学 位 論 文 の 要 旨

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学 位 論 文 名　Altered Feedback-Related Negativity in Mild Cognitive Impairment

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論 文 内 容 の 要 旨

INTRODUCTION

Mild cognitive impairment (MCI) is a condition in which a person experience memory issues and mild cognitive deficits without meeting the criteria for dementia. Around 50% of MCI patients develop dementia in 5 years, with 10–15% progressing to Alzheimer's disease (AD) annually. Although intact daily functioning is a criterion for MCI, recent studies have revealed difficulties in complex daily tasks for MCI patients. This study focuses on the executive functions which are critical to goal-directed behavior. Feedback-related negativity (FRN) is a key indicator of brain processes in executive functions. FRN is generated by external feedback and has been studied in relation to age, with changes observed in the elderly. A previous study found delayed FRN latency and increased amplitude in mild Alzheimer's disease (AD) patients. The current study aims to examine FRN changes in MCI, hypothesizing similarities to AD due to MCI as a prodromal stage of AD.

MATERIALS AND METHODS

Thirteen amnestic mild cognitive impairment (MCI) patients (MCI group) and thirteen age-matched healthy elderly volunteers (HC group) were examined. The MCI

patients were diagnosed based on Petersen's criteria, which include a clinical dementia rating (CDR) score of 0.5, a memory score of 0.5 or 1 on CDR, and an MMSE score between 24 and 30 points. The healthy controls had a CDR of 0 and an MMSE score above 27 points. All participants had normal vision and underwent neuropsychological assessments, including the frontal assessment battery, self-rating depression scale, and apathy scale. During EEG recording, participants completed a gambling task in which they chose between two squares for potential rewards. The EEG data were analyzed for event-related potentials (ERPs), with a specific focus on FRN. Statistical analyses included t-tests, repeated-measure ANCOVA, and partial correlation analyses. The study aimed to investigate changes in FRN among individuals with MCI during the gambling task. The study protocol was approved by the Research Ethics Committee of Shimane University. (No. 20100526-1)

RESULTS AND DISCUSSION

The groups with amnestic MCI and HC had similar age and gender distributions. However, MCI patients had significantly lower scores on the mini-mental state examination (MMSE) and frontal assessment battery (FAB) compared to the HC group. The apathy score was higher in the MCI group, while depression scores were comparable. Reaction time to choice stimuli did not differ between the two groups. The analysis of event-related potentials (ERPs) showed that MCI patients had a more negative shift in the feedback-related negativity (FRN) waveform than the HC group in response to loss conditions. The difference in FRN amplitude between the two groups was significant, with MCI patients showing a more negative peak. However, there were no significant differences in FRN peak latency. Partial correlation analyses revealed a slight correlation between FRN amplitude and MMSE score, indicating that lower MMSE scores were associated with a more negative FRN amplitude. However, this correlation diminished when accounting for group differences. No significant correlations were found between FRN measures and other neuropsychological measures (FAB, SDS, and AS scores).

In this study, it was revealed that a significant increase in FRN amplitude in amnesic MCI presumed to have AD pathology. The hypothesis that FRN would already be elevated in MCI due to increased FRN amplitude in mild AD patients was supported. This suggests a link between the change in FRN amplitude and cognitive impairment with the neurodegenerative process rather than simple aging. FRN, involved in monitoring one's behavior, may be uniquely affected by neural degeneration compared to other cognitive functions.

A plausible explanation for this finding is that the increased FRN amplitude is

generated by the phase reset of the elevated slow waves. EEG studies of AD and MCI have shown a common increase in slow waves, suggesting an underlying network dysfunction in patients with cognitive impairment. Another explanation is a compensatory mechanism for cognitive decline, supported by fMRI and neuropathological studies. The frontal cortex, which is responsible for monitoring functions, may undergo a compensatory response and explain the increased FRN amplitude in MCI. The positive correlation between FRN amplitude and MMSE supports this interpretation, but further validation is needed. In addition, the emotional response during the task, particularly to negative feedback, may contribute to the increased FRN amplitude. The latency of the FRN was not delayed in MCI, suggesting that changes in neural activity to negative stimuli precede a decrease in processing speed. Limitations include small sample size, uncertainty about MCI pathology, and the need for longitudinal follow-up to confirm underlying Alzheimer's pathology.

CONCLUSION

In conclusion, our findings suggest that MCI patients also had augmented neural activity evoked by negative feedback information, possibly reflecting an intact neural reserve mechanism against cognitive deterioration. The alteration in FRN amplitude could be a good biomarker for the early detection of dementia, and this study provided one of the cornerstone findings.