CNS Neuroscience & Therapeutics

EDITORIAL

Imaging Brain Networks in Neurodegenerative Diseases

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doi: 10.1111/cns.12466

Neurodegenerative diseases affect millions of people worldwide and include many different types, such as Alzheimer's disease (AD), frontotemporal dementia, semantic dementia, amyotrophic lateral sclerosis, and Parkinson's disease (PD). Patients suffering from these diseases show declines in a variety of cognitive functions, as well as disruptions of brain structures and functions, in parallel with a molecular and pathological progression, such as the accumulation of specific proteins. Despite the differences in the underlying biological mechanisms, important commonalities have been observed among these diseases, leading some researchers to argue that neurodegenerative diseases are brain disorders with misfolded protein aggregates between regions over time as a consequence of diffuse network dynamics [1,2]. Recent advances in multimodal neuroimaging techniques (e.g., structural MRI, functional MRI, diffusion MRI, and positron emission tomography) provide unique opportunities to explore the structural and functional brain abnormalities in patients, in particular from a network perspective, to improve our understanding of the pathophysiological mechanisms of neurodegenerative diseases, and to assist in developing diagnostic biomarkers and assess treatment effects [3,4]. While there are still many challenging issues, such as the extraction of reliable brain connectivity from various imaging modalities and the analyses of the topological properties (e.g., the selection of global and regional metrics), network analysis of neuroimaging data in neurodegenerative diseases has significantly advanced in the past decade, mainly due to the rapid development of imaging analysis methodologies and computational models of brain networks.

In this special issue, we aimed to compile works representing recent studies regarding imaging brain networks in neurodegenerative diseases. We collected eleven articles, including five review articles and six original research articles. The article topics covered various research directions in structural and functional brain network studies using neuroimaging data in neurodegenerative diseases such as AD, semantic dementia, and PD.

(i) We assembled five review articles. In the first review article, Agosta et al. [5] provided a comprehensive review regarding the recent progress on the most common neurodegenerative diseases (e.g., AD, frontotemporal dementia, amyotrophic lateral sclerosis, and PD) involving the main molecular and pathological substrates of these diseases and neuroimaging findings based on structural and functional brain connectivity analyses. They highlighted the "network-based neurodegeneration" hypothesis in these disorders by representing the large-scale brain network alterations, as well as the microscopic abnormalities of structural pathways. They emphasized that characterizing network breakdown using multimodal MRI data in combination with molecular imaging techniques would be crucial to understanding the biological mechanisms of these neurodegenerative diseases, and they may even help to identify new therapeutic targets to slow or stop the disease progression.

Sun et al. [6] and Li et al. [7] provided systematic reviews regarding behavioral, biochemical, and neuroimaging studies in subjective cognitive decline and mild cognitive impairment, respectively. Neurodegeneration due to AD can progress over years before dementia appears. Individuals with mild cognitive impairment have a high risk of progressing to AD, which represents the prodromal stage of this disease. Furthermore, most individuals with mild cognitive impairment are preceded by subjective cognitive decline characterized by self-reported memory complaints. By summarizing the recent progress on structural and functional imaging studies, Sun et al. [6] and Li et al. [7] highlighted that brain network dysfunctions have appeared in both subjective cognitive decline and mild cognitive impairment and emphasized the importance and necessity of considering these early stages in disease diagnosis. Given that both subjective cognitive decline and mild cognitive impairment are heterogeneous and some individuals will not convert to dementia, they also emphasized that longitudinal studies using multimodal neuroimaging techniques are vital for the discovery of diagnostic biomarkers.

Yang et al. [8] conducted an exhaustive review of studies that directly or indirectly assessed the structural and functional connectivity alterations of semantic dementia. Their synthesized analyses showed that semantic dementia is associated with extensive changes in terms of both structural and functional networks, encompassing, but not restricted to, regions that are strongly atrophied in semantic dementia, such as the anterior temporal lobe. They highlighted that the relationship between structural and functional connectivity changes, and between these network changes and the core behavioral symptoms of semantic dementia, that is, semantic deficit, is not yet established, marking critical new research directions for the study of this disorder.

Finally, Baggio et al. [9] systematically reviewed the recent progress on brain functional network studies using resting-state functional MRI in Parkinson's disease. Resting-state functional MRI provides a unique opportunity to explore the brain's spontaneous or intrinsic functional architecture in healthy and disease populations (e.g., AD and PD). By summarizing the findings using resting-state functional MRI, they suggested that there were a number of variabilities in the results across studies. Nonetheless, they emphasized that the resting-state fMRI technique and network analysis approaches are vital for evaluating the pathophysiological mechanisms underlying the clinical and cognitive

manifestations of PD patients, as well as for discovering potential biomarkers for early diagnosis, treatment evaluation, and clinical outcomes.

(ii) We assembled six original research articles. As mentioned above, the combination of resting-state functional MRI and network analysis approaches, such as graph theory, has emerged as a promising tool for characterizing the topological organization of functional brain networks in neurodegenerative diseases. In this issue, Du et al. [10] performed an important resting-state functional MRI study by systematically evaluating the test–retest reliability of various graph metrics in the high-resolution (voxel level) functional networks in 53 healthy participants. Specifically, using different nodal metrics, they identified functional hubs of the brain networks mainly located at the default-mode, salience, and executive control systems. These regions exhibited high test–retest reliability in the high-resolution functional networks, which were not sensitive to the selection of preprocessing factors such as head motion and global signal removal. Thus, this study provides valuable guidance for choosing reliable network metrics and analysis strategies in future longitudinal imaging studies of neurodegenerative diseases.

Age is a key factor in neurodegenerative diseases. In this issue, Huang et al. [11] used a group-level independent component analysis and dual regression approaches to study resting-state networks derived from resting-state functional MRI data from a large group of healthy elderly participants (n = 430). They showed age-related decreases in many functional systems, including the ventral default-mode network, frontoparietal, auditory, sensorimotor, and visual medial networks. Most of these have been found to be disrupted in many neurodegenerative diseases, such as AD and PD. Thus, this work provides insights into age-related network breakdown, which would be helpful to understand the impact of aging on the biological mechanisms and clinical manifestations of neurodegenerative diseases.

The hippocampus is a deep-brain structure involved in learning and memory. Structural and functional abnormalities in the hippocampus have been commonly observed in various neurodegenerative diseases. Specifically, neurodegenerative changes in AD have been suggested to begin at this structure and then to propagate in a stereotypical fashion. Automated and precise segmentation of the hippocampus is thus valuable for clinical studies. In this issue, Li et al. [12] introduced a novel segmentation method that utilized a manifold learning technique under the multiatlas-based segmentation scenario. Compared with two representative local weighted label fusion methods using structural MRI data of 28 healthy adolescents (age range: 10–17 years) and two ADNI datasets with 100 participants (age range: 60–89 years), the proposed method obtained consistent and significant improvements over the previous label fusion strategies, showing promising potential for future structural and functional connectivity studies of the hippocampus in neurodegenerative diseases.

Mallio et al. [13] performed an intriguing study by investigating whether the disruption of structural connectivity in AD is centered on the hippocampus and whether this disruption propagates from this structure to others. Using diffusion-weighted imaging data, they first built structural brain networks in 14 amnestic mild cognitive impairment, 13 mild patients with AD, 15 moderate patients with AD, and healthy controls. They then calculated the percentages of affected connections directly linking to the epicenter (defined as the first ring) and to nodes with the topological distance 2 from the epicenter (defined as the second ring). They showed that both the first and the second rings were significantly affected in both the mild and the moderate AD groups but less affected in the mild cognitive impairment group, providing empirical support for the "network-based neurodegeneration" hypothesis in this disease.

Numerous neuroimaging studies have suggested focal structural and functional abnormalities in many regions in patients with subcortical vascular mild cognitive impairment. However, it remains largely unknown whether and how brain network organization is disrupted in this disease. In this issue, Yi et al. [14] directly addressed this important issue by constructing brain functional networks using resting-state functional data in 21 patients with subcortical vascular mild cognitive impairment and 26 healthy controls. They found that compared with the controls, the patients exhibited disrupted global network topology with significantly increased path length and modularity. Disrupted modular structure was also observed in patients, with a notable reorganization of the executive control module. The parietal regions were split into different modules. Finally, they showed disrupted within-module and between-module connections involving the middle cingulate gyrus, anterior insula, medial prefrontal cortex, and lateral parietal regions. Collectively, this study highlighted the topological disorganization of functional brain networks in subcortical vascular mild cognitive impairment, providing implications for the biological mechanism of this disease.

Postural instability with gait difficulty and tremor dominant are the two main subtypes of Parkinson's disease. Many studies have demonstrated that patients with these two subtypes exhibit different clinical manifestations, but the underlying neural substrates remain incompletely understood. In this issue, Chen et al. [15] addressed this interesting question by exploring the subtype-specific patterns of spontaneous brain activity in PD. Using resting-state functional MRI data, they measured the amplitudes of low-frequency fluctuations in 31 PD patients (12 tremor dominant /19 postural instability with gait difficulty) and 22 healthy controls. The two groups of patients showed different resting-state activities in the bilateral putamen, the cerebellar posterior lobe, and the lateral temporal and parietal regions. These differences were correlated with clinical variables (e.g., tremor score and the postural instability with gait difficulty score). Although not a direct assessment of network dysfunction, this study provided preliminary evidence for abnormal spontaneous activities in the cerebellum and putamen, which may underlie the neural substrate of the motor subtypes of PD.

Collectively, the works of this special issue cover a great range and depth of the network studies of neurodegenerative diseases, constituting exciting exemplars of how the new advances in multimodal neuroimaging and network analysis can be powerful approaches to studying diseased brains. We anticipate that these works will provide critical insights into the field of neurodegenerative research. Future works are important to collect a large sample of longitudinal clinical and

imaging data and develop novel network analysis approaches to fully decipher brain network dysfunction in neurodegenerative diseases. Lastly, we would like to thank all of the authors, reviewers, and the editorial office for their great contributions to this special issue.

Acknowledgments

This work was supported by the National Key Basic Research Program of China (973 Project, No. 2014CB846102) and the National Science Fund for Distinguished Young Scholars (No. 81225012).

References

1. Raj A, Kuceyeski A, Weiner M. A network diffusion model of disease progression in dementia. *Neuron* 2012;**73**:1204–1215.
2. Zhou J, Gennatas ED, Kramer JH, Miller BL, Seeley WW. Predicting regional neurodegeneration from the healthy brain functional connectome. *Neuron* 2012;**73**:1216–1227.
3. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci* 2009;**10**:186–198.
4. He Y, Evans A. Graph theoretical modeling of brain connectivity. *Curr Opin Neurol* 2010;**23**:341–350.
5. Agosta F, Weiler M, Filippi M. Propagation of pathology through brain networks in neurodegenerative diseases: from molecules to clinical phenotypes. *CNS Neurosci Ther* 2015;**21**:754–767.
6. Sun Y, Yang FC, Lin CP, Han Y. Biochemical and neuroimaging studies in subjective cognitive decline: progress and perspectives. *CNS Neurosci Ther* 2015;**21**:768–775.
7. Li X, Zhang ZJ. Neuropsychological and neuroimaging characteristics of amnestic mild cognitive impairment subtypes: a selective overview. *CNS Neurosci Ther* 2015;**21**:776–783.
8. Yang Q, Guo QH, Bi YC. The brain connectivity basis of semantic dementia: a selective review. *CNS Neurosci Ther* 2015;**21**:784–792.
9. Baggio HC, Segura B, Junque C. Resting-state functional brain networks in Parkinson's disease. *CNS Neurosci Ther* 2015;**21**:793–801.
10. Du HX, Liao XH, Lin QX, et al. Test–retest reliability of graph metrics in high-resolution functional connectomics: a resting-state functional MRI study. *CNS Neurosci Ther* 2015;**21**:802–816.
11. Huang CC, Hsieh WJ, Lee PL, et al. Age-related changes in resting-state networks of a large sample size of healthy elderly. *CNS Neurosci Ther* 2015;**21**:817–825.
12. Li XW, Li QL, Li SY, Li DY, ADNI. Local manifold learning for multiatlas segmentation: application to hippocampal segmentation in healthy population and Alzheimer's disease. *CNS Neurosci Ther* 2015;**21**:826–836.
13. Mallio CA, Schmidt R, de Reus MA, et al. Epicentral disruption of structural connectivity in Alzheimer's disease. *CNS Neurosci Ther* 2015;**21**:837–845.
14. Yi LY, Liang X, Liu DM, et al. Disrupted topological organization of resting-state functional brain network in subcortical vascular mild cognitive impairment. *CNS Neurosci Ther* 2015;**21**:846–854.
15. Chen HM, Wang ZJ, Fang JP, et al. Different patterns of spontaneous brain activity between tremor dominant and postural instability gait difficulty subtypes of Parkinson's disease: a resting-state fMRI study. *CNS Neurosci Ther* 2015;**21**:855–866.