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Characterization of task-free and task-performance brain states via functional connectome patterns

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ABSTRACT

Both resting state fMRI (R-fMRI) and task-based fMRI (T-fMRI) have been widely used to study the functional activities of the human brain during task-free and task-performance periods, respectively. However, due to the difficulty in strictly controlling the participating subject's mental status and their cognitive behaviors during R-fMRI/T-fMRI scans, it has been challenging to ascertain whether or not an R-fMRI/T-fMRI scan truly reflects the participant's functional brain states during task-free/task-performance periods. This paper presents a novel computational approach to characterizing and differentiating the brain's functional status into task-free or task-performance states, by which the functional brain activities can be effectively understood and differentiated. Briefly, the brain's functional state is represented by a whole-brain quasi-stable connectome pattern (WQCP) of R-fMRI or T-fMRI data based on 358 consistent cortical landmarks across individuals, and then an effective sparse representation method was applied to learn the atomic connectome patterns (ACPs) of both task-free and task-performance states. Experimental results demonstrated that the learned ACPs for R-fMRI and T-fMRI datasets are substantially different, as expected. A certain portion of ACPs from R-fMRI and T-fMRI data were overlapped, suggesting some subjects with overlapping ACPs were not in the expected task-free/task-performance brain states. Besides, potential outliers in the T-fMRI dataset were further investigated via functional activation detections in different groups, and our results revealed unexpected task-performances of some subjects. This work offers novel insights into the functional architectures of the brain.

1. Introduction

Functional magnetic resonance imaging (fMRI) techniques have been widely used to study the functional activities and cognitive behaviors of the brain in recent years. Generally, fMRI studies can be differentiated into various categories based on the stimulus used, e.g., resting state fMRI (R-fMRI) (task-free) (Raichle et al., 2001; Fox and Raichle, 2007) and task-based fMRI (T-fMRI) (task-performance) (Linden et al., 1999; Heeger and Ress, 2002; Calhoun et al., 2001; Koshino et al., 2005; Gailard et al., 2004). For these fMRI studies, the quality of fMRI data is vital because it strongly influences the reliability of conclusions inferred from the fMRI data (Simmons et al., 1999; Stocker et al., 2005). During fMRI scans, there are several factors which may affect the fMRI data qualities (Stocker et al., 2005), such as fMRI hardware related factors, experimental designs, and participating subject's issues (e.g., motion, lack of attention or any other unexpected cognitive behaviors which are not related to the experimental designs). A variety of fMRI data quality control studies have focused on fMRI imaging quality, which already made significant contributions to the quality assurance of fMRI data (Simmons et al., 1999; Foland and Glover, 2004; Stocker et al., 2005; Friedman and Glover, 2006). Furthermore, there were many studies that aimed to optimize and improve experimental designs, especially in event-related task fMRI studies (Anders 1999; Wager and Nichols, 2003; Savoy, 2005; Amaro and Barker, 2006). These task-based experimental designs were expected to provide a statistically meaningful contrast between the neuronal activity at task-performance and the background condition. In addition, the reliability and variability of the results based on fMRI data were investigated and analyzed in a variety of papers (McGonigle et al., 2000; Specht et al., 2003; Schuyler et al., 2010).

An important but underexplored issue in T-fMRI/T-fMRI is how to ascertain the performance of the participating subject's functional brain behaviors during fMRI scans. It is an ideal case that

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researchers design experimental fMRI paradigms appropriately such that participating subjects collaboratively pay close attention and strictly responds to stimulus events. However, it is difficult to strictly control every subject's mental status and cognitive behaviors all the time during fMRI scan sessions. As a consequence, the analysis results derived from fMRI data based on the assumption that every participating subject was strictly complying with the experimental design could be doubtful to some extent, due to the critical lack of effective approaches that can accurately assess the performance of the participant during fMRI scans. For instance, if a participating subject's brain was actively thinking during R-fMRI scans, how different this R-fMRI data will be from other strict resting state fMRI data acquired during task-free states? Similarly, if a participating subject's brain was in resting state, that is, not following the administered task-performance paradigm, how different this T-fMRI data will be from other strict task-based fMRI data acquired during task-performance states? If these differences are substantial, can we quantitatively characterize and automatically differentiate those unreliable R-fMRI/T-fMRI data from strict R-fMRI/T-fMRI data? The answers and possible solutions to these questions can significantly enhance our understanding of the function mechanisms of the brain and help us better monitor and control the quality of R-fMRI/T-fMRI data in the subsequent quantitative analysis, e.g., inference of resting state networks (RSNs), functional connectivity analysis, and task-based functional region localization.

In response to the above unanswered questions, this paper presents a novel computational framework to characterize the brain's task-free and task-performance functional states by learning from both R-fMRI and T-fMRI datasets. Our computational pipeline is composed of three major components. First, the structural connectome of each subject is constructed via our recently developed and validated 358 Dense Individualized and Common connectivity-based Cortical Landmarks (DICCCOL) (Zhu et al., 2013) based on DTI data. Second, a sliding window approach was employed to construct each subject's temporally varying functional connectomes based on the structural connectome and coincident fMRI data, which was further interactively divided into quasi-stable segments. Third, we represent the brain's functional status by a set of whole-brain quasi-stable connectome patterns (WQCPs), and then apply the Fisher discriminative dictionary learning (FDDL) sparse coding approach (Yang et al., 2011) to learn the atomic connectome patterns (ACPs) of both task-free and task-performance states from large-scale temporally segmented WQCPs. Essentially, the integration and pooling of many WQCPs from different brains are enabled by the DICCCOL system (Zhu et al., 2013), which provide intrinsic structural and functional correspondences across different individuals and populations. Consequently, the WQCPs from the different temporal segments of multiple brains can be readily pooled and effectively compared via sparse coding and representation methods, which will learn the most descriptive atomic patterns in forming a combined meaningful dictionary to represent and discriminate those WQCPs. Therefore, the major methodological novelties of this paper lie in the DICCCOL-based structural/functional connectome construction and the sparse coding and representation of functional brain states.

The computational pipeline has been applied on two separate multimodal DTI/R-fMRI/T-fMRI datasets of 26 healthy adolescents and 37 healthy adults. Our experimental results demonstrated that the learned ACPs for R-fMRI and T-fMRI datasets are substantially different, as expected, and that the ACPs learned from independent R-fMRI datasets of healthy adolescents and adults are quite reproducible. Importantly, a certain portion of ACPs were overlapped between the two datasets, suggesting that some participating subjects were not in the expected task-free/task-performance states during the R-fMRI/T-fMRI scans and should be considered as potential outliers in the following steps of data analysis. As examples, some potential outlier WQCP segments from the T-fMRI dataset within resting state ACP patterns were further examined. Our activation detection results on T-fMRI datasets demonstrated that the subjects with outlier resting state ACPs have almost no group activation regions, while the subjects without outlier resting state ACPs exhibit consistent task-related activations. This result suggests that the ACP patterns could be potentially used to infer whether the participating subjects were following the administered experimental tasks or not during T-fMRI scans. In general, our experimental results revealed interesting phenomena of the regularity, diversity and dynamics of functional connectomes in task-free and task-performance states. Notably, an early short version of this methodology *was presented in* the MICCAI 2012 conference (Zhang et al., 2012).

2. Materials and methods

2.1. Overview

The flowchart of the proposed computational framework is summarized in Fig. 1. First, the 358 consistent DICCCOL landmarks that have been discovered and validated in our recent study (Zhu et al., 2013) are located in the DTI data of each brain (green bubbles[1] in the left panel of Fig. 1) via an effective functional landmark prediction approach (Zhang et al., 2012; Zhu et al.,2013). After pre-processing (Zhu et al., 2011b, 2013), both R-fMRI and T-fMRI images are co-registered into the DTI space using FSL FLIRT, and the representative R-fMRI/T-fMRI time series in each DICCCOL were extracted (Fig. 1(1)). Second, by using a sliding time window approach (Li et al., 2013), the dynamic functional connectivity time series between each pair of DICCCOLs are measured and thus the time-varying functional connectomes are constructed (Zhu et al., 2013). Furthermore, the cumulative functional connectivity strength of each landmark with all other DICCCOLs at each time point is summed, and the functional connectome is thus compactly represented by a column as shown in Fig. 1(2). Third, as extensive observations show that the functional connectome strengths are relatively stable in a continuous time period, therefore, they are interactively segmented into quasi-stable segments (called WQCP above), which form a set of WQCP training samples (Fig. 1(3)). Fourth, the WQCP samples from both R-fMRI and T-fMRI datasets were pooled together for sparse representation and classification via the Fisher discriminative dictionary learning (FDDL) method (Fig. 1(4)) (Yang et al., 2011) and a set of representative ACPs were obtained. Finally, each WQCP segment is classified to one ACP and the distributions of ACPs can be examined at the individual and population levels, as illustrated in Fig. 1(5).

2.2. Data acquisition and pre-processing

Two populations including 26 healthy adolescents (ages 11–17) and 37 healthy adults (ages 23–46) were recruited in Sichuan, China, under the IRB approvals of the Second Xiangya Hospital and the Central South of University. Multimodal DTI/R-fMRI/T-fMRI datasets for each participant were acquired on a 3T MRI scanner in West China Hospital, Huaxi MR Research Center, Department of Radiology, Chengdu, China. Acquisition parameters were as follows: DTI: 256×256 matrix, 3 mm slice thickness, 240 mm FOV, 50 slices, 15 DWI volumes, *b*-value = 1000; fMRI: 64×64 matrix, 4 mm slice thickness, 220 mm FOV, 30 slices, TR = 2 s. The

[1] For interpretation of color in Figs. 1, 5 and 6, the reader is referred to the web version of this article.