Real-time tomography from magnetoencephalography (MEG)? experimental and theoretical challenges, possible physiological basis and evidence from the analysis of real data

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Abstract. Magnetoencephalography (MEG) and electroencephalography (EEG) were the Cinderellas of neuroimaging. On the one hand they are endowed with unparallel temporal resolution, while on the other they are in theory unable to uniquely determine the generators, even when a complete and exact set of measurements is available. Yet, study after study from our laboratories and others demonstrate that with modern hardware and software a very accurate estimate for the generators can be derived, at least from the MEG data. In this work we first review briefly theoretical arguments and the methods of source reconstruction. We then list experimental evidence for localization accuracy of a few millimeters from real MEG data using magnetic field tomography and a recent phantom study where a number of these techniques have been compared. We then put in context the accepted view of the electrophysiological basis of the EEG and MEG signal generation, adding caveats that must be considered given our incomplete knowledge of the anatomy and electrophysiology. We finally present results for processing of facial information that link the localization measures derived from MEG to the fMRI data at one end and invasive electrophysiology at the other and put them in the proper neurophysiological context.

Keywords: canonical circuit, open field, close field, localization, magnetic field tomography (MFT), single trial analysis.

1. Introduction

In all scientific endeavours, the reductionistic exploration of detailed experimental findings and the generalizations needed to extract principles and rules out of these findings resemble the two sides of a continuously turning coin. Like in coins the former side bears the value and the latter the origin of the credit for this value. The two sides are inseparable; more than anywhere else in brain research. On one side we have the results, the raw data and the processed output of their analysis that provide us with a value (in the form of numbers and images, often in the background of anatomy). On the other side of the coin there is an often implicit notion of what these numbers and images might represent. This side of the coin is influenced by the biological reality assumed (what might possibly be the physical generators and how they function) and the theoretical framework that defines the limits of what can and cannot be measured by the hardware and derived from the data analysis. Interpreting what we read in the literature is often difficult, partly because of our own prior assumptions about

what each side might represent and partly by a mismatch in the actual coin (paper) about what value one side is portraying and how this value is described implicitly or explicitly on the other side.

The end product of an EEG or MEG experiment is some measure of activity. Even if we assume that the contribution emanating from the brain has been successfully separated from other interfering sources, considerable ambiguity remains about the data and results of their analysis. The MEG or EEG signal is a coarse measure that in its raw form can only produce global and abstract measure of brain activity, for example global field power. As we will shortly recount, it is nevertheless possible to derive surprisingly accurate estimates of activity pooling information from a large number of sensors. It is even possible to design linear combinations of signals to extract timecourses of focal generators, in a rather direct way from the raw data [Liu and Ioannides, 1996; Tesche et al., 1995; Laskaris et al., 2003]. It is however unclear what is measured by a sensor of interest (SOI) analysis [Liu et al., 2002] which depends critically on the differences between conditions at the level of individual sensors. Ambiguities of this type abound in the literature, where the raw signal of one or more sensors is directly used to index activity. The ambiguity is augmented when such raw signal is linked to localized measures of activity derived from methods like fMRI or invasive electrode recordings. For example, in many papers the EEG N170 or the corresponding MEG M170 signal component elicited by face stimuli is often described as an index of activity from the fusiform gyrus or even the more restricted fusiform face area (FFA) [Kanwisher et al., 1997].

An ambiguity of a different kind is encountered when the data are heavily processed. Averaging and filtering are two powerful pre-processing operations that however lead to huge loss of information some of critical importance for the interpretation of the results. It is believed that by heavy filtering and averaging the signal quality is improved. There is no doubt that these pre-processing operations improve signal to noise ratio (SNR). The question however remains unexplained on the other side of the coin: what is the underlying signal and what is the noise? Animal experiments and our own studies have demonstrated that stimuli produce responses that can be very brief [Moradi et al., 2003; Ioannides et al., 2005] and highly variable from trial to trial [Liu et al., 1999; Liu and Ioannides, 1996; Ioannides et al., 2002; Laskaris et al., 2003; Ioannides et al., 2004b], even in the primary sensory areas. Labile, task relevant responses in one area are co-occurring with other similar responses, some are also task-relevant while others are not. It is then inevitable that averaging and filtering mix together responses that should have been studied separately.

The use of different reconstruction methods leads to a third category of ambiguities, especially when models are employed that are too simple to represent accurately the underlying biological reality. Equivalent current dipole modeling (ECD) has been the most widely used method of analyzing EEG and MEG data, and continues to be very popular. ECD can lead to misleading conclusions, especially when applied to heavily filtered and averaged data. For example, many studies using ECD modeling of /and/or heavily averaged and low pass filtered EEG or MEG data have failed to identify early modulations within 100 ms, e.g. for attention in V1 [Martinez et al., 1999] or face specificity in the Fusiform Gyrus (FG). We have suggested that such failures may reflect the influence of pre-processing and source modeling rather than true absence of early modulations [Ioannides, 1995; Ioannides, 2001]. We have recently demonstrated early attentional modulation in V1 [Poghosyan et al., 2005] and face specific responses from the FG [Okazaki and Ioannides, 2008], both within 100 ms.

A fourth type of ambiguity arises when results are compared with stimuli presented to different parts of the visual field. There is no reason to expect that the early processing of visual stimuli is the same when stimuli are presented to the center and the periphery, left and right, upper and lower parts of the visual field. Animal experiments have demonstrated that stimuli presented in the periphery reach the striate cortex 10 to 20 ms earlier than stimuli presented at the center of the visual field [Mitzdorf and Singer, 1979; Schmolesky et al., 1998]. We have recently provided the first convincing demonstration of earlier arrival of peripheral stimuli in humans. Specifically, we showed that a simple checkerboard pattern activates V1 about 10 ms earlier when it is presented in peripheral than parafoveal locations. Furthermore, by the time the response in V1 reaches its peak (around 70 ms) activity has already reached almost all areas of the visual hierarchy [Poghosyan and Ioannides, 2007]. In a separate study using emotional facial expressions in a face recognition task we showed that the first detectable link between activities in V1 and the FG (within 100 ms) proceeds from V1 to the FG for stimuli presented at the center or the lower parts of the visual field, but from the FG to V1 for stimuli presented in the upper part of the visual field [Liu and Ioannides, 2006]. In a third project we studied the information transfer between V1/V2 and the motion area V5. We found that for high contrast, responses to stimulus motion and position began first in V1/V2, and then in V5. At low contrast however, lateralized responses in V5 came first, with those in V1/V2 lagging with a delay of 27 ms [Maruyama.M. et al., 2007]. In a fourth study, we showed that processing and task effects

proceed in different ways when subjects view Kanizsa figures and their controls. Stimuli presented at the fovea elicit an automatic, attention-independent, sweep from V1 to extrastriate areas beginning with separation of the responses for illusory figures and their controls in V1/V2 within 100 ms. For stimuli presented at the periphery, the differentiation of responses to illusory figures and their controls begins late in the FG, while a task (attentional) modulation spreads outwards from V1, beginning within 100 ms [Bakar et al., 2007].

In the next section, Material and Methods, we will go to a more basic level, beyond the ambiguities regarding the detailed interpretation of the reconstructed activity described above. We will discuss briefly the very feasibility of obtaining reliable information from the non-invasive MEG signals, first at the theoretical level, and then at the practical level using results from the analysis of phantom and real MEG data. We will then describe physical processes, implemented by the neuronal machinery that might be responsible for the generation of the EEG and MEG signal. We will describe the view for the canonical cortical circuit, and consider the wide range of variability of neurons and their roles. We will then outline the widely accepted view about the generation of the EEG and MEG signal. In section 3, Results, we will use the processing of face stimuli to demonstrate how MEG analysis can bridge the gap from the macro- and multi-subject descriptions derived from functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) to very precise timing focal activations in real time that can be related to information derived from invasive electrode recordings. These results provide yet one more validation for the MEG localization using the fMRI data as gold standard, and also demonstrate that estimates of activity derived from the same MEG data can be linked to hemodynamic measures and invasive electrophysiology. In the final section, Discussion, we will point out gaps in our knowledge that might be critical for the interpretation of electrophysiological data and end with some speculations about what we might reasonably expect from MEG in the future.

2. Material and Methods

2.1. Theoretical mountains .. or hills?

Given the long established fact that there is no unique solution to the biomagnetic inverse problem [von Helmholtz, 1853], it would appear that working on the reconstruction problem in EEG and MEG is an exercise in futility. Yet, practical experience shows that the non-uniqueness hanging over the field may be a real "sword of Damocles" in theory but only a paper one in practice. There is no doubt, that selecting one of the infinite number of possible solutions demands the use of constraints and that each constraint will bias the solution in a different direction. The key question is then how large is the range of ambiguity when the set of possible constraints are considered. Focusing only on theoretical monsters or on generator types that will generate negligible signals is an interesting theoretical exercise, but not necessarily very helpful in practice. We separate in two parts the question how large a range of ambiguity different reconstructions allow. First, we consider finding a "best method", call it X, that has good theoretical credentials <u>and</u> can produces accurate source reconstructions, as can be judged by a gold standard comparison and our knowledge of the underlying biological reality. Second, we examine how other methods compare with method X, when tested in situations where the generator configuration is known, i.e. either with computer generated or phantom data.

We begin with the optimal choice of method and how it measures against real data. After long debates in the 80s and 90s the field has slowly accepted that distributed models offer a more realistic, albeit more difficult to handle, way of describing brain activity. Distributed source models are naturally described by the set of lead field functions. Each lead field function, $\varphi_m(r)$, describes the sensitivity profile of one (the mth) sensor within the region of space that can accommodate generators [Tripp, 1982]. Expressing the unknown current density vector, $\mathbf{J(r)}$, as a linear sum of lead fields seems the natural way to proceed, $J(r) = \sum_m A_m \varphi_m(r)$. This formulation is known as the minimum norm method (MN) [Hamalainen and Ilmoniemi, 1984] and it effectively provides a 2D projection of the underlying currents. Information about the distribution of generators in the third dimension is limited because the MN solution inherits the bias of the lead fields for superficial generators. Guided by how an analogous limitation was overcome by a successful application of an iterative-perturbative approach to the inverse scattering problem in nuclear physics [Ioannides and Mackintosh, 1985], a

new framework for the biomagnetic inverse problem was proposed [Ioannides et al., 1990]. The new framework introduced three new ingredients. The first two compensate obvious limitations of the MN method, by controlling for noise in the data through a regularization procedure and eliminating the bias favoring superficial sources by the introduction of an *a priori* probability weight [Clarke et al., 1989; Ioannides et al., 2007]. The third ingredient is a subtle one, and it follows the realization that an expansion in terms of lead fields alone, even with the addition of a J-independent weight is not justified a priori. Different expansions were tested with successive iterations weighted by different powers of the current density modulus of the last iteration [Ioannides et al., 1990]. Simulations with computer generated data demonstrated that multiplying the a priori probability weight by the modulus of the current density vector lead to the best solutions, capable of recovering distributions in three dimensions [Ioannides et al., 1990; Ioannides et al., 1995]. The method was named magnetic field tomography (MFT) [Ribary et al., 1991]. The name reflected the capability to recover details of superficial and deep brain regions, with no prior assumptions about their format, equally well for single focal activation, a few focal activations or distributed activity. The mathematical justification for these results was provided by a detailed analysis of the lead field expansions [Taylor et al., 1999]. This analysis produced a principled way of arranging the range of available methods for distributed sources by considering them as variants of the assumed *a priori* form for the unknown current density vector, $\mathbf{J(r)}$. In the new framework, MFT was generalized to encompasses many of the other distributed methods available today [Ioannides and Taylor, 1999]. The key concept in this generalized hierarchy of distributed models is that the unknown current density is expressed

by $J(r) = |J(r)|^{p+1} \sum_m A_m \varphi_m(r) \omega_p(r)$. The choice $p = -1$ leads to the family of linear models

that includes (weighted) minimum norm, LORETTA, and beamformer techniques. The choice $p = +1$ leads to a version of the FOCUSS algorithm (corrected for gauge invariance) [Gorodnitsky and Rao, 1992]. Standard MFT, refer to simply as MFT hereafter, corresponds to $p = 0$ and it leads to a highly non-linear system of equations that must be solved independently for each single timeslice of data. Linear methods allow statistical analysis and other linear pre-processing operations at the level of MEG signals. As a result the inverse problem can be solved for a much reduced "clean" signal, than the massive set of original raw data. The underlying non-linearity of MFT does not allow such a shortcut. For MFT, the inverse problem must be solved for each timeslice of data independently. Statistics and measures of how timecourses in different areas are related to each other are derived from the resulting huge volumes of tomographic solutions. The obvious limitation of MFT is the complexity and size of the computational problem that must be tackled. Nowadays however, solving this problem is manageable and more than compensated by the maximal use of the information in the MEG data. Voxel-by-voxel statistical parametric mapping (SPM) of the MFT solutions allows comparisons of short segments of post-stimulus activity with similar segments drawn either at the same latencies but from other conditions (active test) or drawn from the pre-stimulus interval or some other control data set (baseline test). Such comparisons can be made either from sets of average data or from single trial (ST) MFT solutions. Post-MFT SPM analysis allows a time-dependent generalization of the same methods that are routinely applied to PET and fMRI data to be applied to MEG. This has allowed us to compare the MFT localization accuracy directly with fMRI data using identical stimuli and paradigms and the same analysis methods (albeit at vastly different timescales). This methodology allows the same subjects to be studied in separate fMRI and MEG experiments, thus removing the need for anatomical averaging across subjects. Two recent SPM studies with MFT have demonstrated accurate localization at both cortical [Moradi et al., 2003] and sub-cortical [Ioannides et al., 2004a] levels.

For the second part of our key question, we compared the localization accuracy of ECD, MFT and two other popular source identification methods, using data generated by brief transient activations of dipoles implanted in a realistically shaped phantom. The first, Synthetic Aperture Magnetometry (SAM) is a minimum-variance beamformer algorithm that estimates the source and noise power from a full-rank covariance matrix [Robinson and Vrba J., 1998]. SAM requires long time windows for the computation of an accurate estimate for the covariance matrix of the signal. The other technique, MUSIC, estimates a signal subspace from the recorded MEG data using singular value decomposition. The MUSIC algorithm scans a single dipole model through the 3D head volume and for each position estimates the projection of model MEG signal onto the signal subspace [Mosher et al., 1992]. More details of this study can be found in this volume (Papadelis, Poghosyan and Ioannides). Figure 1 shows the main results for two of the four source location studied. In all cases the forward problem was solved using the sphere model but with center adjusted individually for each sensor.

The first, PhS1, corresponds to a superficial generator, at the level of primary sensory areas or supplementary motor cortex (SMA). The other, PhS3, corresponds to a fairly deep source, roughly at the level of the hippocampus and amygdala. In summary this study demonstrated that for superficial sources all four methods (except ECD applied to ST data) produce results with localization accuracy of a few millimeters, for source strengths producing signals in the range of typical MEG signals recorded from humans. Differences were more pronounced for deep sources where MFT provided the best results, maintaining an accuracy of a few millimeters. The advantage of MFT was maintained when multiple sources were simultaneously active and when reconstructions were made using a small number of trials.

The accuracy reported in our analysis of real data [Moradi et al., 2003; PoghosyaN and Ioannides, 2007] and the phantom study is not unexpected. A meaningful description of activity cannot be extracted from either a snapshot of PET or fMRI data, but only after many such images are compared statistically to each other. In contrast, MFT provides a pretty good tomographic image of the activity in the brain from just one snapshot of MEG data [Ioannides, 2006]. MEG generates huge number of such snapshots, each with a slightly different background activity. Reconstruction of generators using methods, like MFT, that can exploit this information reliably should produce accurate reconstructions with high statistical significance. Of course such accuracy is only possible from data that have been recorded with corresponding accuracy all the way through, from the coregistration with the anatomical (MRI) data to the calibration of the head location relative to the sensors and the stability of the subject position during the measurements.
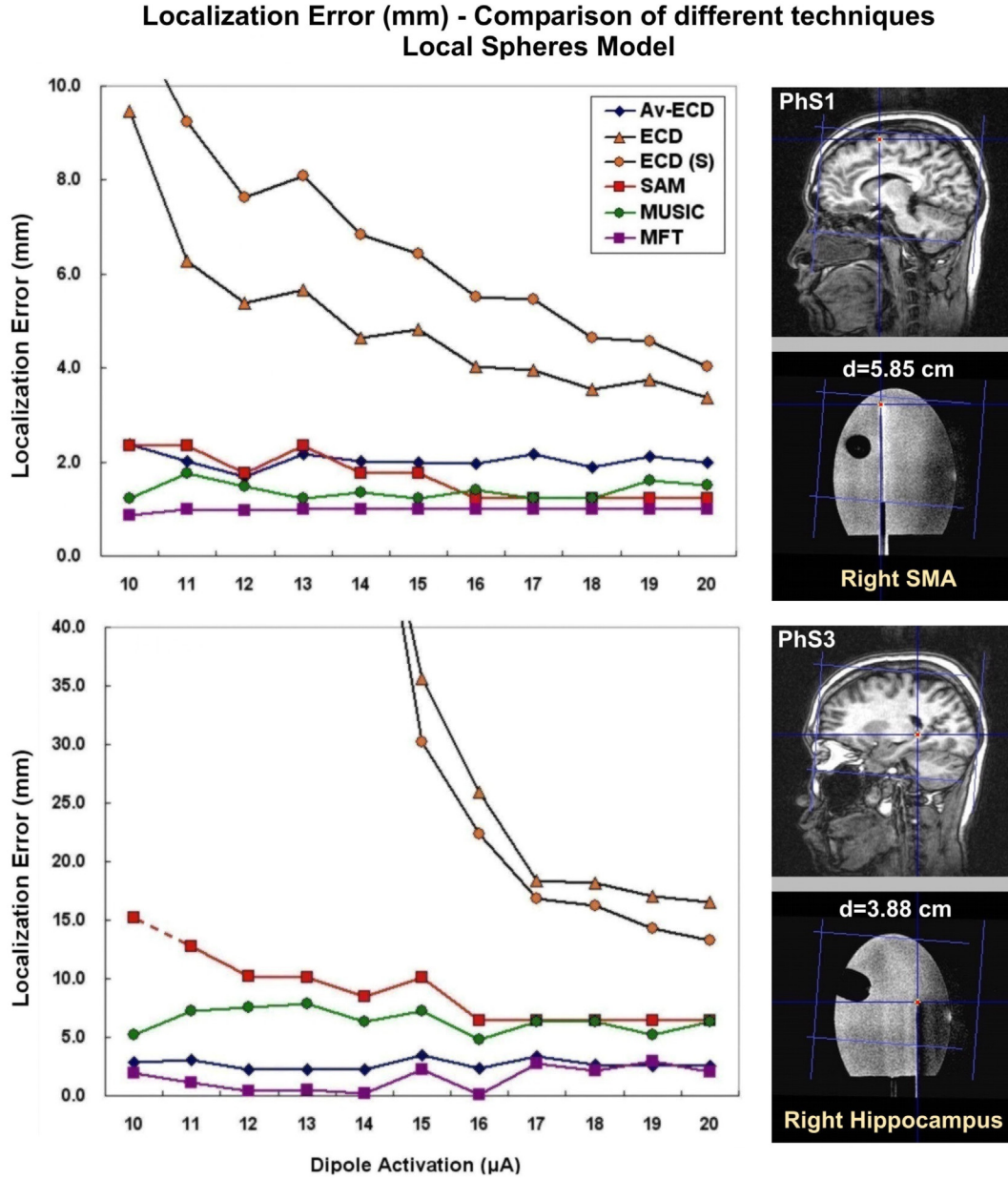
Figure 1. *Localization accuracy for transient activations of a single source in a realistically shaped phantom. All four methods studied produce excellent results for the superficial source (placed roughly where the human SMA would be found). For the deeper source (roughly at the level of the hippocampus and amygdala) the accuracy of different methods varies with the best results obtained for MFT and ECD (from average data). Note also that the ECD model fails when applied to single trial data. The distance, d, of each implanted dipole from the (nearly) silent center of the "head" is printed in the phantom figurine.*

2.2. The neural reality

It is thought that cortical neuronal assemblies are the main generators of EEG/MEG activity. Understanding of how EEG/MEG fields are generated therefore relies on knowledge of the architectonics of cortical neuronal assemblies and the elementary principles of their functional organization. Studies of cortical cyto- , myelo- and chemoarchitectonics have distinguished with considerable consistency tens of different neocortical areas [Toga et al., 2006]. Considering a canonical circuit of the cortex is surely an oversimplification of a system made up of 10^9 cortical neurons engaged in dynamic interactions with each other via 10^{12} synapses. Extracting simplifying principles is however a practical guide necessary for directing future investigations and in our case for

understanding the most likely mechanisms of EEG sources creation. Most (>70%) neurons are spiny (pyramidal and stellate) with assymetric synaptic junctions containing round vesicles and releasing glutamate; they are excitatory. Smooth neurons on the other hand have no spines, they make synaptic junctions with pleomorphic vesicles releasing γ-aminobutyric acid; they are inhibitory. Common is also the presence of 6 cortical layers; 2-6 containing principal neurons toped by the first layer containing long axons from brainstem and non-specific thalamic nuclei terminating on apical dendrites [Jones, 1998]. In primary sensory cortex the densest projections end in layer 4, where specific thalamocortical input also arrives. Excitation appears to spread from layer 4 to 3 to 5 to 6 and reenters in 4 [Douglas and Martin, 2004]. Variations and enrichment of this sequence of events abound, but the essence lies with the gradual recognition of the dynamics which the considerable convergence and divergence of connections impose on any such scheme. An average layer 4 neuron could receive input from more than 1000 thalamic relay cells, each of which has terminal arbors extending several mm on the cortical surface. In addition to thalamus 20 other subcortical areas project to the cortex. However more than 99% of inputs to cortical neurons are from other cortical neurons. Neighboring neurons are sparsely coupled, but can be potentially activated by hundreds of others, most connections being relatively local and only restricted subsets of neurons being involved in long-distance connections. Most connections are between excitatory neurons and so weak thalamocortical inputs can be amplified by recurrent collateral excitation. This activity will be specifically shaped by feedback, feed forward and lateral (surround) inhibition. In parallel to structural studies, the discovery of collumnar organization [Mountcastle, 1998] led to a functional categorization of neurons, which were complemented later by work in slices revealing the intrinsic membrane properties characterizing certain neuronal types [Llinas, 1988]. Four main types have been described: regular spiking, intrinsically bursting, fast-rhythmic bursting and fast spiking neurons [Connors and Gutnick, 1990; Gray and McCormick, 1996]. Although serving elementary communication such categorization is criticized as not taking into account the continuum of firing patterns observed as the membrane potential changes. It has been demonstrated that different brain states are associated with changes in intrinsic properties and transformations from firing patterns that define one neuronal type into discharge characteristics of other cell types [Steriade, 2004]. Hypotheses of how the generic cortical circuits might express themselves functionally, have been further elaborated [Douglas and Martin, 2004]. Superficial cortical patches have been allocated the role of sampling, selecting ("winner-take-all"), distributing and interpreting inputs. Deeper layers receive this information, put it in context thus forming an integrated output. While the ubiquity of such generalizations is debated, structural studies have endowed neurophysiology with few but solid principles, which have been exploited in interpreting brain's electric field generation, i.e. the statistical predominance of pyramidal neurons, the parallel arrangement of their apical dendrites, the sequential activation of different layers etc. Also very decisive have been the explorations of intrathalamic circuits including the nucleus reticularis, the estimations of the quantitative importance of corticothalamic influences and the role of cortico-thalamic re-entry for cortico-cortical interactions [Jones, 2002; Sherman and Guillery, 2002].

We often complain about the inability of EEG to reflect brain activity unambiguously. Considering however the complexity of the system as sketched above, the multitude, the variety and the minute strength of brain electric sources it is more appropriate to marvel that we see anything at all non-invasively. It almost seems that all forces of evolution have conspired to make EEG (and MEG) possible. Consider the case of the large EEG delta waves of deep sleep (Fig. 2). Under what conditions can they be generated? We will consider the creation of elementary dipoles in single neurons, their orientation/polarity and their numbers i.e. their arrangement relative to each other and the skull and their synchronization, so that they add up in space and time and create electrical currents big enough to be produce measurable correlates outside the scalp.
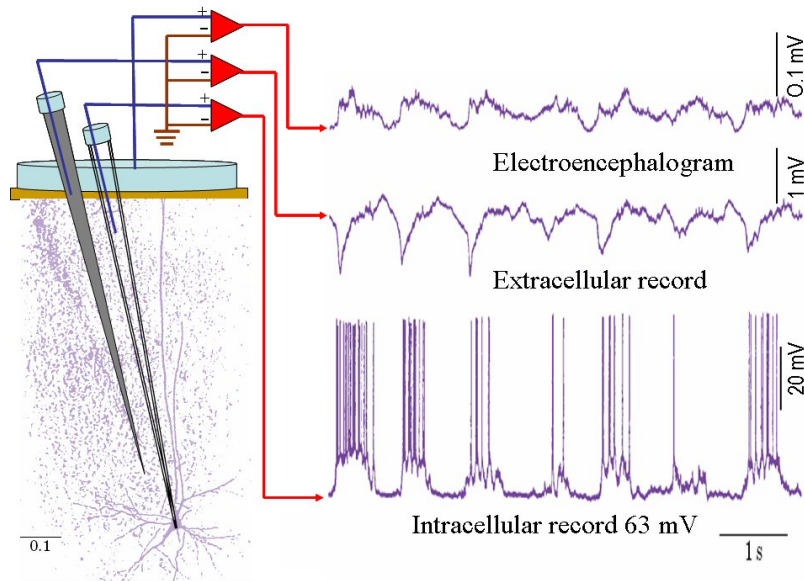
Figure 2. *Fluctuations in the membrane potential of a cat pyramidal neuron (bottom recording trace) when synchronous enough create local electric fields (middle trace), which can be recorded outside the scalp (yellow) as EEG but substantially diminished (about 10:1) due to the intervening resistances. The 3 electrodes in light blue: epidermal disk, extracellular metal (dark) and intracellular (transparent) glass micropipette. The activity recorded corresponds to deep sleep (delta waves). Modified from [Jones, 2002; Amzica and Steriade, 2002].*

Figure 3 shows the flow of current generated by the activation of a hypothetical axosomatic synapse. Positive current is rushing in the cell as the binding of the released glutamate to its postsynaptic receptor opens Na+ channels, leaving a relatively negative charge in the extracellular space in the vicinity of the synapse.
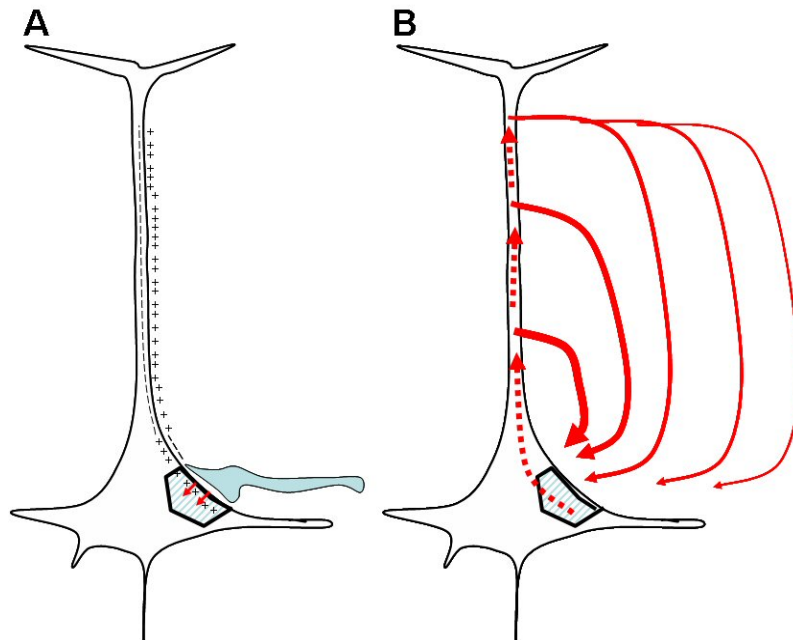

Figure 3. *A. Excitatory synaptic activation of a patch (striated blue area). Positive ionic current through the synaptic channels will depolarize the local membrane and create a potential difference with other areas of the cell. B. As a result current will flow intracellularly away from the activated area and extracellularly towards it.*

The local membrane is depolarized, i.e. compared to other areas of the same neuron the local membrane will present an excess of positive charges on its interior and a decrease on its exterior (Fig. 3A). Ionic current driven by the electrical potential gradient will flow intracellularly, depolarizing remote parts of the membrane by a capacitative current. The resulting increase of positive charges in

extracellular space around these remote dendrites will drive ionic current flowing in the extracellular space from these areas with relative excess of positive charges (serving as sources) towards the area of the activated synapses which serve as sink (Fig. 3B). The circuit thus formed is made up of two parts: a highly concentrated intracellular current balanced by a diffused extracellular current. An electrode placed in the extracellular space close to distal dendrites will be expected to record a positivity relatively to a remote neutral electrode. If this positivity was strong enough it might be recorded as a positive EEG wave.

The example represents the most usual case of an excitatory postsynaptic potential (EPSP) creating an active sink at the soma level (deep layers) and a passive source at the level of apical dendrites. In the case of an inhibitory postsynaptic potential (IPSP) at the soma level we would have entrance of Cl- through synaptic channels and creation of an extracellular dipole with passive source at the soma level and the apical dendrtites area serving as sink. The opposite polarity dipoles will be respectively created when EPSPs and IPSPs are created by synapses in the apical dendrites. It becomes evident that theoretically, the depolarization (EPSP) from synapses on the body of a pyramidal neuron will produce such current flow – a dipole positive at the surface and negative in the deeper layers - that an EEG electrode would record a minute positive wave. Similarly, positive EEG wave would be produced by a hyperpolarization (IPSP) on the dendrites. On the contrary, an EPSP on the dendrites or an IPSP on the body would produce a negative EEG wave. Biphasic EEG waves may be created when apical and basal parts of pyramidal neurons are successively activated. Note that according to this static view, sources in a cell a stellate cell, with symmetrically distributed dendrites, will not create an electrical disturbance in the extracellular space because different contributions will cancel each other (fig. 4A).
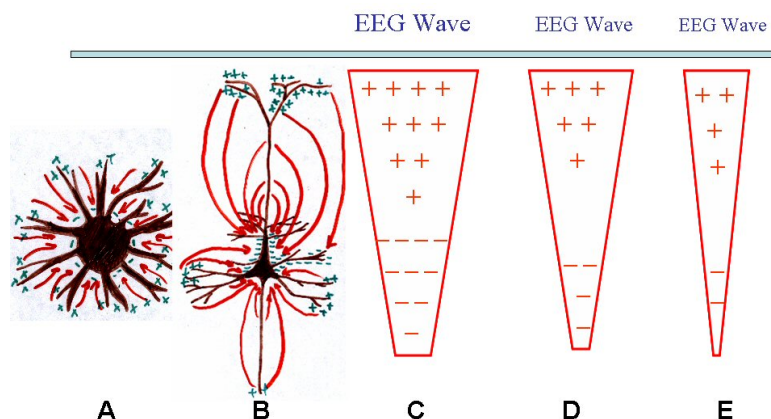

Figure 4. *A stellate cell (A) producing no external electric field and a pyramidal cell (B) capable of producing extracellular flow of current that can be seen as an **elementary current dipole.** The polarity depends on the position of sinks and sources that in turn depend on the location and nature of synaptic activation. The strength of the extracellular effect diminishes quickly with distance (C-E). The EEG will reflect the polarity close to the surface.*

On the contrary, a strongly asymmetrical neuron like the pyramidal ones will create an electric dipole (fig. 4B), strong close to the activated neuron but rapidly diminishing with distance with decay constant of few hundreds of μm (fig. 4 C-E). The potential contribution to surface recorded EEG is accordingly decreased, although an even more critical factor for EEG is how the signal is further distorted by the intervening material. The effective (electrical) distance for an electrode on the scalp is dominated by the distortions and attenuation produced by the high resistance of the skull. From this point of view sources in the brain appear equally distant. If the shape and resistance of the skull is known exactly this effect can be allowed for and thus a much cleaner view of the generators can be achieved.

In extending the discussion to MEG, it is useful to consider the source activity at the mesoscopic level, and separate the full current density into two terms. The first term, is determined by what are known as impressed currents because they describe the active currents generated by energy-demanding neuronal activity. Remaining currents make up the second term; they describe the passive currents that flow as a result of the impressed currents in the biological medium. At the spatial scale relevant to EEG and MEG signal generation, the full current density can be separated into active and passive elements, referred to as primary current density and volume or return currents respectively. The primary current density depends on both intracellular currents and the local extracellular currents. The intracellular currents are closely related to the local impressed currents. As we already described the net contribution from a single neuron is a sum of vectors each pointing along the long axis of the

corresponding active dendrite or axon. The overall primary current density generated by intracellular currents is the vector sum of contributions from active neurons, which is therefore strongly dependent on the overall arrangement of neurons. The extracellular currents flow along the local conductivity gradients, determined mainly by cell membranes. For each focal neuronal activity, the local arrangement of cells determines the combined effect of both intracellular and extracellular currents and therefore shapes the resulting primary current density. Primary currents can be thought of as the generators of the volume or return currents, i.e., the large-scale passive electrical current flowing in the "volume conductor", in the brain at large and bounded by the highly resistive skull. These large-scale passive electrical currents generate the EEG, but they do not contribute to the magnetic field, except where they "twist" at boundaries with sharp changes in conductivity, especially the skull. Figure 5 summarizes the classical view of the generation of the MEG and EEG signal, ignoring complications due to the secondary sources for MEG and the sensitivity to precise paths for the current flow in the non-homogeneous brain volume that strongly influence the EEG signal. The view acknowledges that the majority of neurons in cortex (>70%) are strongly asymmetrical, i.e. pyramidal neurons with a long apical dendrite and they are conveniently arranged in parallel (perpendicular to the neocortical surface). The MEG signal in this simplified view is created by the nearly macroscopic primary current density with direction lying in the tangential plane.
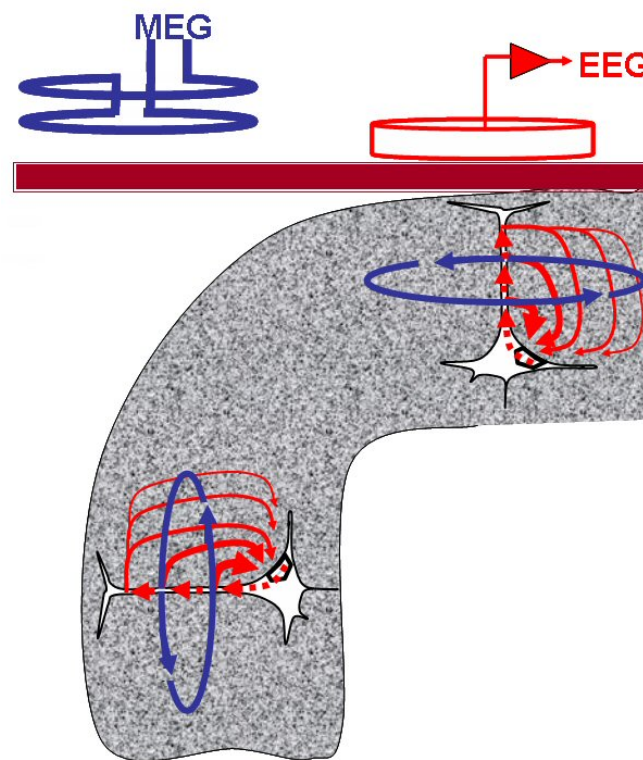
Figure 5. *Gray matter of a part of a cortical gyrus with two exemplary pyramidal neurons at the crown and the side of the gyrus (scalp is in brown). Each neuron represents the collection of similar neurons nearby and the local geometry their arrangement defines. Following an excitation at the soma level as in previous figures, the electric current flow is shown with red - continuous line extracellular and interrupted intracellular branches of the circuit.The EEG electrode will record any part of the field that will reach it (the volume currents conducted through the resistance of brain tissue and fluid, meninges,skull and scalp). To this field the intracellular current contributes relatively very little due to the high resistance of the neuronal membranes. In contrast, The magnetic field (blue) is created largely by the intracellular current in a plane perpendicular to the direction of the intracellular current.*
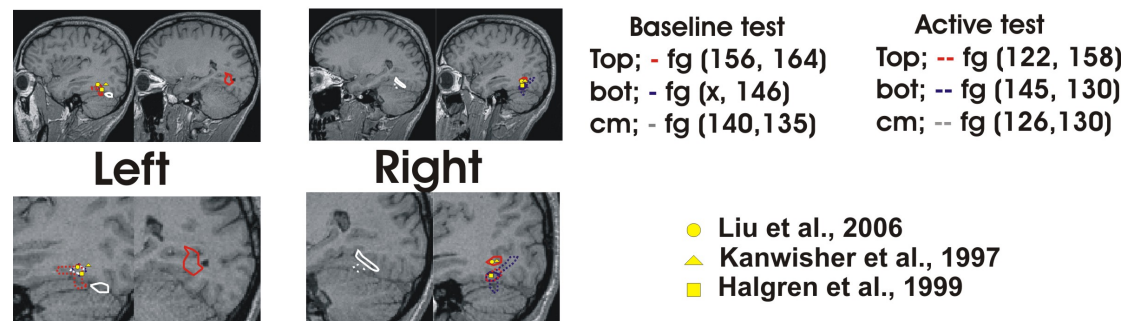
For a perfectly spherical conductor boundary, the magnetic field generated by primary currents in the radial direction is completely compensated by a term that mathematically appears as secondary currents induced on the inner surface of the skull (surface of sharp electrical resistance). Therefore, neurons in the sulci which are oriented tangentially to the scalp surface are maximally represented in MEG record and the radial ones minimally. No such discrimination holds for EEG, which on the contrary will be influenced by neurons from both sulci and gyri, but more so from the gyri. In both

cases the source can be described by an **elementary current dipole.** Another difference between EEG and MEG is the blurring of the generators caused by the high resistance of the skull, but only for EEG. The EEG and MEG do therefore have a common source but they reflect radically different processes and they are therefore truly complementary techniques.

EEG waves are considered to reflect mostly synaptic potentials rather than action potentials. EPSPs and IPSPs typically last more than 10 ms and often much longer. So they may create elementary dipoles across the pyramidal dendrites with a considerable time window of opportunity for synchronization. Although action potential are relatively larger in amplitude (100 mV as compared to 10 mV or less) they have much shorter duration (1-2 ms), so they are less likely to synchronize. Finally action potentials are "quadrupolar", they form two currents flowing towards a node of Ranvier from opposite directions and thus they at least partly cancel out, so they dissipate quicker with distance. The discovery of dendritic back-propagation of the action potential [Stuart et al., 1997] suggests the need to reconsider participation of somatodendritic action potentials in the potential sources of EEG and MEG; especially for the later. For MEG the contribution from action potentials may be important for high frequencies, capturing synchronous input or output volleys of action potentials in white matter bends just outside gray matter [Ioannides et al., 2005].

3. Results

We have demonstrated the high accuracy of MFT SPM localizations (in V1) by comparing them with fMRI SPM localizations of the same subjects under near-identical stimulus conditions [Moradi et al., 2003]. Much of neuroimaging today is concerned with identifying common foci of activity across subjects for brain areas that specialize in a specific function. Functional segregation has been demonstrated repeatedly by PET and fMRI using stimuli designed to preferentially excite specific areas. One of the most spectacular demonstrations of specialization is the identification of a circumscribed area showing preferential activation for faces, often referred to as the fusiform face area (FFA) [Kanwisher et al., 1997]. Numerous PET and especially fMRI studies have provided the "common" coordinates for the FFA across a pool of subjects, as reproducibly as can be expected by the use of common Talairach space. Figure 6 demonstrates that common SPM localizations obtained with MFT for the FFA are consistent with the fMRI findings.


Baseline test
Top; - fg (156, 164)
bot; - fg (x, 146)
cm; - fg (140,135)

Active test
Top; -- fg (122, 158)
bot; -- fg (145, 130)
cm; -- fg (126,130)

● Liu et al., 2006
▲ Kanwisher et al., 1997
◻ Halgren et al., 1999

Figure 6. *Statistical parametric maps for the FFA from fMRI (yellow triangle) and MEG (yellow dot and square). The solid and dash outline show the SPM results for the baseline(solid) and actve(dash) tests respectively.The results for center presentation are shown together with the results for contralateral upper and lower quadrant field stimulation. The numbers in brackets on the right correspond to the latencies for left and right results.*

We use for this analysis data from two MEG [Okazaki and Ioannides, 2008; Liu and Ioannides, 2006] and two fMRI studies [Kanwisher et al., 1997; Halgren et al., 1999]. In fMRI studies it is almost obligatory to identify the FFA using a localizer scan where the activations between faces and other objects, typically houses are compared. With MEG timing provides additional options. For example in the first MEG [Liu and Ioannides, 2006] study only face stimuli were used, and the fusiform activity was identified by comparing the responses between 100 and 200 ms to the pre-stimulus period. The yellow symbols in Fig. 6 show the centers of SPM foci identified by the MFT SPMs (circles) and the centers for FFA identified in the two fMRI studies (triangles and squares). In the second MEG study [Okazaki and Ioannides, 2008] we used both the baseline (solid outlines) and active test (dash outlines). In the active test we compared the responses elicited by faces to responses elicited by hands. The contours in Fig. 6 define the first appearance of common FG activations for the center (white contours) and for contralateral top (red) and bottom (blue) visual fields. For the active comparison, the same focal common areas emerge slightly earlier.

We have repeatedly demonstrated that the ST responses are highly variable, especially in areas beyond the primary sensory cortex. For strong stimuli, for example a high contrast pattern reversal, or checker board pattern covering a large part of one quadrant of the visual field, MFT solutions show response in the expected retinotopic locations in V1 extracted from the average of a small number of trials [Tzelepi et al., 2001], and even in individual STs [Ioannides, 2006]. A stimulus like a face presented to part of a quadrant of the visual field is not optimal for V1 and it produces a much more labile response. Figure 7 shows the instantaneous MFT reconstructions around the M70, the first strong response in V1, for the same face stimuli used in Fig. 6 [Okazaki and Ioannides, 2008]. The left part of the figure shows the M70 response extracted from three successive timeslices of the average signal. The right part of the figure shows the instantaneous MFT solutions extracted from one of the STs. This ST is one of the few that showed the response clearly. The magnitudes of the responses in the average and ST at the different timeslices is printed on the bottom of each sagittal slice, normalized to the overall maximum (at 74 ms for the single trial on the right).
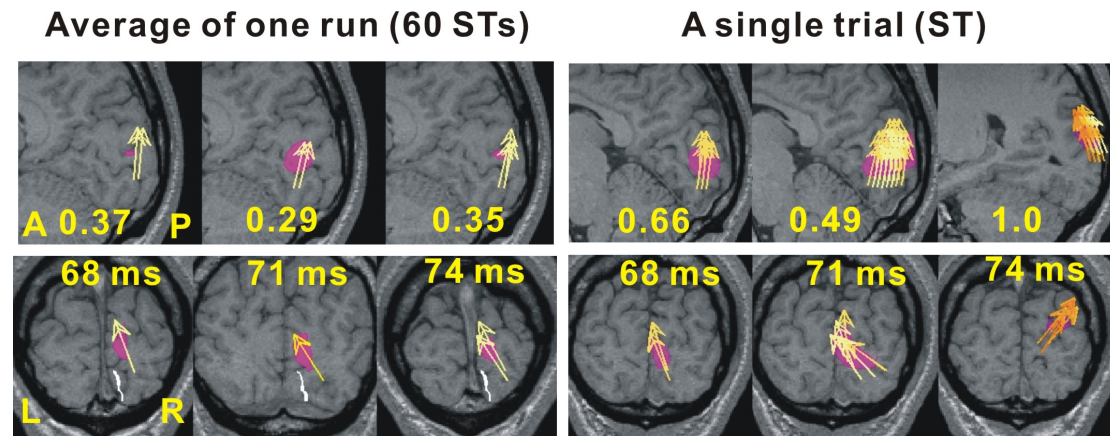
Figure 7. *Instantaneous MFT solutions in and around V1 for a single subject elicited by a face stimulus presented in the bottom left (BL) part of the visual field. Solutions extracted from the average MEG signal (about 60 STs) are on the left and from a ST with clear response on the right. In each case instantaneous solutions are displayed at 68, 71 and 74 ms,with sagittal on top and coronal on bottom panels. The slices vary with latency because they are cut at the level of maximal V1 activity. On the lower sagittal slices the V1/V2 border defined from a separate fMRI experiment is marked by the white outline. The numbers on the lower part of each sagittal display give the maximum value of the activation rlative to the overall maximum (the ST activation at 74 ms).*

4. Discussion

The brain is a fast and accurate machine. If an image of a familiar face is presented to our visual system many times, each time the brain will arrive at the correct interpretation, seemingly with little effort. Our brain can do this even when the images are presented in different sizes, from different angles, isolated or in a crowded environment, in full detail and color or in rough outline. Our brains can accomplish this with accuracy and speed that no man-made machine can match (yet). Numerous PET and fMRI experiments have shown that activity in specific brain areas, especially in the FG, correlates with processing of faces. Figure 6 has provided evidence that our tomographic analysis of MEG signals can identify the same area in individual subjects (not shown in the figure) and also in the common activations across subjects after suitable transformation to a common anatomical space.

The brain is also a complex machine that can appear to operate in capricious ways. The responses of a single neuron or a population of neurons varies considerably each time the same identical stimulus is presented, even in a highly controlled environment (in terms of physical properties of the stimulus and background, and for the same subject state and task). We have seen the same variability demonstrated in the V1 responses to a simple face image presented in one of the quadrants of the visual field. The results in Fig. 7 are examples with the most consistent responses; in other runs and in most STs the V1 response is not clearly identified. For some trials this is because a much stronger response can be seen in another nearby area, but in others no such interfering activity can be traced. A clue about what might be happening is the fact that the V1 response in the ST solution is typically about three times the size of the response in the average. The discrepancy cannot be attributed to amplification of irrelevant signals because the average of the MFT instantaneous ST solutions is almost indistinguishable from the MFT solution extracted from the average signal.

Our results demonstrated that the MFT analysis of the same set of MEG data can provide measures that relate on the one hand to hemodynamic macro-measures and electrophysiological invasive recordings. The MFT solutions provide to the fMRI data the missing information about timing. Different properties of the MFT solutions provide to the invasive electrode recordings a wider spatial context for the localization of the activity. While the results for responses in the FG and V1 described above do not contradict the models for the generation of the MEG signal described earlier, they also suggest that these models must be extended. The models we have described were based on an understanding of basics that is woefully incomplete. In terms of anatomy we have no idea how synaptic connections are organized at the spatial scale of many millimeters [Rockland, 2004]. We are equally ignorant about how activity is organized in time over the same spatial scales. We can not even be sure about the details of individual neuron activations. For example, the closed field nature of the activity of a stellate cell is based on the assumption that the probability of activation is uniform along the dendritic tree and soma. If the activation is spatially asymmetric at each instance of time, and if this asymmetry reflects an anatomical organization over large distances, the activation could easily become open field. These speculations begin to have some plausibility as recent evidence from two photon two-photon microscopy suggests that temporal synchrony of large neuronal populations is much higher than previously assumed [Ikegaya et al., 2004]. It is only a small step from there to assume that a spatial organization might exist (long-lasting or transient, just a few milliseconds long) that would produce a powerful MEG signal.

It seems that the side of the coin that we were most worried about the images and numbers side is relatively in good shape. It is the other side that defines what these really mean that requires most attention. The possibility of alternative ways of source creation cannot therefore be ignored. On the contrary, they are becoming increasingly plausible with discoveries like the dendritic hot spots of action potential generation and the non-synaptic influences on membrane potential of transmission through gap junctions, changes in extracellular space and ionic concentrations and glial as well as metabolic and vascular contributions. All these influences appear to become important and dramatically increase as synchronization and local fields increase and spread and dynamically feed back reinforcing this increase. Therefore one can no more exclude the possibility of open fields created not by simple addition of elementary single cell dipoles but rather emerging (beyond some threshold local field) as a result of such dynamic interaction of various influences at the mesoscopic level, e.g. at the trajectory of gap junctions distribution in many different cells etc. With the multitude of possibly interacting influences the space-time development of a current source would have a predictability closer to that of a lightning rather than that of a falling object. This accommodates the ST variability even in early somatosensory evoked potentials [Ioannides et al., 2002]. The crucial question is how the interaction of such not yet accounted for aggregate factors with individual neuronal activity may have implemented structure to function adaptation in brain evolution and ontogenetic development. It is unlikely that the mechanisms underlying the creation of strong enough to be recorded outside the head were developed and preserved for the sake of electrophysiologists. The coupling of local moment to moment mesoscopic currents to the overall electrical flow of activity might provide a useful global communication channel across the brain. As previously proposed such coupling of local and global brain electrical activity could be important in maintaining the organism unity by establishing a common reference, in a way analogous to how nucleons create a mean field that in turn keeps each nucleon bound to the nucleus [Ioannides, 1995]. Understanding the role they may play in brain function is a goal inseparable from understanding the nature of these current sources.

In conclusion the ability of MFT to localize brain activity reasonably accurately in much of the brain at widely different timescales promises to provide a much needed link between the detailed invasive electrode recordings and the more macroscopic (in space and time) hemodynamic data that are nevertheless closer to behavior.

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