

Multimodal integration: constraining MEG localization with EEG and fMRI

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Abstract— I review recent methodological developments for multimodal integration of MEG, EEG and fMRI data within a Parametric Empirical Bayesian framework [1]. More specifically, I describe two ways to incorporate multimodal data during distributed MEG/EEG source reconstruction under linear Gaussian assumptions: 1) the simultaneous inversion of EEG and MEG data using a common generative model [2], and 2) the addition of spatial priors from fMRI data when inverting MEG or EEG data [3]. In the former, the addition of EEG data was shown to increase the conditional precision of source estimates relative to MEG alone; in the latter, the inclusion of each suprathreshold cluster in the fMRI data as a separate spatial prior was shown to increase the Bayesian model evidence for MEG and EEG reconstruction. The former is an example of “symmetric” integration, or “fusion”, in which a single generative model of all data modalities is inverted; the latter is an example of “asymmetric” integration, in which the data from one modality is used to inform inversion of another. I will conclude by considering whether symmetric fusion of MEG/EEG and fMRI data is worthwhile.

Keywords— MEG, EEG, fMRI, multimodal, fusion.

I. INTRODUCTION

There is much recent excitement in formal methods to integrate, or “fuse”, data from different, non-invasive neuroimaging modalities, such as magnetoencephalography (MEG), electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), in order to achieve more accurate spatiotemporal descriptions of human brain activity than is possible with any one modality alone. EEG/MEG data provide a relatively direct measure of (synchronous) neuronal local field potentials (LFP) and ensuing currents with millisecond (or higher) resolution, as recorded outside the scalp. Localizing this electrical activity within the brain is an ill-posed, inverse problem however [4]. Furthermore, EEG and MEG have different sensitivities to the orientation of electrical sources and to the different conductivities of skull and scalp [5]. fMRI on the other hand, normally relies on a blood oxygen level dependent (BOLD) signal that can be localized in the range of millimeters, but integrates over several seconds of neuronal activity.

Fusion of multimodal data can take several forms (Fig 1). A full integration, or “fusion”, would entail inverting a single “generative” model that explains both types of data. This model must relate the same hypothetical neural causes

(e.g., timecourses of neuronal activity in circumscribed brain regions) to each type of data, using modality-specific “forward models”. In this framework, usually Bayesian, different data-types are treated symmetrically, and the priors on model parameters are not based upon the data in either modality [6]. This approach will be illustrated for simultaneous inversion of MEG and EEG data in Section III.

Developing such a generative model is the ultimate goal of multimodal fusion. In some cases however, these models can become complex and difficult to invert. For example, in order to integrate MEG/EEG data with fMRI data, one needs to relate the physiological causes of EEG/MEG signals to the physiological causes of the BOLD signal. While there is empirical evidence for a close relationship between LFPs and BOLD [7], accepted and accurate models do not yet exist. Furthermore, if the modalities are differentially sensitive to different dimensions of the neuronal causes, such as the temporal and spatial dimensions, it remains unclear whether the modalities can mutually constrain each other. In other words, the traditional complementarity of MEG/EEG and fMRI in terms of temporal and spatial resolution respectively makes the value of full fusion unclear (see Section V).

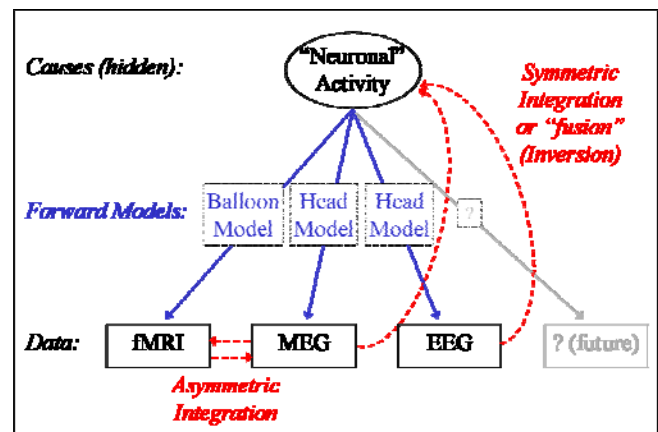


Fig. 1 Schematic illustrating distinction between symmetric and asymmetric multimodal integration within a generative model

An alternative approach therefore is to use data from one modality as a predictor (independent variable) for the data of another modality (dependent variable). For example, one might use some summary measure of EEG/MEG power at

each fMRI sample point as a regressor in a voxel-wise, classical statistical analysis of the fMRI data [8]. This type of ‘‘asymmetric’’ approach taken for MEG and fMRI integration in Section IV, except that we use partitions of the fMRI data as spatial priors on the localization of the sources of the EEG/MEG data (see also [9]).

II. A PARAMETRIC EMPIRICAL BAYESIAN FRAMEWORK

The approach to multimodal integration reviewed here benefits from a recent convergence of analysis methods for MEG/EEG and fMRI towards a common Variational Bayesian framework, specifically a Parametric Empirical Bayesian (PEB) framework [10]. The ‘‘Parametric’’ refers to the assumption of multivariate Gaussian distributions, e.g., for random error terms; while the ‘‘Empirical Bayesian’’ refers to hierarchical models in which the parameters at one level function as priors on those at lower levels. This means that the ‘‘hyper-parameters’’ that scale the Gaussian priors can be estimated directly from the data (e.g., through expectation-maximization, [10]).

In the context of distributed unimodal inversion of MEG (or EEG) data – i.e. estimation of the spatial distribution of activity over the brain that gives rise to the data recorded at the sensors – the PEB framework entails a two-level, linear, hierarchical model, where the first level represents the sensors and the second represents the sources [1]:

$$\begin{aligned} Y &= LJ + E^{(1)} \\ J &= 0 + E^{(2)} \end{aligned} \quad (1)$$

where Y is a n (sensors) by t (time points) matrix of sensor data; L is a n by p (sources) ‘lead-field’ matrix, or ‘forward model’, based on Maxwell’s equations, and J is a p by t matrix of unknown dipole currents; i.e., the model parameters that we wish to estimate. These normally correspond to the amplitudes of several thousand dipoles distributed over a 2D tessellated surface of the neocortex (and are often, though not necessarily, assumed to be oriented normal to that surface). The fact that $p \gg n$ means that inversion is ill-posed without additional constraints (i.e. regularization). These come from constraints on the random terms, E , which are assumed to be sampled from zero-mean, multivariate Gaussian distributions whose covariance factorizes into temporal components, V , and spatial components; $C^{(1)}$ and $C^{(2)}$ at the sensor and source level respectively.

The spatial covariance matrices are represented by a linear combination of covariance components:

$$C^{(i)} = \sum_{j=1}^N \lambda_j^{(i)} Q_j^{(i)} \quad (2)$$

where $\lambda_j^{(i)}$ is the ‘hyperparameter’ (regularization coefficient) for the j -th component of the i -th level. At the source-level, $C^{(2)}$ represents a spatial prior, and it can be shown that the standard ‘minimum norm’ solution corresponds to setting it to a p -by- p identity matrix [11]. Other assumptions are possible however, such as the use of multiple sparse priors (MSP), where each $Q_j^{(2)}$ represents a small ‘patch’ of coherent activity [12]. For the sensor-level components, $Q_j^{(1)}$, one might assume white noise (an n -by- n identity matrix) or an empirical estimate of sensor noise (e.g., from MEG empty-room data, [2]).

The hyperparameters can be estimated using a Restricted Maximum Likelihood (ReML) algorithm. The objective function maximized by ReML is identical to the (negative) variational free-energy, F . For such linear models with Gaussian assumptions, the optimized free-energy provides a tight bound on the marginal log-likelihood of the generative model, M , or its ‘log-evidence’ [10]:

$$\ln p(Y|M) = \ln \int p(Y, J | M) dJ \approx F \quad (3)$$

This log-evidence can be used to evaluate the advantage of asymmetric integration (Section IV). The hyperparameter estimates in turn allow Maximum A Posteriori (MAP) estimates of the source parameters (J), in addition to estimates of their posterior covariance, which quantifies the conditional precision of the source estimates. These conditional precisions can be used to evaluate the advantage of symmetric integration (Section III).

III. SYMMETRICAL FUSION OF MEG AND EEG

Several studies have shown that MEG and EEG data provide non-redundant information, both theoretically [13], and practically, in the sense that simultaneous inversion of both affords more accurate reconstructions than unimodal inversions (e.g., [14]). We recently reinforced these claims by outlining a new PEB method for full MEG-EEG fusion, and applying it to three types of evoked data recorded simultaneously [2]. These were two types of MEG data, from 1) 102 magnetometers and 2) 204 planar gradiometers, and 3) EEG data from 70 scalp electrodes.

Assuming that a lead-field matrix can be created for each of d sensor-types, then Eq. (1) can be extended as:

$$\begin{bmatrix} \tilde{Y}_1 \\ \tilde{Y}_2 \\ \vdots \\ \tilde{Y}_d \end{bmatrix} = \begin{bmatrix} \tilde{L}_1 \\ \tilde{L}_2 \\ \vdots \\ \tilde{L}_d \end{bmatrix} J + \begin{bmatrix} E_1^{(1)} \\ E_2^{(1)} \\ \vdots \\ E_d^{(1)} \end{bmatrix} \quad (4)$$

where the data of each type have been scaled (see below) and stacked into a single matrix; similarly for the modality-specific lead-field matrices. Note the sources (hidden neuronal causes) in J are common to all sensor-types. Likewise, the spatial covariance matrix of the sensor error, $C^{(1)}$, is formed by concatenating the covariance matrices for each sensor-type, which are themselves formed by linear combination of variance components, as in Eq. (2).

To accommodate different scaling and measurement units across the different sensor-types, the data and the forward model are re-scaled as follows:

$$\begin{aligned} \tilde{Y}_i &= \frac{Y_i}{\sqrt{\frac{1}{m_i} \text{tr}(Y_i Y_i^T)}} \\ \tilde{L}_i &= \frac{L_i}{\sqrt{\frac{1}{m_i} \text{tr}(L_i L_i^T)}} \end{aligned} \quad (5)$$

where tr is the trace of a matrix. This effectively normalizes the data so that the average variance (if the data are mean-corrected) is one for all sensor-types, and, in the absence of sensor noise, the average variance expected under independent and identical sources with unit variance is one.

Note that these scalings are not based on any distinction between “signal” and “noise”, the ratio of which (SNR) has been used previously to weight the relative contributions of MEG vs. EEG to source estimates (e.g., [9]). Such SNRs are often estimated from pre- versus post-stimulus periods; however, this confounds true “sensor noise” with endogenous “brain noise”. In the present framework, the weightings (hyperparameters) of the sensor noise ($E^{(1)}$) for each modality, relative to the signal (J), are estimated automatically from the data, by optimizing the model-evidence, hence obviating the need for empirical SNR estimates.

Using this framework, Henson et al. [2] used statistical comparisons across twelve participants to show that the conditional precision of the source estimates (Section II) based on any one sensor-type generally improved with the addition of others. More specifically, while sensor-level error was greatest for EEG, the inclusion of EEG data increased the conditional precision of the underlying source estimates relative to MEG data alone. This is expected a priori from the ability of EEG to detect radial components of the electromagnetic field. The source reconstructions from fusion also had greater face-validity, in recovering both ventral and lateral posterior temporal activity related to

the processing of faces (relative to scrambled faces); generators that are supported by independent data (such as fMRI and intracranial EEG; see [2] for further discussion).

IV. ASYMMETRICAL FUSION OF MEG AND FMRI

There have been several sophisticated attempts at symmetrical integration (fusion) of MEG (or EEG) data with fMRI data, using biologically-realistic generative models (e.g., [15,16]). We recently proposed a simpler, asymmetric approach, in which the partitions of the fMRI data function as separate spatial priors on the MEG (or EEG) inversion, using the PEB framework [3]. This way, we can estimate any temporal property of the MEG/EEG sources at any location in our solution space.

The use of priors in this context (rather than, say, fixing source activity at fMRI hotspots) is important in that MEG/EEG and fMRI data have different sensitivities to certain source configurations: For example, sources deep in the brain (far from the sensors) are likely to be represented only weakly in the MEG/EEG data, whereas very transient source activity may have minimal BOLD correlates. In other words, the fMRI data should impose “soft” rather than “hard” constraints on the MEG/EEG inversion [4].

Furthermore, the ability to use multiple spatial priors within the PEB framework allows each suprathreshold “cluster” from the fMRI data to form a separate prior (rather than entering all fMRI clusters, or even all voxels, as a single prior). Each suprathreshold cluster becomes a separate component, Q_j (Eq. (2)) for the source-level covariance, $C^{(2)}$, such that their relative weighting (hyperparameters) can differ (analogous to the relative weighting of the sensor-level covariances, $C^{(1)}$, for each sensor-type in Section III). This allows the “Automatic Relevance Detection” (ARD) behavior of our ReML algorithm to emphasize priors that are relevant, and de-emphasize priors that are not. In addition to possible discrepancies between the neuronal causes of the MEG/EEG and BOLD signals described above, irrelevant fMRI priors might reflect neuronal activity that occurs before or after the critical timewindow being localized (given the poor temporal resolution of BOLD).

Because the data (Y) are fixed (unlike for MEG+EEG fusion in Section III), and because the spatial priors are part of the generative model (M), the model evidence in Eq. (3) can be used to compare different types of fMRI prior. The log-evidence increases with the accuracy of the model (fit to the data), but decreases with complexity (favoring more parsimonious models). Using the same MEG+EEG dataset as in Section III, together with fMRI data on the same paradigm, Henson et al [3] showed that adding five suprathreshold fMRI regions as separate priors improved the log-evidence

relative to no fMRI priors (just a minimum norm prior; Section II). This was true for all three sensor-types (magnetometers, gradiometers and electrodes), and was accompanied by more plausible source reconstructions for the face-evoked responses (deeper within the ventral temporal lobe).

Furthermore, this improvement in log-evidence was greater than when the suprathreshold clusters were entered as a single prior (despite the greater model complexity, and consistent with the down-weighting of some of the fMRI priors when entered separately, possibly because they reflected activity occurring outside the epoch of MEG/EEG data localized). Also important was the fact that adding invalid priors (by artificial displacement of the fMRI clusters) did not necessarily improve the model-evidence, particularly when added together with valid priors. This reinforces the ability of our PEB framework to ignore irrelevant (unhelpful) priors, and penalize overly-complex models. Finally, it was interesting to note that, for these data at least, the fMRI priors did not help so much when combined with multiple sparse priors rather than a single minimum norm prior (Section II), presumably due to the even greater flexibility of the former (see [3] for further discussion).

V. CONCLUSIONS

I have outlined a symmetric method for integrating (fusing) source reconstruction of MEG and EEG data, and an asymmetric method for integrating fMRI data as spatial priors on MEG/EEG source reconstruction. Both methods arise naturally within a Parametric Empirical Bayesian framework, in terms of multiple covariance components at either the sensor-level or source-level respectively.

The question remains as to whether symmetric (full) fusion of MEG/EEG and fMRI data is worthwhile. Unlike the fusion of MEG and EEG data, the parameters of generative models for hemodynamic and electromagnetic signals may not be shared. Put simply, if all one can estimate from fMRI data is “where” signals are coming from (i.e., spatial parameters) and all one can estimate from MEG/EEG data is “when” those signals are expressed (i.e., temporal parameters), then there is no point in using a common generative model. This is because multimodal fusion provides multiple constraints on the estimation of unknown causes generating data. If these quantities are constrained by only one modality, the conditional precision of their estimates will not be increased by adding another. The only way that fusion can work is if the spatial parameters estimated precisely by fMRI depend on the temporal parameters estimated precisely by MEG/EEG (or vice versa). Unfortunately, there is no principled reason to think that there will be strong dependencies of this sort, because the dynamics of electromagnetic sources are formally similar in different parts of

the brain. If this argument turns out to be true, then the most powerful approaches may be asymmetric: i.e., using MEG/EEG as temporal constraints in whole-brain fMRI models, or using fMRI as spatial priors on the EEG/MEG inverse problem, as considered here.

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REFERENCES

1. Phillips C, Mattout J, Rugg M et al. (2005) An empirical Bayesian solution to the source reconstruction problem in EEG. *NeuroImage* 24:997-1011.
2. Henson R, Mouchlianitis E & Friston K (2009). MEG and EEG data fusion: Simultaneous localization of face-evoked responses. *NeuroImage* 47: 581-589.
3. Henson R, Flandin G, Friston K et al. (in press). A Parametric Empirical Bayesian framework for fMRI-constrained MEG/EEG source reconstruction. *Human Brain Mapping*.
4. Baillet S, Garnero L., Marin G. et al. (1999). Combined MEG and EEG source imaging by minimization of mutual information. *IEEE Trans. biomed. eng.* 46: 522-534.
5. Nunez P (1981). *Electric fields of the brain: the neurophysics of EEG*. New York: Oxford University Press.
6. Daunizeau J, Jbabdi S, Grova C et al. (2007). Symmetrical event-related EEG/fMRI information fusion in a variational Bayesian framework. *NeuroImage* 36:69-87.
7. Logothetis N, Pauls J, Augath M. et al. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412:150-157.
8. Debener S, Ullsperger M, Siegel M et al. (2006). Single-trial EEG-fMRI reveals the dynamics of cognitive function. *TICS*, 10:558-63.
9. Liu A, Belliveau J & Dale A (1998). Spatiotemporal imaging of human brain activity using functional MRI constrained magnetoencephalography data. *Proc Natl Acad Sci U S A.* 95:8945-50.
10. Friston K, Penny W, Phillips C et al (2002). Classical and Bayesian inference in neuroimaging: theory. *NeuroImage* 16:465-483.
11. Hauk O (2004) Keep it simple: a case for classical minimum norm estimation in analysis of EEG and MEG. *NeuroImage* 21:1612-21.
12. Friston K, Daunizeau J, Kiebel S et al. (2008) Multiple sparse priors for the M/EEG inverse problem. *NeuroImage* 39:1104-1120.
13. Molins A, Stufflebeam S, Brown E & Hamalainen M (2007) Quantification of the benefit from integrating MEG and EEG data in minimum L2-norm estimation. *NeuroImage*, 42:1069-1077.
14. Sharon D, Hamalainen M, Tootell R et al. (2007). The advantage of combining MEG and EEG: comparison to fMRI in focally stimulated visual cortex. *NeuroImage*, 36:1225-1235.
15. Riera J, Wan X et al. (2006). Nonlinear local electrovascular coupling I: A theoretical model. *NeuroImage* 27:896-914.
16. Sotero R & Trujillo-Barreto N (2008). Biophysical model for integrating neuronal activity, EEG, fMRI and metabolism. *Neuroimage*. 39:290-309.

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