significantly to the surface signals and to exclude inactive areas from the multiple dipole model. The different methods were compared using real somatosensory evoked potentials (SEP), for which brain activities are known to be localized.

Methods

Subjects and data

SEPs were recorded from 16 volunteers in a 32-channel montage using constant current stimulation of the left median nerve. Details on the subjects and recording procedures have been published elsewhere (Buchner and Scherg 1991). In this study we used the grand averaged data (8400 sweeps, digital filter bandwidth 20-416 Hz, average referenced) of 2 subjects to test the different analysis methods as described below using the Brain Electromagnetic Source Analysis program (BESA, NeuroScan, Inc., Herndon VA).

Reference-free mapping

Surface maps (figure 1d) were constructed using spherical splines, which provide an optimal interpola-
tion for the estimation of the surface potential and of the scalp current density (Laplacian) at points interspaced between the electrodes (Pascual et al. 1988; Perrin et al. 1989). Maps are displayed in a top equidistant meridian projection up to an angle of 110 degrees from the vertical z-axis, thus covering an area down to the nasion, inion and the earlobes. Maps were made reference-free in two alternative ways: First, equipotential lines are drawn in black to illustrate the "landscape" rather than the distance from "sea level" in color, thus obviating the need for a reference. Second, the best fit multiple dipole model was used to estimate the potential at the (average) reference electrode. When adding this signal to the waveforms in each channel, they become approximately zero-referenced (figure 3).

Single-time-point source imaging

Figure 1 illustrates two different instantaneous imaging methods, moving (single) dipole fitting and surface spline mapping. Single dipoles were fitted to the 32 potential values independently at each time point using the simplex algorithm and an approximated 3-shell head model (Scherg 1990). The fitted locations are shown by dots and the dipole moment vector by small lines pointing away from the dots. Dipoles are displayed for each time point during the computing epoch (12-26 ms) only if the residual variance (RV) is less than 10%.

The principle of minimum norm imaging is also illustrated in figure 1. Current density vectors are estimated from a lead field representation of the sensor space (Hämäläinen and Ilmoniemi 1984). Lead fields describe the sensitivity of each electrode with respect to the current flow in any direction at any point in a predefined brain volume. In terms of a discrete voxel model of the SEP, this method can be viewed as estimating the magnitude and orientation of the source density vector in each of very many voxels comprising the predefined volume or brain region from only 32 voltage differences measured at the scalp. Two assumptions are necessary to render this estimation unique. First, the current density is assumed to be zero outside of the predefined volume. Second, the sum of the squares over all dipole moments must be minimal. Both assumptions impose arbitrary constraints which need not conform with the true physiological properties of the brain activity under study.

Spatio-temporal imaging

Three different spatio-temporal imaging methods are illustrated in figure 2. The data form a matrix the dimen-

![Spatio-temporal Imaging Diagram](image-url)
sions of which are electrodes and temporal sampling points (space x time). For the recorded SEP, linear spatial operators can be formed in a mathematical space defined by the 32 spatial dimensions. The goal of imaging is to find significant axes in this space, given by the linear operators, which lead to a decomposition and representation of the data in terms of a subspace or a reduced set of source waveforms which explain the signal variance in the data set (Mosher et al. 1992). The source waveforms are the result of a linear transformation of the scalp waveforms which depends only on the selected set of spatial operators. These can be defined either by external constraints, e.g., orthogonality of spatial vectors and source waveform vectors, as in principal components analysis (figure 2c), or by properties of the system itself, i.e., by the physical volume conductor mechanisms describing the voltage differences at the scalp due to localized brain currents, as in multiple dipole models (figure 2b). There are various ways to obtain such linear spatial operators: multiple dipole imaging, regional source imaging and multiple signal classification (MUSIC) are presented here.

Multiple fixed dipole imaging (Scherg 1990; Scherg and Picton 1991) uses dipoles that do not change location and orientation over time. Therefore, the spatial image (figure 2b) holds for the whole epoch of analysis. Of course, such an image can only be schematic, because each equivalent dipole may represent the activity of quite a large area of the brain (figure 1a) the extent of which is almost impossible to estimate from the outside (De Munck and Spekreijse 1988 a,b; Scherg 1990). In this context, "activity" means the macroscopic activity of a circumscribed brain region that contributes significantly to the surface signals. The magnitude of the estimated source current of each modeled brain region is shown in terms of source potential (Scherg and von Cramon 1986) or source current waveforms (figure 2b, left).

The source waveforms image the time pattern of activity in different brain regions, provided that at least one equivalent dipole is included in the model for each active region. The activity of a non-modeled brain region is distributed amongst all other dipoles in the model. The time course of the residual variance (logarithmic plot, figure 2b, bottom) illustrates the goodness of fit, i.e., the sum of the squares of the difference waveforms (measured-model) divided by the sum of the squares of the measured waveforms. The goodness of fit can also be viewed when the model and measured waveforms are

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Figure 3. Measured (dotted lines) and modeled (solid lines) scalp waveforms of subject 1 using a 3-dipole model (dipoles 1, 3 and 4 of figure 1). Displayed epoch 5-35 ms post-stimulus. Top view with Cz at the pole of an equidistant meridian projection.
shown in overplot mode. Figure 3 depicts the contributions of each source waveform to the scalp signals and their sum, i.e., the model waveforms, with the measured waveforms overplotted (dotted lines) for a three dipole source model of the SEP.

Principal components analysis (PCA; Glaser and Ruchkin 1976; Maler et al. 1987) is illustrated in figure 2c. First, the spatial vector which explains most of the variance in the data is defined. Then the next vector is sought which explains the next highest amount of variance, and so on. In BESA, singular value decomposition is used to compute the spatial factor weights and the basic waveform scores. The variance explained by each principal component is shown along with the cumulative variance. According to the signal-to-noise ratio a cutoff can be defined at a certain threshold (horizontal marker). The waveforms above the threshold are attributed to the signal subspace and the waveforms below to the noise subspace. These spaces provide a mathematically unique representation of the spatio-temporal data matrix.

When using one regional source (Scherg and von Cramon 1986) as a probe to scan the brain along horizontal slices, a probability function for localized currents can be defined. The probability is based on the proportions of the regional source waveforms that can be projected either into the noise or the signal subspaces of the PCA. This method of multiple signal classification (MUSIC) was first applied to the MEG (Mosher et al. 1992) and derives from mathematically similar inverse problems in acoustics. MUSIC implicitly assumes activities of the multiple sources that are not correlated over time. This is a limitation similar to that of the single dipole model, but not as severe. Figure 2d depicts probability maps (isocontour lines at p=0.994, 0.99, 0.98, 0.937, 0.887, 0.8, 0.64 etc.) for horizontal slices that are parallel to the Fpz-Oz/T3-T4-plane. i.e., approximately parallel to planes defined by the anterior and posterior commissures. Probabilities above 0.98 are shaded.

Regional Source Imaging

The new method of regional source imaging (RSI), as illustrated in figure 4, is a special variant of multiple dipole imaging having certain constraints on each source. A regional source consists of three collocated orthogonal dipoles. Such a source model can image the current flow of a localized brain volume in any direction (Scherg and von Cramon 1986). Successively one, two, three and more regional sources are used to scan the brain, the volume of which can be divided up into a set...
of discrete voxels. During RSI the sources reside at the
centers of the voxels and, thereby, maintain a minimal
distance from each other. Thus, the spatial vector matrix
is always non-singular and can be inverted. The good-
ness of fit is invariant to any rotation of the local co-
ordinate system of each regional source. Hence, the local
axes can be selected for each regional source such that
the first dipole reflects the initial activity, the second dipole
the next (orthogonal) activity and the last dipole the
remaining activity of the local brain volume surrounding
it. This local orientation process can be automated in the
BESA program. At the end of the scanning process, those
voxels are selected for which each regional source images
a maximal amount of variance while having the least
amount of covariance with the other regional sources
(energy and variance constraints in the BESA program,

If the number of regional sources exceeds the number
of underlying macroscopic areas of activity, one or more
regional sources begin to show source waveforms of low
amplitude (figure 4, bottom). This indicates that there is
little contribution from these brain regions while there is
localized contribution from the active regional sources.
The inactive sources act like probe sources which check
the surrounding brain region for the presence of source
currents. If there were source currents in this region, they
ought to be imaged by the probe source rather than by
any other regional source because the inverse linear
operators are implicitly constructed to be orthogonal to
the forward spatial weights of each other regional source.
Each regional or probe source has unity covariance only
with its own spatial forward vectors while having zero
covariance with all others. This principle has been used,
for example, to develop a very efficient method for the
correction of eye and cardiac artifacts in the EEG (Berg
and Scherg 1991).

Results

Scalp waveforms and mapping

The SEP scalp waveforms of subject 1 are shown in
figure 3 along with the model waveforms of the best fit
3-dipole model, described below. Prominent peaks
occur at the upper neck electrode (N14), over the right
parietal (N19) and frontal (F10) scalp and at C4 (F22).
Maps are shown for the interval of 19-21 ms in figure 1.
They show an apparent rotation from a tangential to a
radial field distribution, but neither the potential nor the
current-source-density maps are capable of separating
the underlying cortical sources.

Single moving dipole fitting

A single moving dipole was fitted in the time range
of 12-30 ms. For subject 1 the fit was stable (RV<10%) in
the intervals of 12-15.5 ms and 18.5-30 ms. Figure 1 shows
clusters of dipoles at the lower brainstem (minimum of
RV=1.95% at 13.5 ms) and a trace all the way through the
depth of the right central sulcus (minimum of RV=1.0%
at 24 ms). For subject 2 the fit was stable in the intervals
of 12-16 ms, 23.25 ms and 26-30 ms. At the peaks of N20
and P22 the fit was unstable because of the overlapping
activities from the source at the low brainstem level and
from the sources in the vicinity of the central sulcus.

Multiple dipole imaging

A minimum of 3 dipole sources was needed to model
the SEP in the interval of 12-30 ms (RV=1.82%, whole
epoch). Model waveforms and the contribution of each
source to the scalp are depicted in figure 3. The model
consisted of one source at the level of the posterior fossa
and of two sources in the region of the right central sulcus
that were approximately tangential (2) and radial (3).
These sources correspond to dipoles 1, 3 and 4 of the more
detailed 5-dipole model of figure 2 b (RV=1.03%). Only
small deflections at the right frontal and parietal scalp in
the 24-35 ms range were not accounted for by the 3-dipole
model. Zero reference was computed on the basis of
the 3-dipole model. Source 1 explains the large N14-P20
complex at the upper neck electrode and the widespread
P15 over the frontal-central scalp as well as a small
amount of N19 at the parietal scalp. The tangential
source 2 in the depth of the central sulcus provides the
major contribution to the parietal N19 and to the frontal
P20. P22 has its maximum at C4 and is almost exclusively
due to the radial generator 3, because this electrode was
located precisely on top of the deep tangential source, i.e.,
at a location where no potential field can be sensed from
this source while the radial source is maximally recorded.

The 5-dipole model (subject 1) in figure 2 b shows that
the deep source in the central sulcus could be broken up
into two closely located sources with different onsets and
initial peaks at 19 ms (dipole 3) and 23.3 ms (dipole 5),
similar to previous findings in other subjects (Buchner
and Scherg 1991; Scherg and Buchner 1992). The radial
dipole 4 peaked at 21.3 ms. Dipole 2 was located centrally
in the head with its orientation pointing towards the
active cortical areas. It imaged an initial deflection at 153
ms (shown with an enhanced scale in the schematic
illustration of figure 2 a). This deflection, occurring 2 ms
after the N14 peak of source 1, was quite small in subject
1 but consistently present and most often larger in the
other subjects.
Regional source imaging

Figure 4 shows the results of RSI for subject 2 and the control of the 5-dipole solution of subject 1. One regional source was an insufficient model of the data (RV=15.2%), because all activities were lumped together at a location that was intermediate between the brainstem and the upper central sulcus. However, the source waveforms already separated the N14 and N19-P25 processes by their different orientations. The scanning with 2 regional processes provided a reasonable model (RV=1.52%) which separated the lower and deep sources from the cortical sources by location. For each regional source several distinct processes were recognizable by difference in orientation (2 deep processes with initial peaks at 14 and 16 ms, 3 cortical processes peaking at 19, 21 and 22.5 ms). When a third regional source was added, it located centrally (RV=1.28%) and accounted for the thalamo-cortical dipole activity (peaking at 16 ms, dipole 2 in the 5-dipole model) previously imaged by dipole 2 of the deep regional source (figure 4 b).

Because of the lack of electrodes at lower head locations the horizontal dipoles 2 and 3 of the deep regional source which showed only very small activities had to be switched off when further regional sources were added. Also, because most of the variance was already explained, the additional regional sources acted as probe sources checking the validity of the previous solutions. For example, when a regional source was used to scan the ipsilateral somatosensory cortex, the flat source waveforms documented the absence of significant source currents in this brain region, thereby justifying the exclusion of these voxels from the model (figure 4 c).

Finally, the control of the 5-dipole solution of subject 1 is depicted in figure 4 d. The source waveforms are not affected by the added three regional sources (the small waveform of dipole 2 is not shown for clarity). Further, they disprove the presence of activity at the lower temporal lobes bilaterally and at the parietal cortex ipsilateral to stimulation. In fact, when the three regional sources were present, the 5-dipole fit could be improved and shown to be stable by using the variance constraint (Scherg and Berg 1991) to minimize the source activities in the waveforms of the regional probe sources.

PCA and MUSIC

Figure 4 depicts the results of PCA and MUSIC for subject 1. The variance of the principal components decreased rapidly with every subsequent component, indicating that the SEP data could indeed be represented by only a few source components. Also the orthogonal and, therefore, independent basic waveforms of the PCA illustrated that about 4-5 sources were sufficient and necessary to model all signal in the data. However, in comparison to the 5-dipole model, the basic waveforms were much less distinct in their onset.

MUSIC images were computed for horizontal slices at 5 mm intervals ranging from -35 mm to 55 mm in vertical distance from the zero plane defined by the Fpz-Oz and T3-T4 axes. High probabilities, indicated by shading, were found at the deep slices in the center of the head (the lateral shadings are artifacts due to the lack of low electrodes) and at upper slices (10-45 mm) in the region of the right central sulcus, thus confirming the 2-regional source model. The central dipole 2 was more clearly visible in the MUSIC images of subject 2.

Discussion

The word “imaging” is mainly associated with structural images such as MRI or CT. In this sense, the terminology of “Brain Source Imaging” or “Electromagnetic Source Imaging” could be misleading, because source localization is: a) schematic, since the equivalent dipole(s) may represent the activity of extended or even remote cortical areas (figure 1 a), and b) approximate, because the dipoles are computed within a spherical volume conductor model that only approximates the real geometry and conductivity of the head. With certain types of source models, e.g., the single moving dipole, localization may be wrong by up to or even more than 50 mm.

However, “Brain Source Imaging” obtains a different meaning if applied to a gross voxel model of the brain with a discrete number of regional sources or a multiple dipole model that has been validated by regional probe sources to exclude the occurrence of source currents at any other voxel. Only when such validation is missing (e.g., in moving dipole fitting), is the critique of Snyder (1991) on source modelling appropriate. However, if all the voxels surrounding discrete dipole sources have been shown to be inactive, localization can be accurate at about the voxel level (8-30 mm), depending on the number of electrodes and on the signal-to-noise ratio. Even then, localization still occurs within the idealized spherical volume conductor. This can lead to further errors of about 10-20 mm unless more precise realistic head models become available that are based on the individual anatomy.

The most important justification to use the terminology of “Brain Source Imaging” for spatio-temporal source analysis derives from the capability of regional sources or multiple dipoles to create a dynamic functional image of the macroscopic source currents in the different active regions of the brain. This dynamic image is a valuable tool to visualize the pathological decrease or delay of source processes in dysfunctional brain areas (Scherg and von Cramon 1986). “Brain Source Imaging” is a unique
functional imaging technique with a high temporal resolution.

The regional source imaging technique tackles the inverse problem in a bottom-up fashion. Rather than proving the correctness of each of the sources found by multiple dipole fitting, RSI attempts to exclude brain areas as major contributors to the surface signals. Due to the orthogonality of the inverse operators to each of the forward dipole operators, RSI has the capacity of proving the accuracy of a model by eliminating others: If local activity cannot be imaged, the probed brain region or voxel can legitimately be excluded from the potential set of discrete sources. Multiple dipole models provide three quite different results: equivalent localization, orientation and source waveforms. Orientation has to match the geometry of the underlying cortical folds. If this is known, e.g., from MRI, the number of generator candidates for a certain regional or dipole source can be substantially reduced. Therefore, when MRI information is combined with the orientation and localization data of the model, localization can be improved indirectly and interpretation of the dipoles in terms of the individual cortical anatomy becomes possible.

Single-time-point analysis methods, such as moving dipole fitting or minimum norm estimates, are likely to lump together activity at an equivalent "center of gravity" when multiple brain areas are active simultaneously, because they ignore differences in the evolution over time of each source process. Minimum norm imaging, in addition, has the tendency to smear out the source current over a more extended area than necessary. On the other hand, spatio-temporal methods like MUSIC and multiple source imaging achieve a 100% separation of the source processes in the ideal case when they are not correlated over time. In this case, PCA achieves the same result. However, in realistic situations with fairly synchronous activities in distant areas, e.g., in the auditory cortices of both hemispheres, MUSIC and PCA fail, whereas regional and multiple source imaging still works (Scherg and Berg 1991). MUSIC, as applied here, thus also leads to a midline center of gravity.

A comparison of assumptions inherent in the different presented methods reveals that the single-time-point methods need stricter assumptions than do not conform with brain physiology. Single moving dipole models assume that only one brain structure is active at a time. This assumption is almost never tested, for example in MEG analyses. Minimum norm estimates are based on an underdetermined system of linear equations that is stabilized by a statistical constraint minimizing the total sum over the source currents in the brain. Regional and multiple dipole models assume a discrete number of sources that must be less than the number of recording channels. The number of sources needed for an appropriate model is sequentially increased and tested: PCA gives an a priori objective estimate of the lowest number of possible sources. Sources are then added until the last source becomes the probe source and does not reveal any significant activity at any voxel unoccupied by another source of the model. When this procedure is applied, the number of macroscopic sources that can be extracted from a given data set is not any more assumed, but analyzed from the data itself. In this case, regional and multiple dipole imaging are based on no other assumptions than: a) there are localized regions of brain activity and b) the localized currents lead to potential differences at the scalp according to the physics of volume conduction in the head. The accuracy of the head model does not affect the separability of the source activities by multiple dipole models, but rather affects the precision in localization and orientation and the quality of the signal separation.

The moving dipole fit of the SEP data of subject 2 was not stable in the N20-P22 range in subject 2, whereas the spatio-temporal analysis revealed multiple overlapping processes from sources in the brainstem, thalamus and in the region of the contralateral central sulcus. A detailed discussion of these results and analyses of the SEP in other subjects can be found elsewhere (Buchner and Scherg 1991; Scherg and Buchner 1992). When comparing the regional source images in subject 1 with the 5-dipole model, it became evident that the multiple dipole model can get ambiguous, if multiple sources reside within a region with an extension that is at or above the voxel level (diameter about 2 cm). In the "fine tuning" process of defining multiple dipoles within such a small volume, the ambiguity arises from the invariance of the local regional source to a rotation of the dipole axes. It can be overcome by external knowledge (Scherg and Berg 1991). Such knowledge can be based on physiology (wavelength of source processes) or anatomy (orientation of the underlying structures). The MEG senses the source currents only in the two tangential dimensions. Therefore, it may be more severely affected by this "fine tuning" problem than the EEG (Scherg and Buchner 1992).

Brain source imaging is a non-invasive and inexpensive functional diagnostic technique that can be repeatedly applied to patients. However, to increase reliability, EEG and event-related potentials ought to be regularly recorded from more scalp locations (>30). Faster techniques for electrode placement and more precise measurement of electrode locations will allow functional RSIs to be matched with structural MRI-images. Two results can derive from this match: a) the sources may be more accurately related to the anatomy, and b) the anatomy may be given a functional meaning by the time course of its activation.
References


