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Disrupted functional connectivity of striatal sub-regions in Bell's palsy patients

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ABSTRACT

The striatum plays an important role in controlling motor function in humans, and its degeneration has the ability to cause severe motor disorders. More specifically, previous studies have demonstrated a disruption in the connectivity of the cortico-striatal loop in patients suffering from motor disorders caused by dopamine dysregulation, such as Parkinson's disease. However, little is known about striatal functional connectivity in patients with motor dysfunction not caused by dopamine dysregulation. In this study, we used early-state Bell's palsy (BP) patients (within 14 days of onset) to investigate how functional connectivity between the striatum and motor cortex is affected by peripheral nerve injury in which the dopamine system remains fully functional. We found a significant increase in the connectivity between the contralateral putamen, and the ipsilateral primary sensory (S1) and motor cortex (M1) in BP patients compared to healthy controls. We also found increased connectivity between the ventral striatum and supplementary motor area (SMA), and the dorsal caudate and medial prefrontal lobe in BP patients compared to healthy controls. Our results demonstrate that the entirety of the striatum is affected following acute peripheral nerve injury, and suggests that this disrupted striatal functional connectivity may reflect a compensatory mechanism for the sensory-motor mismatch caused by BP.

1. Introduction

The human striatum is a complex structure that belongs to the extrapyramidal system and is integral to motor, cognitive, and affective functions in humans. The various structures within the striatum such as the putamen, the caudate, and the ventral striatum have been found to play different roles in the brain. More specifically, previous neuroanatomical and neuroimaging studies of the human striatum suggest that the association cortex projects to the caudate, the sensorimotor cortex projects to the putamen, and the limbic area projects to the ventral striatum (Alexander et al., 1990; Vanderah and Gould, 2015; Draganski et al., 2008; Di Martino et al., 2008; Choi et al., 2012; Lehericy et al., 2004).

The striatum, especially the putamen, plays an important role in motor function, by adjusting the amplitude and velocity of muscle contractions through both the corticostriatal loop and the dopamine system (Loonen and Ivanova, 2013; Grillner et al., 2005). In some motor disorders, such as Parkinson's disease and Huntington's disease, degeneration of the central nervous system can cause a disorder of the dopamine system and affect the functional connectivity between the striatum and motor cortex (Hacker et al., 2012; Helmich et al., 2010; Kwak et al., 2010; Luo et al., 2014; Unschuld et al., 2012), thereby suggesting that the corticostriatal motor loop is impaired due to the reduced dopamine levels in the striatum (Helie et al., 2013). These results further prove that the striatum is a crucial region in motor function, and plays an important role in the development of motor diseases. In Parkinson's disease the lesion is directly in the striatum, which allows us to explore the function of the striatum, but limits our exploration of how the striatum modulates movement, especially when motor dysfunction occurs with a completely normal dopamine system.

Bell's palsy (BP) is the paralysis of the unilateral facial expression muscles caused by reactivation of the herpes virus in the facial nerve. This reactivation impairs the signaling from the motor cortex to the affected facial muscle, which results in the paralysis of the facial muscles. In turn, the sensory cortex detects that the facial muscles do not move,

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despite the motor cortex giving the muscle the command. We call this discrepancy the sensory-motor mismatch. Compared to other conditions such as Parkinson's disease, BP has fewer complications, fewer or no medications, and importantly, no effect on the dopamine system, thereby allowing researchers to explore the physiological function of the striatum following peripheral nerve injury (Vakharia and Vakharia, 2016). BP offers an ideal model to investigate how the striatum modulates motor function following peripheral nerve injury.

Recently, investigators have applied resting state functional connectivity (rsFC) analysis to sub-regions of the striatum (Di Martino et al., 2008). More recently, rsFC has also been used to investigate the pathological changes of different disorders such as Parkinson's disease, depression, autism, and obsessive-compulsive disorder (Di Martino et al., 2011; Felger et al., 2015; Gabbay et al., 2013; Hacker et al., 2012; Harrison et al., 2009; Helmich et al., 2010; Padmanabhan et al., 2013). The results obtained have significantly enhanced our understanding on the pathophysiology of these disorders and the function of the striatum.

In this study, we compared the rsFC changes in 12 sub-regions of the striatum (left and right side, each with 6 sub-regions), which were identified (Di Martino et al., 2008) and applied in previous studies (Kwak et al., 2010; Subira et al., 2016; Lin et al., 2015; Kerestes et al., 2015; Bell et al., 2015; Di Martino et al., 2011; Gabbay et al., 2013; Wang et al., 2017), in BP patients. Our objective was to explore if the rsFC between the striatum and the rest of the brain, especially the motor cortex, was similarly affected in BP patients as with patients with reduced dopamine levels in the striatum. We hypothesized that the functional connectivity between the striatum and other brain regions, especially between the putamen and motor cortex, would be increased at the contralateral side in BP patients. Additionally, we aimed to test if there was any disruption between the ipsilateral and contralateral striatum in BP patients. We hypothesized that the connectivity between the ipsilateral and contralateral striatum should also be moderately disrupted in the early stage of BP.

2. Method

2.1. Subjects

Twenty-five right-handed patients with left or right side Bell's palsy (House-Brackmann Scale ≥3, age 36 ± 7 years old ranging from 23 to 50, 15 males, 10 females, 14 right side facial paralysis) were recruited from the First Affiliated Hospital of Zhejiang Chinese Medical University. All patients with Bell's palsy onset of fewer than 14 days underwent an MRI scan (He et al., 2014). We recruited 25 age- and gender-matched healthy controls. No participants had a history of physical or mental disorders. The study was approved by the ethics committee of the First Affiliated Hospital of Zhejiang Chinese Medical University.

2.2. fMRI imaging acquisition

All scans were performed with a 3.0 Tesla MR scanner (Magnetom Verio, Siemens, Germany) in order to obtain T1-weighted structural images and echo-planar T2*-weighted images (EPI). Structural images were obtained by MP-RAGE sequence: TR = 1900 ms, TE = 2.45 ms, FA = 9 degrees, voxel size = 1 × 1 × 1 mm, matrix = 256 × 256. Two hundred time points of functional resting state data were acquired by EPI session: TR = 2000 ms, TE = 30 ms, FA = 90 degrees, slices = 33, voxel size = 4.0 × 4.0 × 4.0 mm, matrix = 256 × 256. All subjects were required to keep their eyes open during the scan.

2.3. fMRI data preprocessing

Before any processing, all patients with left-side Bell's palsy and their matched healthy controls were flipped along the y-axis (R-L flip) in order to directly compare them to the patients with right-side Bell's palsy (Klingner et al., 2014).

Functional MRI data analysis was carried out by applying a seed-based approach using the CONN toolbox v15.g (Whitfield-Gabrieli and Nieto-Castanon, 2012) (http://www.nitrc.org/projects/conn). Similar to our previous study (Tao et al., 2016), the preprocessing of fMRI data was performed using Statistical Parametric Mapping (SPM8) (Welcome Department of Cognitive Neurology, University College, London, UK) in MATLAB (Mathworks, Inc., Natick, MA, USA). The preprocessing steps included realignment, coregistration of subjects' respective functional and structural images, normalization, and smoothing with an 8-mm full width at half maximum (FWHM) kernel. In addition to these steps, we employed segmentation of gray matter, white matter, and cerebrospinal fluid (CSF) areas in order to remove temporal confounding factors (Whitfield-Gabrieli and Nieto-Castanon, 2012). Band-pass filtering was performed with a frequency window of 0.008–0.9 Hz.

To eliminate correlations caused by head motion and artifacts, we identified outlier time points in the motion parameters and global signal intensity using ART (http://www.nitrc.org/projects/artifact_detect). For each subject, we treated images as outliers if composite movement from a preceding image exceeded 0.5 mm, or if the global mean intensity was >3 SDs from the mean image intensity for the entire resting scan. Outliers were included as regressors in the first-level General Linear Model along with motion parameters.

2.4. Functional resting state connectivity analysis

We used six striatum sub-regions in each hemisphere as 3 mm spherical seeds. The centers of the seeds were: dorsal caudal putamen (DCP, NMI coordinate, ±28, 1, 3), dorsal rostral putamen (DRP, ±25, 8, 6), ventral rostral putamen (VRP, ±20, 12, −3), dorsal caudate (DC, ±13, 15, 9), inferior ventral striatum (VSi, ±9, 9, −8), and superior ventral striatum (VSs, ±10, 15, 0) (Di Martino et al., 2008). Seeds were selected using WFU-Pick Atlas software (Maldjian et al., 2003) according to NMI coordinates.

First-level correlation maps were produced by extracting the average BOLD time course from each striatum seed and by computing Pearson's correlation coefficients between that time course and the time courses of all other voxels in the brain. Correlation coefficients were Fisher transformed into “Z” scores, which increased normality and allowed for improved second-level General Linear Model analyses.

A whole brain group analysis was performed using two-sample *t*-tests to compare changes in the 12 striatal sub-regions' functional connectivity between the healthy control group and the BP patient group. To explore the association between the observed clusters and the House-Brackmann Scale (HBS) scores of the BP patients, we extracted average Fisher z-values for the survived clusters and performed multiple regression analyses across all patients using SPSS 18.0 Software (SPSS Inc., Chicago, IL, USA). Age, gender, and duration of onset (days) were included in the analysis as covariates of non-interest. A threshold of voxel-wise $p < 0.005$ uncorrected and cluster-level $p < 0.05$ family wise error (FWE) correction was applied to all fMRI data analyses.

In addition, we also calculated the functional connectivity between the 12 (6 × 2 hemispheres) seeds to explore the network change within the striatum between the healthy controls and patients. We applied a threshold of $p < 0.05$ FDR (false discovery rate) corrected.

3. Results

3.1. Behavioral results

All patients' had lost their left or right facial muscle function due to BP, with HBS grades ≥3. The MR scan was performed 3–14 days after onset.