Gamma oscillatory activity in relations to memory impairment

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ABSTRACT

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in relation to memory impairment

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Human gamma-band activity over 30Hz is thought to reflect attention, memory and higher cognitive processes. It has been widely reported that the gamma band shows increased activation during tasks involving memory, but it is not clear whether gamma oscillations truly reflect memory ability. We investigated the gamma oscillation changes during the maintenance phase in memory tasks and analyzed the differences between amnestic and multiple domain mild cognitive impairment (MCI, n=16) subjects and controls (CTR, n=19). Verbal and spatial delayed match to sample tasks were performed with simultaneous EEG recording and we specifically looked for gamma event-related desynchronization (ERD) during maintenance phase. There were no significant differences between the two groups in verbal delayed match to sample task. In spatial delayed match to sample task, gamma-ERD was stronger in controls than MCIs, and it was significantly correlated with memory ability scores and behavioral performance. We then investigated the gamma oscillation during memory tasks and its correlation with clinical measures of memory. Our result suggested that gamma oscillations reflect not only brain activity related to memory processes, but also the memory ability of subjects, with lower gamma oscillation activity reflecting greater efficiency of information processing. Gamma band activity may be a potential bio-physiological marker of memory function.

Key words: Gamma oscillation, ERD (Event-related desynchronization), Memory, Mild cognitive impairment.

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I. INTRODUCTION

Rhythmic synchronization of neural discharges in the gamma band over 30Hz may provide the necessary spatial and temporal information that link together processing in different brain areas to build a concept of coherence. Human gamma-band activity (GBA) is thought to be a sign that synchronized cortical networks exist that are involved in the generation of mental representations. Oscillatory activity in this area is generated by networks of interconnected GABAergic interneurons.[2]

Event-related modulation can be quantified by event-related desynchronization (ERD) and event-related synchronization (ERS), relating to a relative decrease or increase in oscillation power respectively after a stimulus compared to baseline.[3] Gamma ERS has been proposed as a physiological indicator of attention, memory, coherent perception, and higher cognitive functions.[1] Fewer studies investigate gamma ERD than gamma ERS, but some recent studies report that it may reflect activation of language processing.[4-6] Gamma ERD is also thought to reflect the continuous and parallel activities of neuronal networks within areas or between separation areas.[6]

Traditionally, recent or working memory is thought to involve both central executive processes, governing encoding and retrieval of information, and active maintenance of information in sensory buffer or “slave” systems. Both single-cell recording studies and brain imaging studies have demonstrated working memory-dependent activation of prefrontal and posterior brain regions. In line with these findings, GBA during recent memory of visual objects was located under occipito-temporal and frontal electrodes.[7] The posterior activity was interpreted as reflecting the rehearsal of the stimulus representation, whereas the frontal GBA may have indicated active maintenance processes.[8] Apparent representation of the spatial position of a sound source is associated both with synchronization of networks in parietal areas involved in the auditory dorsal stream and with increased coupling between networks serving representation of audio-spatial information and frontal executive systems.[9]

It has been widely reported that gamma activity reflects memory processes.[1,7,8,10] However it is still unclear whether gamma oscillations are related to memory ability or are able to reflect memory impairment. Current evidence suggests that EEG values such as theta activity,[11] alpha activity[12] and synchronization likelihood[13] may reflect memory ability, therefore gamma activity may be also a useful value.

Memory impairment is considered one of the first signs of dementia. The criteria of mild cognitive impairment (MCI) are as follows: memory disturbance preferably corroborated by an informant, objective memory impairment for age and education, normal general cognition, preserved activities of daily living, and not demented. Neuropsychological testing can also assist in the diagnosis of MCI.[11] In this study, we especially focused on amnestic and multiple domain MCIs with impairment of the memory domain diagnosed by neurophysiological tests such as verbal recall, visuo-spatial recall and visual recognition. In clinical psychiatry, many studies have been performed using EEG as a biological marker of memory ability, but sufficient evidence is still lacking for its use in initial evaluation of subjects with memory impairment.[14]

We hypothesized that decreased memory would cause changes in gamma oscillation and in order to prove this, we investigated changes in gamma oscillations during maintenance phase in memory tasks and analyzed the differences between amnestic and multiple domain MCIs and controls. In addition we also studied the correlation between gamma oscillation and clinical variables related to memory.

II. MATERIALS AND METHODS

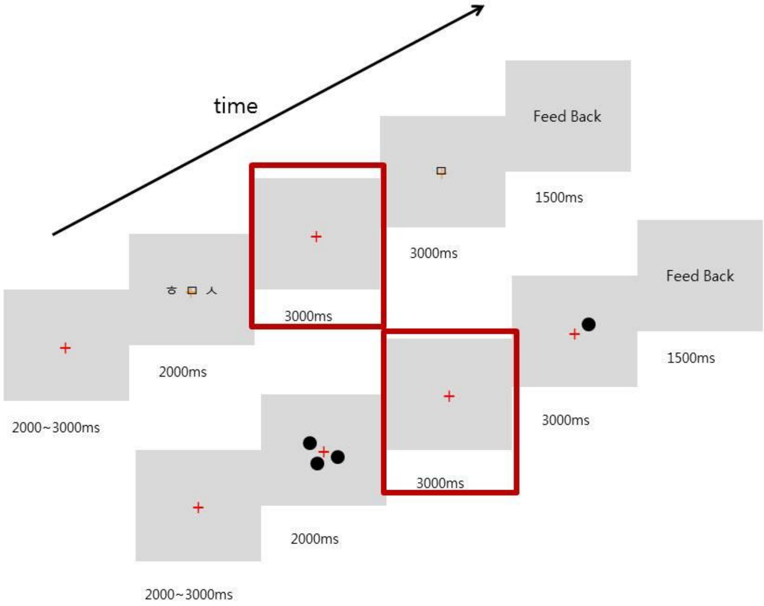
1. Subjects

Sixteen MCI subjects (M:F 7:9; age, mean: 66.63 SD: 4.88 years; education, mean: 7.94 SD 3.92 years) and nineteen normal controls (M:F 9:10; age, mean: 67.05 SD: 4.92 years; education, mean: 8.79 SD 4.13 years) registered in a program for the early detection and management of dementia at Gongju-National Hospital participated in this study. None of the subjects exhibited signs of dementia based on the neuropsychological examinations used in the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K).[14] The degree of working memory deficit was measured by performing letter-number sequencing and spatial span in the recruited subjects. This study was performed following the ethics guidelines described by the Institutional Review Board of Gongju National Hospital and the Declaration of Helsinki (World Medical Association: Ethical Principles for Medical Research Involving Human Subjects, 1964).

2. Delayed Match to Sample Tasks

In this study, verbal (VDMST) and spatial (SDMST) delayed match to sample tasks was used (Fig. 1). At the beginning of each trial, a small red cross was presented in the center of a computer monitor to achieve eye fixation. For the encoding period, three consonants of the Korean alphabet were presented in the verbal task, or three black circles (6.8° x 6.8° maximum visual angle; distance from monitor = 100 cm) randomly located among 16 points (a 4 x 4 matrix) in the spatial task for 2,000 ms. Following a 3,000 ms delay period, a probe (one consonant in the verbal task and one black circle in the spatial task) was presented for 3,000 ms to test the maintenance phase.

Figure 1. Verbal and Spatial Delayed Match to Sample Task. The maintenance phase was analyzed (red square) in this study.



Subjects were instructed to judge whether the consonant or the location of the black circle matched the location of one of the three consonants or black circles presented during the encoding phase. In addition, subjects were told to react as quickly and accurately as possible. Responses were made by pressing one of two buttons with the right and left index fingers, and the response hands were counterbalanced. The feedback on correct/incorrect responses and the accuracy rates were presented at the end of each trial for 1,500 ms. The next trial then began after an inter-trial interval of 2,000-3,000 ms. The experiment consisted of two blocks of 80 trials (160 trials in total). The proportion between match and non-match trials was 50% within each condition. The accuracy rate and reaction time of the two tasks were used to evaluate the relationship between gamma oscillations and behavioral performance.

3. EEG data recording

During the task, EEG measurements were taken from the scalp using a SynAmps2 DC-amplifier and a 10/20 layout 64-channel Quik-cap electrode placement system (Neuroscan Inc, USA). EEGs were recorded from 19 electrodes (standard 10/20 system based) at a sampling rate of 1,000 Hz. We used the linked mastoid for reference and two bipolar electrodes to measure horizontal and vertical eye movements. The impedance of each electrode was maintained below 10 kOhm. We used Matlab 7.0.1 (MathWorks, USA) with the EEGLAB toolbox[15] to preprocess and analyze the data. Firstly, the data were detrended and mean-subtracted to remove the DC component, then segmented into 10,000 ms intervals (including the 2,000ms segment preceding the encoding stimulus). The epochs including incorrect answers were also removed. Independent component decomposition and visual inspection of data were performed to eliminate artifacts and bad epochs.

We used EEGLAB software[15,16] to reference, analyze and illustrate independent components and time frequency. We first removed channel baseline means from the unepoched EEG dataset of each subject and re-referenced it to a common average reference. Data were epoched from 1000 ms prestimulus to 9000 ms poststimulus. Applying independent component analysis, we removed the eye movement component. We used the event-related spectral perturbation measure (ERSP) as the gamma amplitude value, as ERSP may correspond to a narrow-band of event-related desynchronization (ERD) or event-related synchronization (ERS). In short, the power spectrum was calculated over a sliding latency window on each epoch, each of them was normalized by its respective mean baseline spectra and then averaged across all data trials. Each trial contained samples from -1000 ms to 9000 ms of the onset of an encoding stimulus and the size of the sliding window was 600 data points. ERSP images provide a color code at each image pixel indicating the power reached (in dB) at a given frequency and latency relative to the stimulus onset.

$$ERSP(f,t) = \frac{1}{n}\sum_{k-1}^{n}\left|F_k(f,t)\right|^2$$

For statistical analysis, we used an independent t-test between MCIs and normal controls (CTRs) during maintenance phase, and we calculated Pearson's correlation coefficient to examine the relationships between gamma oscillations and memory measurements. Statistical significance was defined as $p<0.05$. We estimated the standard q-value and controlled the false-discovery rate (FDR) with it using the original Benjamini & Hochberg approach to multiple testing.[17,18] All statistical comparisons were performed using the Statistical Package for the Social Sciences (SPSS) 13.0 (SPSS Inc., USA), and all other computations were performed using Matlab (MathWorks Inc., USA).

III. RESULTS

VDMST ($t(33)=5.647$, $p=<0.001$) and SDMST ($t(33)=3.093$, $p=0.004$) accuracy in the MCI group was significantly lower than in the CTR group. Reaction time in the MCI group was slower than CTRs during VDMST ($t(33)=2.902$, $p=0.007$) and number letter sequence scores in the MCI group were lower than CTRs. There were no significant differences in SDMST reaction time or spatial span between the two groups (Table 1).

MCIs were significantly lower than controls in various subsets of the CERAD-K scoring criteria: verbal fluency ($t(33)=3.834$, $p=0.001$), Boston naming test ($t(33)=2.114$, $p=0.048$), word list memory ($t(33)=3.378$, $p=0.002$), constructional praxis ($t(33)=3.227$, $p=0.003$), word list recall ($t(33)=3.437$, $p=0.002$), word list recognition ($t(33)=3.570$, $p=0.001$), and constructional recall ($t(33)=3.305$, $p=0.002$). There was no significant difference in MMSE score ($t(33)=1.560$, $p=0.128$) (Table 2).

Table 1. Group differences in Behavioral Data & Working Memory Test Scores

	MCIs		CTRs		Analysis	
	Mean	SD	Mean	SD	t	p
VDMST Acc (%)	85.55	6.87	95.33	2.91	5.647	**<0.001**
VDMST RT (ms)	1380.51	324.83	1093.19	261.08	2.902	**0.007**
SDMST Acc (%)	80.71	17.27	93.19	3.31	3.093	**0.004**
SDMST RT (ms)	1272.16	324.31	1146.4	408.72	0.994	0.327
Number Letter Seq.	4.19	2.97	6.05	2.48	2.041	**0.049**
Spatial Span	12	4.12	14.21	2.76	1.892	0.067

MCI, Mild Cognitive Impairment; CTR, control subjects; VDMST, Verbal Delayed Match to Sample Task; SDMST, Spatial Delayed Match to Sample Task; RT, Reaction Time; Acc, Accuracy. Statistically significant values are presented in bold.

Table 2. Group differences in CERAD-K scoring subsets

	MCIs		CTRs		Analysis	
	Mean	SD	Mean	SD	t	p
Verbal fluency	12.63	2.96	16.89	3.53	3.834	**0.001**
Boston Naming Test	11.06	2.02	12.37	1.64	2.114	**0.048**
MMSE	26.38	2.47	27.89	1.29	1.560	0.128
Word List Memory	16.25	3.51	20.16	3.32	3.378	**0.002**
Constructional Praxis	9.75	1.69	11.00	0.00	3.227	**0.003**
Word List Recall	4.25	2.21	6.58	1.80	3.437	**0.002**
Word List Recog.	7.56	1.71	9.21	0.98	3.570	**0.001**
Constructional Recall	5.19	2.64	8.37	2.67	3.305	**0.002**

MCI, Mild Cognitive Impairment; CTR, control subjects; MMSE, Mini-Mental Status Examination. Statistically significant values are presented in bold.

In topography, we observed gamma ERD of the frontal and occipital area in the MCI group, but only the frontal area in CTRs. However, there was no significant difference between the two groups during VDMST (Fig. 2(a)). We also found that the ERD in the MCI group was more prominent in the frontal area during SVMST under the FDR threshold (Fig. 2(b)). Eleven channels (FPz, AF3, F3, F1, Fz, F2, F4, F6, F6, FC1 and FC2) clustered as significantly different between the MCI and CTR groups and we selected these eleven channels as the region of interest (ROI) for further analysis (Fig. 2(b), right, Fig. 3).

Figure 2. Topography of gamma ERD and p-map in Verbal Delayed Match to Sample Task (a) and in Spatial Delayed Match to Sample Task (b).

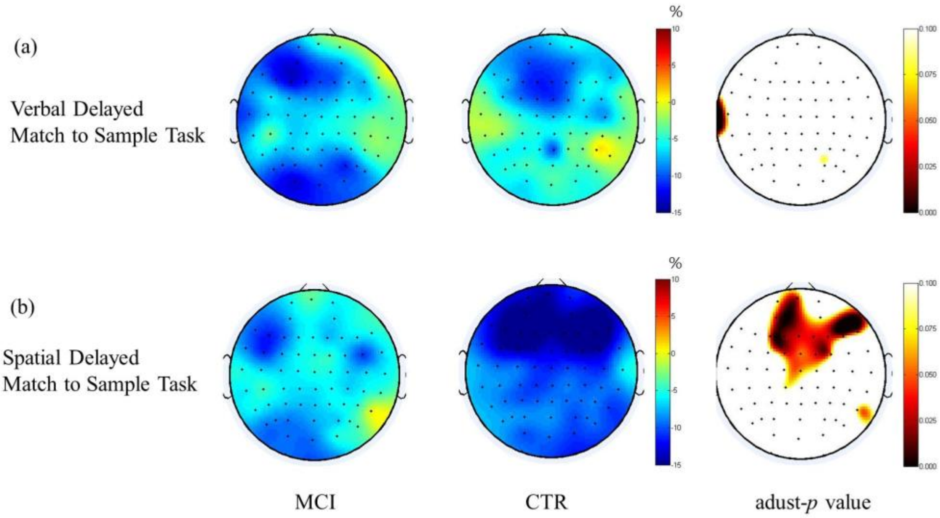
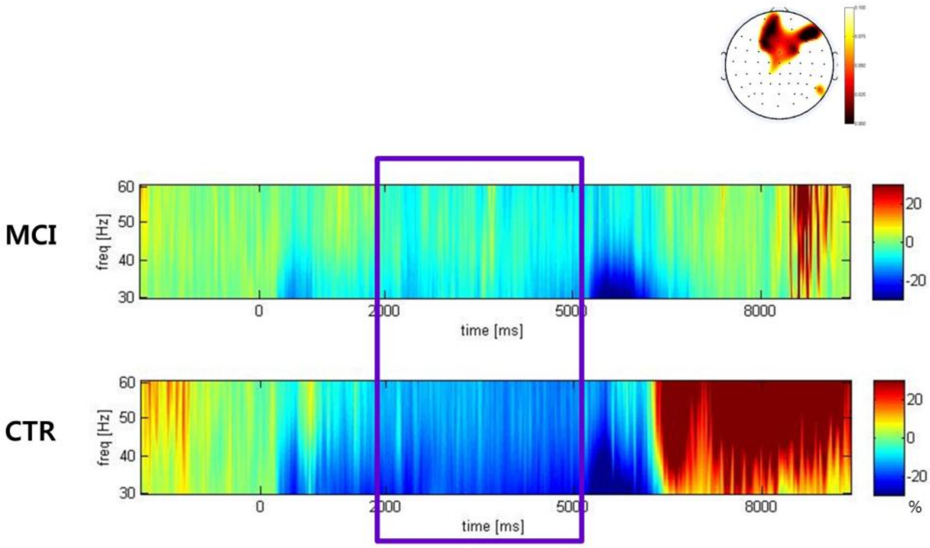


Figure 3. Averaged Time-Frequency Plots of ROI channels and subjects in Spatial Delayed Match to Sample Task



Gamma ERD mean during SDMST was significantly correlated with spatial span score (*r*= -0.357, *p*=0.035), accuracy (*r*= -0.365, *p*=0.031), verbal fluency (*r*= -0.387, *p*=0.022), word list recall (*r*= -0.384, *p*=0.023), word list recognition (*r*= -0.439, *p*=0.008), and constructional recall (*r*= -0.375, *p*=0.027) (Table 3, Fig. 4).

Table 3. Summary of correlation between ERD of the ROI window and clinical variables

		r	p
Demographics	Age	-0.150	0.933
	Education	-0.158	0.363
Working Memory Test	Number-Letter Sequence	-0.266	0.122
	Spatial Span	-0.357	**0.035**
Behavioral Responses	Accuracy	-0.365	**0.031**
	Reaction Time	0.239	0.167
Subsets of CERAD-K	Verbal fluency	-0.387	**0.022**
	Boston Naming Test	-0.251	0.146
	MMSE	-0.193	0.268
	Word List Memory	-0.167	0.118
	Constructional Praxis	-0.384	0.336
	Word List Recall	-0.384	**0.023**
	Word List Recognition	-0.439	**0.008**
	Constructional Recall	-0.375	**0.027**

ERD, Event-related Desynchronization; ROI, Region of Interest; r, Pearson's Correlation Coefficient; SDMST, Spatial Delayed Match to Sample Task; Mild Cognitive Impairment; MMSE, Mini-Mental Status Examination. Statistically significant values are presented in bold.

Figure 4. Correlation between ERD mean and spatial span (upper left), accuracy (upper right), and word list recognition (bottom)

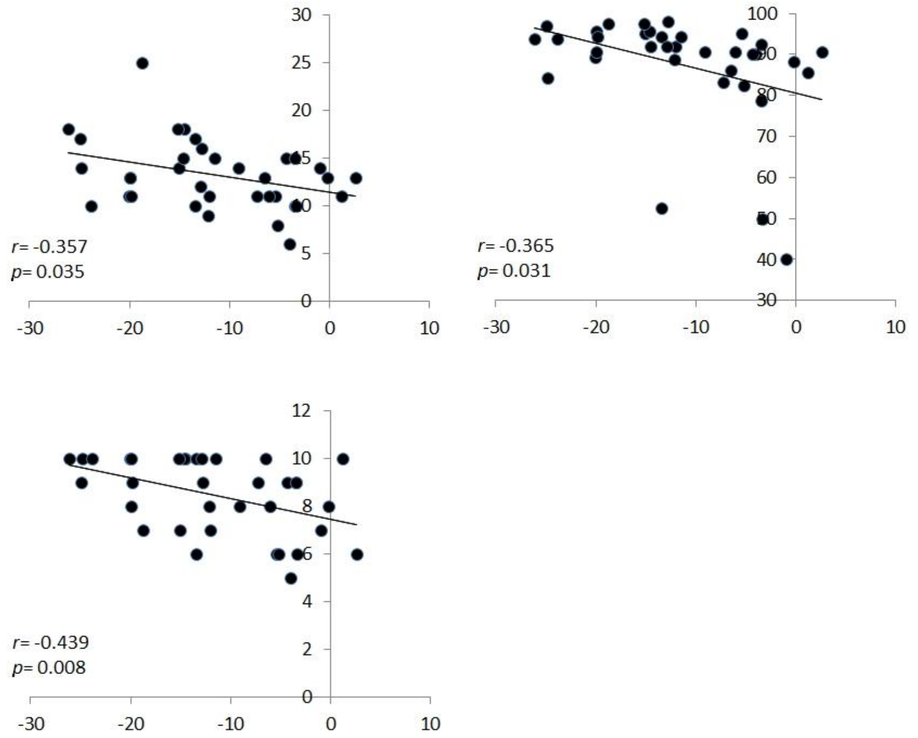
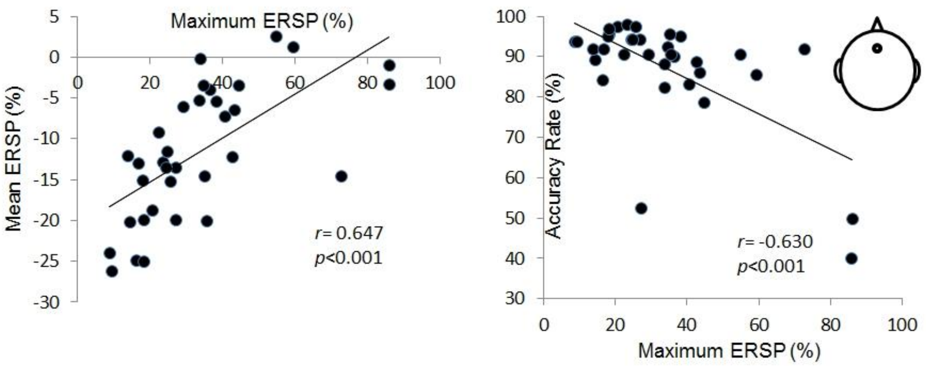


Figure 5. Correlation between maximum ERSP and mean ERSP (left), and word list recognition (right)



We analyzed relationships between maximum ERSP (which reflects ERS) and mean ERD (mean ERSP) and maximum ERSP and accuracy rate (Fig. 5). There was significant correlation between maximum ERSP and mean ERSP (r= 0.647, p<0.001) as well as with accuracy rate (r= -0.630, p<0.001).

IV. DISCUSSION

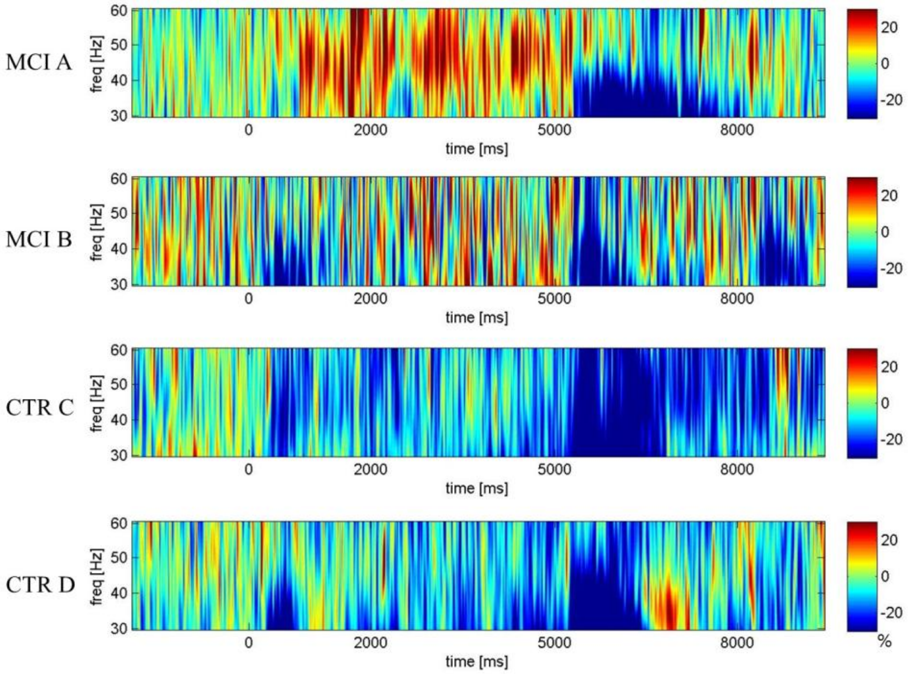
As expected, we observed a difference in gamma band activity dependant on memory ability, and gamma band activity was significantly correlated with neuropsychological test and behavioral scores. It has been widely reported that gamma oscillations reflect memory processes[7,8,10,19] and previous studies have investigated the relationship within single subjects by comparing cognitive and non-cognitive tasks.[7,8] In this experiment, however, we studied gamma activity between subjects with or without memory impairment. Our results are in line with previous studies and show additional evidence that gamma oscillations reflect memory processing as well as memory ability.

In this study, greater gamma ERD was observed in the group with a high memory ability than those with mild cognitive impairment. This result might reflect that neural efficiency in subjects performing a task well may result in a limited number of brain circuits and/or fewer neurons used, while poor performers use more circuits and/or neurons.[20] According to neural efficiency theory, intelligent groups can efficiently use neural resources and show lower activation compared to lower intelligence groups. This has been confirmed by various methodological approaches such as PET, MRI and EEG,[21] and could also be theoretically applied to the memory domain.

Some studies using fMRI reported that both activation in the dorsal prefrontal cortex and the extent of activation are significantly correlated with behavioral reaction time,[22] and that high performers showed less overall activation than low performers.[23] In addition, well educated subjects responded more efficiently with less neuronal network activation during two back working memory tasks.[13] Upper alpha power was also more prominent in high performers as measured by scalp EEG.[12] The results of these studies show that controls in our study would be expected to use less neural resources than the lower performing MCI group and as a result, gamma ERD was more prominent in controls than MCIs.

As mentioned in the introduction, previous studies have tended to use gamma ERS, but recent studies have showed that gamma ERD may also reflect active neural processing[4-6] and seems to measure the continuous and parallel activities of neuronal network within areas or between separation areas.[6] It is possible then, that the average of continuous and parallel activities result in negative values causing ERD. Individual time frequency plots in single channnels showed ERS phenomena during maintanence phase (Fig. 6), in contrast to the average plots of ROI channels and subjects showing ERD in the gamma area (Fig. 2). In addition, ERSP maximum, which reflects the highest value of ERS during maintanence phase, was positively correlated with mean ERS and behavioral performance (Fig. 5). These findings suggest that the gamma ERD happens concordantly with the neural activation process.

Figure 6. Time-Frequency plots of individuals at Fz during Spatial Delayed Match to Sample Task



In our study, differences in gamma ERD appeared only during SDMST, not during VSMST and we can provide a partial explanation for this. It is known that the difficulty of the task may affect neural efficiency[21] and indeed, we observed a tendency for lower accuracy in the SDMST compared to VDMST by paired t-test (t(34)=1.702, p=0.098, data not shown). To clarify this issue, further studies using tasks of various memory loading are necessary.

Our study has shown that gamma oscillation sensitively reflects memory ability and implicates it as an important biological marker. The initial symptom of dementia is often impairment in recent memory in older subjects[11] and until now there were no useful biological tools that could reliably measure memory function.[22] Many studies have been performed in order to find a neurophysiological biological marker using resting background EEG,[20-22,24] but the pattern of electrical activity at rest and during cognitive effort is remarkably different. Thus, studies such as ours investigating EEG activity during memory performance should provide a more accurate approach to memory impairment.

V. CONCLUSION

Using scalp EEG, we investigated the gamma oscillation during memory tasks and found that it correlated well with clinical measures. We focused on the clinical applicability of this phenomenon and anticipate the potential use of gamma band activity as a bio-physiological marker for screening and diagnosing memory-related disorders.

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ABSTRACT (IN KOREAN)

기억력 저하에 관련된 감마 진동의 활성

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뇌파 측정시 나타나는 30Hz이상의 고주파인 감마파는 집중력, 기억력, 고차원적인 인지능력과 관련이 있는 것으로 알려져 있다. 감마파는 기억을 요하지 않는 과제를 수행했을 때에 비해 기억을 필요로 하는 과제를 수행했을 때 더 활성화되는 것으로 알려져 있다. 하지만 개개인별 기억 능력에 따른 감마 진동 활성의 차이에 대한 연구는 아직 부족하다. 이에 본 연구에서는 기억력 관련 과제를 수행할 때 기억력 지수가 저하되어 있는 경도 인지 장애 군과 정상 대조군 사이에 감마 진동 활성의 차이가 있는지를 밝혀보고자 이 연구를 진행하였다. 기억력저하가 있는 경도인지장애 환자 16명과 19명의 정상 대조군을 모집했다. 언어적, 공간적 지연매치 반응을 하면서, 뇌파를 측정하였고, 유지기에서의 두 군간 감마 밴드의 활성에 차이가 있는지를 분석했다. 언어적 지연매치 반응 검사를

했을 때 두 군간의 유의미한 차이가 관찰되지 않았다. 공간적 지연매치 반응을 했을 때 정상군에서 경도인지장애 군에 비해서 감마 사건 유발비동기화가 강하게 나타났다. 유지기에서의 감마 사건 유발비동기화는 기억능력검사 소척도 및 행동 반응점수들과 유의미한 상관관계를 나타냈다. 이 연구 결과는 감마 밴드가 기억 수행 과정에서의 뇌활성뿐 아니라 각 객체 간의 기억 능력도 반영하는 것을 시사한다. 감마 진동은 정보처리를 효율적으로 할 때, 덜 활성화되어 나타나는 것으로 추정되며, 감마 밴드의 활성은 기억관련 능력을 구분하는 유용한 생물학적인 지표로 활용 될 수 있을 것으로 보인다.

핵심되는 말 : 감마 진동, 사건 유발 비동기화, 경도인지장애, 기억.