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Bayesian network models in brain functional connectivity analysis

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ABSTRACT

Much effort has been made to better understand the complex integration of distinct parts of the human brain using functional magnetic resonance imaging (fMRI). Altered functional connectivity between brain regions is associated with many neurological and mental illnesses, such as Alzheimer and Parkinson diseases, addiction, and depression. In computational science, Bayesian networks (BN) have been used in a broad range of studies to model complex data set in the presence of uncertainty and when expert prior knowledge is needed. However, little is done to explore the use of BN in connectivity analysis of fMRI data. In this paper, we present an up-to-date literature review and methodological details of connectivity analyses using BN, while highlighting caveats in a real-world application. We present a BN model of fMRI dataset obtained from sixty healthy subjects performing the *stop-signal task* (SST), a paradigm widely used to investigate response inhibition. Connectivity results are validated with the extant literature including our previous studies. By exploring the *link strength* of the learned BNs and correlating them to behavioral performance measures, this novel use of BN in connectivity analysis provides new insights to the functional neural pathways underlying response inhibition.

1. Introduction

Biomedical imaging, including computed tomography, positron emission tomography, and magnetic resonance imaging has become important tools for medical diagnosis, surgical planning, and/or neuroscience research. In particular, brain imaging has provided important new information to the operations of the complex human brain, and improved our understanding of many psychiatric and neurological diseases, such as Alzheimer and Parkinson diseases, schizophrenia, addiction, and depression. In a recent review, Friston [1] referred to *neuroimaging* as the predominant technique in human behavioral and cognitive neuroscience, and highlighted the exponentially growing number of publications in the field. In particular, functional connectivity analysis, the study of how different parts of the brain are integrated during execution of cognitive tasks, is of growing importance in neuroscience research [1,2].

Several computational and statistical tools, from basic image processing to complex network analysis, have made possible these advances in neuroimaging. Approximate reasoning and Bayesian statistics are a *de facto* standard when dealing with complex and uncertain data, which often requires the use of expert and prior knowledge [3–6]. Although much progress has been made in the field, the interdisciplinary dialogue between statistician, computer scientist, physician and psychologist only began recently. For instance, although investigations have successfully applied Bayesian network (BN) and probabilistic graphical models in functional connectivity analysis [2,7], suggesting a large venue of opportunities to be explored, few

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functional connectivity studies systematically addressed the use of BN modeling in magnetic resonance imaging (fMRI) of a large number of subjects executing a cognitive task [8,9].

The goals of this paper are two-fold. First, we provide an up-to-date review of the current BN methodology in fMRI connectivity analysis, and highlight the practical issues involved in these applications. Second, and more importantly, we present a BN group modeling of fMRI dataset obtained from sixty healthy subjects performing the *stop-signal task* (SST) [10,11], to demonstrate the real-world application of this approach. By showing the *link strength* [12,13] of the learned BNs and their correlation to group behavioral measures, these new data provide novel insights to the brain networks of response inhibition. This application also highlights the caveats and potential pitfalls, and suggests plausible solutions to these issues.

The paper is organized as follows. In Section 2, we present a summary of BN applications in functional connectivity analyses, and provide a critical review of the caveats and methodological alternatives. In Section 3, we describe the details involved in a functional connectivity analysis of real fMRI data set using BN. In Sections 4 and 5, we demonstrate the results and conclude with a few additional remarks.

2. Bayesian networks (BN) in connectivity analysis of fMRI

In this section, we describe the methodology for applying BN in connectivity analysis of fMRI data. We review extant works of BN in Section 2.1, present the caveats and challenges in Section 2.7, and list available software tools in Section 2.8.

2.1. Literature review

The application of BN in connectivity analysis of fMRI data has a comparatively short history, and became a relatively established approach around 2000s [1]. The development of efficient fMRI data preprocessing methods and accessible software's made possible a more reliable execution of group connectivity analyses. Pioneering studies applying BN to functional connectivity analysis of fMRI were published by Labatut and colleagues [14], followed by others [15,16,9,17,18]. Recently, BN and its methodological extensions were suggested to be useful in inferring causal relationships between activations by Glymour and colleagues [7]. The causal inference in fMRI is closely related to *effective connectivity* (influence that one neuronal system has on another [1]). On the other hand, Lindquist and Sobel [19] disagreed with Glymour and colleagues [20], and expressed their concern in using directed graphical models for revealing causal relations between regional activations. Pearl [21] entered in the discussion by clarifying the relation between the Structural Equation Modeling (SEM) [22] and causal graphical models in the analyses of brain connectivity. In particular, Lindquist and Sobel [23] demonstrated their concern about inferring causal relationships using graphical models in a data-driven fashion without prior substantive assumptions.

In the following, we revisit most of these works, by detailing the different approaches that are possible when applying BN in functional connectivity analysis.

2.2. fMRI data acquisition

FMRI provides an indirect measure of brain activity by means of a blood-oxygenation-level dependent contrast or BOLD signal in short, as discovered by Ogawa and colleagues [24]. The BOLD signal measures changes in the amount of deoxygenated hemoglobin, resulting from a larger consumption of oxygen when neurons are activated, and increased blood flow and volume. Active neurons generate an increase in the amount of deoxygenated hemoglobin, leading to brighter MR images or an increase in BOLD signal. The term BOLD *hemodynamic response* (HR) is commonly used to refer to the shape of the BOLD signal following a neuronal event, and could be conceptualized as the *impulse response* of BOLD. The hemodynamic response shows its peak in 6s and an undershoot around 10s after the stimulus is presented, as a result of the changing dynamics of cerebral blood flow and volume. It must be noted that the hemodynamic response will vary depending on the duration and number of the environmental stimuli driving neuronal responses. Complex image acquisition and reconstruction processes are involved to turn BOLD signals into 3D images. Paul Lauterbur and Peter Mansfiled, recipients of the 2003 Nobel Prize in Medicine, developed the echo-planar imaging (EPI) technique, which made rapid collection of BOLD signals possible. An excellent introduction and review of fMRI is available in Huettel et al. [25].

In terms of image acquisition, two main issues apply to BOLD fMRI:

- *Spatial resolution*: the ability to distinguish signal differences between nearby spatial locations. In fMRI, images are usually obtained in 64×64 or 256×256 matrix (referred as *slice*). For a field of view of 220 by 220 mm and a matrix of 64x64, the in-plane voxel size would be 3.44 by 3.44 mm. The third dimension is generally the same as or larger than the in-plane voxel size, and depends on how many slices one might want to obtain for one particular study. The term *echo time* (TE) is used to refer to the time interval between excitation pulse and data acquisition, and it is related to image reconstruction.
- *Temporal resolution*: the ability to distinguish signal differences between sequential observations. Temporal resolution is given by the *repetition time* (TR). TR is usually between 500ms and 3s, and is the time necessary for the scan to resample from the same voxel. One of the MR scanner parameters related to temporal resolution is the *flip angle*, which is the change in net longitudinal magnetization after excitation pulse. The shorter the TR is, the smaller the flip angle has to