学位論文の要旨

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学　位　論　文　名　Multiscale Entropy of Resting-state Functional Magnetic Resonance Imaging Differentiates Progressive Supranuclear Palsy and Multiple System Atrophy

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論文内容の要旨

INTRODUCTION

Progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) are neurodegenerative diseases with diverse brain pathologies: PSP is characterized by tau filaments with four repeats, globular neurofibrillary changes, and glial fiber changes in the astrocytes and oligodendrocytes; conversely, MSA is characterized by fibrillar inclusions of α-synuclein (termed glial cytoplasmic inclusions) in the oligodendrocytes. However, both of their gross pathological features display atrophy in common regions, such as the brainstem, cerebellum, basal ganglia, and frontal lobe, which represent the structural basis for clinical magnetic resonance imaging (MRI) examination. Distinguishing progressive supranuclear palsy (PSP) from multiple system atrophy (MSA) in the early clinical stages is challenging; few sensitive and specific biomarkers are available for their differential diagnosis.

Recently, the resting-state functional MRI (rs-fMRI) technique using spontaneous neuronal activity has revealed functional brain networks. Regions that are functionally related or co-activated during a cognitive task display temporally correlated activities at rest. Spontaneous neuronal activities are estimated by slow fluctuations in the blood oxygen level-dependent (BOLD) signals, and functional neural networks are represented by spatial maps of the correlations of the aforementioned signal fluctuations between anatomically separate brain regions. These highly correlated brain regions are functionally connected, and the strength of their connections is represented by the

correlation values between specific regions. Functional connectivity is reportedly associated with the severity of dementia and aging-related illnesses, and cognitive decline. We aimed to examine whether rs-fMRI data could differentiate between PSP and MSA via a multiscale entropy (MSE) analysis of BOLD signals, which estimates the complexity of temporal fluctuations in brain activity.

MATERIALS AND METHODS

We recruited 14 patients with PSP and 18 with MSA who had been referred to the Department of Neurology at the Shimane Medical University Hospital. All patients had one or more symptoms of parkinsonism, cerebellar ataxia, postural retention disorders, dementia, and visited Shimane Medical University Hospital for diagnosis and scrutiny. They were evaluated by neurologists specializing in neurodegenerative diseases and were clinically diagnosed with PSP or MSA.

All patients were assessed using neuropsychological test batteries, including the Mini-Mental State Examination (MMSE), frontal assessment battery (FAB), self-rating depression scale (SDS), and Apathy Scale (AS). We used a General Electric 3.0T scanner to acquire the brain MRI data. First, all patients underwent rs-fMRI examinations for a total of 5 min, and were instructed to stay awake, relax, and remain calm with their eyes closed during the examination. We conducted an ROI-to-ROI analysis to examine the differences in functional connectivity between PSP and MSA. To define the brain nodes, we used an automated anatomical labeling (AAL) atlas to divide the entire brain, except the cerebellum, into 90 regions. The average time courses of the voxels in each region were extracted, and a network was constructed. In addition to the Complexity Toolbox (http://loft-lab.org/index-5.html) was used to calculate the MSE of the rs-fMRI data.

We performed analyses of covariance with the age, sex, and measurement period as covariates to compare the entropy maps of each scale between the PSP and MSA groups. All statistical analyses were performed using IBM SPSS Statistics version 26 (IBM, Armonk, NY, USA). The study protocol was approved by the Research Ethics Committee of Shimane University.

RESULTS AND DISCUSSION

PSP patients demonstrated greater cognitive function impairments, particularly in the frontal executive function. The mean disease duration was slightly longer for patients with MSA than were those for patients with PSP; however, the difference was not significant. We also estimated the incidence of silent brain infarction, cerebral microbleeds, periventricular hyperintensity, and deep and subcortical white matter hyperintensity, and did not observe significant differences in these pathological MRI findings between the groups.

We conducted ROI-to-ROI analysis, which is one of the basic analyses for rs-fMRI data, to assess the functional connectivity between the multiple brain regions. We compared the functional connectivity matrix of 90 regions between PSP and MSA based on the AAL atlas. Both groups demonstrated similar functional connectivity maps in the group-level analysis. There were no significant differences in the connectivity patterns between the groups in the network-based analysis.

We subsequently compared the MSE between the groups. For all scales, the entropy of the frontal, temporoparietal junction, and medial regions were relatively higher than those of the other regions. A comparison of the entropy between the groups revealed a robust decrease in the entropy in the bilateral prefrontal cortex for PSP. Furthermore, we performed correlation analyses between the MSE values and neuropsychological test scores. Correlation analyses revealed an association between the entropies in the prefrontal cortex and cognitive function. .

Despite no clear difference in the brain network types affected by PSP and MSA with the ROI-to-ROI or network-based analyses of BOLD signals at rest, our study demonstrated a significant difference between the two diseases in the entropy analysis, where signal complexity was considerably reduced in the bilateral prefrontal cortex in PSP compared to that observed in MSA. In particular, the right lateral prefrontal cortex displayed a significant decrease in complexity in patients with PSP in multiple time window ranges. Furthermore, neuropsychological test scores, particularly the FAB score, positively correlated with the entropy value in the prefrontal cortex. The reduced complexity of BOLD signals in the prefrontal cortex in patients with PSP was associated with low FAB scores. Our results support the previously established significant relationship between cognitive function and the complexity of BOLD activity at rest. Thus, our study indicates that an MSE analysis of rs-fMRI could differentiate between PSP and MSA, and the reduced complexity of BOLD signals could be associated with cognitive impairment. In particular, a subtle and subclinical functional brain impairment could be identified by the entropy analysis, leading to help clinical differential diagnosis.

CONCLUSION

MSE analysis of rs-fMRI could differentiate between PSP and MSA, and the reduced complexity of BOLD signals could be associated with cognitive impairment. Patients with PSP exhibited reduced complexity of signals compared to those of patients with MSA, and this reduction was associated with greater impairment of frontal executive function.