이학석사 학위논문

Hippocampal Theta-based Neurofeedback Enhances Associative Memory

: A Case Study on Theta Variability upon Epilepsy Patients

해마 세타파에 기반한 뉴로피드백에 의한 연합기억 향상

: 뇌전증 환자에 따른 세타파 가변성에 대한 사례 연구

2023년 8월

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이 논문을 이학석사 학위논문으로 제출함
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송인정의 이학석사 학위논문을 인준함
2023년 7월

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Abstract

Hippocampal Theta-based Neurofeedback Enhances Associative Memory
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Introduction: Being able to predict memory encoding outcomes from electrocorticography (ECoG) during real-time encoding has a significant value from a neuropsychological perspective. One previous study showed that increased hippocampal theta activity (4-10 Hz) is linked to better verbal associative memory (Jun et al., 2020). Delivering real-time neurofeedback based on previous findings would allow subjects to self-regulate their memory ability and optimize their overall performance outcome. However, no study using ECoG has yet investigated neurofeedback approaches to enhance memory in verbal memory tasks.

Materials and Methods: In this study, we aimed to investigate the effect of theta (4-10 Hz) neurofeedback on memory encoding performance. We recorded ECoG from the hippocampus while three epilepsy patients performed a word pair associative memory task.

Memory task included three encoding blocks with different conditions and one retrieval block. Each encoding block corresponded with the following three conditions: no feedback, random alarm, and real-time neurofeedback based on theta power. Subjects had to memorize the given word pairs during the encoding block. After encoding, the subjects went through a distractor block which contained some simple arithmetic questions. Then, in the retrieval block, the subjects were asked to answer among the three options: intact, rearrange, and new.

Results and Conclusion: In our behavioral results, memory recollection and familiarity were measured. Memory recollection increased while memory familiarity decreased among all subjects. For the electrocorticography (ECoG) theta power analysis, the theta (4-10 Hz) frequency power increased after theta-based neurofeedback compared to before. On the other hand, no feedback and random alarm condition did not show a difference between before and after feedback was given. The results also suggested that delivering theta-based neurofeedback in prediction to memory outcome, will enhance theta power, which is highly related to memory performance. In addition, it demonstrated the effect of increasing memory task performance using theta-based neurofeedback, while confirming that feedback should be delivered at a desired time point to lead to increase theta and memory performance.

Keywords: Associative memory, Neurofeedback (NF), Theta activity, Hippocampus, Electrocorticography (ECoG), Human brain

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Chapter 1. Introduction

1.1. Study Background

Hippocampus is a well-known brain region that supports the formation of learning and memory. The right and left hippocampus appeared to be involved in memory formation, such as memory for locations within an environment, and in context-dependent episodic or autobiographical memory (Burgess et al., 2002). Since learning and memory is very crucial in our daily lives, adjusting the process in aware of knowing and forgetting a certain information is an essential factor in learning. But it has been only relied on individual's ability of recognizing the learning outcome throughout prior studies. If people knew that they would fail to learn or memorize ahead of time, there would no need to be concerned about forgetting and could spend more time on the learning process. So, it would be useful to predict that memory encoding will fail before acknowledging the memory outcome, or even prior to process memory encoding. Knowing ahead of time of memory failure could be done by decoding the neural features during encoding; thus, real-time neurofeedback would allow the subjects to self-regulate their memory ability and to train a successful performance outcome.

1.1.1. Prediction of Memory Encoding by Neural Signals

It is significant to know which brain signals are related to successful memory processing, then, predict whether success or failure of memory encoding would follow suit. Jun investigated that intracranial hippocampal stimulation enhanced associative memory during retrieval (Jun et al., 2020). When the subjects were performing associative memory task of paired words, hippocampal theta power was associated with successful memory improvement. Another relevant theta power study has identified success or failure of memory encoding in the right frontal cortex associated with increased theta band activity in human scalp-recorded EEG (Friese et al., 2013). Rutishauser also found that human memory strengthening is predicted by theta band power of single neurons (Rutishauser et al., 2010). Note that most of the previous studies reported that there was a high relevance between human memory performance and the theta frequency band.

1.1.2. Previous Real-time Neurofeedback Memory Studies

Neurofeedback training is a widely used type of biofeedback that utilizes brainwaves, and is reported to improve memory. Neurofeedback is based on the brain's electrical activity and involves training and learning self-regulation of brain activity (Nazer et al., 2018). Many real-time neurofeedback training research has been studied using diverse modalities such as fMRI (functional magnetic resonance imaging) and EEG (electroencephalogram). Recent studies have shown fMRI based real-time neurofeedback manipulated memory performance; in advance, it improved cognitive effectiveness in neuropsychological functions for instance attention and motivation (Scharnowski et al., 2015). Happy memories toward healthy participants were able to learn how to self-regulate their own emotion using fMRI neurofeedback (Zotev & Bodurka, 2020). Another emotion regulation fMRI neurofeedback study provided a new methodology in terms of application and clinical treatment of emotional disorders (Zhu et al., 2019). While memory and emotion studies were put together, fMRI neurofeedback training also have been used towards posttraumatic stress disorder (PTSD) studies which also provided methodological implications of delivering real-time neurofeedback (Cisler et al., 2015). In EEG studies, there was a report that human episodic memory was enhanced during early consolidation using EEG neurofeedback (Rozengurt et al., 2017). Improvement of attention and working memory performance study also used EEG neurofeedback to train the participants (Wang & Hsieh, 2013). Real-time neurofeedback studies were commonly done by using EEG or fMRI separately, but the development of simultaneous EEG-fMRI could lead to combine those two methods. Applying real-time EEG-fMRI neurofeedback which is on the basis of the system for real-time fMRI and EEG data combination could train the subjects to self-regulate their memory encoding (Zotev et al., 2014). Previous studies of neurofeedback training have confirmed that providing neurofeedback through EEG or fMRI or even combined technologies could improve memory performance and also self-regulate the subjects' memory ability.

Nevertheless, these prior studies towards neurofeedback training have not been explored the disruption in giving feedback during memory processing. If the feedback was delivered when a subject is successfully performing in a memory task, it could not support memory formation but rather interrupt it. It is a necessary step to check if the feedback is required at an exact time, which we could also call when the theta frequency is low, during a memory formation.

1.2. Purpose of Research

Modalities such as fMRI and EEG provide great advantage towards researchers since both modalities does not require any clinical processes. While these modalities are widely used across researchers, when studying brain and especially hippocampus, it also comes along with several weaknesses. For example, fMRI has a weakness in limited temporal resolution which does not allow exquisite time-based analysis on a millisecond scale. But in real-time brain studies, time-based analysis is frequently and bound to use as it has a characteristic of a real-time process. Also, EEG has a weakness in terms of collecting brain waves since the occupying equipment is placed outside of the brain and the brain signal has to reach out towards the equipment. During this process, because the brain signal has to go through many layers such as the cerebrospinal fluid and the skull, the collected brain wave may not be the desired signal.

To escape from these weaknesses, it is highly required to use electrocorticography (ECoG) which could interact with neural membrane potentials and provide neural correlates of cognitive processes (Parvizi & Kastner, 2018). Although studies using ECoG is still not yet used widely compared to fMRI and EEG, so evidence for memory performance enhancement of neurofeedback training system is lacking (Campos da Paz et al., 2018; Jirayucharoensak et al., 2019). ECoG comes along with some assistance in brain studies such as determining the exact location of the existing electrode placed on the surface of the brain and spatial sampling of the cortical surface (Jobst et al., 2020). Some previous studies practically used ECoG to control higher cognitive functions such as learning and memory performance enhancement (Jun et al., 2019; Wang et al., 2014).

More recently, ECoG signal was used to achieve closed-loop decoding and enhancement of cognitive control in a non-verbal memory task (Basu et al., 2021). Non-verbal memory task is an inappropriate task to test the course of learning and memory; and to test the process of it, it is required to design a verbal memory task which is available to verify the learning outcomes. However, no study using ECoG has ever investigated neurofeedback approaches in verbal memory tasks. This study would deliver real-time auditory neurofeedback by tracking subject-specific theta (4-10 Hz) activity in the hippocampus to observe enhancement in theta power and whether it would enhance memory encoding performance. We will also be reviewing the presence of feedback at a given time point and discuss the importance of it.

Chapter 2. Materials and Methods

2.1. Participants

Three epilepsy patients (two males and one female) with intracranial depth electrode implanted for localization of the epileptogenic zone were recruited in this study (Fig. 1.). The electrodes were placed in the hippocampal area to measure our hypothesis in memory encoding (Fig. 2.). Prior to the memory task, all subjects underwent pre-operative MRI (magnetic resonance imaging) and post-operative CT (computerized tomography). All procedures have received agreement through Institutional Review Board of Seoul National University Hospital (H-2106-063-1225). The direct consent was received from all subjects and experiment instructions were guided before the experiment was handled.

Subject	Demographics			Clinical characteristics		
	Age	Gender	IQ/MQ	Seizure onset	Depth	Epilepsy Diagnosis
Subject 1	10-20	F	55/57	Temporal lobe	Lt hippocampus	TLE
Subject 2	40-50	M	59/43	Temporal lobe	Lt hippocampus	TLE
Subject 3	50-60	M	90/93	Temporal lobe	Rt hippocampus	TLE

Abbreviations: IQ, intelligence quotient; MQ, memory quotient; Lt, left; Rt, right; TLE; temporal lobe epilepsy

Figure 1. Subject information. Each subject’s age range, gender, IQ / MQ, and clinical characteristics are included in the table.

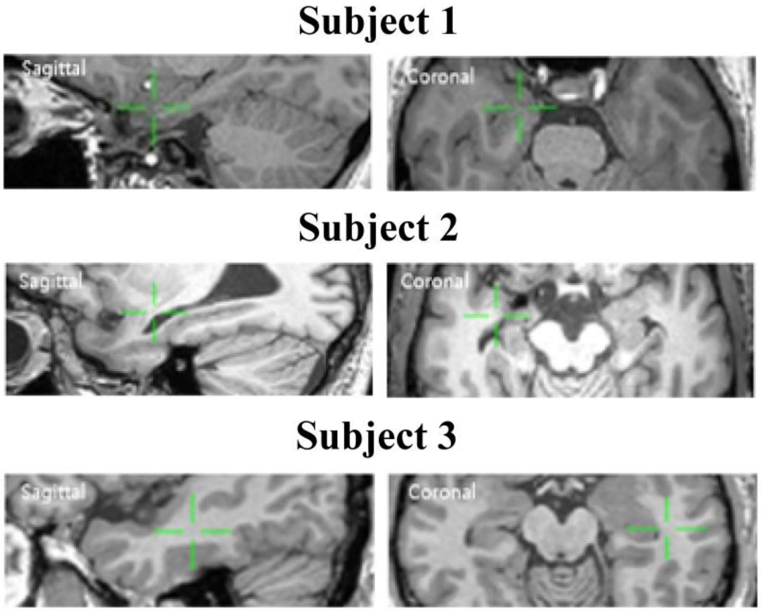

Figure 2. Hippocampal depth electrode localization of all subjects. Electrodes were implanted in different hippocampal area.

2.2. Experimental Design

In this study, we aimed to investigate the effect of theta (4-10 Hz) neurofeedback on verbal associative memory encoding performance and whether the feedback should be given at a desired time point. We recorded ECoG from the hippocampus, while three epilepsy patients performed a word pair associative verbal memory task.

The associative verbal memory task experiment set up contained several equipment. We used the hospital monitor to track the subjects' EEG recording through Profusion EEG Software (Compumedics). The Neuvo amplifier (Compumedics Neuroscan) was connected to the Profusion monitor for event markers. The light sensor attached to the subject screen sent every event happened during the experiment to Profusion and the StimTracker (Cedrus Corporation) recorded all the events marked on Profusion (Fig. 3.). The feedback was delivered ten times at a random trial for the random alarm block, but for the theta-based neurofeedback block the feedback was delivered every trial when the threshold hit below the criteria.

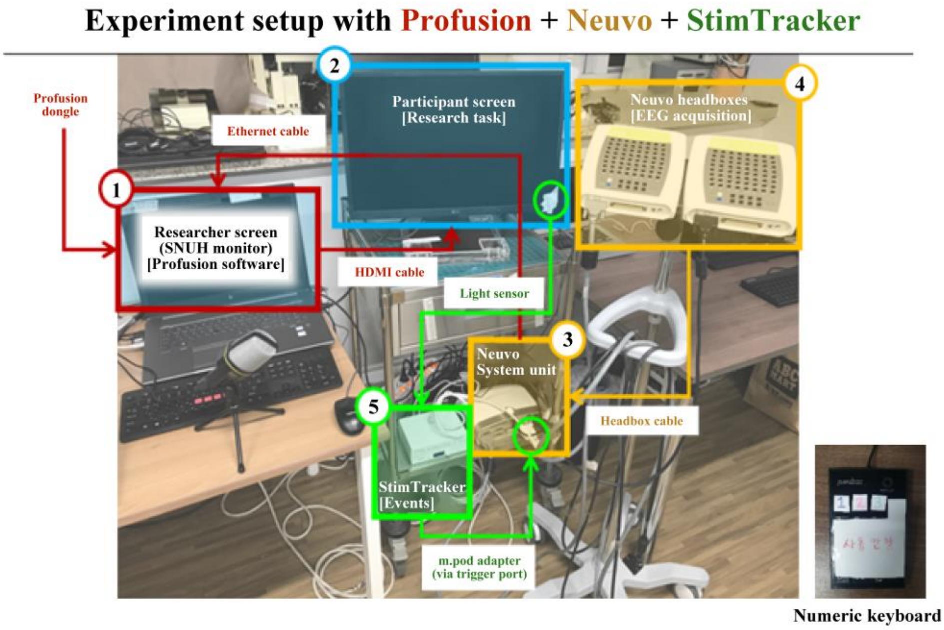

Figure 3. Experiment setup for the verbal associative memory task. **(1) Profusion** was used to monitor the **(4) subject's EEG recording**, which **(3) Neuvo amplifier** was connected. **(2) The light sensor** was attached to the **subject's screen** and sent every events that happened during the experiment to Profusion. **(5) The StimTracker** recorded all events that were imprinted on Profusion. Subjects were instructed to use the **numeric keyboard** to answer to the memory task.

Memory task included three encoding blocks and one retrieval block. Each encoding block corresponded with the following three conditions: no feedback, random alarm, and theta-based neurofeedback. The order of the three conditions were randomized for the two main experiments (Fig. 4.).

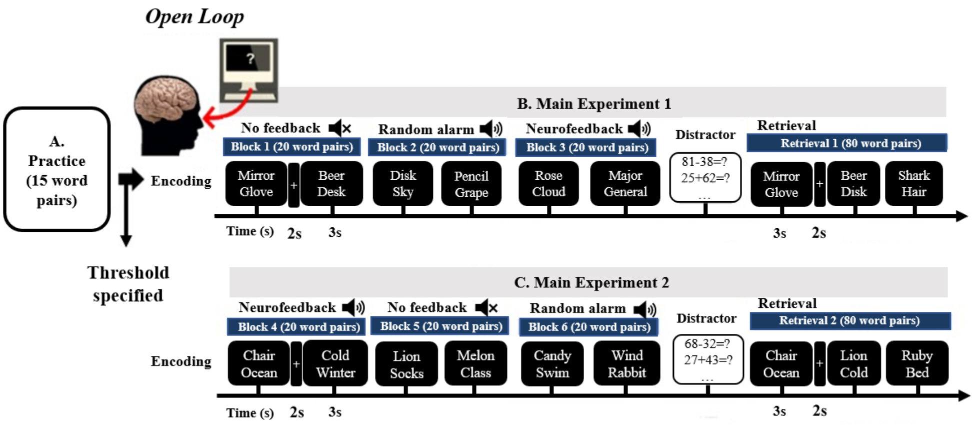

Figure 4. The experimental design of the study. Steps **A** through **C** shows the whole experimental paradigm. **(A)** During practice, the subjects went through 15 word pairs of encoding and retrieval to gather the subject specific sample theta power. The median of the sample theta power was used as a threshold value throughout the whole experiment. The threshold value was the criteria for present or absent of the feedback. **(B)** and **(C)** are the main experiments of associative verbal memory task. The order of the three conditions were replaced between the two main experiments.

At the beginning of the experiment, subjects were guided to pay attention to the given word memory task and if their attention decreases, the 'beep' sound will be delivered to support them in performing the task. During the encoding block, the subjects had to memorize the word pairs shown up on the subjects' screen. After encoding, the subjects went through some simple arithmetic questions as a distractor. Then, at the retrieval block, the subjects faced a word pair memory test that was asked to answer among the three options: intact, rearrange, and new (Fig. 5.).

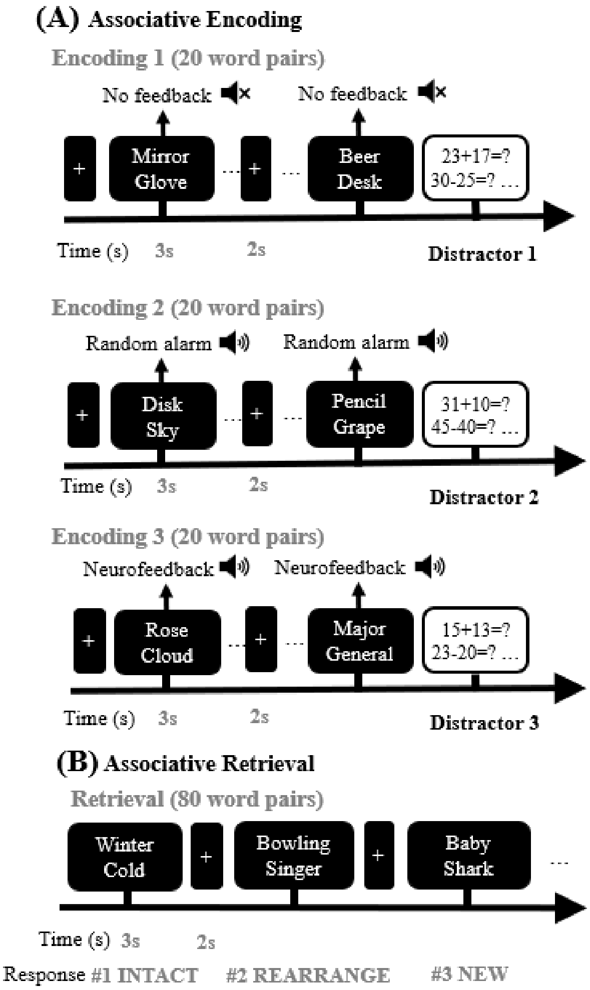

Figure 5. (A) The encoding block. Subjects were instructed to memorize the given word pairs that are shown for three seconds. Each encoding blocks contained 20 word pairs. The word pairs were organized with related and unrelated words in a 50% / 50% ratio. The subjects went through a distractor block which asked two-digits add or subtract questions for 3 minutes. **(B)** The retrieval block. Subjects were instructed to respond to the word pair recall test by pressing the numeric keyboard: intact (#1), rearrange (#2), and new (#3).

The decoding model used the inputs of the theta frequency power values in the hippocampus. The number of inputs depended on subject-specific electrode placement within the hippocampus. For the theta-based neurofeedback condition, the feedback was given when the subject's threshold level dropped below the criteria. The criteria were selected from the median value in the practice set of word pairs since the theta frequency was inconsistent or unregular during the whole time. If the threshold value was put as a mean value, the threshold could be too high or too low to define as an ordinary theta value of a subject. For the random alarm condition, the alarm was given randomly. We provided auditory feedback (a pure “beep’ tone) rather than visual because it allowed subjects to avoid confusion in task performance since the visual stimulation has already existed on the subject screen (Fig. 6.).

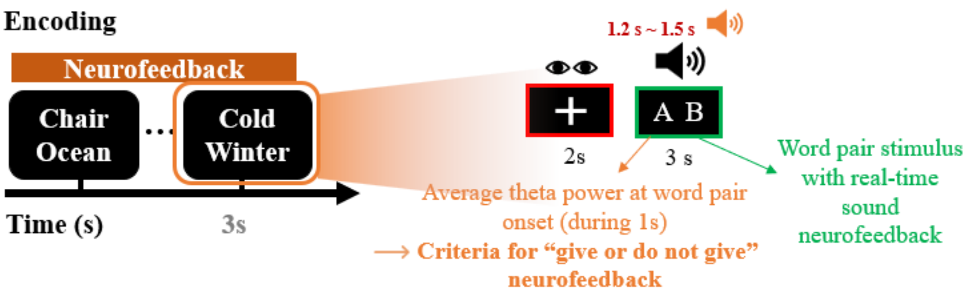

Figure 6. Neurofeedback was delivered during the encoding block after the word pair onset for 1.2 seconds to 1.5 seconds. A feedback was provided when the classifier determined the theta value at the moment of word pair onset was below the threshold. We later tested if the neurofeedback was appropriately delivered at the desired trials by MATLAB software (version 2021b, MathWorks, Natick, MA, USA) script and also analyzed if the trials that have received neurofeedback practically increased.

We used MATLAB software (version 2021b, MathWorks, Natick, MA, USA) script to collect the theta values for all trials in the practice set to check the threshold (median) value. Then we verified if the theta-based neurofeedback was given at the right time point likewise we constructed the experiment concept. We found out that the theta-based neurofeedback was delivered in the trials below the threshold value from the practice set. We will be discussing later in the results if the theta value in the trials which received theta-based neurofeedback practically increased.

2.3. Neural Signal Preprocessing

Before we started the post-hoc analysis, we used CURRY software (version 9.0, Compumedics) to delete out the unused events. Then the data which have removed the events was saved as a CNT file. Other than deleting events, most of the data pre-processing procedures were performed through MATLAB software (version 2021b, MathWorks, Natick, MA, USA). The event tracker (StimTracker, Cedrus Corporation) tracked the offset of events, so aligning the event offset timing to onset timing was performed. Electrodes that were located in the hippocampus were used for the analysis. Bad channels with epileptiform activities or unable to measure due to technical issues were defined as bad electrodes and were rejected from the data set. The impedance of depth electrodes was in the range of 1 through 15. The data set was re-referenced using common average referencing (CAR) to average each scalp channels. Through this process, each channel amplitude would be added up to zero in each time point. We did not used high-pass filtering since we are targeting the lower range of the data and if high-pass filter situates, a distortion in the targeted area could occur. Since we are targeting the lower region of the frequency, we used low-pass filtering to filter out higher frequency range. Lastly, notch filtering was done at a higher range in 60, 120, 180 Hz each to eliminate or weaken the single or narrow range frequency. We performed down sampling since we are using a huge volume of dataset, and down sampling helps to reduce processing time or computer memory by scaling out the sampling rate or sample size. The data was epoched with window size of -4 to 5 seconds of fixation cross and the word pair onset. The epoched data went through a continuous wavelet transformation (CWT) to determine how rapidly the wavelet oscillations decayed from one wave to another and removed all noises. After that, baseline normalization was done at the range of -0.9 to -0.2. Then the data was averaged at the theta (4-10 Hz) range to calculate out the theta power.

2.4 Decoding Model using SVM

The decoding model was a binary support vector machine (SVM) classification model. Model inputs were theta frequency power values in the hippocampus that was monitored in real-time. The number of inputs depended on subject-specific electrode placement, which was based on requirements of clinical evaluation. Model outputs were either "success" or "failure" labels. To find the most appropriate decoding model, the training sets were split into five folds, and decoding accuracies were calculated using a 20-80 train-test ratio. The SVM model with the highest accuracy was kept for subsequent predictions in the real-time experiment. Finally, a closed-loop system was implemented to process intracranial signals and made predictions in real time (Kevin Meng, 2022).

2.5. Hippocampal Depth Electrode Selection

Hippocampal depth electrodes were localized with MRI-CT co-registration from CURRY software (version 9.0, Compumedics). The subjects had different number labeled to their hippocampal depth electrodes since the operation took place in different day and time. Based on the previous ECoG research done prior to this study, we selected the depth electrode that could be seen through MRI-CT co-registration and was placed in the hippocampal area.

Chapter 3. Results

3.1. Enhancement of Memory Recollection and Performance Accuracy

In the behavioral results, we calculated the effect of neurofeedback compared to no feedback in two ways. First, we determined the hit rate and false alarm rate of associative memory; second, we examined whether theta-based neurofeedback would enhance theta which relates to memory performance. Memory recollection and memory familiarity for each subject were compared to determine whether subjects' memory recollection increased compared to memory familiarity.

We calculated the recollection index which consists the hit rate of associative memory (i.e., intact word pairs correctly identified as intact and rearranged word pairs correctly identified as rearranged) minus the false alarm rate in associative memory (i.e., rearranged word pairs identified as intact). The familiarity index was measured by dividing the false alarm rate in associative memory (i.e., rearranged word pair identified as intact) by 1 minus the recollection index (Fig. 7. Table). Since we only had three subjects, statistical analysis was not necessary and we rather observed the result consistency between all three subjects. We observed increasing tendency of memory recollection while memory familiarity did not show any changes across all subjects (Fig. 7. Graph).

Subject	*d'*	Recollection		Familiarity	
		NF	No FB	NF	No FB
Subject 1	0.66	**0.42**	-0.06	0.5	0.5
Subject 2	0.18	**0.06**	-0.01	0.5	0.5
Subject 3	0.7	**0.45**	0.43	0.5	0.5

Abbreviations: NF, neurofeedback; FB, feedback.

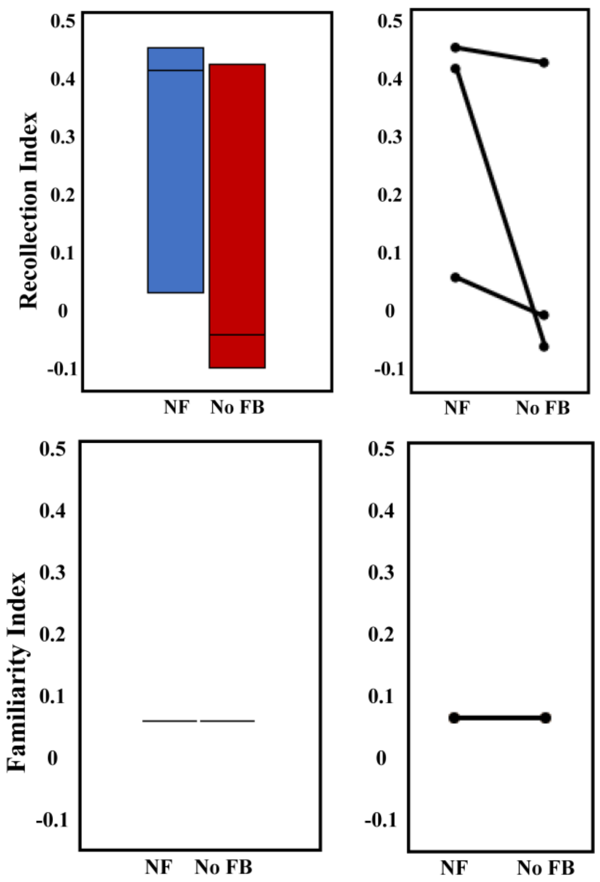

Figure 7. For the behavior results, it reviewed recollection, familiarity, and *d-prime* value over all subjects. All subjects showed enhancement of memory recollection. On the other hand, memory familiarity did not showed difference between neurofeedback and no feedback condition. For the sake of few numbers of subjects, statistical analysis was not performed and rather reviewed the result consistency over subjects.

We also analyzed the accuracy of each subject's response to the memory task. We used the equation of *d-prime* (*d'*) from the signal detection theory (SDT). The *d-prime* analysis is commonly used for memory index to measure the discriminability or sensitivity that is unaffected by the response biases. The value of *d'* indicates the performance of the memory task and the accuracy of the responses achieved from the subjects. The following is the equation of the z-score that was needed prior to calculate the *d'* value:

$$z = (x-\mu)/\sigma$$

where x = score, μ = mean, and σ = standard deviation. Z-score value was used to analyze the hit rate and false alarm of each subject (subject 1: hit rate; $z(H)$ = 0.33, false alarm; $z(Fa)$ = -0.33, subject 2: hit rate; $z(H)$ = 0.44, false alarm; $z(Fa)$ = 0.25, subject 3: hit rate; $z(H)$ = 0.95, false alarm; $z(Fa)$ = 0.25).

Value of *d'* equals the difference between the distributions of probabilities for scoring a hit in relation to a false alarm. If *d'* value is above zero, it indicates that subject's signal detection was above chance level. We used the following equation to calculate the *d'* value of all three subjects:

$$d' = z(H) - z(Fa)$$

where $z(H)$ = hit rate, and $z(Fa)$ = false alarm. The *d'* value for each subject were: subject 1, *d'* = 0.66; subject 2, *d'* = 0.18; subject 3, *d'* = 0.7. All three subjects showed a *d'* value above zero, which meant that the hit rate of all subjects was above chance level, thus, was not in coincidence (Fig. 7. Table).

We next observed the correct number of word pair trials and the performance accuracy of each subject. The retrieval result shown in the graph on the top is the number of correct trials of each subject. The number of correct trials in the neurofeedback trials rated higher score compared to other conditions. The following results are the correct number of trials in a condition of each subject in order: no feedback: 15, 17, 24; random alarm: 10, 12, 22; and neurofeedback: 18, 19, 25 (Fig. 8. Top). The performance accuracy is shown in the bottom bar graph. The following results are the performance accuracy in a condition of each subject in order: no feedback: 37.5, 42.5, 60; random alarm: 25, 30, 55; neurofeedback: 45, 47.5, 62.5 (Fig. 8. Bottom). Performance accuracy was calculated through correct number of trials divided by the whole number in the memory task. Performance accuracy also rated highest in the neurofeedback condition among the conditions. There was not a huge difference between the conditions and we could not go through a statistical significance analysis due to small number of subjects, but the result consistency explained that theta-based neurofeedback gave alarm to the subjects to increase or maintain a theta value above threshold. Furthermore, results viewed that alarm should be given at a desired time point when the theta droped below the threshold;

in other words, if the feedback is delivered randomly unrelated to the theta value, it would disrupt memory performance.

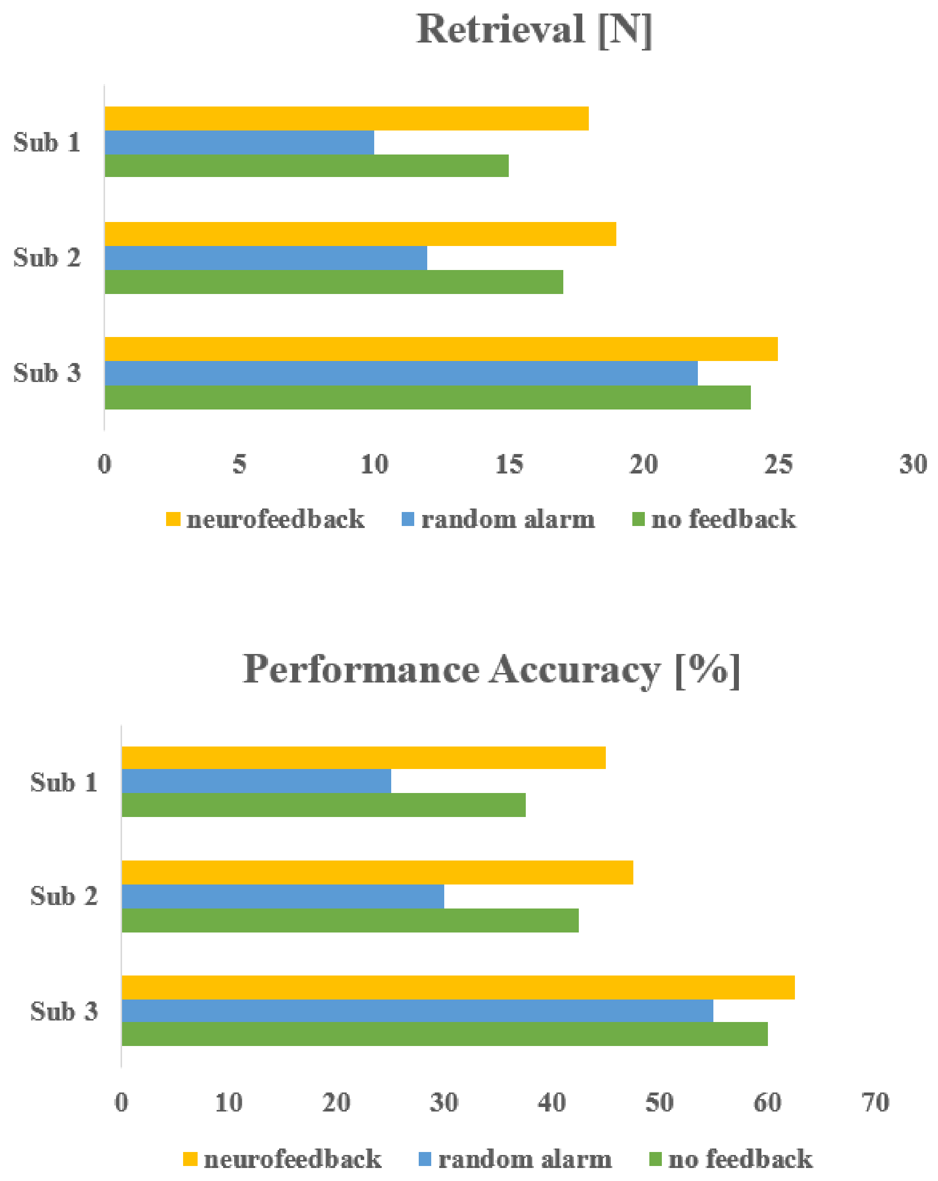

Figure 8. Performance accuracy during retrieval of no feedback, random alarm, and neurofeedback conditions. The top bar graph shows the correct number of trials during retrieval in each condition and the bottom graph shows the performance accuracy. It showed that all subjects recorded higher correct trial numbers during neurofeedback condition compared to other conditions. Also all subjects' performance accuracy has increased for neurofeedback condition. We could not calculate the statistical significance due to small number of subjects.

3.2. Theta Power in a Time Series

We also analyzed the theta power flow during the memory encoding blocks of all subjects in a time series. When the subjects' theta power decreased lower than the threshold value, the theta-based neurofeedback was given to up-regulate the theta power to a state where it is higher than the threshold. In the post-hoc analysis, we plotted each subject's averaged theta power during the neurofeedback condition and observed if the theta power increased after receiving theta-based neurofeedback (Fig. 9.).

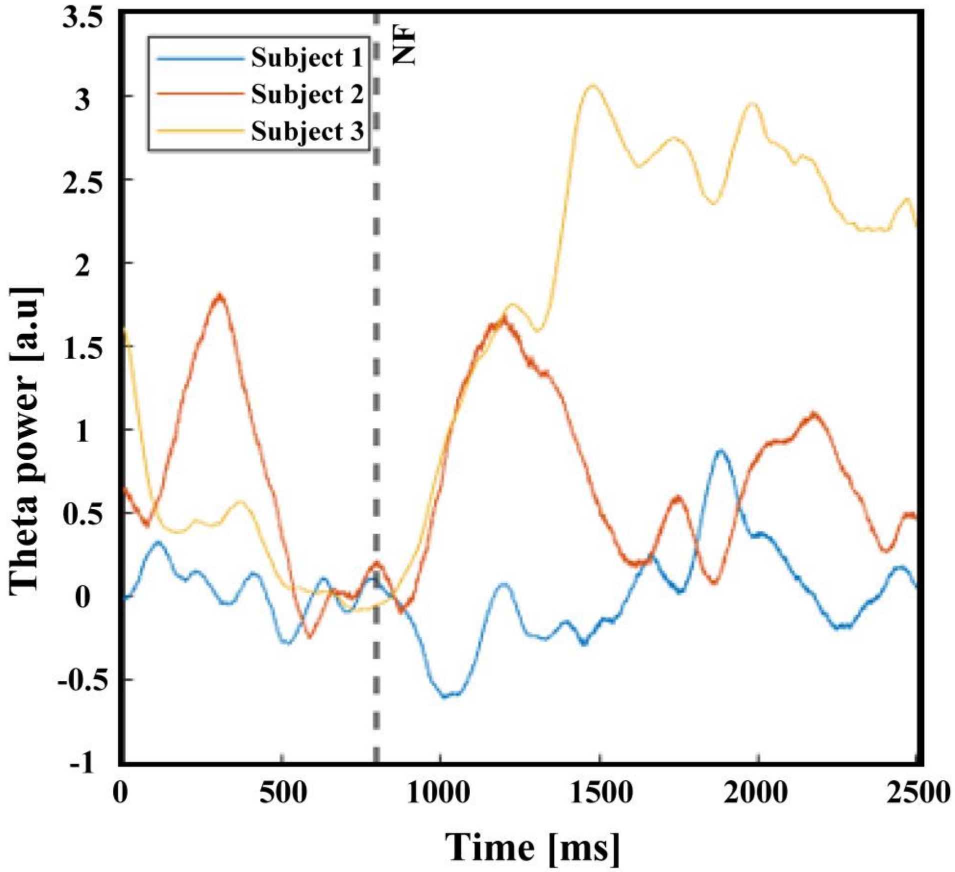

Figure 9. The line plot of all three subjects were drawn through custom made MATLAB code. When there was a decrease in theta power and the neurofeedback was given, it was able to increase the theta power back to the normal or the higher state before the neurofeedback was given.

We discovered that when decrease in theta was captured, then the neurofeedback was given to the subject. And when the neurofeedback was delivered to the subject, the following theta power of all subjects was up-regulated. The conditions have undergone *Wilcoxon rank sum test* (*ranksum test*) to test whether it is statistically significant and resulted in $p<0.05$.

3.3. Theta Frequency Change in Different Conditions

We next observed the theta (4-10 Hz) frequency change in those three different conditions. We drew a time frequency map that interprets the theta frequency flow in a time series. The theta frequency in the no feedback condition showed no other changes during the whole trials. Since the theta frequency is the band which is highly related to the memory functioning, and the no feedback condition is the control group with no other theta-related alarm, it was an expected outcome. For random alarm condition, the theta frequency showed a decrease. The range in the heat bar from the time frequency map did not exactly fit in with the results in the before and after neurofeedback box plots due to a narrow interval between the values. We could determine that delivering feedback at a random time point, would not affect in increasing theta power but it could rather disturb the memory formation. Lastly, the theta-based neurofeedback condition increased during the whole trials. Comparisons between three conditions revealed that only theta-based neurofeedback given condition was increased (Fig. 10. Sub 1. – Sub 3., *Wilcoxon rank sum test*, $p < 0.05$).

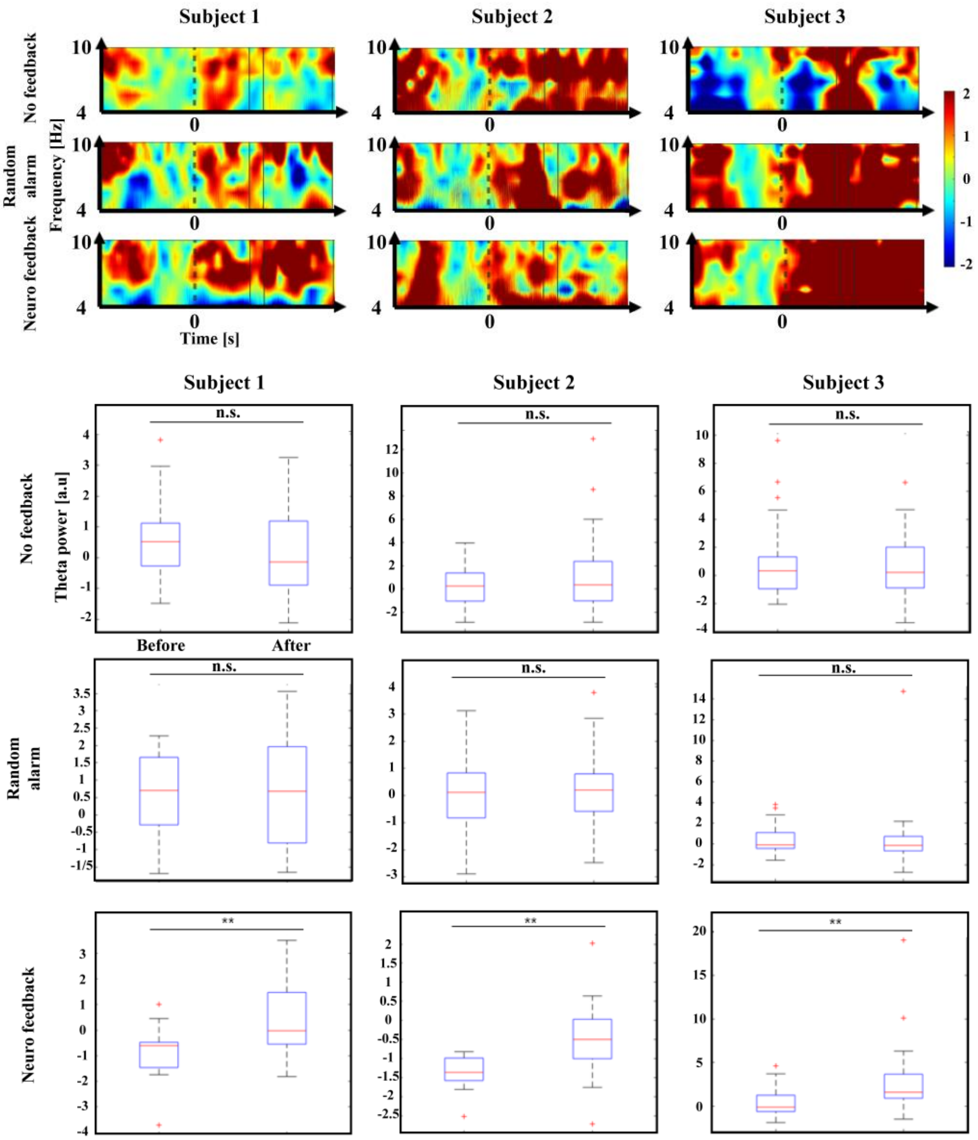

Figure 10. The time frequency map and box plot comparing before and after feedback for subjects 1 through 3. The time frequency map drawn here has the window of 4 to 10 Hz and time range of -2 to 3 seconds. The box plot shows the theta power before (left) and after (right) the feedback was given. All subjects showed increase in theta power for theta-based neurofeedback. *Wilcoxon rank sum test* (*ranksum test*) was performed and all subjects were statistically significant ($^{**}p<0.05$) for increase in theta-based neurofeedback. The + in the box plots represents the outliers.

Chapter 4. Discussion

This study demonstrated the memory self-regulation through real-time auditory neurofeedback is available, and that compared to no feedback condition and delivering theta-based neurofeedback condition during a memory task, the memory recollection increased but memory familiarity did not show any changes.

Hippocampal theta (4 - 10 Hz) frequency was used as a reliable predictor of success or failure during memory encoding. Neurofeedback gave alarm to the subjects to maintain a high level of theta frequency power above a threshold. During the retrieval phase, the subjects statistically performed better for word pairs contained in the encoding block with neurofeedback. However, we had a limitation within the technical issue which brought up a slight miss regarding the number of trials in each block. The number of feedbacks given during the random alarm and theta-based neurofeedback were not the same, which is highly connected to different environmental issue to be compared. The environment such as number of feedbacks in each block should be same to reveal the effect of theta-based neurofeedback.

The prediction accuracy was significantly above chance level in this study, so the framework could be seen as appropriate to address the main research question regarding the neurofeedback model. However, if prediction accuracy remained around chance level, the initial assumptions may not be valid and the results must be discussed with additional limitations. Although we had small number of trials in the training set, the decoding accuracy remained significantly above chance level.

We also discussed if the threshold value that was used in this experiment was reasonable. We used the median theta value out of the practice word pairs before starting the main experiment. If the median theta value that we obtained from the practice word set located exactly between the success group and the failure group, the median theta value we used as a threshold was appropriate. But if the median theta value did not locate exactly between the success group and the failure group, it could be seen that it was not valid for the use of the criteria for delivering feedback. For further analysis, it is needed to plot the success only or failure only trials from the practice word set and see if the median value is positioned between the two groups.

The behavior results showed that all three subjects' memory recollection increased compared to memory familiarity in the case of neurofeedback condition. Also, the result of performance accuracy revealed that the subjects' correct rate was a reasonable data that they did not guess the word pairs but rather memory recollection and familiarity was successfully examined. In the theta power analysis, we found that no feedback and random alarm condition both showed theta decrease during the encoding phase but theta-based neurofeedback condition increased theta power during encoding (*Wilcoxon rank sum test,* $p < 0.05$). Lastly, in our theta power time series analysis, when subject's theta power tends to decrease during memory encoding, and the theta-based neurofeedback was delivered, subject's theta power was up-regulated to the normal range which is higher than the range where theta decrease occurred. However, the theta fluctuation was observed before delivering neurofeedback which could be an effect of similar baseline of each subject. To measure more accurate theta flow in a time series, the baseline of subjects should be designated differently. Also, the bias in regard to individual variety such as intelligence quotient (IQ) and memory quotient (MQ) could not be ignored. These results suggested that delivering theta-based neurofeedback enhanced memory performance. In addition, it demonstrated the effect of increasing memory task performance using feedback, while confirmed an increased recollection when receiving a theta-based neurofeedback compared to no feedback delivered.

Previous neurofeedback training studies explored the hippocampal theta oscillation and the relationship between memory enhancement (Rozengurt et al., 2017), and memory stability within the EEG activity in the hippocampus (Shtoots et al., 2021). Also, attention and working memory could be improved through neurofeedback training (Wang & Hsieh, 2013). Nevertheless, previous studies that made up the background of this study have been using EEG or fMRI which comes along with various difficulties in brain studies. Studies also has not been mentioned the possible existent of error in providing feedback during memory task.

This present study has discovered that real-time auditory neurofeedback enhanced human associative memory, while on the other hand the feedback should be needed to deliver at a desired time point. Limitations to this study brought out small number of subjects, which extended to impossibility in statistical analysis. However, we were able to observe the consistency in our overall results. Our findings confirmed that further study in memory encoding disturbance through feedback is required. Whether feedback would disturb memory encoding during a memory task could be studied through analysis on the theta value distribution of success or fail trials in the random alarm condition.

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초 록

연구 배경: 실시간으로 기억을 입력하는 동안 두개 내의 뇌피질뇌파 (ECoG)에서 기억 입력 결과를 예측할 수 있다는 것은 신경 심리학적 관점에서 중요한 가치가 있다. 이전 연구에서는 해마에서의 증가된 세타 파 (4-10 Hz) 활성이 단어 연합 기억의 향상과 관련이 있음을 발표하였다 (Jun et al., 2020). 이러한 연구 결과를 바탕으로, 실시간 세타 뉴로피드백을 제공하면 피험자들이 기억력을 스스로 조절하고 전반적인 인지 기능을 최적화할 수 있을 것이다. 그러나 단어 기억 과제에서 기억력을 향상시키기 위한 뉴로피드백 훈련 방법에 아직은 두개 내 뇌피질뇌파 (ECoG)를 이용한 바가 없다.

실험 장비 및 방법: 본 연구에서는 세타 (4-10 Hz) 기반 뉴로피드백이 기억 입력 기능에 미치는 영향을 실험하였다. 3명의 뇌전증 환자의 해마에서 ECoG로 뇌피질뇌파를 기록했고, 환자 모두가 단어 쌍 연합 기억 과제를 수행하였다.

기억 과제에는 조건이 다른 3개의 입력 단계와 1개의 인출 단계가 포함되어 있다. 각 입력 단계는 피드백이 없는 상태 (no feedback), 무작위 알람 (random alarm), 그리고 세타 파 기반 실시간 뉴로피드백 (real-time theta based neurofeedback); 이 세 가지 컨디션을 가지고 있다. 피험자들은 입력 단계 동안 주어진 단어 쌍을 연합하여 암기해야 했고, 암기한 내용을 장기 기억화 하기 위하여 입력 단계 후 몇 개의 간단한 산수 문제를 풀도록 하였다. 그런 다음 인출 단계에서 피험자는 본래의 단어 쌍 (intact), 재배열된 단어 쌍 (rearrange) 또는 새로운 단어 쌍 (new) 등 이렇게 세 가지 보기 중 하나를 선택하여 응답하도록 안내를 받았다.

결과 및 결론: 인출 단계에서 피험자들의 행동 결과를 기억 회상 (memory recollection)과 기억 친숙도 (memory familiarity)로 비교하였다. 모든 피험자에서 기억 친숙도가 감소할 때, 기억

회상도는 증가하였다. 두개내 뇌피질뇌파 분석에서는 세타 파워 기반 뉴로피드백을 받은 후 세타 (4-10 Hz) 주파수 파워가 증가하였지만, 피드백이 없는 상태와 무작위 알람 상태의 경우에는 피드백 구간의 전과 후에 세타 파워가 떨어지거나 반응을 보이지 않았다. 또한 세타 기반 뉴로피드백을 부여하면 기억 기능과 밀접한 관련이 있는 세타 파워를 향상시킬 수 있음을 시사하였다. 본 연구에서는 세타 기반의 뉴로피드백을 이용하여 기억 작업 수행 능력을 높이는 효과를 입증하였으며, 피드백은 반드시 적절한 시점에 주어져야 뉴로피드백의 효과를 볼 수 있음을 확인하였다.

주요어: 연합 기억, 뉴로피드백, 세타 활성화, 해마, 뇌피질뇌파 (ECoG), 인간 뇌 기능

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