学 位 論 文 の 要 旨

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学位論文名　Altered Resting-state Functional Connectivity of the Frontal-striatal Circuit in Elderly with Apathy

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論 文 内 容 の 要 旨

INTRODUCTION

Apathy is defined as a state of diminished motivation and goal-directed behavior, not attributable to decreased level of consciousness, cognitive impairment or emotional distress. Investigations of apathy mainly in neuropsychiatric diseases have been tried to explain its neural substrate with anatomical and functional alterations of brain circuits using different neuroimaging modalities. The previous results suggest that abnormalities within frontal-striatal circuits are relevant to apathy in the clinical population. Although apathy is also observed in older adults with normal cognitive function, only a few neuroimaging studies have attempted to cope with apathetic state in healthy elderly adults. Therefore, it remains unclear whether the neural bases of apathy in normal aged people is the same as those in the neuropsychiatric groups.

In this study, we used resting-state functional MRI (rs-fMRI) technique to assess the frontal-striatal circuit characteristics in elderly people. Rs-fMRI delineates functional connectivity between distant brain regions based on synchronized low-frequency fluctuations of blood oxygen level dependent (BOLD) signal. It has been widely used in both healthy subjects and patients with various neurogenetic and neuropsychiatric disorders. We applied region of interest (ROI)-based analyses for detecting distinct patterns of functional connectivity with/within the striatum. Twelve seeds placed throughout the striatum, six in each hemisphere.

We aimed to investigate the underlying mechanism of apathy focusing on the frontal-striatum circuit disfunction in healthy subjects by the analyses with the multiple seeds in the striatum, and located the alterations of interaction and organization among the different frontal-striatum circuits in the elderly with apathy.

MATERIALS AND METHODS

The study protocol was approved by the Research Ethics Committee of Shimane University. We recruited subjects who voluntarily participated in the brain checkup system at Shimane Institute of Health Science, Izumo City, Shimane Prefecture, Japan. Apathy level was evaluated with the Japanese version of the Apathy Scale (AS). Eighteen subjects with apathy (7 female, 63.7 ± 3.0 years) and eighteen subjects without apathy (10 female, 64.8 ± 3.0 years) who underwent neuropsychological assessment and cranial MRI measurement were included. We performed 5-minute rs-fMRI scan as functional scans and measured T1-weighted structural images of the whole brain.

SPM12 was used for MRI data preprocessing. We adopted 12 striatum seeds and each seed was as follows: the inferior ventral striatum (VSi) (± 9, 9, -8), superior ventral striatum (VSs) (± 10, 15, 0), dorsal caudate (DC) (± 13, 15, 9), dorsal caudal putamen (DCP) (± 28, 1, 3), dorsal rostral putamen (DRP) (± 25, 8, 6), and ventral rostral putamen (VRP) (± 20, 12, -3). The bilateral pairs of seeds were combined into a single ROI in ROI-to-voxel analysis. In ROI-to-ROI analysis, all 12 seeds were independently considered as ROIs.

Data analyses were carried out using the CONN toolbox. In the first-level analysis, we obtained ROI-to-voxel functional connectivity maps for each individual subject. This analysis produced z-score maps of positive and negative correlation coefficients for 6 striatal seeds and whole-brain voxels, combining homologous left and right ROIs to one seed. We also conducted an ROI-to-ROI analysis to examine functional connectivity between 12 ROIs within the striatum for each subject. In the second-level analysis, at first, we conducted one-sample t-test of whole brain functional connectivity for 6 striatal ROIs across 36 participants to acquire the functional connectivity map. Then, to assess the differences in functional connectivity between the apathy and non-apathy group, we conducted two-sample t-test controlling for confounding factors including age and sex with the statistical threshold at the voxel level of $p < 0.001$ and the cluster level of $p < 0.05$ for FDR. Moreover, we added a group comparison of the ROI-to-ROI analysis for the purpose of examining functional connectivity among 12 striatal ROIs with FDR correction of $p < 0.05$.

RESULTS AND DISCUSSION

Demographic data showed that there were no significant differences between the apathy and non-apathy group in age, sex, educational status, and cognitive test scores. The apathy group's mean depression score was higher than the non-apathy group.

The seed-to-voxel group analysis for functional connectivity between the striatum and other brain regions showed that the connectivity was decreased between the VRP and the right dorsal anterior cingulate cortex (dACC)/pre supplementary motor area (SMA) in the apathy group compared to the non-apathy group while the connectivity was increased between the DC and the left sensorimotor area. We also performed ROI-to-ROI analysis within the striatum and compared the functional connectivity between two groups. Compared with the non-apathy group, the apathy group showed reduction of functional connectivity between the right VSs and right DCP, the VSi and dorsal striatum and the right VSi and left DC.

The dACC has been considered to be an important component of the frontal-striatal circuit model. Cumulative evidence suggests that it is associated with self-generated movement or goal-directed behavior. The SMA is considered as a part of the motor-related areas on the medial surface of cerebral hemisphere. The pre SMA is involved in more complex motor and cognitive process associate with goal-directed behavior. Recent conceptual framework of cortico-striatal circuit has speculated that the connections between functionally different frontal areas involved in emotion, cognition and motor function and the striatum are segregated and overlapped, and their interactions enable to carry out goal-directed actions. The projections of the striatum are topographically organized, such that the ventromedial area of striatum is connected to the limbic frontal area, the dorsolateral area of striatum is connected to the motor-related frontal area, and the intermediate area of striatum is connected to the dACC and the pre SMA, which is related to cognitive process. Our study showed that people with apathy had decreased functional connectivity between the dACC/ the pre SMA and VRP which is corresponded to the ventromedial area of striatum.

Furthermore, the current study demonstrated increased functional connectivity between the DC and sensorimotor area in people with compared with people without apathy. The DC is located in dorsal area of the striatum, and is connected to cognitive prefrontal areas like dorsolateral prefrontal cortex. Our result also suggests that functional dysfunction in the cognitive system in apathy could activate motor function area for compensation.

Another finding of the present study was the reduction of functional connectivity among ROIs within the striatum in the apathy group compared to the non-apathy group. Compared with the non-apathy group, the apathy group showed reduction of functional connectivity between the ventral regions of the striatum (including the VSi and the VSs) and the dorsal regions (including the DC and the DCP).Our result, together with other studies, suggests that apathetic state may be attributed to changes of the balance between dorsal and ventral striatum network.

CONCLUSION

Our findings showed that apathetic state in aged people was associated with altered resting-state functional connectivity with/within the striatum, specifically decreased functional connectivity of the striatum with emotional and cognitive frontal-striatal circuits, and between ventral and dorsal regions within the striatum. These results suggest that alteration of interaction and organization among different frontal-striatum circuits contributes to apathy in elderly.