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Featured Article

Advances in functional magnetic resonance imaging data analysis methods using Empirical Mode Decomposition to investigate temporal changes in early Parkinson's disease

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Abstract

Introduction: Previous neuroimaging studies of Parkinson's disease (PD) patients have shown changes in whole-brain functional connectivity networks. Whether connectivity changes can be detected in the early stages (first 3 years) of PD by resting-state functional magnetic resonance imaging (fMRI) remains elusive. Research infrastructure including MRI and analytic capabilities is required to investigate this issue. The NIH/NIGMS Center for Biomedical Research Excellence awards support infrastructure to advance research goals.

Methods: Static and dynamic functional connectivity analyses were conducted on early stage never-medicated PD subjects (N = 18) and matched healthy controls (N = 18) from the Parkinson's Progression Markers Initiative.

Results: Altered static and altered dynamic functional connectivity patterns were found in early PD resting-state fMRI data. Most static networks (with the exception of the default mode network) had a reduction in frequency and energy in specific low-frequency bands. Changes in dynamic networks in PD were associated with a decreased switching rate of brain states.

Discussion: This study demonstrates that in early PD, resting-state fMRI networks show spatial and temporal differences of fMRI signal characteristics. However, the default mode network was not associated with any measurable changes. Furthermore, by incorporating an optimum window size in a dynamic functional connectivity analysis, we found altered whole-brain temporal features in early PD, showing that PD subjects spend significantly more time than healthy controls in a specific brain state. These findings may help in improving diagnosis of early never-medicated PD patients. These key observations emerged in a Center for Biomedical Research Excellence–supported research environment.

Keywords: Resting-state fMRI; Empirical mode decomposition; EMD; Intrinsic mode function; Group ICA; Functional connectivity; PPMI; Parkinson's disease

1. Introduction

Functionally related regions of the resting brain show a high degree of temporal correlation in blood-flow fluctuations, as measured by the blood-oxygenation level-dependent (BOLD) functional magnetic resonance imaging

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(fMRI) signal [1]. Using either seed-based methods or data-driven approaches such as independent component analysis (ICA), brain regions that fluctuate in synchrony and constitute reliable and reproducible functional networks in the human resting brain can be identified [2–6], named resting-state networks. Resting-state networks were assumed to be static in nature in the past, and approximately a dozen of such static networks have been discovered and investigated in relation to how they are impacted by neurodegenerative disorders. However, more recently, it has been shown that resting-state networks are dynamic in character and change on a time scale of several seconds to a minute [7–10]. Analyzing the temporal dynamics of resting-state connectivity provides a more accurate picture of the working brain and can help in the early detection of neurological disorders and in monitoring effects of potential treatments.

Both static and dynamic analysis methods have been applied to study resting-state functional networks in major neurodegenerative diseases, for example, Alzheimer's disease (AD). One of the major brain networks affected in AD is the so-called default mode network (DMN), which is heavily involved in memory formation and retrieval [11]. In normal subjects, the DMN shows functional connections between the posterior cingulate cortex, angular gyrus, hippocampus, and the medial prefrontal cortex. In AD patients, amyloid-beta (Aβ) protein has been found to accumulate in DMN and other regions, which may disrupt connections and lead to the symptoms of memory and cognitive impairment [12–14]. Early Aβ accumulation is associated with reduced static functional connectivity within the DMN and between the DMN and the frontoparietal network (FPN), a network that is involved in attention-demanding tasks [15,16]. The dynamic aspect of the DMN shows significant changes in AD as well [17]. It has been reported that AD subjects spend less time in brain states with strong posterior DMN contributions and more time in states with dorsal medial prefrontal cortex contributions.

Parkinson's disease (PD) is, after AD, the second most common neurodegenerative disorder in the elderly and is characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta with resulting striatal dopaminergic deficiency [18]. Previous neuroimaging studies of PD patients have shown that whole-brain functional networks such as the DMN and networks involving the motor pathway are affected, leading to different functional connectivity patterns when compared to those found in normal controls (NC) [19]. Studies of the temporal characteristics of fMRI resting-state brain networks have also shown abnormal spontaneous low-frequency content in PD [20]. The dynamic aspects of brain networks have been widely studied using electrophysiological recordings. Intraoperative electrophysiological data have shown that the occurrence of motor symptoms in PD is associated with changes in synchronizations within and between brain regions and changes in phase-amplitude coupling between brain regions [21,22]. However, it is not clear if *static* changes in resting-state networks are present in the very early stages (first 3 years) in drug-naïve never-medicated patients with PD. Furthermore, whether changes in temporal dynamics occur in resting-state functional networks in de novo PD subjects is unknown.

In the present study, as part of the NIH/NIGMS Centers of Biomedical Research Excellence grant to the Center for Neurodegeneration and Translational Neuroscience, we investigated low-frequency BOLD fluctuations of major resting-state networks in early PD using data from the Parkinson's Progression Marker Initiative (www.ppmi-info.org). Previously, frequency-specific analysis of resting-state networks has been carried out using bandpass filtering in which the frequency intervals were specified using information from electrophysiological data [23] or simply by dividing the possible frequency range into equal intervals that were specified by the user [24,25]. An alternative approach toward finding frequency intervals in resting-state data is by Empirical Mode Decomposition (EMD) [26,27]. EMD is a data-adaptive analysis method for studying the naturally occurring frequency bands in time series [28]. EMD can be used, in particular, for nonstationary signals and allows the decomposition of time series into nearly orthogonal modes spanning narrow frequency bands. The oscillatory modes are called intrinsic mode functions (IMFs) and are obtained by a sifting algorithm. The novelty of our EMD approach lies in the adaptive decomposition of fMRI data using EMD and identification of resting-state networks based on energy and period (inverse of frequency) characteristics of IMFs. These novel energy-period relationships of resting-state networks in PD may allow use of imaging biomarkers in characterizing or detecting PD in the early stages of the disease. Early stage identification of PD may improve diagnostic accuracy, enrollment in clinical trials of disease-modifying agents, and allow for more effective treatments.

In a second investigation, we explored the dynamic aspects of functional connectivity using the same data set. In previous research studies, dynamic functional connectivity analysis was carried out mainly by using a sliding-window method, in which pairwise linear correlations among network components are captured in subsequent temporal windows with a fixed window size and further clustered into multiple dynamic functional brain states [29,30]. To find an appropriate window size is challenging because the windows size should be small enough to capture existing temporal transients and large enough to produce stable results [10]. The EMD method, however, provides us an alternative way to compute a time-dependent optimum window size in the sliding-window analysis. IMFs obtained from EMD track local periodic changes of nonstationary time series and an optimum window size can be determined at each time point. We incorporated the optimum window size in the sliding-window method to explore dynamic