学 位 論 文 の 要 旨

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学　位　論　文　名　Enhanced Feedback-Related Negativity in Alzheimer's Disease

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論 文 内 容 の 要 旨

INTRODUCTION

Executive function is a set of cognitive processes including attentional control, working memory, and planning, and so on, and is necessary for selecting and successfully monitoring behavior. Monitoring is a part of the executive function, and is the ability to monitor one's own actions and responses during task performance in order to detect and correct errors. Alzheimer's disease (AD), the most common cause of dementia in the elderly, results in the impairment of executive function, including that of performance monitoring.

Feedback-Related Negativity (FRN) is a neurophysiological index that reflects the monitoring process associated with feedback inputs, and is generated from the anterior cingulate cortex. FRN is elicited by feedback stimuli (particularly negative stimuli) in a gambling task or a time production task. This negative potential appears at a latency of 200 to 300 ms after feedback stimuli and is primarily distributed over the frontal-central scalp area. Many studies have revealed that FRN amplitude is reduced and its latency prolonged in the elderly compared to that in young individuals, which means that the elderly is impaired in monitoring process and it might cause cognitive decline.

Based on the prior aging studies, we hypothesized that FRN would decrease in AD patients, and we investigated the monitoring system of AD patients using FRN in a gambling task.

MATERIALS AND METHODS

Twenty-four patients with Alzheimer's Disease (AD; 15 males, 9 females, age range from 66 to 75, mean age = 71.5, SD = 2.8), twenty healthy older subjects (HO; 13 males, 10 females, age range from 62 to 79, mean age = 69.6, SD = 6.0), and nineteen healthy young subjects (HY; 10 males, 9 females, age range from 19 to 28, mean age = 22.2, SD = 2.2) participated in this study. The AD patients met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and

Related Disorders Association (NINCDS/ADRDA) criteria for individuals with AD. Participants in the HO and HY groups had no history of neurological or psychiatric diseases. The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was obtained from all subjects.

AD and HO participants were assessed using neuropsychological test batteries that included the Mini Mental State Examination (MMSE), the Frontal Assessment Battery (FAB), the Word Fluency Test (WFT; vegetable for the semantic category), the Self-rating Depression Scale, and the Apathy Scale (AS).

Each participant performed a simple gambling task. The experiment consisted of 120 trials (two blocks of 60 trials each). The probabilities of winning and losing for each trial was equal (50%), and this was same in all three groups. Participants were told that they would be participating in a virtual game; they were instructed to try to maximize their monetary rewards.

The electroencephalogram (EEG) was obtained from 21 electrodes at the positions of the international 10-20 system. Horizontal and vertical electrooculograms (EOG) were recorded at sites lateral to the left and right outer canthi, and above and below each eye. In addition, each participant's reaction time (RT) was measured simultaneously with the EEG recording.

EEG data were analyzed off-line, and EEG epochs were extracted beginning 200 ms before and ending 800ms after the presentation of feedback for win and loss conditions, separately. A baseline was set at the duration of 200 ms prior to feedback stimulus onset. ERP peak amplitude and latency were derived from each individual's average waveform. The FRN was semi-automatically measured as the most negative peak within the time window of 150 to 400 ms after feedback presentation, and was finally identified by visual inspection.

We conducted t-tests on the demographic and neuropsychological data to allow comparison of AD and HO, and compared the switching ratios between preceding negative and positive feedback using paired t-tests in each group. A one-way ANOVA was used to analyze the RT data, and a two-way repeated measures ANOVA (group x channel, or group x feedback condition) was performed (separately) for the amplitudes and latency of ERP components. The statistical criterion was set at a p value of less than 0.05, and Tukey method analysis was used for post-hoc tests. Partial correlation analyses were also conducted to examine the relationships between the ERP components and the neuropsychological data.

RESULTS AND DISCUSSION

There were no significant differences in age and gender ratios between AD and HO. However, independent t tests revealed that there were significant differences between AD and HO on the cognitive function scores (MMSE, FAB, WFT), and that AD showed reduced cognitive function compared to HO (ts (45) > 5.0, ps < 0.001). However, affective function scores did not differ between those groups (ts (45) < 1.9, ps > 0.068). RT in the gambling task was delayed significantly in AD and HO compared to that in HY (ps < 0.001). Switching response ratio was higher for following negative feedback than positive feedback in every three groups (ps < 0.05).

The FRN in the AD group showed larger amplitude and prolonged latency compared to that in the HO group. However, the FRN amplitude in HY group was almost the same as that in the AD group, but its latency was shorter than in the latter group. Finally, HO showed smaller FRN amplitude and delayed latency compared to HY. The ANOVA revealed that the main effect of group for amplitude was significant (F (2, 63) = 4.1, ε = 0.69, p = 0.021). Post-hoc tests indicated the amplitude in AD was significantly larger than that in HO (p = 0.015). However, the main effect of channel did not reach significance (F (2, 63) = 3.0, ε = 0.69, p = 0.053), nor was interaction of group by channel significant (F (4, 126) = 1.2, ε = 0.69, p = 0.296). Regarding the latency, the main effects of group and channel were significant (Fs (2, 63) > 6.3, ε = 0.73, ps < 0.003). Post-hoc tests denoted that the latency was prolonged significantly in AD compared to HY (p = 0.002), although there was no significant interaction of group by channel (F (4, 126) = 0.7, ε = 0.73, p = 0.602).

The aim of this study was to examine the changes in the monitoring system of AD patients and healthy control participants (HO) during gambling tasks using FRN. Results reveal that the AD group showed a larger amplitude and a delayed latency of FRN compared to the HO group. This study revealed electrophysiological abnormalities of the monitoring function in AD. The original hypothesis relating to changes in FRN for the AD group was based on prior evidence of aging effects on FRN. Many researchers have reported decreases in FRN amplitude associated with aging, and our results also replicated this aging effect. However, the increased amplitude of FRN in AD was unexpected, and it is the opposite to predictions derived from the original hypothesis. We speculate that this may reflect the existence of a compensatory mechanism against the decline in executive function.

Also, there was a significant association between FRN amplitude and depression scores in AD, and the FRN amplitude tended to increase insomuch as the SDS was higher. This result suggests the existence of a negative bias in the affective state in AD. Thus, the impaired functioning monitoring system in AD is a more complex phenomenon than we thought.

CONCLUSION

The present study demonstrated that the FRN in AD patients showed larger amplitude and delayed latency compared to age-matched controls, and correlated with depressive tendency. This indicates that enhanced monitoring response in AD patients might reflect a compensatory mechanism and/or negative bias in outcome evaluation. Psychophysiological measures in the feedback process could provide a clue to understand the neurobehavioral changes in AD patients.