EDITORIAL

Electromagnetic Brain Imaging

Riitta Salmelin[1]* and Sylvain Baillet[2]

[1]*Brain Research Unit, Low Temperature Laboratory, Helsinki University of Technology, Espoo, Finland*
[2]*Department of Neurology, Froedtert Hospital & the Medical College of Wisconsin, Milwaukee, USA*

INTRODUCTION

There is a long history to detection of neural current flow via specific changes in the electromagnetic field that is measured outside the brain. Electroencephalography (EEG) has been extensively investigated and utilized for the last 80 years [Berger, 1929] and electrocorticography (ECoG) for 60 years [Jasper and Penfield, 1949]. Magnetoencephalography (MEG) was introduced 40 years ago [Cohen, 1968] and it has since experienced intense technical development and growing interest in various fields of neuroscience. Clinicians and basic scientists who have chosen to utilize these time-sensitive techniques have always appreciated their great potential and pertinence to questions in both the clinical domain and integrative neuroscience, while understanding their respective limitations.

These electromagnetic techniques have recently fostered increasing interest from investigators who originally entered the field of human brain mapping via other modalities, particulary functional magnetic resonance imaging (fMRI). An aspiration to reach beyond the hemodynamic response and its limited time resolution is likely to be at the origin of such interest which has also manifested as notable investments in cutting-edge MEG and fMRI-compatible EEG systems. For example, the organization and internal mechanisms of brain-wide functional networks are considered by many investigators a tough problem of great interest that can ultimately not be addressed with the time scale of several hundreds of milliseconds that is accessible with blood oxygen level dependent (BOLD) effects. Consequently, the functional neuroimaging community now seems to increasingly encompass the relevance of *timing*—in a very broad sense—as a natural complement to *spatial mapping*, when seeking to characterize and understand human brain function and its disorders as well as the relationship between neural processes and behavior.

Each new development in electromagnetic methods and the more recent interplay between electromagnetic and hemodynamic techniques has brought along new views, challenges and disputes that have, eventually, moved the field forward. EEG was initially collected with a relatively small number of electrodes and, for several decades, the focus was set primarily on the identification and chronometry of typical scalp waveforms or components, with only indirect concern of the areas in the brain the signals would originate from—although there has been an unwarranted tendency to associate changes in EEG signals (or event-related potentials, ERPs) at specific electrodes with activation of the brain areas directly underneath. Emergence of the MEG technique, particularly devices covering large areas of the scalp (cortex), resulted in a palpable tension between EEG and MEG users and developers, akin to the brawls witnessed in the hemodynamic imaging community between users of positron emission tomography (PET) and the proponents of the rapidly emerging fMRI technique. Early MEG investigators—mostly from physics laboratories sought to localize—from the outset, the neural sources of the surface signals and determine the temporal variation of their activation. The prominent spatiotemporal (or source localization) emphasis in MEG had strong foundations: the volume currents that are generated by the intracellular (primary) currents and circulate within the head tissues have markedly less influence on the surface magnetic fields (MEG) than surface electric potentials (EEG), as

*Correspondence to: Riitta Salmelin, Brain Research Unit, Low Temperature Laboratory, Helsinki University of Technology, FIN-02015 TKK, Finland. E-mail: riitta@neuro.hut.fi

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do variations of electric conductivity across the brain, skull and scalp. The EEG community correctly emphasized cost-effectiveness and mobility of the EEG instrumentation and some relative limitations of MEG, such as poorer sensitivity to sources in deeper brain regions and uneven sensitivity to the orientation of neural current flow (the upside of these limitations is that they facilitate localization of the active areas). Most importantly, these "electromagnetic" confrontations have precipitated an abundance of developments in MEG/EEG methodology and led to recognition of their respective strengths and mutual benefits.

The newest, on-going phase of development was prompted by the increasing number of investigators with access to both fMRI and EEG and/or MEG systems and wishing to capitalize on both electrophysiological and hemodynamic techniques. Bridging these methodological approaches that have, so far, developed essentially in parallel may still be considered an open challenge. In fMRI, the need to detect small signal changes across experimental conditions and/or subjects even for a first impression of task-related brain responses has necessitated strong modeling and inference-based statistical analysis. In most MEG/EEG experimental setups, however, event-related signal changes are readily detectable even at the sensor level through mere signal averaging across experimental trials. Basic MEG/EEG data analysis has been largely driven by developments in time-series analysis to take full advantage of the temporal resolution and multidimensional nature of the data (time-frequency analysis, coherence and phase-locking indices, blind source separation techniques, etc.).

Electromagnetic brain imaging, i.e., moving from the sensor to the source level, provides an estimate of spatial distribution of activation as a function of time, within the spatial resolution afforded by the recording and analysis methods and the data set. It addresses the so-called inverse modeling (or inverse problem) of MEG/EEG source estimation that can be performed using a great variety of apparently different approaches; those have been a source of endless (and largely artificial) disagreements within the MEG/EEG community. Fortunately, the field now starts to show a fair degree of maturity, which has been further sharpened by the increasing contact with and challenges from the fMRI community.

MEG/EEG source modelling is often reduced to source localization through exploratory data analysis, where effects are first visually identified at the sensor level, then the signals are modeled by simple source models that are adjusted to the corresponding sensor data often based on multiple elementary current dipole fits and finally, the source-level effects are tested for significance by contrasting experimental conditions in an individual subject or across a group of subjects. This approach is, foremost, an efficient means of dimension reduction. Note that the point-like equivalent current dipole (ECD) model is a mathematically and physiologically simple account of a spatially extended cortical activity of a few square centimeters and should be interpreted as such, not misleadingly as an avatar of a strictly focal neural activation. Distributed approaches to MEG/EEG source modeling typically operate on sets of elementary dipoles placed across the individual cortical surface or volume, as identified from structural magnetic resonance images. The ill-posed nature of MEG/EEG source estimation is somewhat emphasized in this scenario as the typical number of model parameters largely outnumbers the original dimensions in the data. This issue is generally addressed through regularizing schemes that are also encountered in other areas of image reconstruction (e.g., astrophysics, geophysics and tomographic medical imaging) and aim at representing a given set of surface recordings by a unique (distributed) source model [Baillet et al., 2001].

Distributed maps can be subjected to group-level statistical inference that resembles fMRI data analysis, but the underlying models require substantial adaptation to the spatiotemporal properties of electrophysiological currents. Control of the error rate on hypothesis testing is certainly important in all functional imaging modalities; in the case of MEG/EEG one needs to consider not only 3D space but also time and frequency. Recent methodological developments further propose to bring neurophysiological and hemodynamic measurements into a similar conceptual framework that would ultimately yield a fully multimodal approach to the exploration of brain function. We anticipate very active discussions on the benefits and risks of within-modality versus multimodal analysis schemes of fMRI and MEG/EEG data that will surely, again, move the entire field of brain mapping forward.

This Special Issue introduces a selection of topical examples of multiple approaches to electromagnetic brain mapping; for more basic-level descriptions see, e.g., [Baillet et al., 2001; Hansen et al., 2009; Niedermeyer and Lopes da Silva 1993]. The contributions have been divided into two main sections, Experimental Reports and Methods. In the experimental section, cutting-edge examples of electrophysiological basic research are followed by studies addressing the relationship of electrophysiological and hemodynamic measures and a mini-review of established and emerging clinical applications. The methodological section focuses on novel approaches to estimating neural flow and connectivity, on extensions of the general Bayesian framework in reaching from sensor signals to the source level, on multivariate statistical inference and on the general problem of dimension reduction and feature extraction in MEG/EEG data and source models.

EXPERIMENTAL REPORTS

Theoretically, a specific electromagnetic field pattern may be generated by an infinite number of possible combinations of source currents, although physiological and anatomical realities set strong constraints on the solution of this so-called inverse problem in the human brain. Because of this element of uncertainty, direct recordings from the brain with intracranial electroencephalography (iEEG) are often seen as a gold standard. Jerbi et al. [2009] review state-of-the-art iEEG work, with a strong focus on high gamma band activity (60–200 Hz) that seems to be particularly tractable with invasive recordings. The mini-review further discusses the methodological limitations of iEEG and its agreement—and possible discrepancies—with surface MEG/EEG measures. Another much discussed issue in electromagnetic mapping is the difficulty of localizing sources deep in the brain or, in MEG, even detecting a signal from them. In this issue, Parkkonen et al. [2009] demonstrate localization of auditory brainstem sources with MEG. This feat required detecting very weak responses that was achieved with signal averaging over thousands of stimulus repetitions and focus on very high frequencies at which background noise from the cortex is negligible.

Oscillatory components in cortical activity are receiving much interest, as signatures of cortical activation and as measures of connectivity within networks of brain areas, and electromagnetic techniques are the obvious imaging methods to shed light on these phenomena and their role in brain function. In MEG/EEG reports to date, these effects have been typically most prominent at frequencies from 5 to 30 Hz, well below the gamma range. Coherent activation in sensorimotor networks, in particular, has been identified successfully, as is also demonstrated by Pollok et al. [2009] in their study of auditorily and visually paced finger tapping. In an otherwise largely similar network of interacting areas, modality-specific differences in frequency range and node location were observed in premotor involvement, suggesting that tapping to auditory stimulus occurs largely via predictive motor control whereas visually paced movements rely more on feedback control. Mazaheri et al. [2009] used the time-varying power of rhythmic activity to evaluate whether and how the state of the brain influences stimulus perception and response. In a Go-no-Go task, elevated levels of occipital alpha (~10 Hz) and sensorimotor mu (~10 Hz and ~20 Hz) activity predicted an erroneous response. An error was followed by enhanced theta activity (~5 Hz) in the frontal cortex and diminished alpha activity; furthermore, the theta and alpha power changes were correlated on a trial-by-trial basis, thus implying functional connectivity between the frontal and occipital cortex after an error had been committed.

Bodily self-perception may break down in neurological conditions, such as an out-of-body experience. In their EEG study, Schwabe et al. [2009] varied both the perspective and angle from which an image of a life-sized human was viewed and asked the subjects to imagine that it was there own body. A sequence from perspective-dependent posterior temporal to perspective-independent (but rotation-dependent) bilateral temporoparietal and frontal activation suggested a transition from a mentally embodied to a mentally disembodied state. This type of clinically-related or clinically-informed investigations form a strong part of MEG/EEG research. Routine clinical use requires specifically developed experimental and analysis approaches that are simple and robust, as described for MEG in the mini-review by Stufflebeam et al. [2009].

Meaningful combined use of the time-sensitive MEG/EEG data and spatially accurate fMRI data is an attractive and valuable goal in neuroimaging. A popular approach is to use fMRI BOLD maxima as seeds for MEG/EEG localization [e.g., Auranen et al., 2009; Dale et al., 2000] or, in simultaneous EEG-fMRI recordings, to use the EEG signal level (oscillations in a certain frequency range, specific components in evoked responses) as a regressor in fMRI analysis and, thus, localize the sources of the EEG features [e.g., Eichele et al., 2005; Laufs et al., 2003]. These approaches implicitly assume that the electromagnetic and hemodynamic measures detect, by and large, the same neural phenomena. The articles included in this Special Issue do not make this assumption but directly compare the two measures in the same individuals. Nangini et al. [2009] address the observation that an increasing stimulus rate typically results in decreased MEG/EEG responses but increased fMRI BOLD signals. Using trains of tactile stimuli in MEG and fMRI they found that MEG energy densities, convolved with the hemodynamic response function, accounted well for the BOLD signal. Neural processes of reading have been studied intensively with both MEG/EEG and fMRI. Both methods implicate the left inferior occipitotemporal cortex in early letter-string or word-form processing, but not in a fully similar way. Brem et al. [2009] asked how the visual word processing system develops from childhood via adolescence to adulthood according to EEG (ERP) and fMRI views. Interestingly, while the identified brain area was largely convergent, the electrophysiological measure showed a marked effect of age whereas the hemodynamic measure exhibited a dependence on reading skills, instead. Liljeström et al. [2009] report on a whole-head MEG vs. fMRI comparison in an action/object picture naming task. They analyzed the MEG data using both focal ECDs and a distributed source model. At the group level, the overall pattern of activation and task effects were relatively similar in MEG and fMRI, although with some systematic discrepancies, but in the individual subjects the correspondence was less compelling.

METHODS

Over the past few years, multiple approaches have been proposed (and applied) for extracting functional or effective connectivity from MEG/EEG signals. Schoffelen and Gross [2009] review the current state of this exciting field of research and argue why the connectivity analysis should be performed at the source level, and not at the sensor/electrode level, and why caution is essential in source space as well. The mini-review by Kiebel et al. [2009] describes the use of an MEG/EEG modification of the dynamic causal modeling framework that was initially developed for analysis of fMRI connectivity. It provides an alternative view to deciphering sensor-level MEG/EEG signals in which one first constructs models that extend from generation of the neural signals to choice of the brain areas involved and the types of connectivity between the areas and then uses Bayesian model comparison to decide which of the tested models best accounts for the measured MEG/EEG data. Lin et al. [2009] offer a means of optimizing the Granger-Geweke estimate of directional causality to allow estimates in both the time and frequency domains with high temporal resolution. The result was tested against a clinically verified case of epileptic spike propagation.

Development of methods for MEG/EEG source analysis and the companion problem of feature extraction continues actively. Lefèvre and Baillet [2009] have introduced the technique of surface-based optical flow in the description of brain dynamics, which also led them to revisit the concept of successive brain microstates [see, e.g., Brem et al., 2009; Schwabe et al., 2009 in this issue for examples of source analysis built on that idea]. The Bayesian framework is currently very popular in electromagnetic imaging as well. Valdés-Sosa et al. [2009] provide an up-to-date example of Bayesian source modeling, in form of a novel source imaging technique that proposes to perform an independent components decomposition of cortical activity at the source level by generalizing existing techniques to have both spatial and temporal priors. Modeling the neural sources as ECDs is a mathematically transparent approach, with the minimum number of assumptions, but it generally requires manual intervention and benefits from expertise. Sorrentino et al. [2009] now propose an algorithm which, based on multitarget Bayesian tracking and the theory of Random Finite Sets, automatically recovers the location, timing and strength of a set of ECDs. As always, all these new methods for source-level description [including the method by Kiebel et al., 2009 above] need to be compared with earlier, generally accepted analysis methods to understand how they work in different theoretically and practically relevant situations. In most experiments, the absolute source-level truth is not known because we cannot reach into the whole brain at once, nor can we trust that there is an exact correspondence between the intracranial and noninvasive measures. The section closes with Soto et al. [2009], who discuss an approach to identify statistically significant effects in cortically-constrained distributed MEG maps, akin to methods used in analysis of hemodynamic data. The focus is on detection of event-related modulation of oscillatory activity but the general considerations are equally relevant for evoked responses.

The field is in a constant motion. This Special Issue will hopefully give the reader an impression of the present possibilities and future potential of electromagnetic brain imaging. We are extremely grateful to the authors, reviewers, editors and staff at the Human Brain Mapping for their valuable contributions to making this Special Issue . . . very special. Happy reading!

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