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State-space model with deep learning for functional dynamics estimation in resting-state fMRI

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ABSTRACT

Studies on resting-state functional Magnetic Resonance Imaging (rs-fMRI) have shown that different brain regions still actively interact with each other while a subject is at rest, and such functional interaction is not stationary but changes over time. In terms of a large-scale brain network, in this paper, we focus on time-varying patterns of functional networks, i.e., functional dynamics, inherent in rs-fMRI, which is one of the emerging issues along with the network modelling. Specifically, we propose a novel methodological architecture that combines deep learning and state-space modelling, and apply it to rs-fMRI based Mild Cognitive Impairment (MCI) diagnosis. We first devise a Deep Auto-Encoder (DAE) to discover hierarchical non-linear functional relations among regions, by which we transform the regional features into an embedding space, whose bases are complex functional networks. Given the embedded functional features, we then use a Hidden Markov Model (HMM) to estimate dynamic characteristics of functional networks inherent in rs-fMRI via internal states, which are unobservable but can be inferred from observations statistically. By building a generative model with an HMM, we estimate the likelihood of the input features of rs-fMRI as belonging to the corresponding status, i.e., MCI or normal healthy control, based on which we identify the clinical label of a testing subject. In order to validate the effectiveness of the proposed method, we performed experiments on two different datasets and compared with state-of-the-art methods in the literature. We also analyzed the functional networks learned by DAE, estimated the functional connectivities by decoding hidden states in HMM, and investigated the estimated functional connectivities by means of a graph-theoretic approach.

Introduction

A human brain can be understood as a complex system with different structural regions dedicated for different functions, which are locally segregated but globally integrated to process various types of information. Over the last decades, it has been one of the major concerns to investigate the underlying functional mechanism of a human brain in the fields of basic and clinical neuroscience. The functional Magnetic Resonance Imaging (fMRI) that measures the changes of Blood Oxygen Level-Dependent (BOLD) signal in a non-invasive manner has become one of the most successful investigative tools to explore the functional characteristics or properties of a brain.

In the meantime, ever since Biswal et al. (1995) discovered that different brain regions still actively interact with each other while a subject is at rest, i.e., not performing any cognitive task, resting-state fMRI (rs-fMRI) has been widely used as one of the major tools to investigate regional associations or brain networks (Rombouts et al., 2005; Fox et al., 2005; Buckner et al., 2008). The rs-fMRI provides insights to explore the brain's functional organization and to examine altered or aberrant functional networks possibly caused by brain disorders such as Alzheimer's Disease (AD) (Greicius et al., 2004; Li et al., 2002), Mild Cognitive Impairment (MCI) (Rombouts et al., 2005; Sorg et al., 2007; Wang et al., 2007; Zhang et al., 2012; Chase, 2014), autism spectrum disorder (Monk et al., 2009; Khan et al., 2013), schizophrenia (Liang et al., 2006; Zhou et al., 2007; Garrity et al., 2007; Lynall et al., 2010), and depression (Anand et al., 2005; Greicius et al., 2007; Craddock et al., 2009). In this work, we focus on the early diagnosis of MCI based on the computational analysis of rs-fMRI. Due to a high rate of progression from MCI to AD in one year, approximately 10 to 15% according to Alzheimer's Association's's (2012)), it has been of great importance for early detection or diagnosis of MCI and seeking a proper treatment to prevent from progressing to AD. From a clinical point of view, it is advantageous to use rs-fMRI to investigate functional characteristics in the rs-fMRI of patients, who may not be able to perform complicated cognitive tasks during scanning. In these regards, the analysis of functional characteristics inherent in rs-fMRI is playing a core role for brain disease diagnosis

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or prognosis (Handwerker et al., 2012; Li et al., 2012; Leonardi et al., 2013; Hjelm et al., 2014; Wee et al., 2014; Suk et al., 2015c).

To date, the functional characteristics in a brain have been studied in two different approaches. The *effective connectivity* (Friston et al., 1993) investigates the causal relations between regions, e.g., one region exerts over another. The *functional connectivity* (Van Dijk et al., 2010), the other type of approach, measures functional associations between regions by means of temporal coherence or correlation. In this paper, we mainly consider the functional connectivity, which is computationally less intensive for whole-brain network analysis. It is worth noting that recent studies investigating the complex brain functions have observed the phenomenon that functional connectivity spontaneously changes over time (Chang and Glover, 2010; Bassett et al., 2011; Hutchison et al., 2013), i.e., dynamic rather than stationary. Functional dynamics include changes in the strength of connection between regions, and also the number of connections linked to regions. Motivated by those studies, there have been efforts to estimate temporal changes in functional connectivities and then use functional properties extracted from the estimated dynamic functional connectivities for disease diagnosis.

To our best knowledge, many existing methods for MCI diagnosis with rs-fMRI typically assumed stationarity on a functional network over time and explicitly modelled it by different methods such as Pearson's correlation, partial correlation (Liang et al., 2012), independent component analysis (Jafri et al., 2008; Li et al., 2012), and sparse linear regression (Wee et al., 2014). Recently, (Faisan et al., 2007; Hutchinson et al., 2009), and (Janoos et al., 2011) independently devised different types of state-space models to explore the dynamic characteristics of functional activation and applied for event-related fMRI data analysis. Due to the use of variables related to external stimulus, i.e., event, those models are not suitable for rs-fMRI data analysis. Meanwhile, Leonardi et al. devised an Eigen-decomposition based method to model functional dynamics with a sliding-window technique (Leonardi et al., 2013) and Eavani et al. proposed to model sparse basis learning within a Hidden Markov Model (HMM) framework (Eavani et al., 2013).

In this paper, we propose a novel method of modelling functional dynamics inherent in rs-fMRI by means of probabilistic models. Specifically, rather than computing correlation matrices and extracting graph-theoretic features (Rubinov and Sporns, 2010) such as clustering coefficients and modularity as commonly performed in the literature, we explicitly model dynamic changes of functional characteristics obtained from regional mean time series of rs-fMRI. In a testing phase, our model estimates the likelihood of a testing sample as MCI and Normal healthy Control (NC), based on which we diagnose MCI. Note that, compared to Eavani et al.'s work, where they utilized the original high-dimensional features, in our method, we devise a Deep Auto-Encoder (DAE) that hierarchically discovers non-linear relations among regional features and helps circumvent the problem of high dimensionality, a common in neuroimaging analysis, and then train a dynamic state-space model, i.e., HMM. While Leonardi et al.'s method fails to reflect the spontaneous changes due to the use of a sliding window strategy, the proposed method probabilistically determines the spontaneous changes based on an observation.

It should be noted that the preliminary version of this work was presented in (Suk et al., 2015a). Compared to the preliminary version of this manuscript, we have extended our work by: 1) carrying out more extensive experiments with an additional dataset from the ADNI2 cohort and 2) analyzing the learned models and the estimated functional connectivities in various perspectives. Although, in this paper, we deal with MCI data only, our method can be also used to understand the functional characteristics of other diseases such as autism, schizophrenia, and depression. In addition, thanks to its capability of estimating dynamic functional connectivities from rs-fMRI, our method can be used for neuroscientific studies on functional organization in a brain.

Materials and preprocessing

In this work, we use two independent rs-fMRI datasets, namely, an ADNI2 dataset publicly available online[1] and an in-house dataset.

ADNI2 cohort

We used a cohort of 31 early MCI subjects (14F/17M) and 31 age-matched NC subjects (17F/14M) from ADNI2[2]. The mean ages of MCI and NC groups are 73.9 ± 4.9 and 73.8 ± 5.5, respectively. All subjects were scanned at different centers using 3.0 T Philips Achieva scanners with the same scanning protocol and parameters of Repetition Time (TR) = 3000 ms, Echo Time (TE) = 30 ms, flip angle = 80°, acquisition matrix size = 64×64, 48 slices, 140 volumes, and a voxel thickness = 3.3 mm.

In-house cohort

It is recruited for 37 participants of 12 MCI subjects (6F/6M) and socio-demographically matched 25 NC subjects (16F/9M). The mean ages of MCI and NC are 75.0 ± 8.0 and 72.9 ± 7.9, respectively. The data were acquired on a 3.0 T GE scanner (Signa EXCITE, GE Healthcare) using a SENSE inverse-spiral pulse sequence with the parameters of TR = 2000 ms, TE = 32 ms, flip angle = 77°, acquisition matrix size = 64×64, 34 slices, 180 volumes, and a voxel thickness = 4 mm.

Preprocessing

The prevalent preprocessing procedure for rs-fMRI was performed using the SPM8 software package[3]. Specifically, we discarded the first 10 rs-fMRI volumes of each subject prior to further processing to ensure magnetization equilibrium. The remaining volumes were then corrected for the staggered order of slice acquisition that was used during echo-planar scanning so that the data on each slice correspond to the same point in time. The images were realigned with the image at the time point of TR/2 as reference to minimize relative errors across each TR. After correcting acquisition time delay, the rs-fMRI volumes of each subject were realigned by means of a least squares technique and a rigid body spatial transformation. The first volume of each subject was used as the reference to which all subsequent volumes were realigned for the purpose of head-motion artifact removal in the rs-fMRI time-series. We assessed the rotation and translation of every subject and found that all the participants showed no excessive head motion with a displacement of less than 1.5 mm or an angular rotation of less than 1.5° in any direction. There were no significant group differences in head-motion for all subjects[4]. To further minimize the effects of head motion, we also applied Friston 24-parameter model (6 head motion parameters, 6 head motion parameters from the previous time point, and 12 corresponding squared items). After realignment, the volumes were resliced such that they match the first volume voxel-by-voxel. We then normalized rs-fMRI images to the MNI space with a voxel size of $3 \times 3 \times 3$ mm^3.

To further reduce the effects of nuisance signals and focus on the signals of gray matter, we regressed out ventricle and white matter signals as well as six head-motion profiles based on (Van Dijk et al., 2010). Due to the ongoing controversy of removing the global signal in the processing of rs-fMRI data (Fox et al., 2009; Murphy et al., 2009), we omitted the process of global signal regression (Supekar et al., 2008; Lynall

[1] Available at 'http://www.loni.ucla.edu/ADNI'.

[2] There are 3 different subtypes of MCI subjects in ADNI2 dataset, i.e., early MCI, normal MCI, and late MCI. In this study, to minimize the effect of different image sizes and resolutions, we selected images from early MCI and healthy normal subjects with the same image dimension and image resolution.

[3] Available at 'http://www.fil.ion.ucl.ac.uk/spm/software/spm8/'.

[4] The smallest p-value for 6 head motion parameters between patient and healthy subjects was 0.218.