学 位 論 文 の 要 旨

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学 位 論 文 名　Gray Matter Volume Changes in the Apathetic Elderly

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論 文 内 容 の 要 旨

INTRODUCTION

Apathy is defined as lack of motivation, which is not caused by consciousness disturbance, cognitive impairment or emotion distress, and it can cause dysfunctions in elaboration, execution and management of goal-directed behaviors. Nowadays apathy becomes an increasingly frequent neuropsychiatric symptom, which could not be ignored in clinical scene. It occurs not only in neurodegenerative disease such as Parkinson disease (PD), Huntington's disease and progressive supranuclear palsy (PSP), but also stroke, dementia, brain injury, depression and malnutrition. Studies have shown that it does influence on patients' quality of life and recovery from diseases. In addition, to patients suffering from apathy, there are also large numbers of healthy old who are struggling with it. But there are few studies on apathy in healthy subjects without related organic diseases. Although the mechanism is still not clear, prefrontal-basal ganglia system is thought to play a key role in apathy. Most lesion studies located prefrontal cortex or basal ganglia as target regions responsible for apathy symptoms. Recently, there is only one study on apathetic healthy to the best of our knowledge, and they did not find changes in the basal-ganglia except frontal, temporal lobes and thalamus. Here we want to explore whether apathetic healthy subjects showed any structural changes in the brain including within the prefrontal-basal-ganglia system.

MATERIALS AND METHODS

Participants were selected from brain doc database with 445 subjects, who participated in health screening at the Shimane Institute of Health Science from the year 2007 to 2013. The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was obtained from all subjects. We got 36 subjects with the inclusive criteria

(They should have no history of neurologic or psychiatric conditions such as cerebrovascular disease, dementia, depression, or other psychiatric illnesses. The corresponding ages ranged from 60 to 70 years old. The MRI did not show any brain lesions including silent brain lesions, silent brain infarctions, pathological white matter lesions, and microbleeds.), and divided them into two groups (apathy group and non-apathy group) according to the apathy score, and each group had 18 people. The 1.5 T MRI T1 images were used for Voxel-based morphometry (VBM) analysis. And here we used VBM with diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL), an improved VBM analysis method, which can achieve more accurate inter-subject registration, realignment of small deformations, and better spatial normalization. The main steps of the analysis were including manual reorientation, segmentation, creating template using DARTEL, being changed into MNI space, normalization and spatial smooth operation. The whole brain analysis between groups was performed first using age and gender as covariates of no interest. And later we added self-rating depression scale (SDS) scores as covariates in order to look for the regions changes without the influence from it.

RESULTS AND DISCUSSION

There were no significant differences of age and gender ratio between apathy and non-apathy groups (ps>0.05). But depression score and apathy score between two groups had significant difference (ps<0.05) and correlated with each other (r=0.58, p<0.001). The depression scores of our subjects were in the normal range according to our severity classification (0–39 normal, 40–59 suspected depressive, and 60–80 possible to be depression). It might indicate that apathy and depression share similar brain mechanisms reported in some studies. But in the second part of our analyzing results indicated that apathy could happen independently, which was referred to in previous studies.

In the VBM analysis regarding the whole brain, significant gray matter volume changes were found in four clusters (p uncorrected <0.01 with the number of voxels more than 100). They were bilateral inferior frontal gyrus, left inferior occipital gyrus and right putamen. Our results showed that in the first three regions the gray matter volume increased in apathy group compared with non-apathy group, while the gray matter volumes of putamen decreased in apathy group. The regions in frontal lobe and occipital lobe had been already reported in the previous studies of the patients of apathetic Parkinson's disease and amyotrophic lateral sclerosis, but the gray matter volume decreased in the apathetic group. These findings for neurological diseases are intriguing because the patterns of structural changes associated with apathy are in part opposite to our pattern for healthy participants. In our healthy participants, the regions with the gray matter volume changes might be responsible for apathy symptoms.

For the healthy elderly, there might be a lot of factors which could affect the execution behavior which related with the two regions, for example, they still have work or take part in some social activities, so that the results would be different from the patients. Gray matter volume reduction of putamen in apathy group was in line with the studies of apathy on blood flow and metabolism of basal-ganglia in Parkinson's disease and stroke. Putamen had been proved to be related to action-reward association learning and storage of motor memories. For apathetic people, they might get the disturbance of these functions and appeared to be lack of goal-directed behavior.

In major depression and neurodegenerative diseases such as AD and PD, apathy and depression were associated with each other in the structural changes of the brain. The results of the next analysis showed that without the affection of depression score, we only got the significant difference between groups was in the right precentral gyrus (p uncorrected <0.01 with the number of voxels more than 100). Compared with non-apathy group, apathy group had decreased gray matter volume in this region. The result that apathetic symptoms were associated with the gray matter volume changes in the right precentral gyrus we got was in line with the VBM study on apathy in PD, which presented significant negative correlations between gray matter volumes and apathy scores in the bilateral precentral gyrus. In a study of rCSF in AD between apathy group and non-apathy group, the reduction of rCSF was found in bilateral precentral gyrus, which could be in support of our finding here. In a task-based study of planning performance in patients with schizophrenia, the precentral gyrus of patients with high level of apathy showed lower task-related activation than healthy control. Thus, our researching results expand the previous studies and are in line with the notion that apathy and depression have a different neuroanatomical basis. This point was already reported by previous studies in neurodegenerative diseases, while we got the same view in healthy elderly.

CONCLUSION

The identification of regions affected in the apathetic healthy old is very important in the mechanism underlying brain pathological changes inside brain with apathy symptoms, because more and more studies have proved that apathy could be the sub-clinical symptom of the diseases which are very serious and common to old people such as dementia, PD, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and stroke. Also, it would be one key potential biomarker for predicting the development period of the stages of cognitive impairment to AD, and PD, which will be helpful to the treatment plan. Our work is also quite meaningful for the diagnosis and treatment of apathy and depression due to their very different medication plans, and it would also make reference for the mechanism of the symptoms which will affect people's life quality seriously.