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Research report

Abnormal cortical-basal ganglia network in amyotrophic lateral sclerosis: A voxel-wise network efficiency analysis

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ABSTRACT

Evidence suggests that dysfunctional cortical-basal ganglia (CBG) network plays important roles in the motor symptoms in amyotrophic lateral sclerosis (ALS). However, little effort has been made to investigate the functional abnormalities of CBG network in ALS. Here, we constructed voxel-wise CBG networks using the resting-state fMRI data of 20 patients with ALS and 21 normal controls, and characterized the differences of their efficiency parameters between the two groups. Compared to normal controls, patients with ALS exhibited decreased nodal efficiency in the right thalamus (THA), the left caudate (CAU) and the right precentral gyrus (preCG), and increased nodal efficiency in the left preCG. In the patient group, we observed a significant negative correlation between the nodal efficiency of the right preCG and disease progression rate. These results demonstrate that both ineffective information transfer and compensatory mechanisms are involved in the pathophysiological mechanism underlying the motor dysfunctions in patients with ALS. In summary, the present study provides a novel perspective on pathophysiological explanation for the motor symptoms in patients with ALS.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a common neurodegenerative disease characterized by loss of upper motor neurons of the primary motor cortex and corticospinal tract projections, together with lower motor neuron loss in the spinal anterior horns and pontomedullary nuclei [1,2]. Although a large number of findings have illustrated that ALS is the most common motor disease, the exact pathophysiological mechanism of this disorder remains unknown. Functional neuroimaging studies showed that alterations in the primary motor cortex (M1), primary somatosensory cortex (S1), and the right supplementary motor cortex (SMA) were closely linked to impaired motor execution in ALS [3–6]. MRI-based morphometric analysis [7,8] reported reduced gray matter volume in sensorimotor cortical areas and premotor cortex in patients with ALS. Furthermore, increasing evidence suggested that regions associated with abnormal brain functions or structures involve not only the cortical motor regions but also the subcortical extra-motor regions [5,9–12], such as the putamen (PUT) and thalamus (THA), known as cortical-basal ganglia (CBG) pathway. According to previous study [13], the CBG network comprises (1) the PUT, which receives input from cortical motor areas and projects directly to the basal ganglia, (2) the globus pallidus (GP), which receives input from the PUT and transmits projections directly to THA, (3) the THA, which receives projections from the internal segment of the GP and in turn projects back to the cortical motor areas [14–16], and (4) cortical motor regions, including the M1, lateral premotor cortex (LPMC), SMA and S1.

Abbreviations: CBG, cortical-basal ganglia; ALS, amyotrophic lateral sclerosis; THA, thalamus; CAU, caudate; preCG, precentral gyrus; M1, primary motor cortex; S1, primary somatosensory cortex; SMA, supplementary motor cortex; PUT, putamen; GP, globus pallidus; LPMC, lateral premotor cortex; MoCA, Montreal Cognitive Assessment; ALSFRS-R, ALS Functional Rating Scale-Revised; MNI, Montreal Neurological Institute; FDR, false discovery rate

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Since the CBG network plays an integral role in movement execution, dysfunctional CBG network was thought to underlie the classical motor signs and symptoms of several neurodegenerative diseases [11,13,17]. Therefore, targeted investigations of the CBG network may provide new insights into the neural mechanisms underlying the motor dysfunctions in ALS.

Recently, advance in the graph theory-based network analysis has offered us a number of parameters to characterize the topological organization of the brain network. Among these parameters, the network efficiency provides a more biologically relevant metric to describe brain networks from the perspective of information flow, which can identify and track the pathophysiology of disease at a network level [18]. In brief, the global efficiency of a network is defined as the mean of the inverse of shortest path length in the network, measuring how efficiently information is exchanged at the global level [19,20], whereas the nodal efficiency of the network is calculated as the averaged reciprocal shortest path length between the node and the other nodes, representing the ability of information transfer from itself to other nodes in the entire network [21]. Alterations in these parameters were observed in a various psychiatric and neurological disorders [18,22,23], which indicated that the network efficiency has the potential of detecting subtle changes in the information transfer of the brain networks. Notably, in ALS, most of existing network analyses were conducted by averaging the time series across a brain region of moderate size [24–26], which could lead to significant losses of spatial information. By contrast, voxel-wise brain network analysis enables the characterization of the large-scale brain network with a higher spatial resolution ($>$ 3 mm isotropic) and thus brings us closer to map the neuronal-level network of the human brain.

In this study, we constructed voxel-wise CBG network for a cohort of 20 patients with ALS and 21 normal controls. Using graph theoretical approach, voxel-wise nodal efficiency and global efficiency were calculated and compared between the two groups. Here, we hypothesized that patients with ALS would show decreased efficiency parameters within the CBG network, especially in the precentral gyrus, given that this region includes a large number of motor neurons [27], and plays important roles in motor function.

2. Materials and methods

2.1. Participants

Twenty patients (14 male, 6 female) with the diagnosis of sporadic probable or definite ALS were recruited from the Department of Neurology at Southwest Hospital, Chongqing, China. All the patients were diagnosed according to the revised El Escorial criteria of the World Federation of Neurology [9], whose exclusion criteria were the following: (1) family history of motor neuron diseases; (2) clinical diagnosis of frontotemporal dementia [28]; (3) presence of other major systemic, psychiatric, or neurological illnesses; and (4) cognitive impairment as determined by Montreal Cognitive Assessment (MoCA) score $<$ 26 [29]. Clinical status of the patients was assessed by the ALS Functional Rating Scale-Revised (ALSFRS-R) [30] within 12 h from MRI scanning. All patients had clinical signs of upper and lower motor neuron involvement, resulting 4 patients with bulbar onset, 15 with limb onset, and 1 with both bulbar and limb onsets [31]. The rate of disease progression was calculated by (48-ALSFRS-R)/time from symptom onset. Twenty-one (15 male, 6 female) gender- and age-matched normal controls with no previous history of neurological or psychiatric diseases and with normal brain MRI were recruited. The demographic and clinical characteristics of the ALS and normal controls were shown in Table 1. The research was carried out in accordance with the Code of Ethics of the World Medical Association. All the participants signed an informed consent according to the research protocol, which was approved by the Medical Research Ethics Committee of Southwest Hospital.

2.2. MRI data acquisition

The fMRI images were acquired using a 3T Siemens scanner (Trio; Siemens Medical, Erlangen, Germany) with an eight-channel head coil. During data acquisition, subjects were instructed to simply close their eyes, to avoid thinking of anything in particular, and to not fall asleep. The functional images were collected transversely using an echo planar imaging sequence with the following settings: repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, field of view = 192 mm × 192 mm, slices = 36, in-plane matrix = 64 × 64, thickness = 3 mm, slice gap = 1 mm, and voxel size = 3.0 mm × 3.0 mm × 3.0 mm. For each subject, a total of 240 vols were acquired, resulting in a total scan time of 480 s.

2.3. Resting-state fMRI data pre-processing

Imaging preprocessing was carried out using the MATLAB toolbox named Data Processing Assistant for Resting-State for “pipeline” data analysis of resting state fMRI (DPARSF, http://rfmri.org/DPARSF). For each participant, the pre-processing steps were: (1) the first 10 vol were discarded to allow for magnetization equilibrium; (2) the remaining 230 consecutive images were corrected for the acquisition delay between slices and for the head movement (subjects whose head motion parameters exceeding 1.5 mm in any dimension or 1.5° of angular motion through the resting-state run were excluded from further analysis. In current study, no participants were excluded based on this criterion); (3) all data were spatially normalized to the Montreal Neurological Institute (MNI) template and resampled to $3 \times 3 \times 3\ mm^3$; (4) linear trending and temporal band-pass filtering (0.01–0.08 Hz) were performed to reduce the effect of low-frequency drift and high-frequency noise; (5) nuisance signals, such as averaged signal from white matter, averaged signals from the cerebrospinal fluid, averaged signals from whole brain, and six motion parameters obtained by rigid body correction of head motion, were regressed out.

2.4. Construction of CBG network

As in previous studies [13,32,33], the CBG network was extracted as a mask containing Brodmann areas 1, 2, 3, 4, 6, PUT, GP and THA using WFU-pickAtlas package (Wake Forest University). Each voxel within the mask was defined as network nodes. Pearson correlation coefficient between the preprocessed time series of every two voxels within the CBG mask was defined as network edges. The correlation matrix was then binarized with a threshold obtained by false discovery rate (FDR) of $p < 0.05$.

2.5. Voxel-wise efficiency map of the CBG network

As previous studies suggested that the graphs to be compared must have the same number of nodes and the same number of edges, that is to say the same sparsity [34], we selected the minimum sparsity value (sparsity = 0.06529) as the final sparsity threshold across all the subjects to generate functional connectivity networks. The sparsity was defined as the ratio of the number of existing edges divided by the maximum possible number of edges in a network. Finally, the global and nodal efficiency were calculated using the brain connectivity toolbox (BCT, http://www.brain-connectivity-toolbox.net/). In the network G, the global efficiency was defined as:

$$E_{global} = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{L_{i,j}} \quad (1)$$

where N is the number of nodes, and $L_{i,j}$ is shortest path length between node i and j. The nodal efficiency was defined as the inverse of the harmonic mean of the shortest path length $L_{i,j}$ between node i and all other nodes in G: