

# Predicting individual brain functional connectivity using a Bayesian hierarchical model



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## ABSTRACT

Network-oriented analysis of functional magnetic resonance imaging (fMRI), especially resting-state fMRI, has revealed important association between abnormal connectivity and brain disorders such as schizophrenia, major depression and Alzheimer's disease. Imaging-based brain connectivity measures have become a useful tool for investigating the pathophysiology, progression and treatment response of psychiatric disorders and neurodegenerative diseases. Recent studies have started to explore the possibility of using functional neuroimaging to help predict disease progression and guide treatment selection for individual patients. These studies provide the impetus to develop statistical methodology that would help provide predictive information on disease progression-related or treatment-related changes in neural connectivity. To this end, we propose a prediction method based on Bayesian hierarchical model that uses individual's baseline fMRI scans, coupled with relevant subject characteristics, to predict the individual's future functional connectivity. A key advantage of the proposed method is that it can improve the accuracy of individualized prediction of connectivity by combining information from both group-level connectivity patterns that are common to subjects with similar characteristics as well as individual-level connectivity features that are particular to the specific subject. Furthermore, our method also offers statistical inference tools such as predictive intervals that help quantify the uncertainty or variability of the predicted outcomes. The proposed prediction method could be a useful approach to predict the changes in individual patient's brain connectivity with the progression of a disease. It can also be used to predict a patient's post-treatment brain connectivity after a specified treatment regimen. Another utility of the proposed method is that it can be applied to test-retest imaging data to develop a more reliable estimator for individual functional connectivity. We show there exists a nice connection between our proposed estimator and a recently developed shrinkage estimator of connectivity measures in the neuroimaging community. We develop an expectation-maximization (EM) algorithm for estimation of the proposed Bayesian hierarchical model. Simulations studies are performed to evaluate the accuracy of our proposed prediction methods. We illustrate the application of the methods with two data examples: the longitudinal resting-state fMRI from ADNI2 study and the test-retest fMRI data from Kirby21 study. In both the simulation studies and the fMRI data applications, we demonstrate that the proposed methods provide more accurate prediction and more reliable estimation of individual functional connectivity as compared with alternative methods.

## 1. Introduction

Brain functional connectivity research based on fMRI, especially resting-state fMRI (rs-fMRI), has become an important approach for understanding brain organization and has revealed intrinsic neural functional connections that can be found consistently across groups of subjects and in repeated scanning sessions (Smith et al., 2009;

Damoiseaux et al., 2006; Shehzad et al., 2009). Clinically, functional connectivity has also shown great promises for studying pathophysiology of the development and progression of psychiatric diseases and their response to treatments (Biswal et al., 1995; Greicius et al., 2003; Fox et al., 2005; Smith et al., 2009 among many others). Numerous studies have identified distinct patterns of functional connectivity in brain networks among subjects with psychiatric disorders as compared

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to a healthy comparison population that support a neuropathophysiology of cognitive/behavioral problems associated with these disorders (Wang et al., 2007; Woodward and Cascio, 2015). Studies report mental disorders such as Alzheimer's disease affect brain functional connections across time with the disease progression (Damoiseaux et al., 2012; Yao et al., 2014). Furthermore, several studies have found significant pre- to post- treatment changes in brain connectivity following psychiatric treatments (Gay et al., 2014; Sarpal et al., 2015). These collective findings strongly implicate alterations in functional connectivity in the pathophysiology of psychiatric disorders and their responses to medical schooltreatment. This provides motivation for the potential utility of forecasting disease progression-related and treatment-related brain functional connectivity reflected in fMRI.

There has been some work aimed to link baseline brain connectivity to disease progression or the eventual clinical response to treatment (Damoiseaux et al., 2012; Yao et al., 2014). In a related manner, several authors (Brody et al., 1999; Goldapple et al., 2004; Kennedy et al., 2001; Lee et al., 2005; Mayberg et al., 2000, 2001; Moresco et al., 2000) showed that changes in brain activity across time were associated with disease progression or treatment response. Hence, important insights can be gained for disease progression or treatment response by evaluating baseline and follow-up scans. However, in clinical practice, these insights are offset due to the unavailability of follow-up scans at the early phase of disease occurrence or at the time when a clinician makes treatment decision for a particular patient. This pragmatic shortcoming suggests the utility of developing a statistical framework to predict disease-related or treatment-related brain alterations, which could then be combined with baseline scans and patients' relevant risk factors to help inform clinical decision-making.

In this work, we present a general framework for predicting individual future resting-state functional connectivity (RSFC) based on his/her baseline rs-fMRI and relevant clinical and demographic characteristics, such as disease stage or treatment group. The proposed prediction method provides a useful tool to predict the changes in an individual's brain connectivity with the progression of the disease or normal aging. It can also be applied to predict a patient's brain connectivity after a specified treatment regimen to help inform individualized treatment plan. The proposed predictive model could potentially have important clinical applications by helping implement early intervention based on predicted disease progression trajectory to prevent severe outcomes from mental illnesses. The method can also help guide the development of a more effective individualized treatment plan by taking into account both the population-level effects as well as a patient's distinct neural connectivity characteristics. Another utility of the proposed method is to provide a more reliable estimator for individual RSFC than the noisy subject-specific estimator in test-retest rs-fMRI data. A reliable RSFC estimate can provide important information about the properties of brain networks and is the basis for many complex network-related analyses. For example, Shou et al. (2014) and Mejia et al. (2015) have shown that by improving the reliability of RSFC estimates, one can improve the reproducibility of individual brain parcellation, which is generated from the RSFC.

The remainder of this paper is organized as follows. In the method section, we first present a general modeling and prediction framework for individual functional connectivity, and then illustrate the model specification for two types of imaging studies: longitudinal imaging studies which investigate disease progression and treatment-related changes in functional connectivity, and test-retest studies which aim to investigate and improve the reliability of estimates for individual RSFC. We conduct simulations studies to evaluate the accuracy of the proposed method using the *K*-fold cross-validation approach. We also illustrate the application of the proposed method using two imaging datasets: the longitudinal resting-state fMRI from ADNI2 study and the test-retest fMRI data from Kirby21 study (Landman et al., 2011).

## 2. Method

The need to predict a subject's future brain connectivity often arises in medical research and clinical practice. Some examples include prediction on how neural connectivity pattern will be affected across time with the progression of a brain disorder or prediction on post-treatment brain connectivity due to treatment-related alterations on neural processing. A subject's future brain connectivity depends on various factors including current disease status, type of treatment, his/her baseline brain connectivity and other relevant subject characteristics such as age, gender and family history, etc. Our aim is to develop an algorithm that utilizes information related to these relevant factors to provide accurate individualized prediction for future brain connectivity. Our approach is to develop a statistical model for characterizing the changes in functional connectivity using a training data set that includes both baseline and follow-up imaging scans. We then derive a prediction algorithm for future brain connectivity using a subject's baseline images and clinical/demographic characteristics based on the developed statistical model. Once the prediction algorithm is established, researchers or clinical practitioners can apply it to predict the future brain connectivity for a new subject by inputting information derived from the subject's baseline scans and relevant individualized traits. With the predicted future brain connectivity, researchers or clinical practitioners can find helpful information in forecasting alterations in a patient's brain networks with the progression of the disease or in deciding whether a treatment is appropriate for a particular patient in the way that it can lead to favorable therapeutical alteration on the patient's brain connectivity. We summarize our proposed approach for developing and applying the prediction algorithm in Fig. 1. Prior to presenting our prediction algorithm, we describe the statistical model underlying the formulation of our

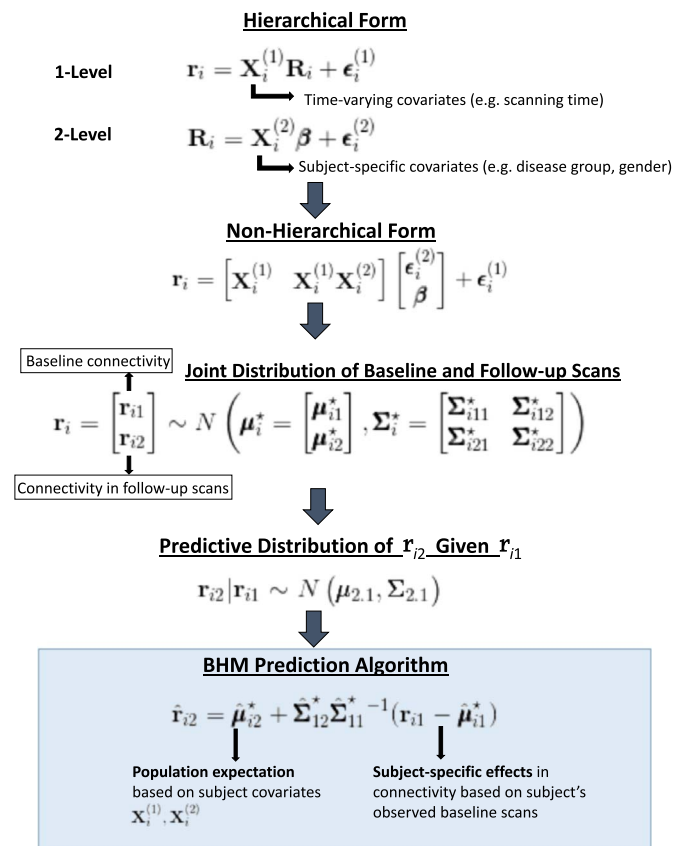


Fig. 1. Schematic illustration of the development of the Bayesian Hierarchical Model and construction of the proposed prediction algorithm for individual brain functional connectivity.

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