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COMPARATIVE STUDIES OF BRAIN ACTIVATION WITH MEG AND FUNCTIONAL MRI

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INTRODUCTION

The past two years have witnessed the emergence of MRI as a functional imaging methodology. Initial demonstrations (Belliveau et al., 1991) involved the injection of a paramagnetic contrast agent and required ultrafast echo planar imaging capability to adequately resolve the passage of the injected bolus. By measuring the local reduction in image intensity due to magnetic susceptibility, it was possible to calculate blood volume, which changes as a function of neural activation. Later developments have exploited endogenous contrast mechanisms to monitor changes in blood volume or in venous blood oxygen content (Kwong et al., 1992). Recently, we and others have demonstrated that it is possible to make such measurements in a clinical imager, suggesting that the large installed base of such machines might be utilized for functional imaging (George et al., 1992).

Although it is likely that functional MRI (fMRI) will subsume some of the clinical and basic neuroscience applications now touted for MEG, it is also clear that these techniques offer different, largely complementary, capabilities. At the very least, it is useful to compare and cross-validate the activation maps produced by these techniques. Such studies will be valuable as a check on results of neuromagnetic distributed current reconstructions and will allow better characterization of the relationship between neurophysiological activation and associated hemodynamic changes. A more exciting prospect is the development of analyses that combine information from the two modalities to produce a better description of underlying neural activity than is possible with either technique in isolation. In this paper we describe some results from initial comparative studies and outline several techniques that can be used to treat MEG and fMRI data within a unified computational framework.

EXPERIMENTAL METHODS AND RESULTS

Experiments to date have employed somatomotor and visual neural activation paradigms. Somatomotor experiments utilized voluntary flexion of the right hand. For MEG, flexion was cued at a rate of .5 to 1 Hz, and precise timing was established using an optical switch. For fMRI, flexion was self-paced, typically at a rate of 2-4 Hz during experimental trial blocks of ~2 minutes. These were followed by control blocks (no flexion) of the same duration.

Visual stimuli consisted of a sector of a circular checkerboard pattern, confined to a single quadrant (typically the lower right) of the subjects' visual field. The pattern occupied an annulus of 2.5 to 10 degrees, and approached but did not touch the vertical and horizontal meridians. A fixation crosshair was displayed continuously during stimulus presentation. In all fMRI experiments, steady state contrast reversal stimulation (7.5 Hz reversal rate) was utilized. MEG experiments utilized contrast reversal at 3.5 Hz or transient stimulation (patterns interleaved with a background screen) with the same transition rate. Computer generated images were displayed by video projection. In some experiments, projected video was focused onto a fiber optic image guide which was routed into a magnetically shielded chamber where the image was reprojected.

Neuromagnetic recordings were conducted using a 7 channel magnetometer (BTi) at the Los Alamos Neuromagnetism Laboratory, or a 37 channel system at the Magnetic Source Imaging (MSI) facility of the Albuquerque Federal Regional Medical Center (AFRMC). Most experiments involved multiple placements of the sensor array, chosen to provide adequate coverage of features apparent in the emerging spatial/temporal field map. Field maps were typically constructed from ~50 to >100 sensor locations, although in some somatomotor experiments a single placement of the 37 channel array captured both extrema in the dipole-like field map. Data were analyzed by single or multiple dipole fitting procedures or using distributed current estimation procedures being developed in our laboratory (e.g. George et al., this volume).

Functional MRI was acquired on a Siemens Magnetom 1.5 T clinical imager at the MRI center of the AFRMC, using a slightly modified FLASH gradient echo image acquisition paradigm. Multislice images (5 or 6 slices, 5-8 mm thick, with 2 mm in-plane resolution) were collected. Local shimming over the slice region was utilized to optimize sensitivity. TR was set at the minimum compatible with interleaved slice acquisition; TE was set at 40 ms (a reasonable compromise between maximal T2* weighting and signal intensity loss), and flip angle was optimized, typically to a value of 70°. Four sets of images were obtained during each stimulus or control block, and the experiment was cycled 2-4 times. Comparable images were averaged, omitting the first image set following a state transition. Stimulus-control difference images were constructed, and a voxel by voxel t-test was performed to assess statistical significance of apparent differences.

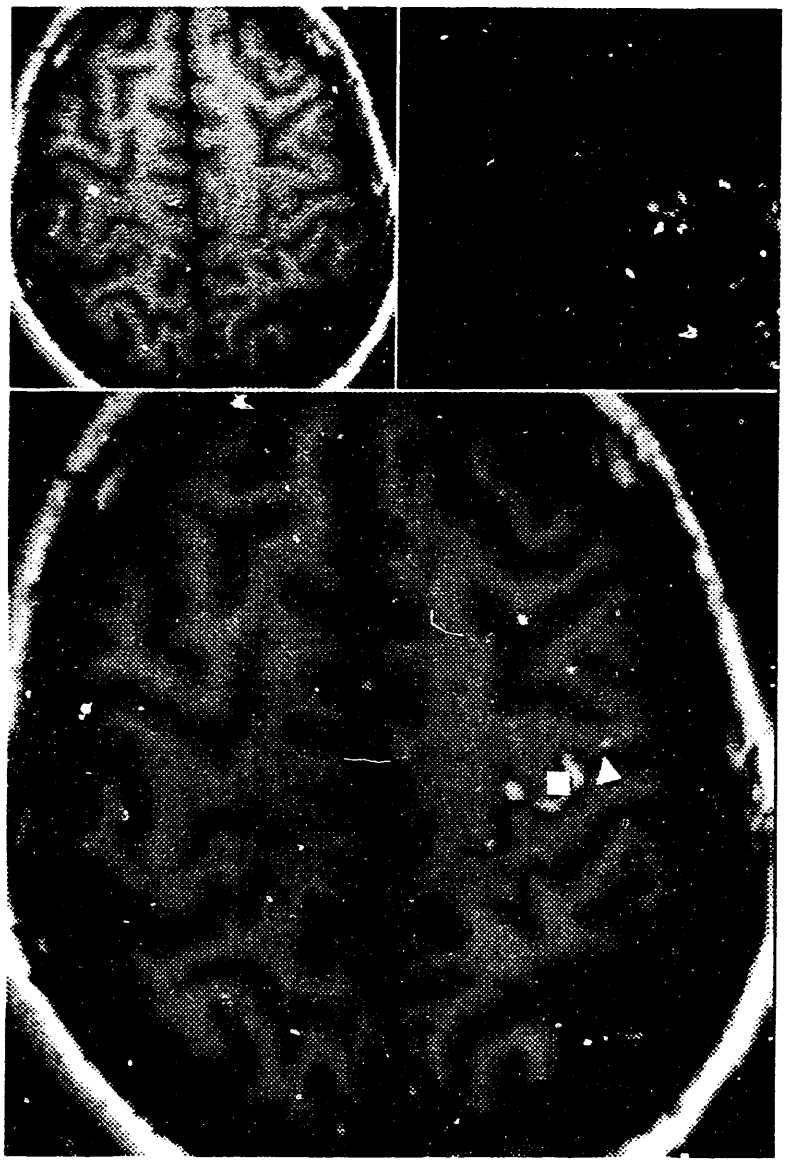

Figure 1. fMRI localization of somatomotor function.
Upper right: A t-statistic difference image from a multiple slice fMRI exam. This slice showed the maximum differences.
Upper left: The anatomical MR Image corresponding to the difference image described above.
Lower panel: The functional difference image thresholded at a 99% confidence level superimposed on the anatomical image. The square indicates the center of mass of the primary activation cluster. The triangle indicates the best fitting MEG dipole location from a comparable experiment with the same subject.

A sharp early component of the MEG somatomotor response was fit with a single dipole model, and the calculated source was located within a volumetric anatomical MRI data set. The necessary coordinate transforms were established by interactively identifying the landmarks defining the MEG head centered coordinate system on head surface renderings generated from the MR data set, using software we have developed. fMRI images were also reconciled with the anatomical data set, based on image definition parameters (if anatomical and functional data sets were collected during the same imaging session), or by identifying common internal anatomical features. The raw images used for fMRI contain considerable anatomical detail that is largely eliminated by the calculation of difference images. In experiments to date, agreement between the estimated center of mass of the region of activation disclosed by MRI, and the equivalent current dipole has been reasonable, typically less than 1 cm. The major discrepancy has been along the radial (depth) axis, which may reflect the fact that for the stimuli used, the region of activation extends between 1 and 2 cm along the cortical surface. Figure 1 shows an example of one such experiment.

MEG visual data were analyzed by sampling the response data at 5 or 10 ms intervals, and then fitting the composite instantaneous field maps with multiple dipole models containing increasing numbers of component sources. Appropriate model order for each map was determined on the basis of reduced chi square statistics, and the minimal sufficient set of source parameter estimates were used for spatial temporal model fitting. Using this technique we consistently identify 4 to 6 sources during the time interval 80-150 ms poststimulus. In general, there was good agreement between calculated locations of dipole sources and corresponding regions of activation apparent in fMRI difference images, with dipoles falling within the activation region. In some cases, it appeared that the dipole fitting procedure was compromised by inappropriate model order, or by the extended nature of the activation region, producing an inaccurate depth estimate; analyses based on the MUSIC algorithm often produced better agreement in these cases.

In most of the fMRI data sets, such as the study illustrated in figure 2, the activation of striate cortex is a dominant feature. In the corresponding neuromagnetic studies, map features associated with V1 activity are typically much less pronounced, presumably reflecting the increased sensitivity of MEG to source orientation, depth, and the possibility of field cancellation in extended, convoluted sources. fMRI is subject to artifacts from instrument instabilities, blood flow, head movement and soft tissue pulsation, among other factors. These possibilities dictate caution about interpretation of difference images. Nevertheless, there is generally good agreement between calculated locations of dipole sources and the corresponding regions of activation apparent in fMRI difference images.

FMRI also provides evidence for multiple visual areas analogous to those observed in neuromagnetic studies. In the fMRI illustrated in figure 3, right panel, we identified regions of activation corresponding to many of the primary sources observed in MEG studies: V1,V2, contralateral and ipsilateral occipital-parietal sources, an occipital-temporal source, and a source on the ventral surface of occipital cortex. We missed a more lateral temporal source, probably due to inadequate coverage in the multislice fMRI exam. The agreement between these data sets is surprisingly good, particularly considering that the data shown is a comparison across individuals.

DISCUSSION

MEG and fMRI provide complementary views of neural functional activation elicited by sensory stimulation or voluntary motor control. Although there is general agreement on the location of activity detected by these methods, there are differences in detail, apparently stemming from differences in sensitivity of the techniques, uncertainties introduced by the neuromagnetic inverse calculation or the possibility of artifact over the long temporal baseline of fMRI studies. Clearly a convergence of evidence from both techniques lends additional credence to observations from either methodology.

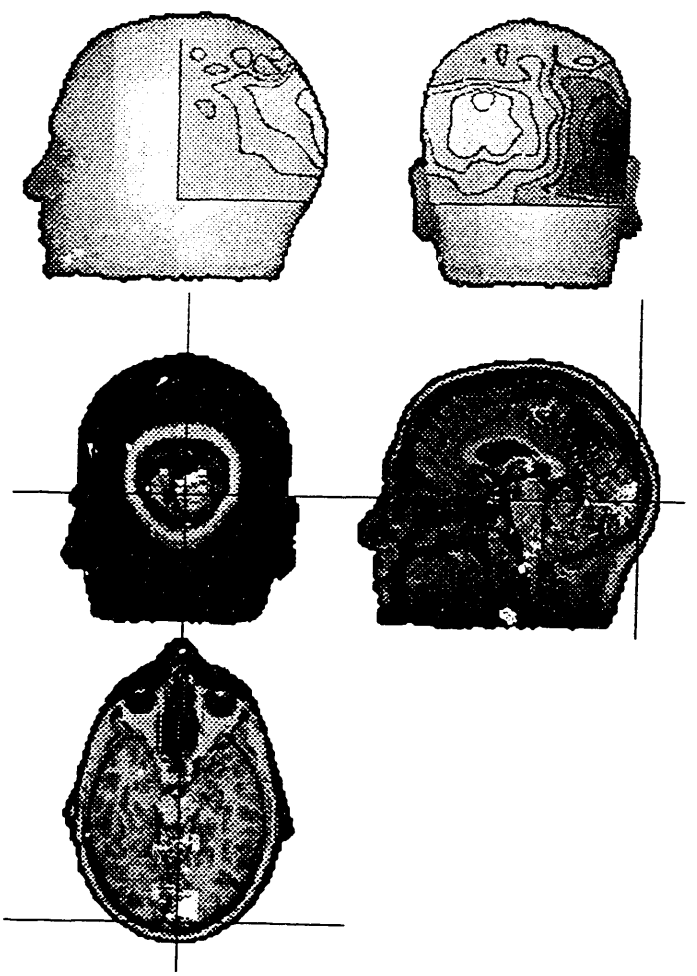

Figure 2. High resolution mapping of human brain structure and dynamic function by combined techniques.
Blocks of 6 parasagittal slices , each 5 mm thick were were collected using a T2* weighted acquisition sequence. Visual stimulation consisted of contrast reversal of an annular sector of a circular checkerboard displayed in the lower right visual field. Control periods were interleaved with stimulation epochs. The primary visual area active from ~70 to 100 milliseconds poststimulus was located on orthogonal projections produced from 3-D anatomical MRI data (crosshairs on lower panels); the field distribution associated with this source is illustrated in the upper panels. Functional MRI measurements disclosing changes in cerebral blood flow are shown as highlighted overlays on anatomical images in the lower panels.

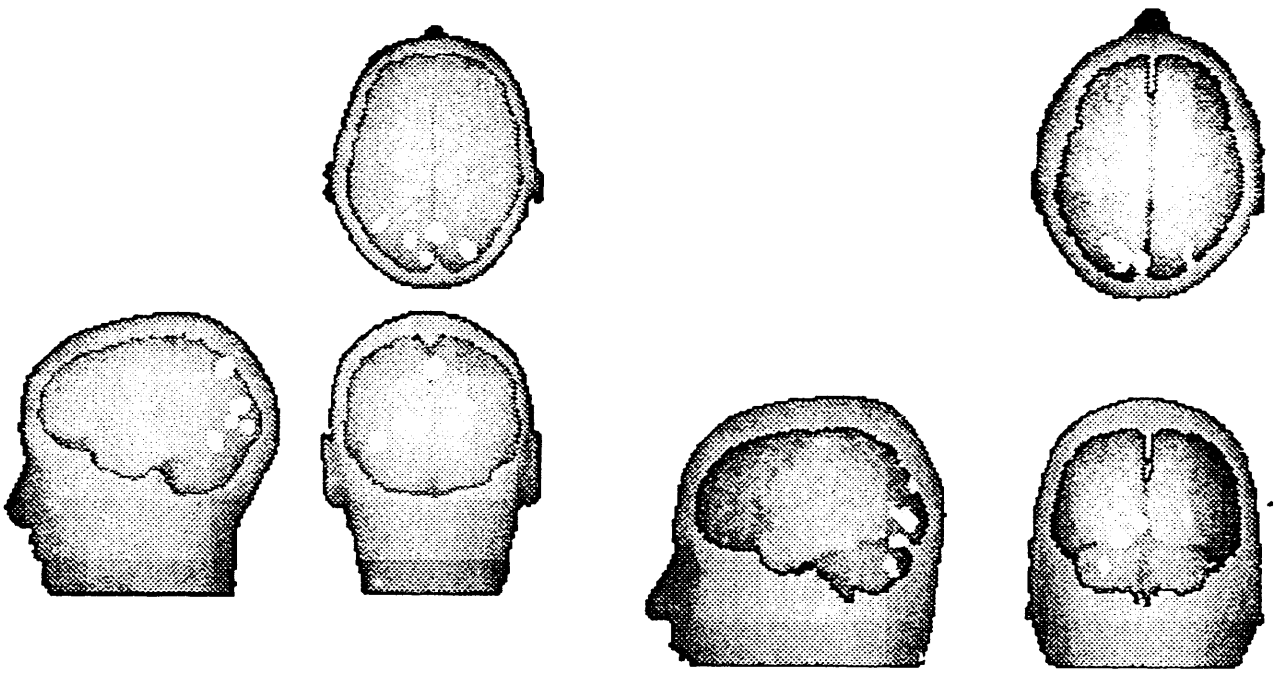

Figure 3. Multiple Visual Areas identified by MEG and fMRI.
Left panels: Neuromagnetic field measurements of neural sources activated by visual stimulation were analyzed by multiple dipole spatial-temporal modeling techniques. Confidence regions determined through Monte Carlo analyses are superimposed on renderings of the head and brain generated from volumetric MRI for this subject.
Right panels: A six (coronal) slice fMRI experiment for a different subject, disclosing regions activated by visual stimulation. Highlighted areas indicate significant differences in the control versus stimulated images.

Differences in the sensitivity of the techniques and the nature of the underlying physical phenomena dictate different optimal designs for the two classes of experiments. fMRI, with temporal resolution on the order of seconds based on the time constants of the hemodynamic responses, is most useful for characterizing the location of steady-state phenomena. MEG analyses often exploit the temporal fine structure (ms) of dynamic neural population responses, and therefore often employ transient stimulus presentation. However, by utilizing relatively slow "steady state" stimulation paradigms it is possible to produce adequate activation for fMRI while retaining unambiguous temporal information for MEG analyses. fMRI has tended to use large stimuli to produce extended regions of activation for compelling identification, whereas the most successful MEG experiments have utilized focal stimuli that more closely approximate the dipole model. However the ultimate limitations on fMRI spatial sensitivity are due to partial volume effects in a single voxel, which can be made quite small, and distributed source modeling will relax the dependence of MEG on the point dipole model.

It may be desirable to use fMRI to precisely define the locations of regions of activation while using MEG to define the temporal dynamics. While existing methods allow us to approach this goal, we are presently implementing methods which will allow explicit analyses of combined data sets. By assuming current orientations normal to the local cortical surface, it is possible to define the field distribution associated with the coherent activation of a contiguous region. Corresponding MEG data can be fit with a small number of such extended sources. Although the more realistic source geometry should improve model accuracy, this procedure does not allow resolution of adjacent, functionally distinct, areas on the basis of timing differences. Alternatively, it is possible to use fMRI to limit the source space for tomographic reconstruction procedures, analogous to the use of MRI-based anatomical constraints we and others have described (George et al. 1991). Though a useful enhancement, such methods will often produce an underdetermined inverse calculation when multiple, extended sources are present. Optimal reconstruction performance may require advanced inverse strategies in addition to source space constraints.

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