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DRIFT IN CENTRALITY OF DIFFERENT BRAIN REGIONS IN AN ANATOMICAL NEURAL NETWORK WITH PARKINSON'S DISEASE: A VIEW FROM COMPLEX NETWORK ANALYSIS

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Abstract—Understanding the role of brain regions in anatomical neural networks with Parkinson's disease (PD) is essential for improving the clinical protocol or finding new targets for deep brain stimulation (DBS). Although numerous changes have been reported in local functional studies, few studies have reported on the anatomical network of the entire brain. Here, by developing a series of algorithms, this study provided a whole anatomical neural network of the macaque monkey. Then, the drifts in centrality from normal to PD networks were described in terms of complex network analysis and summarized with principal component analysis. Results revealed that the areas including the striatum, globus pallidus, amygdala, prefrontal lobe, thalamus, hippocampus, visual cortex, insula, etc., showed relatively notable drifts in their own patterns. The present study also demonstrated that the current targets of DBS shared a common feature: their centrality values being relatively low in the normal brain while intensely drifting with PD.

Key words: network analysis, centrality, anatomical connectivity network, Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is the most common neurodegenerative movement disorder with an incidence of 17.4–93.1 in 100,000 person-years in aged people (Lees et al., 2009). To date, there is no effective cure for this disease, which causes strong impairment to patients' daily lives and imposes a substantial burden on their families and society (Findley, 2007; Kowal et al., 2013). The current understanding of the pathophysiological basis of PD is often considered to be the irreversible loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc), an important dopamine-producing area located in the midbrain. The loss of DA neurons in the SNc then causes the ensuing depletion of dopamine in the striatum (Str), a subcortical part of the forebrain (Carlsson et al., 1957), leading to the symptoms of PD. The first-line treatment of PD is dopamine replacement therapy (including dopamine or DA receptor agonist supplement) (Fahn et al., 2004, Olanow et al., 2004). Because the effects of these medicines are not stable for long-term therapy and also because their complications, especially the motor complications (Rascol et al., 2000; Bezard et al., 2001), are intolerable for some patients, the deep brain stimulation (DBS) which is re-emerging from its original form, the abandoned ablative surgery, is gaining more and more attention as a second-line therapy for advanced PD patients.

For several decades, although the targets of DBS for PD ranged from subthalamic nucleus (STN) (Kumar et al., 1998; Deep-Brain Stimulation for Parkinson's Disease Study, 2001) to internal globus pallidus (GPi) (Deep-Brain Stimulation for Parkinson's Disease Study, 2001), pedunculopontine (PPN) (Stefani et al., 2007), ventral intermediate nucleus (Vim) (Benabid et al., 1991), center median/parafascicular complex (CM/Pf) (Krauss et al., 2002; Peppe et al., 2008), and zona incerta (ZI) (Plaha et al., 2006, Plaha et al., 2008; Smith et al., 2012), the effects of DBS remained below the expectations of both patients and doctors, yielding limited therapeutic effects and unwanted complications (Limousin and Martinez-Torres, 2008). However, the most discussed strategies to improve DBS drew attention away from the search of new targets and the modification of the stimulation parameters, and instead focused on other methods such as the selection of patients, the localization of electrodes, or the upgrading of the device itself. One of the reasons for this shift in strategy has been the lack of a

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Abbreviations: DA, dopaminergic; DBS, deep brain stimulation; GPe, external globus pallidus; GPi, internal globus pallidus; PD, Parkinson's disease; PPN, pedunculopontine; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; Vim, ventral intermediate nucleus; ZI, zona incerta.

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comprehensive understanding of the brain changing from normal to PD brain, especially the changes in the roles of key regions in the neural network. To gain such a comprehensive understanding, the classical region-to-region interaction studies (for example: stimulate one region while recording from other brain regions) may be less effective in forming an overall view than a more systematic approach. Indeed, recent developments in the quantitative analysis of complex networks, which are largely based on graph theories and already widely used in other fields such as social sciences and computer sciences, may offer a better alternative.

Although numerous studies employing noninvasive neuroimaging and electrophysiological recording methods already used network analysis in functional connectivity (Stam, 2014), few reported using this method in anatomical connectivity. This could be attributed to the complexity of undertaking brain research: ''Different studies performed at different times by different groups by using different techniques on different animals and at different resolutions, inevitably lead to a wide variety of nomenclature.'' (Modha and Singh, 2010). For example, the CoCoMac (Bakker et al., 2012), one of the largest connectivity databases for macaque monkeys, provided connectivity information about the thalamus (low resolution), its sub-regions (middle resolution), and its sub-regions' sub-regions (high resolution). This kind of overlapping information causes difficulties in defining nodes for network analysis.

By developing a series of algorithms that merge connectivity data from different studies, especially those with different resolutions, this study established a whole brain connectivity network in monkey, which was firstly available for further network analysis. Then, the whole emulational PD brain network was established for comparing with the normal brain network by using a complex network analysis. This further provided both comprehensive and detailed view of the changes in the centralities of each brain area. The result may help in our understanding of how the brain changes with PD, thus opening the door for future researchers to find new targets for DBS with the aid of the network sciences.

EXPERIMENTAL PROCEDURES

Connectivity database

The initial connectivity matrix in this study was derived from D. S. Modha, and R. Singh's work (Modha and Singh, 2010) (hereafter ''merged CoCoMac''), a matrix carefully merged from the original CoCoMac database (Bakker et al., 2012). In their work, connectivity information was corrected for errors made in the original CoCoMac, and the brain regions were merged to connect previously disconnected path fragments. For example, in their merging process, external globus pallidus (GPe) and GPi were merged into a new item named ''GPe'' and substantia nigra pars reticulata (SNr) and SNc were merged into an item called ''SN''. Furthermore, all the self-loop connections were removed. As a result, their final matrix had 383 nodes and 6602 directed connections. In addition, their work provided a clear hierarchical brain map, which can be conveniently used in network analysis.

However, the resolution remained an issue for network analysis: only nodes that are not overlapping

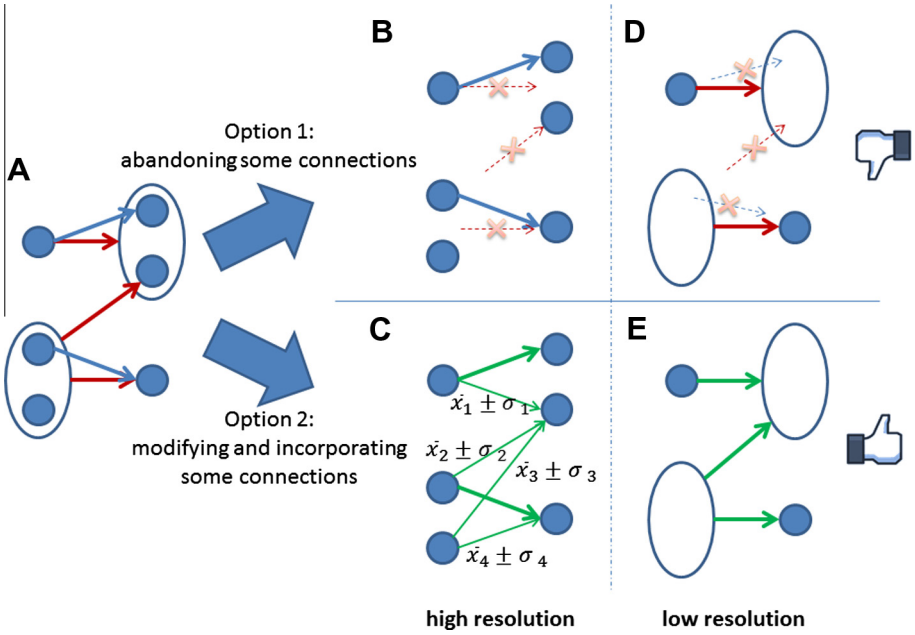

Fig. 1. Approaches for merging connections with different resolutions. The original data (A) contain two kinds of nodes [those who have substructures (parent-region, elliptic) and those who do not (child-region, round)], and two kinds of connections [those with only child-regions involved, in blue, and those with at least one parent-region involved, in red]. In order to merge the network without nodes overlapping in high resolution (B, C) or low resolution (D, E), the first option consists in abandoning some of the connections. However, the resulting networks (B, D) are sparser and disconnected. The second option consists in modifying and incorporating these connections with a degree of uncertainty (C and E, the uncertain edge weights are random variables, the $\bar{x}_i \pm \sigma_i$ here just denotes that it follows a certain distribution with a mean $\bar{x}_i$ and a variance σ_i). In this case, the resulting networks keep their connectivity. This second option is preferred to the first one. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)