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MEG source reconstruction based on identification of directed source interactions on whole-brain anatomical networks

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ABSTRACT

We present an MEG source reconstruction method that simultaneously reconstructs source amplitudes and identifies source interactions across the whole brain. In the proposed method, a full multivariate autoregressive (MAR) model formulates directed interactions (i.e., effective connectivity) between sources. The MAR coefficients (the entries of the MAR matrix) are constrained by the prior knowledge of whole-brain anatomical networks inferred from diffusion MRI. Moreover, to increase the accuracy and robustness of our method, we apply an fMRI prior on the spatial activity patterns and a sparse prior on the MAR coefficients. The observation process of MEG data, the source dynamics, and a series of the priors are combined into a Bayesian framework using a state-space representation. The parameters, such as the source amplitudes and the MAR coefficients, are jointly estimated from a variational Bayesian learning algorithm. By formulating the source dynamics in the context of MEG source reconstruction, and unifying the estimations of source amplitudes and interactions, we can identify the effective connectivity without requiring the selection of regions of interest. Our method is quantitatively and qualitatively evaluated on simulated and experimental data, respectively. Compared with non-dynamic methods, in which the interactions are estimated after source reconstruction with no dynamic constraints, the proposed dynamic method improves most of the performance measures in simulations, and provides better physiological interpretation and inter-subject consistency in real data applications.

Introduction

There are two fundamental functional principles of the brain: functional specialization and functional integration (Tononi et al., 1994; Friston, 1994). Identifying functionally specialized brain regions (e.g., for sensory processing, motor control, and cognitive processing) has been a long-term focus of neuroimaging studies. However, for a true understanding of the mechanisms underlying brain function, elucidating the scheme of dynamic integration between these functionally specialized brain regions is indispensable. This topic has received growing interest in recent years (Hutchison et al., 2013).

Magnetoencephalography (MEG) and electroencephalography (EEG) provide ways to investigate such dynamic integration of brain functions (Schoffelen and Gross, 2009; Palva and Palva, 2012), because of their high temporal resolution and large reflection of neuronal electrical activity (Hämäläinen et al., 1993; Nunez and Srinivasan, 2006). The richness of the temporal information in MEG/EEG allows capturing temporal propagation, or event-related dynamics, of neuronal activity occurring over millisecond time scales, which cannot be easily achieved by functional magnetic resonance imaging (fMRI). In contrast to the excellent temporal resolution, the spatial resolutions of MEG and EEG are limited; the spatial distribution of neuronal current sources cannot be uniquely determined from the measurements, unless a priori knowledge or assumptions are imposed as constraints on current sources (Baillet et al., 2001).

Numerous source reconstruction methods have been developed over the past three decades. These methods can be categorized into three approaches; the equivalent current dipole approach, the linear distributed source approach, and the spatial filtering approach. In the equivalent current dipole approach, a small number of focal sources are pre-determined and their locations and amplitudes are estimated by non-linear optimization algorithms (Scherg and Von Cramon, 1985; Mosher et al., 1992). The linear distributed source approach allocates a large number of sources to grid points over the whole brain volume or surface. The amplitude of all sources is simultaneously estimated by solving a system of linear equations. Since the linear equations are underdetermined, additional constraints or prior information are necessary to obtain a unique solution. Prior assumptions used in linear distributed solvers include a spatial prior forming minimum $l2$ norm regularization (MNE; Hämäläinen and

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Ilmoniemi, 1994), spatial smoothness priors (LORETA and its variant; Pascual-Marqui et al., 1994; Pascual-Marqui, 2002), spatial sparseness priors (Matsuura and Okabe, 1995; Uutela et al., 1999; Sato et al., 2004; Friston et al., 2008; Wipf et al., 2010), temporal smoothness priors (Baillet and Garnero, 1997; Schmitt et al., 2001; Daunizeau et al., 2006), temporal basis function priors (Trujillo-Barreto et al., 2008; Ou et al., 2009; Bolstad et al., 2009), and fMRI-based spatial priors (Dale et al., 2000; Sato et al., 2004; Daunizeau et al., 2007; Henson et al., 2010; Ou et al., 2010). In the spatial filtering approach, an optimal spatial filter, which maps the sensor measurements to the current source amplitude at each single grid point in the brain, is computed. A popular method for this purpose is the linear constrained minimum variance (LCMV) beamformer (Van Veen et al., 1997). LCMV is used to identify resting-state MEG functional connectivity for neuroscience research (Brookes et al., 2011; Hipp et al., 2012). Wipf and Nagarajan (2009) have recently proposed a framework unifying the beamformer method and some distributed source methods.

In source reconstruction from the linear distributed source approach, introducing prior constraints on the spatiotemporal dynamics of source activities is of particular interest; this type of constraint complements other commonly used constraints (typically spatial) and introduces additional knowledge into the source reconstruction process, for example, on dynamic properties of neuronal populations, anatomical connections between brain areas, and transmission delays of neuronal activities. This knowledge potentially facilitates the extraction of information on directed interactions (i.e., effective connectivity) between sources, while reconstructing spatial source distributions from MEG/EEG data. The spatiotemporal dynamics reflects the generative nature of neuronal current sources, and is readily incorporated into a state-space representation. To formulate such dynamics, previous state-space methods have adopted linear autoregressive models with spatially local interactions (Galka et al., 2004; Lamus et al., 2012) and self-interactions (Yamashita et al., 2004; Daunizeau and Friston, 2007; Fukushima et al., 2012). These methods extend an approach that imposes a simple prior assumption (such as a temporal smoothness prior in Schmitt et al., 2001) on the source dynamics (the effectiveness of imposing simple temporal smoothness is critically evaluated by Dannhauer et al., 2013). Nevertheless, these methods still cannot elucidate the long-range interactions across brain areas. This problem was first solved by Olier et al. (2013), who represented these interactions using the full multivariate autoregressive (MAR) model. However, in this model, the spatiotemporal dynamics was formulated in a low-dimensional latent space rather than in the source space.

To allow the long-range interactions to be directly estimated in the source space, we extend the previous state-space methods into a new MEG source reconstruction method. To achieve this goal, the full MAR model is implemented in the high-dimensional source space. The structure of the MAR model is informed by whole-brain anatomical networks inferred from diffusion MRI (dMRI). More specifically, the MAR coefficients (entries of the MAR matrix) associated with pairs of anatomically connected sources according to dMRI, are estimated from the data, while the others are fixed at zero. The time lags of the MAR model are determined from the mean fiber lengths between pairs of source locations. The anatomical long-range connectivity has been used as a constraint in forward modeling of neuronal dynamics (Honey et al., 2007; Ghosh et al., 2008; Deco et al., 2009), and in estimating the effective connectivity from fMRI data (Stephan et al., 2009; Woolrich and Stephan, 2013). The a priori knowledge of anatomical connectivity also reduces the prohibitively large number of model parameters (in our scenario, from order 10^6 to order 10^5 at minimum), thereby improving the feasibility of the estimation. Using this prior information, we can simultaneously estimate the current sources and the source-space effective connectivity. This joint estimation framework distinguishes our method from existing approaches (David et al., 2006; Owen et al., 2009; Hui et al., 2010; Brookes et al., 2011; Hipp et al., 2012; de Pasquale et al., 2012) in which the source time courses and the source connectivity are sequentially estimated. With a low-dimensional MAR model, it was demonstrated that the joint approach yielded better connectivity estimates than the sequential approach (Cheung et al., 2010).

To further improve the reliability of source reconstruction, we apply an fMRI prior on the spatial patterns of source activity. While the fMRI prior is used as a spatial constraint frequently in *non-dynamic* (or not temporally constrained) reconstruction methods (Dale et al., 2000; Sato et al., 2004; Daunizeau et al., 2007; Henson et al., 2010; Ou et al., 2010), it has yet to be applied in the above-mentioned *dynamic* (or state-space) methods. The fMRI prior in the proposed method is implemented similarly to the hierarchical variational Bayesian (hVB) method (Sato et al., 2004; Yoshioka et al., 2008). In forming this prior, the variance of the current noise (an input term driving the spatiotemporal dynamics of the MAR model) is weighted by the fMRI t-values. If all MAR coefficients are fixed at zero, this prior becomes identical to the fMRI prior proposed in Sato et al. (2004) and Yoshioka et al. (2008).

The present study unifies the MAR model, prior knowledge on the model parameters, and the measurement process of the current sources into a Bayesian framework. To improve stability of the estimated source dynamics, this framework also includes a sparse prior on the MAR coefficients. All hidden parameters in the unified probabilistic model (such as source amplitudes and the MAR coefficients) are jointly estimated by a variational Bayesian algorithm (Attias, 1999; Sato, 2001). The update rules are similar to those proposed in Fukushima et al. (2012), enabling inference of a high-dimensional dynamic model within a reasonable computation time.

Our method estimates the effective connectivity in the source space without requiring the selection of regions of interest (ROIs). To this end, the source dynamics are formulated using the full MAR model, and the source amplitudes and interactions are estimated simultaneously over the whole brain. These extensions allow exploratory analysis of the integration of brain functions, which complements the confirmatory approach of dynamic causal modeling (DCM; Friston et al., 2003; David et al., 2006). In contrast to our method, DCM initially assigns a small number of ROIs as network nodes, and then examines the validity of the network solutions by post hoc comparison of the model evidence.

The proposed method is quantitatively and qualitatively evaluated on simulation and experimental data, respectively. The results are compared with those of the hVB method, and of MNE and LCMV as benchmark methods. First, we examine the identification accuracy of the MAR model, using data generated from the adopted dynamic source model. We then investigate the estimation performance under more realistic conditions by mimicking stimulus-evoked responses by a network of neural mass models (Jansen and Rit, 1995; David and Friston, 2003; David et al., 2005). Finally, we examine the physiological plausibility of the estimates by application to a publicly available experimental dataset on face perception (Henson et al., 2011). Since the proposed method is a dynamic extension of the hVB method, we refer to it as the dynamic hVB method when comparing the methods.

This paper is organized as follows. The Theory section explains the model formulation and the adopted estimation algorithm. Model construction from the data and schemes for evaluating the estimation performance are described in the Methods section. The next two sections present the settings and results of the evaluation studies. Next, we investigate whether the free energy can be used for model comparison. Finally, we summarize the significance of the present study and discuss the advantages and limitations of the proposed method.

Theory

Notation

The following notations are used throughout this paper. $P(x)$ denotes the probability distributions of x and $P(x \mid y)$ denotes the

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