Functional MRI as a constraint in multi-dipole models of MEG data
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Abstract
The use of physiological constraints in the solution of the inverse problem of brain electromagnetic fields has received increasing attention in recent years. A priori information is needed to constrain the solution of the electromagnetic inverse problem; other imaging modalities, such as fMRI, can provide information of this kind. The goal is to combine complementary information from different imaging modalities and thus achieve increased resolution in both spatial and temporal domains. In this article, the application of functional MRI data in guiding the construction of multi-dipole models for the interpretation of magnetoencephalographic data is discussed. Comparison of the differences of fMRI and MEG is made and convergence of the results obtained with these methods is described.

Introduction
The electromagnetic inverse problem is notorious in that any magneto- or electroencephalographic data can be explained by multiple different source current patterns. To select from the possible solutions, the use of physiological constraints has become an attractive approach in recent years especially after functional magnetic resonance imaging has become widely available (1-3). Initially, hemodynamic responses from positron emission tomography (PET) were applied to this purpose. In a pioneering study of visual attention, Heinze et al. (4) used PET data with a two-dipole model to find the location for equivalent current dipoles. With its better spatial and temporal resolution and wider availability fMRI appears somewhat more attractive, however. With recent developments in the field of event-related fMRI, it seems possible to use similar experimental setups as those used in electrophysiological studies (5-8). Separation of hemodynamic responses, even to very rapid stimulation rates, may be achievable in fMRI experiments (6, 8).

The goal in combining information from fMRI and MEG is to make the methods to complement each other so that the best resolution of each technique in temporal and spatial domains is achieved. With fMRI, the commonly achievable spatial resolution is about one millimeter; with high field strength MR scanners resolution even at cortical column level has been achieved (9-11). Functional MRI does not provide, however, much information about temporal characteristics of the cortical network in the millisecond scale. Rather, it reflects indirectly the activity of neurons integrated over a period of several seconds. By measuring latencies of hemodynamic responses though, one might be able to measure differences in the onset of activity with a 10-millisecond resolution (10, 12). Given the long time constants of the hemodynamic responses, information about more rapid modulation and offset of activity appears unachievable for fMRI. Electrophysiological measurements are still the only methods able to provide information directly of the neuronal activity on the millisecond time-scale.
Design of experimental setups presents a challenge when hemodynamic and electrophysiological measurements are used in combination. Naturally, it would be desirable to use exactly the same experimental parameters, but usually modified paradigms have to be used. This is due to the different nature of the measured responses. The signal-to-noise ratio may limit the use of similar paradigms. For example, electrophysiological response amplitudes decrease with increasing stimulation rate, while the hemodynamic response amplitudes increase (13, 14). As the hemodynamic response is smaller for shorter stimuli (7), use of short stimulus durations conventionally used in electrophysiology is of limited value. In electrical stimulation of peripheral nerves, for example, it is common to use stimulus durations of 0.2 ms.

**Convergence of the methods**

The use of spatial information from hemodynamic methods as a constraint to the electromagnetic inverse problem necessitates the assumption that the areas that appear active with different methods are to some extent the same. The spatial correspondence has been mostly investigated in the context of motor and somatosensory evoked activity. In the localization of the primary sensory and motor areas using equivalent current dipole modeling, typical spatial differences between the dipole location and the center of fMRI activation have been between 10 to 16 millimeters (15-18). In light of the current limited knowledge, the localization results seem to agree reasonably well when locating responses from primary sensory areas. Extending comparison to more complex cortical networks has indicated mostly converging activation patterns (19, 20). The activation patterns converged better on group level, thus suggesting that improvements in the sensitivities of respective techniques would further increase the convergence of the results.

There are occasions where disagreement in spatial activation patterns could exist. It is not clear, for example, whether very short-lasting synchronous firing, which can be detected in EEG and MEG, will produce a detectable hemodynamic change. Event-related synchronization and resynchronization are phenomena that possibly remain undetected by observing hemodynamic changes. For example, in the study by Ahlfors et al. (19), MEG indicated activity over the frontal cortex bilaterally while fMRI did not demonstrate any activity in similar areas. Using fMRI activation pattern as a strict spatial constraint or guidance in the model construction would obviously lead to incomplete and erroneous source models in these situations. Liu et al. (21) investigated the effect of the spatial constraint weighting to inverse solutions. In Monte Carlo simulations they found 90% weighting of the minimum-norm solution as the best compromise, providing good differentiation of the activity between sources localized correctly by fMRI and minimization of the errors caused by missing source areas in fMRI.

**Applications of fMRI in multi-dipole modeling of MEG data**

Multi-dipole models and continuous current distribution models (18) based on minimum-norm estimates have been applied in efforts to combine electrophysiological data with spatial information from hemodynamic responses. In two studies, we have attempted to model complex cortical networks with interaction from multiple brain areas using multiple ECDs.

**Somatosensory evoked responses.** We used an eight-dipole model constrained with fMRI data to model median nerve somatosensory evoked fields (SEFs) (20). Five normal subjects were studied. Somatosensory evoked fields were recorded with a Neuromag-122 magnetometer. In MEG, the interstimulus interval (ISI) was 5 s, while in fMRI an ISI of 0.25 s was chosen. The goal was to maximize the response amplitude in both imaging modalities, in order to achieve the best possible signal-to-noise ratio. The SEFs were first modeled independently of fMRI results. Thereafter a multi-dipole model was constructed by placing ECDs to fMRI activation centroids. If MEG data indicated activity in some of the eight source areas but no fMRI activation was seen, then ECD location from independent MEG data analysis was used. The eight dipoles were spatially fixed, but were allowed to change their orientation and amplitude to explain the data (rotating dipoles). The ECD orientations were remarkably stable over the whole analysis period (0 to 400 ms poststimulus). The time-courses of activation in the model were found to agree with data, that have been obtained with invasive electrophysiological methods (Table I) (22-25).

**Visual motion processing.** We have also studied temporal dynamics of visual motion areas, combining fMRI and MEG data (19). In this study, the cortical network processing visual motion was modeled with nine ECDs. The stimulus was a set of concentric contracting and expanding rings. The direction of motion changed with 3 s intervals. Four normal subjects were studied. Magnetic evoked responses measured with a Neuromag-122 magnetometer were averaged relative to the time of motion reversal. In fMRI, activation related to visual motion processing was studied by comparison between similar contracting and expanding rings versus stationary rings. The analysis of MEG data was first done independently of fMRI results. Independent MEG analysis indicated activity in occipital (V1, V3A),
occipito-temporal (MT+) and parieto-temporal (posterior superior temporal sulcus) areas as well. The occipito-temporal and frontal sources were found in both hemispheres in all subjects. The field patterns indicated the existence of a frontal source at the latency of 170-190 ms. FMRI indicated activity in similar areas bilaterally, with the exception of frontal activation. A multi-dipole model with ECDs placed to fMRI activation foci centroids was constructed. Figure 1 illustrates that the measured fields are explained unsatisfactorily if sources are constrained only to locations shown by fMRI. This model apparently did not explain the data well when frontal sources were active. A clearly better goodness-of-fit was obtained with a model augmented with frontal ECDs, whose locations were found independently from MEG data (Figure 1).

Both of the above mentioned studies indicated that while complete overlap of activation patterns determined independently from MEG and fMRI did not exist on individual level, the activation patterns did converge at the group level.

When sources are located close to each other, it might prove difficult to separate them into distinct source areas, even though shifts in the dipole location might indicate that multiple generators exist in an area. This is the case, for example, with opercular sources (Figure 2) of SEFs. The source area in postcentral sulcus for somatosensory evoked fields is very close to primary sensorimotor areas. Functional MRI, however, indicates separate areas of activation.

The results from these studies suggest that while fMRI cannot be used as a strict constraint in modeling MEG data, it will be useful in giving further validation for the source configuration used in a model.

Conclusion

Current results indicate that while it may not be possible to simply restrict the source model solutions to areas where fMRI shows activation, it still seems to be a valuable aid in the validation of the source model. Even when the experimental setups in fMRI and MEG were slightly different, a similar activation pattern could be seen with both methods in our studies. Converging lines of evidence from multiple methods will increase the likelihood of correct solution. The ultimate way to validate the inverse solution will be invasive recordings. Data from cortical surface recordings and depth electrode measurements are scarce for obvious reasons. Our experience from somatosensory evoked fields modeled with fMRI guided multi-dipole model shows that the time-course of activation shown by the model agrees with invasive data at least in those areas where reported data are available in the literature.

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References


Table I. Time of onset of activity in cortical areas participating in the processing of somatosensory information. Comparison between mean values obtained from fMRI constrained multi-dipole model and results of invasive recordings found in literature(20-23). SMI: primary sensorimotor cortex, PoCS: postcentral sulcus, AO: Anterior operculum, PO: posterior operculum, SMA: supplementary motor area.

<table>
<thead>
<tr>
<th>Area</th>
<th>Model value</th>
<th>Invasive study</th>
<th>Invasive recording mean value</th>
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<tbody>
<tr>
<td>SMI contralateral</td>
<td>17-22</td>
<td>Allison et al.1989</td>
<td>22</td>
</tr>
<tr>
<td>PoCS contralateral</td>
<td>21-25</td>
<td>Allison et al.1989</td>
<td>25</td>
</tr>
<tr>
<td>PO contralateral</td>
<td>19-32</td>
<td>Lüders et al. 1995</td>
<td>24</td>
</tr>
<tr>
<td>AO contralateral</td>
<td>22-51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMA</td>
<td>24-48</td>
<td>Allison et al.1996</td>
<td>40-50</td>
</tr>
<tr>
<td>SMI ipsilateral</td>
<td>30-70</td>
<td>Allison et al.1989</td>
<td>40-50</td>
</tr>
<tr>
<td>PO ipsilateral</td>
<td>42-92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AO ipsilateral</td>
<td>32-112</td>
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Figure legends

**Figure 1.** Visual evoked magnetic fields at 170 ms after visual motion direction reversal. The recorded magnetic fields are not modeled sufficiently when the dipoles are fixed only at the centroids of fMRI activations. Adding a frontal dipole, whose location is obtained by dipole fitting independently of fMRI data, results in a better goodness-of-fit (modified from Ahlfors et al. 1999).

**Figure 2.** Somatosensory evoked activity in opercular areas is usually modeled with one dipole in each hemisphere. Functional MRI data indicate, however, that activity is distributed in two clusters in each hemisphere: one in parietal operculum and one in frontal operculum and the insula. Using two dipoles bilaterally in the operculum (8-dipole model) clearly improves the model goodness-of-fit in opercular areas.
Measured

Independent MEG Dipole Model $g = 77\%$

fMRI-Constrained Dipole Model $g = 67\%$

fMRI-Constrained & Independent MEG $g = 85\%$