Neuroscience 364 (2017) 212–225

DISRUPTED STRUCTURAL AND FUNCTIONAL CONNECTIVITY NETWORKS IN ISCHEMIC STROKE PATIENTS

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Abstract—Local lesions caused by stroke may result in extensive structural and functional reorganization in the brain. Previous studies of this phenomenon have focused on specific brain networks. Here, we aimed to discover abnormalities in whole-brain networks and to explore the decoupling between structural and functional connectivity in patients with stroke. Fifteen ischemic stroke patients and 23 normal controls (NCs) were recruited in this study. A graph theoretical analysis was employed to investigate the abnormal topological properties of structural and functional brain networks in patients with stroke. Both patients with stroke and NCs exhibited small-world organization in brain networks. However, compared to NCs, patients with stroke exhibited abnormal global properties characterized by a higher characteristic path length and lower global efficiency. Furthermore, patients with stroke showed altered nodal characteristics, primarily in certain motor- and cognition-related regions. Positive correlations between the nodal degree of the inferior parietal lobule and the Fugl-Meyer Assessment (FMA) score and between the nodal betweenness centrality of the posterior cingulate gyrus (PCG) and immediate recall were observed in patients with stroke. Most importantly, the strength of the structural–functional connectivity network coupling was decreased, and the coupling degree was related to the FMA score of patients, suggesting that decoupling may provide a novel biomarker for the assessment of motor impairment in patients with stroke. Thus, the topological organization of brain networks is altered in patients with stroke, and our results provide insights into the structural and functional organization of the brain after stroke from the viewpoint of network topology.

Key words: ischemic stroke, structural connectivity network, functional connectivity network, decoupling, topological properties.

INTRODUCTION

Ischemic stroke, which results from a focal loss of blood supply to brain tissues due to the occlusion of a cerebral artery, is one of the leading causes of adult disability. Damage from ischemic stroke causes structural and functional reorganization of perilesional and remote brain regions, leading to cognitive deficits after stroke (Dacosta-Aguayo et al., 2014, 2015), and damage is linked to poor recovery of motor function during rehabilitation (Li et al., 2015). Hence, the identification of factors that cause cognitive impairment and motor dysfunction would improve interventions that promote the recovery of patients with stroke.

Multiple magnetic resonance imaging (MRI) techniques have been used to investigate the structural and functional changes that occur in the brains of patients with stroke. According to diffusion tensor imaging (DTI) results, damage caused by ischemic stroke leads to the structural reorganization of ipsilesional sensorimotor regions and transcallosal and corticospinal tracts, and the extent of this reorganization has been used to predict the severity of motor skill and neurological deficits in patients with stroke (Li et al., 2015; Huang et al., 2015; Meyer et al., 2015). Resting-state functional MRI (rs-fMRI) has also been used to identify post-stroke changes in brain function. Previous rs-fMRI studies reported changes in the amplitude of low-frequency fluctuations (ALFF) and regional homogeneity (ReHo) in the cerebellum, precuneus, frontal lobe and parietal cortex, brain regions related to motor and sensory function, as well as emotion (Wu et al., 2015; Zhu et al., 2015). As shown in the recent study by Yang et al., patients with stroke primarily showed increased ALFF in the right mesial temporal and lateral temporal cortices (Yang et al., 2016a) and decreased ReHo in the right lingual gyrus, the left calcarine region, the left cuneus, the left superior frontal gyrus, and the left medial area of the superior frontal gyrus, which are some of the

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Abbreviations: AAL, automated anatomical labeling; ALFF, amplitude of low-frequency fluctuations; AUC, area under the curve; AVLT, Auditory Verbal Learning Test; DMN, default mode network; DTI, diffusion tensor imaging; FA, fractional anisotropy; FMA, Fugl-Meyer Assessment; FOV, field of view; MMSE, Mini-Mental State Examination; MPRAGE, magnetization-prepared rapid gradient-echo sequence; MRI, magnetic resonance imaging; NCs, normal controls; PCG, posterior cingulate gyrus; ReHo, regional homogeneity; ROIs, regions of interest; rs-fMRI, resting-state functional MRI; SMA, supplementary motor area; TE, echo time; TR, repetition time.

https://doi.org/10.1016/j.neuroscience.2017.09.009
0306-4522/

brain regions involved in language processing (Yang et al., 2016b). However, a structural or functional alteration in a particular region of the brain does not provide information about how this region interacts with other regions in patients with stroke.

Recent developments in connectivity analyses have provided new insights that improved our understanding of whether intra- and inter-hemispheric interactions are disrupted after stroke (Carter et al., 2012; Yin et al., 2014; Liu et al., 2015; Zhang et al., 2016; Grefkes and Fink, 2011). Based on the results from an increasing number of structural and functional studies of connectivity networks, the interactions among key motor regions are pathologically altered in patients with stroke (Baldassarre et al.,2014; Yin et al., 2012, 2014; Liu et al., 2015; Zhang et al., 2016; Rehme and Grefkes, 2013; Carter et al., 2010; Park et al., 2011). According to Van Meer et al. (2010), reduced structural and functional inter-hemispheric connectivity between the contralesional primary motor cortex (M1) and ipsilesional sensorimotor cortical regions, and increased the structural and functional inter-hemispheric connectivity in the contralesional sensorimotor cortex were found in rats after stroke. A previous review of experimental stroke models also confirmed the pathological alterations of structural and functional connectivity among motor regions (Dijkhuizen et al., 2012). Focal brain lesions resulting from ischemic stroke also result in selective alterations in functional and structural inter-connectivity of other brain circuits that are unrelated to motor function, such as the frontal networks (Mikell et al., 2016), the default mode network (Liu et al., 2014; Dacosta-Aguayo et al., 2015), the dorsal attention network (Baldassarre et al., 2014) and the white matter language pathways (Bonilha et al., 2014; Yang et al., 2016c). As widespread brain regions and extensive networks may be damaged in patients with stroke, studies investigating the integrated network of structurally and functionally interacting brain regions might be more valuable than studies investigating local connections in an attempt to understand the pathological mechanisms of stroke.

Recently, the graph theoretical analysis has been popularly used to characterize the topological properties of whole-brain networks (Salvador et al., 2005; Achard et al., 2006; Hagmann et al., 2008; Gong et al., 2009; Bullmore and Sporns, 2009). Disrupted organization of the brain network has been observed in a wide range of psychiatric disorders and neurological diseases using graph theoretical approaches (Zhang et al., 2011a,b; Long et al., 2013; Sang et al., 2015). Regarding stroke studies, one rs-fMRI study observed interrupted functional connectivity in several speech-processing regions and local topological aberrations in the default mode network in patients with ischemic stroke; these changes likely contribute to abnormal cognitive performance (Zhu et al., 2017). A DTI study observed abnormalities in nodal characteristics within the orbitofrontal cortex and parietal-occipital cortex, as well as a correlation between the betweenness centrality of the right pallidum and the National Institutes of Health Stroke Scale score that also explains cognitive impairment in patients with ischemic stroke (Shi et al., 2013). As shown in another DTI study by Bonilha et al., post-treatment improvements in correct naming were related to the post-stroke preservation of both small-worldness of the global network and the betweenness centrality in temporal lobe cortical regions; thus, the topological properties of structural connectivity networks have been used to screen particular therapies in patients with stroke (Bonilha et al., 2016). The structural and functional connectivity networks in the brain provide a different perspective for studies of the brain (Damoiseaux and Greicius, 2009). Thus, the simultaneous assessment of functional and structural connectivity networks takes advantage of complementary views of the brain and enhances our understanding of the neural information processing reflected in each modality. Most current large-scale network studies involving patients with ischemic stroke focus on a particular modality of the brain and may not have sufficient sensitivity or specificity to detect pathological changes in the brain. Thus, researchers must simultaneously study structural and functional connectivity networks to better understand pathological mechanisms in the brains of patients with ischemic stroke.

Recently, a combined structural and functional connectivity network analysis has also been used to study the relationship between these two networks (Zhang et al., 2011b; Zhu et al., 2016). Functional connectivity is assumed to reflect the structural connectivity of the brain, and structural connectivity is highly predictive of and places constraints on functional connectivity within the brain (Zhang et al., 2011b). The two connectivity modalities have been shown to exhibit large spatial resemblances within the whole-brain large-scale network (Honey et al., 2009, 2010). The coupling of structural and functional connectivity networks increases with age (Hagmann et al., 2010) and decreases in disease-specific states (Zhang et al., 2011b; Zhu et al., 2016). However, the relationship between structural and functional connectivity networks in ischemic stroke remains poorly understood.

In this study, we hypothesized that ischemic stroke is characterized by disrupted topological organization and decoupling of the structural and functional connectivity networks. We collected DTI and rs-fMRI data from fifteen patients with ischemic stroke and twenty-three age- and gender-matched normal controls (NCs) and constructed the structural and functional connectivity networks of these subjects to test this hypothesis. Subsequently, graph theoretical approaches were used to analyze the topological properties of these networks. Finally, nonparametric tests were used to analyze between-group differences in the strength of structural–functional connectivity coupling and the topological properties of connectivity networks.

EXPERIMENTAL PROCEDURES

Participants

Fifteen patients with subcortical stroke (5 females, ranging in age from 47 to 76 years (58.26