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Effective connectivity analysis of fMRI and MEG data collected under identical paradigms

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ABSTRACT

Estimation of effective connectivity, a measure of the influence among brain regions, can potentially reveal valuable information about organization of brain networks. Effective connectivity is usually evaluated from the functional data of a single modality. In this paper we show why that may lead to incorrect conclusions about effective connectivity. In this paper we use Bayesian networks to estimate connectivity on two different modalities. We analyze structures of estimated effective connectivity networks using aggregate statistics from the field of complex networks. Our study is conducted on functional MRI and magnetoencephalography data collected from the same subjects under identical paradigms. Results showed some similarities but also revealed some striking differences in the conclusions one would make on the fMRI data compared with the MEG data and are strongly supportive of the use of multiple modalities in order to gain a more complete picture of how the brain is organized given the limited information one modality is able to provide.

1. Introduction

The morphology and connectivity of neurons define the functional properties of the brain. A combination of short-, mid- and long-range interactions among neurons forms multiscale networks that give rise to high level cognitive functions [1,2].

Anatomical neuronal connections are extensively studied at all scales of brain's interaction network. Initially, *in vitro* studies provided the most of the information. Subsequent advent of noninvasive imaging methods, such as DTI [3], led to an explosion of the number of *in vivo* connectivity studies [4,5] and equipped large mapping efforts, such as the human connectome project [6], with essential tools.

Noninvasive studies of mid- and long-range connections as well as invasive studies of dendritic connections provide information about structural networks in the brain. These connections form a "supporting fabric" for dynamically changing processing networks. Interaction within and among these changing function-induced networks also supports high level cognitive processing. Some of these network-circuits are surprisingly stable under equivalent conditions in single-subject as well as in group studies [7,8].

Functional neuroimaging provides a way to look at these networks by tracking different aspects of dynamical brain behavior [9–11]. Among many currently used functional modalities we have focused this study on magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI). The main advantages of functional neuroimaging in general and of the two selected modalities are in providing spatio-temporal data. These data inform us of brain dynamics at different regions and with different spatio-temporal resolutions.

Among available approaches to extracting neuronal function-induced networks, we are interested in those that result in a graphical model representing regions of interest (ROI) as graph vertices and their connections as edges [12]. A widely accepted approach to extracting such models from functional data involves obtaining a correlation (mutual information, spectral coherence or others) matrix, thresholding its values and using the result as the adjacency matrix of the graph representing the data. This approach only extracts the second order pairwise interactions or functional connectivity, whereas causal relationships involving groups of ROIs acting together (effective connectivity) require more involved approaches [13].

The definition of effective connectivity usually involves extraction of causal relationships among ROIs as well as going beyond

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second order measures to multiple potentially nonlinear interactions. Causality in its strong sense is a difficult concept to handle and it often requires intervention analysis for estimation [14]. However, it is possible to estimate graphical models having causal interpretations from data and prior knowledge [15] or to resort to a specific definition of causality [16,17]. Multiway interactions with a possible causal interpretation are also modeled by Bayesian networks (BN) developed specifically for reasoning about effective connectivity in the field of artificial intelligence [18,19].

The more traditional approaches to effective connectivity estimation in neuroimaging such as dynamic causal modeling [15] have their limitations restricting interactions among variables to bilinear, and posing difficulties for full brain graphical model structure estimation. In this paper we use Bayesian networks with multinomial random variables as our model of effective connectivity and a structure learning algorithm to recover the graphical model from the data. Recent developments in structure learning algorithms [20] allow us to estimate structures of networks covering all cortical ROIs.

Estimated effective connectivity can be used to compare the groups of subjects (such as patients and controls) or/and to make conclusions about interactions among ROIs [21,22]. In the latter case we feel that a special care should be taken to attribute the result to the modality that was used to obtain effective connectivity. Although in essence all neuroimaging modalities with timeseries information measure neuronal activity and connectivity at their core, the degradation of such signals through e.g. the neurovascular transformation in fMRI and volume conduction/mixing in EEG/MEG before detection at the sensors does heavily influence the result. The combination of imaging modalities provides a way to maximize neuronal information although it remains unclear in which way connectivity from multimodal signals should be estimated in an optimal fashion. In order to test this problem, in this work we have estimated effective connectivity from two modalities (MEG and fMRI) of the same subjects performing the same task in MEG and in fMRI collected on separate occasions in a Bayesian network approach. Thus, we attempt to eliminate all differences but functional modality in these datasets. Then we compare the results for MEG and fMRI.

The rest of the paper is structured as follows. Section 2 describes details of Bayesian network modeling and the structure search algorithm as an approach to effective connectivity estimation as well as the data collection. Section 3 gives details of our data processing and application to each modality, and then covers the results of the structure search obtained in this study. We discuss consequences of our findings together with their interpretation in relation to the current literature in Section 4.

2. Methodology

The goal of our work is to study how the choice of a functional modality may affect the conclusions of an effective connectivity study. In the following, we describe the method of Bayesian network structure search used to estimate the connectivity, the metrics originating in the graph community structure research for characterizing graph structure properties, and the MEG and fMRI modalities we apply our comparison to. An overview of how we use the methods and process the data is shown in Fig. 1

2.1. Bayesian networks

Bayesian networks [14,19,23] can be viewed as a way to compactly represent a joint probability distribution by encoding the conditional independence structure of its random variables. This is done through two parts: a directed graph G, and parameters θ of conditional densities. Since all information about a set of random variables and their interactions are encoded in the joint probability density, being able to estimate and reason about it provides a way to understand complex structured data. The joint probability density of a given set of n random variables $\mathbf{X}=\{X_1,X_2,\ldots X_n\}$ in the Bayesian network representation is expressed as

$$P_\theta(\mathbf{X}) = \prod_{i=1}^{n} P(X_i|P_a(X_i);\theta) \quad (1)$$

where $P_a(\cdot)$ denotes the parent set of the argument in the corresponding graph structure G of the BN. Compactness is achieved due to the significant decrease in the number of parameters, θ, required to describe random variable values in conditional densities compared to every possible combination of values for all random variables of the joint density. This, however, is a consequence of the graphical representation, G.

The BN graphical representation G is a directed acyclic graph (DAG) with random variables at nodes and directed edges connecting them according to the independence structure (Fig. 2a). A random variable is called a *parent* if it has outgoing graph edges pointing to other nodes of the graph. A random variable with incident edges is called a *child*. The key property of a BN that gives it an advantage over the functional connectivity approaches is that every variable is conditionally independent of its non-descendants given its parents. This property and the factored form of the joint distribution (1) leads to special importance of a graphical unit called a family: a child node plus its parents (Fig. 2b).

While in functional connectivity studies, the fundamental unit is a pair of ROIs connected by an edge, in effective connectivity analysis the fundamental unit is an entire family. Since it may simultaneously involve several parents and a child, the interactions it is modeling are of higher order than in the pairwise model. Fig. 2c shows an example of modeling higher order nonlinear interactions in the family of three ROIs.

The data arriving from functional measurements is, by nature, continuous: magnetic field and hemodynamic activity are real valued despite being sampled at discrete intervals. Unfortunately, the approaches to treat it in the context of Bayesian networks are either not well developed or limited. In this paper we employ the quantized representation. In terms of generality of relationships a

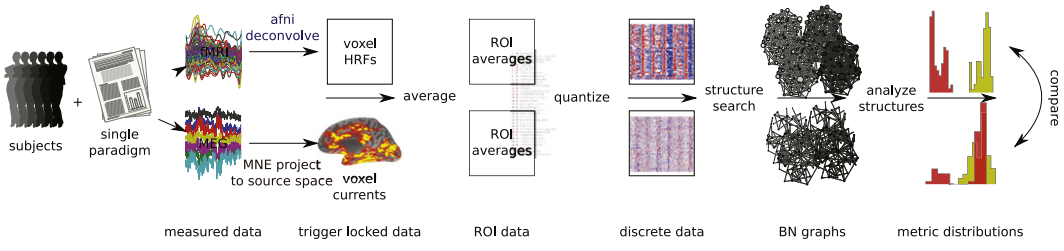

Fig. 1. A cartoon of processing and analysis steps performed in the paper.