# Advances in Electromagnetic Source Imaging

by Srikantan Nagarajan, PhD

Localizing functionally intact brain tissue before surgery guides neurosurgical planning and limits the region of resection, allowing for improved long-term patient morbidity and neurological function. There are various ways to map functional brain organization, including direct electrical cortical stimulation (ECS), functional magnetic resonance imaging (fMRI), and electromagnetic source imaging (ESI).

Reconstruction of the spatiotemporal activation of brain sources from non-invasive magnetoencephalography (MEG) and electroencephalography (EEG) measurements is referred to as ESI, and it is increasingly being used for preoperative functional brain imaging. When combined with magnetic resonance imaging (MRI) data, preoperative functional localization with ESI can be integrated with neuro-navigational systems to guide the surgical team. ESI mapping complements intraoperative mapping by delineating retained areas of function non-invasively and in advance, reducing the time needed for intraoperative mapping.

In contrast to other functional brain techniques that measure indirect hemodynamic and metabolic changes due to neuronal activity, MEG and EEG measurements offer the unique capability to measure direct neural activity in the millisecond time-scale with high temporal resolution. ESI is the only function imaging technique to provide spatiotemporal brain activation profiles that reflect not only where activity occurs in the brain, but also when it occurs in relation to the presentation of the external stimulus and the activity in other brain regions.

## Forward Models

ESI is achieved by reconstruction algorithms that involve two major components: a forward model and an inverse model. The forward model has three sub-components: a source model, a volume conductor, and a measurement model. Inverse modeling refers to the algorithm or procedure used to reconstruct sources based on a forward model and MEG/EEG measurements.

Typical source models assume that the MEG and EEG measurements outside the head are generated primarily by electric current dipoles located in the brain. This model is consistent with available measurements of coherent synaptic and intracellular currents in cortical columns that are thought to be major contributors to MEG and EEG signals. Although several more complex source models have been proposed, the electric current dipole remains dominant.

Volume conductor models refer to the equations that govern the relation between the source model and the sensor measurements – i.e. the electric potentials or the magnetic fields. These surface integral equations, obtained by solving Maxwell's equations under quasi-static conditions, can be solved analytically for special geometries of the volume conductor, such as a sphere or ellipsoid. For realistic volume conductors, numerical techniques such as finite-element and boundary-element methods are used. These time-consuming methods may appear impractical in clinical settings because knowledge about specific parameters is lacking in these models. However, several speed-up efforts involving fast numerical methods, pre-calculations, look-up tables and interpolation of pre-calculated fields have been proposed. These models are expected to be used soon in clinical practice.

Measurement models refer to the specific measurement systems used in EEG and MEG. For instance, different MEG systems measure axial vs. planar gradients of the magnetic fields with respect to different locations of reference sensors. The measurement model incorporates such information about the type of measurement and the geometry of the reference sensors.

The source, volume conductor, and measurement models are typically combined and embodied in a "forward-field" that describes a linear relationship between sources and the measurements. Usually, we assume that the forward-field matrix is known. We can easily calculate the forward-field for electric current dipoles in a spherical volume conductor model for a whole-head axial gradiometer MEG system. In this model, MEG is sensitive only to the tangential component of the primary current dipoles, whereas EEG is sensitive to all components. Simultaneous MEG and EEG can be acquired in most modern MEG systems. This requires some modification to the forward-field matrix for combined MEG/EEG measurements especially for more realistic source, volume conductor, and measurement models.

## Inverse Models

Inverse algorithms are used to solve the bioelectromagnetic inverse problem i.e., estimating neural source model parameters from MEG and EEG measurements obtained outside the human head. Because the source distributions are inherently four-dimensional (three in space and one in time)

The Neurodynamic Utility Toolbox for Magnetoencephalography – NUTMEG – was designed to reconstruct and visualize the dynamics of brain activity. Developed by the Biomagnetic Imaging Laboratory, the toolbox runs under MATLAB and can be used with Linux/UNIX, Mac OS X, and Windows platforms. NUTMEG uses raw MEG recordings (see Fig B.1) to generate a tomographic reconstruction of neuromagnetic activity over desired time intervals and brain regions. This technique produces activity maps akin to fMRI and PET, but with the added dimension of time. The results can be thought of as an array of virtual depth electrode recordings. NUTMEG allows the MEG coordinate frame to be easily co-registered with an MRI volume, which facilitate a convenient visual correspondence to neuroanatomy. Navigating through the MRI volume automatically displays the time course of neural activity arising from the selected voxel. Animations can be generated to view the evolution of neural activity over time. Because NUTMEG is an open-source MATLAB package, the end user can add customized functions. NUTMEG is available for download at ***http://bil.ucsf.edu/***.

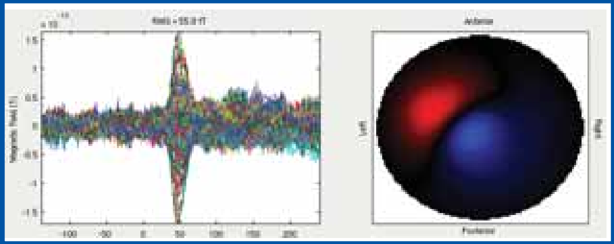

Figure B.1. MEG recordings. Left panel – Averaged magnetic field response to a somatosensory stimulus whose onset is at 0 ms. The response peaks at ~50ms following stimulus onset. Right panel – The magnetic field profile on the sensor array consisting of 275 MEG sensors. Here, sensor locations on the three-dimensional surface of the sensor array are mapped non-linearly to point in a circle. Red shows magnetic field lines pointing into the plane of the sensor array; blue shows magnetic field lines pointing outward.

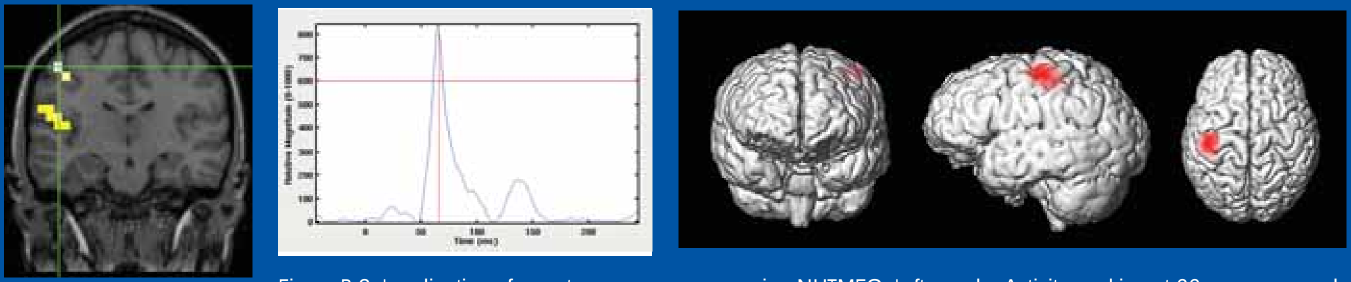

Figure B.2. Localization of somatosensory response using NUTMEG. Left panel – Activity peaking at 66 ms corresponds to primary and secondary somatosensory cortex (SI and SII). Center panel – Time course of activity in SI. Right panel – Three-dimensional overlay of the SI activity rendered on the cortical surface for this subject.

and only a few measurements are made outside the head, estimation is inherently ill-posed, i.e. there are many more unknown than known quantities. To reduce this ill-posedness and to improve the spatial resolution of ESI, estimation procedures incorporating prior knowledge and constraints about source characteristics (e.g., possible source locations, the source spatial extent, the total number of sources, or the source frequency/time-frequency characteristics) have been developed.

Inverse algorithms can be broadly classified into two categories – parametric dipole fitting and tomographic imaging methods. Parametric dipole fitting methods assume that a small set of current dipoles (usually two to five) can adequately represent an unknown source distribution. The dipole locations and moments form a set of unknown parameters, typically found using a non-linear least square fit, multiple signal classification algorithms (MUSIC), or maximum likelihood estimation method. Parametric dipole fitting has been used clinically with success to localize early sensory responses in somatosensory and auditory cortices, and interictal epileptiform activity. However, the localization of higher cognitive functions such as sensorimotor, language and memory has not been consistent or reliable.

There are two major problems in dipole fitting procedures. First, are problems of local minima when more than two dipole parameters are estimated. This is usually manifested by sensitivity to initialization. A second, more difficult, problem is that parametric methods often require *a priori* knowledge of the number of dipoles. In the case of MUSIC and maximum-likelihood methods, this is the rank of the signal sub-space dimension. The model order often is not known *a priori*, especially for complex brain mapping conditions. Although information and decision theoretic criteria have been proposed to address this problem, the success of these approaches is unclear. While parametric dipole methods are ideal for point or focal sources, they perform poorly for distributed sources and non-dipolar sources.

Tomographic imaging is an alternative approach to the ESI inverse problem. It imposes constraints on source locations, based on anatomical and physiological information derived from information obtained with other imaging modalities. Anatomical MRI provides excellent spatial resolution of head and brain anatomy, whereas fMRI techniques provide an alternative measure of neural activation based on associated hemodynamic changes. Because of the high degree of overlap in activity measured using multiple modalities, multimodal imaging data can be used to improve solutions to the inverse problem. If we assume that the transmembrane and intracellular currents in the apical dendrites of the cortical pyramidal cells are the dominant sources, the source image can be constrained to the cortex, which can be extracted from a registered volume MRI of the subject's head. Furthermore, the orientation of the cells normal to the cortical surface can be used to constrain the orientation of the cortical current sources. By tessellating the cortex into disjoint regions and representing sources in each region by an equivalent current dipole oriented normal to the surface, the forward model relating the sources and the measurements can be written as a linear model with additive noise. Such a formulation transforms the inverse problem into a linear imaging method, since it now involves the estimation of electrical activity at discrete locations over a finely sampled reconstruction grid based on discrete measurements. This imaging problem, although linear, is also highly ill-posed because of the limited number of sensor measurements available in comparison to the number of elements used in the tesselation grid.

## Tomographic ESI Algorithms

Several groups of researchers have expounded the bio-electromagnetic inverse problem using a Bayesian formulation, an approach that is common in modern statistical signal processing and estimation theory. In this formulation, a prior distribution is introduced on the source and these priors are used to resolve ambiguities inherent in the inverse problem. This prior, with its pre-specified set of parameters, is usually combined with a Gaussian likelihood model for the data (based on a linear forward model and an assumption of additive white Gaussian noise). Maximization over the resulting posterior probability distribution results in a maximum *a posteriori* (MAP) estimate of the primary current sources and is achieved using Bayes rule (hence the term Bayesian).

Various priors have been proposed for ESI. Assuming a Gaussian prior for sources, i.e. each source is assumed to be drawn from a normal distribution with known variance, the posterior distribution is also Gaussian and can be computed analytically. Several ESI algorithms assume Gaussian priors for sources. Examples are minimum-norm methods and their variants. For Gaussian priors, it can be shown that the MAP estimators can be expressed as a non-adaptive spatial filter that operates on the spatiotemporal data to obtain reconstructions.

Basic studies of functional imaging reveal the sparse and highly localized nature of activation in the cerebral cortex. Nevertheless the idea of sparsity is appealing to enable functional interpretation of specific brain regions in various tasks. Several priors have been designed to reflect sparse and focal sources in the brain. For these non-Gaussian (sparse) priors, MAP estimators can be computed using advanced Bayesian methods.

In recent years, several papers from the Biomagnetic Imaging Laboratory, as well as other independent groups, have published alternative ESI algorithms called "adaptive spatial filtering" or "beamforming." The idea is to construct a spatial filter or beamformer that is a linear operator on the data used to estimate the strength of activity at different spatial locations within the head. In contrast to previously mentioned non-adaptive spatial filters, the beamformer spatial filters depend on the spatiotemporal covariance of the data, hence the term adaptive spatial filtering.

By scanning all locations inside the head, this method can be used to localize source activity within a particular scan volume. In the past several years, we have analyzed the performance of beamformers and demonstrated their superiority – zero localization bias, spatial resolution, signal-to-noise ratio – and analyzed their sensitivity to lead-field errors, low- and high-rank interference, and coherent sources.

Although the traditional derivations of the beamformers are based on spatial filtering theory, it can easily be shown that beamformers also are MAP estimators for a Gaussian prior with three additional assumptions. First, sources in the brain are uncorrelated; second, the prior variance of these Gaussian sources is equal to the posterior variances after reconstruction (also referred to as a unit gain constraint). A third, more implicit and less understood assumption is that there are fewer active sources when compared to the number of sensors, i.e. sparsity.

The Biomagnetic Imaging Laboratory has developed a software toolbox called NUTMEG (see sidebar, page 13) for use by the MEG research community for source localization using beamforming. This open-source software is available for free downloading.

## Application of Novel ESI Algorithms

ESI reconstruction methods, primarily involving single dipole fitting, have been used with success clinically to localize somatosensory and auditory cortices, and to localize interictal epileptiform activity. However, these methods are not adequate for mapping other brain functions.

In recent studies we show that novel ESI algorithms, such as beamforming, can be used for automated, accurate localization of motor cortex and interictal epileptogenic zones. Several previous electrocorticography (ECoG) studies have shown that voluntary movement results in event-related desynchronization (ERD) in the _ (~10Hz) and _ (~20Hz) bands in the sensorimotor cortex. This desynchronization starts ~2 s prior to movement onset over the contralateral rolandic region. ECoG studies have shown that _-band ERD is more discrete and somatotopically specific compared to _ERD. ERDs can be interpreted as an electrophysiological correlate of activation of cortical areas involved in the production of motor behavior. Power changes in the _ and _ bands during brisk finger extension and hand grasping can be observed in MEG. They also can be localized to the precentral sulcus, corresponding to the hand motor cortex using adaptive spatial filtering methods (Figure 1).

## Conclusion

The development of novel algorithms for ESI has helped realize the ultimate promise of MEG and EEG — namely exquisite spatiotemporal localization of normal and abnormal cortical networks. ESI is now considered an essential functional brain imaging tool to study sensorimotor, language, memory, and higher cognitive functions.

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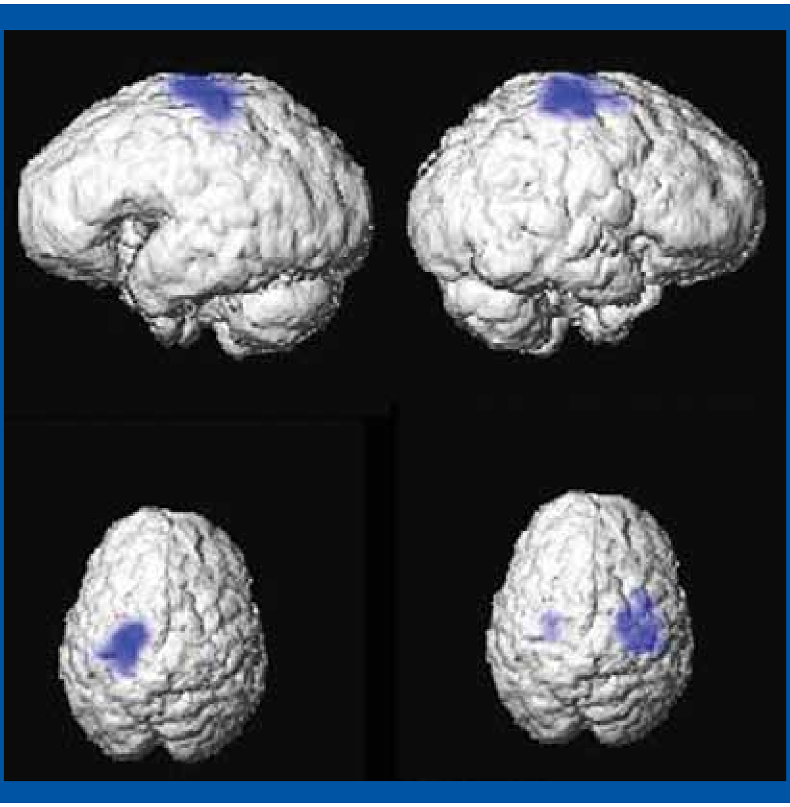

Figure 1. Localization of _-band desynchronization preceding hand movement in a patient with a brain tumor. Activity measured during a self-paced button press task shows the location of contralateral hand motor cortex. Left column – Activation from right index finger flexion. Right column – Activation from left index finger flexion. MEG measurements obtained 600ms prior to movement onset was used for localization with adaptive spatial filtering. Reconstructed images are overlaid on a rendered cortical surface that is extracted from the subject’s MRI.