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Review article

Aberrant regional homogeneity in Parkinson's disease: A voxel-wise meta-analysis of resting-state functional magnetic resonance imaging studies

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ABSTRACT

Studies of abnormal regional homogeneity (ReHo) in Parkinson's disease (PD) have reported inconsistent results. Therefore, we conducted a meta-analysis using the Seed-based *d* Mapping software package to identify the most consistent and replicable findings. A systematic literature search was performed to identify eligible whole-brain resting-state functional magnetic resonance imaging studies that had measured differences in ReHo between patients with PD and healthy controls between January 2000 and June 4, 2016. A total of ten studies reporting 11 comparisons (212 patients; 182 controls) were included. Increased ReHo was consistently identified in the bilateral inferior parietal lobules, bilateral medial prefrontal cortices, and left cerebellum of patients with PD when compared to healthy controls, while decreased ReHo was observed in the right putamen, right precentral gyrus, and left lingual gyrus. The results of the current meta-analysis demonstrate a consistent and coexistent pattern of impairment and compensation of intrinsic brain activity that predominantly involves the default mode and motor networks, which may advance our understanding of the pathophysiological mechanisms underlying PD.

Contents

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease in the aging population (de Lau and Breteler, 2006), and the worldwide data indicate that the prevalence of PD increases with age (Pringsheim et al., 2014). PD causes serious health, economic, and social problems and continues to be a debilitatingly progressive and incurable condition (Miller and O'Callaghan, 2015). PD is characterized by a selective loss of nigrostriatal dopaminergic neurons that results in classically extrapyramidal motor impairment; however, more widespread involvement of other structures in the central nervous system as well as peripheral tissues, which is associated with various non-motor symptoms, has been widely documented in recent years (Miller and O'Callaghan, 2015; Reichmann et al., 2016). Despite much progress, however, the pathophysiology of PD has yet to be fully elucidated (Michel et al., 2016; Sulzer and Surmeier, 2013).

During the past decade, resting-state functional magnetic resonance imaging (RS-fMRI) has become a promising tool for the *in vivo* exploration of brain activity and connectivity, greatly enhancing our understanding of the pathophysiology of PD (Barkhof et al., 2014; Griffanti et al., 2016; Jiang et al., 2015; Prodoehl et al., 2014; Tahmasian et al., 2015). Such fMRI research has revealed that PD is associated with functional abnormalities in large-scale intrinsic connectivity networks such as the corticostriatal-thalamic-cortical network (including the sensorimotor network and the basal ganglia network), default mode network (DMN), dorsal attention network, frontoparietal network, and ventral attention network (Baggio et al., 2015a; Sharman et al., 2013). In recent years, regional homogeneity (ReHo) has been used as an efficient and reliable neuroimaging marker in the exploration of resting-state regional brain activity in neuropsychiatric disorders, including PD (Jiang et al., 2015; Jiang and Zuo, 2016; Prodoehl et al., 2014). ReHo is a whole-brain RS-fMRI analysis algorithm used to examine local synchronization of spontaneous blood oxygenation-level-dependent (BOLD) signals by calculating the similarity of the time series of one voxel with those of its nearest neighbors in a voxel-wise manner (Jiang and Zuo, 2016; Zang et al., 2004). ReHo alterations in PD have been observed to correlate with both symptom burden (Wu et al., 2009; Yang et al., 2013) and illness duration (Choe et al., 2013), which may be modulated by currently available treatments (Wu et al., 2009; Yeo et al., 2012). However, findings from these ReHo studies of PD so far have been inconsistent. Many studies have observed both areas of decreased and increased ReHo in patients with PD relative to healthy controls (Choe et al., 2013; Jiang et al., 2016; Li et al., 2016; Liu et al., 2011; Wu et al., 2009; Yang et al., 2013; Zhang et al., 2015), while several other studies have only detected decreased or increased ReHo (Borroni et al., 2015; Sheng et al., 2014; Yeo et al., 2012). In addition, the affected brain regions identified in these studies were diverse (Borroni et al., 2015; Choe et al., 2013; Jiang et al., 2016; Li et al., 2016; Liu et al., 2011; Sheng et al., 2014; Wu et al., 2009; Yang et al., 2013; Yeo et al., 2012; Zhang et al., 2015) with different studies sometimes reporting increased or decreased ReHo in the same brain regions (Supplementary Table S1 in the online version at DOI: http://dx.doi.org/10.1016/j.neubiorev.2016.11.018). These reported inconsistencies regarding changes in ReHo in patients with PD can potentially be ascribed to factors such as sample size, illness severity, illness duration, and imaging protocols. Identifying the core regions of functional change may advance our understanding of the neural mechanisms underlying this disorder.

In this context, we considered it timely to conduct a meta-analysis to identify the most consistent and replicable ReHo changes in PD. In the present study, we utilized Seed-based *d* Mapping (SDM), a well-established and validated meta-analytic tool for neuroimaging studies that has been widely used to detect the most spatially consistent structural and functional brain changes in a number of neuropsychiatric diseases (Iwabuchi et al., 2015; Radua and Mataix-Cols, 2009; Sheng et al., 2015). In addition, we conducted meta-regression analyses to examine the potential effects of age, illness severity, and illness duration on ReHo changes.

2. Methods

2.1. Data sources, study selection, and quality assessment

A comprehensive search of studies published between January 2000 and June 4, 2016 was conducted in the PubMed, Embase, and Web of Science databases using the keywords "Parkinson" OR "Parkinson's disease"; AND "regional homogeneity" OR "ReHo" OR "local connectivity" OR "coherence". In addition; the references of the included studies and relevant review articles were checked for additional relevant studies. Studies that satisfied the following conditions were included in the meta-analysis: (i) patients had been diagnosed with idiopathic PD; (ii) ReHo comparison of patients with idiopathic PD versus healthy controls was conducted; (iii) three-dimensional coordinates (Talairach or Montreal Neurological Institute [MNI]) were reported for the whole-brain ReHo analysis; (iv) significant results were reported using thresholds for significance corrected for multiple comparisons or uncorrected with spatial extent thresholds; and (v) the study was published as an original article (not as a letter or an abstract) in a peer-reviewed English language journal. Datasets were excluded if they explicitly indicated patients with PD diagnosed with comorbid neurological or psychiatric diseases (i.e.; cognitive impairment or depression). For longitudinal studies; only the baseline data were included. For studies reporting both on- and off-state results; only the off-state datasets were included. In cases where patient datasets overlapped between separate articles; only the dataset with the largest sample size and the most comprehensive information was included. The corresponding author of each included study was contacted via email when additional information was required. The quality of each study selected for this meta-analysis was assessed with a 20-point checklist used in a previous meta-analysis of RS-fMRI studies (Iwabuchi et al., 2015) (Supplementary Table S2 in the online version at DOI: http://dx.doi.org/10.1016/j.neubiorev.2016.11.018). Literature search; study evaluation and selection; and data extraction were independently performed by two investigators.