



Unveiling the Contributions of the Hippocampus to Associative Memory: Evidence from Resection Study and EEG Connectivity Study

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Abstract

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Associative memory refers to the ability to remember the relationships between unrelated items. The hippocampus (HC) is known to play a critical and irreplaceable role in associative memory. However, it is important to note that the HC does not operate in isolation when it comes to performing associative memory; instead, it interacts with various regions of the brain. Therefore, in the context of associative memory, the functional connectivity between the HC and memoryrelated networks may be more important than the mere activation of specific regions.

To investigate the specific contribution of the HC to associative memory, I examined the relationship between hippocampal resection and postoperative memory changes on various memory tests in patients who underwent surgery for medial temporal lobe epilepsy (MTLE). Through a voxel-based analysis that accounts for individual differences in the resection, it was found that resection of the HC was associated with a decline in associative memory rather than item

memory. This finding emphasizes the specific involvement of the HC in associative memory processes.

Expanding upon this understanding, I utilized single-trial EEG connectivity between the HC and neocortical regions to predict memory success and failure. The results achieved an average accuracy of over 90% in predicting subsequent memory performance. Notably, this level of accuracy was higher compared to utilizing brain activity in specific regions. In summary, this thesis highlights the significant role of the HC and its connectivity in associative memory. It underscores the significance of hippocampal communication with large-scale brain networks, rather than solely focusing on specific brain regions, in understanding memory processes.

Key words: Hippocampus, Large-scale Network, Functional Connectivity, Memory Prediction, Associative Memory, Subsequent Memory EffectsStudent Number: 2016-20436

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List of Abbreviations

- AAL, automated anatomical labeling
- AG, angular gyrus
- AH, amygdalohippocampectomy
- ATL, anterior temporal lobectomy
- DMN, default mode network
- DMPFC, dorsomedial prefrontal cortex
- EEG, electroencephalography
- HC, hippocampus
- K-RAVLT, Korean version of Rey auditory verbal learning test
- K-RCFT, Korean version of Rey complex figure test
- MI, mutual information
- MNI, montreal neurological institute
- MRI, magnetic resonance imaging
- MTG, middle temporal gyrus
- MTL, medial temporal lobe
- MTLE, medial temporal lobe epilepsy
- PCC, posterior cingulate cortex
- PET, positron emission tomography
- PFC, prefrontal cortex
- ROI, region of interest
- SAH, selective amygdalohippocampectomy
- SMEs, subsequent memory effects

SPECT, single photon emission computed tomography

TPR, temporal pole resection

WMS, Wechsler Memory Scale

I. INTRODUCTION

1.1 Associative Memory and the Hippocampus

The human memory system consists of several subsystems (**Figure 1**). Among them, episodic memory is a type of explicit memory that involves the recall of specific events, experiences, and personal circumstances that occurred at a particular time and place in a person's life (Tulving 2002). The HC and medial temporal lobe (MTL) have been recognized to play an essential role in episodic memory following the famous case of Henry Gustav Molaison, widely known as H.M., a patient who became severely amnesic following the surgical resection of a large part of bilateral MTL (Scoville and Milner 1957). Specifically, he was unable to form new episodic memories, but he was able to learn simple sensorimotor skills and hold information for very short periods of time. These findings demonstrated that MTL structures, including the HC, are specialized in forming and maintaining episodic memories.

Episodic memory is essentially associative, connecting various elements such as words and objects, either directly or through relationships based on space or time. Associative memory is defined as memory for the relationship between initially unrelated items. It primarily involves the recollection of associations, relationships, and interactions between objects or concepts. For example, when we see a particular object, associative memory allows us to recall related events or ideas associated with it. The HC is widely believed to play a critical role in binding and relating different attributes to form a comprehensive memory trace (Battaglia et al. 2011; Konkel and Cohen 2009).

Many studies have investigated the relationship between the HC and associative memory. Neuroimaging studies have shown that the HC exhibits stronger activation during the process of encoding associative information compared to encoding individual items (Brown and Aggleton 2001; Giovanello, Schnyer, and Verfaellie 2004). Additionally, patients with selective damage to the HC and amnesia demonstrate more pronounced difficulties in remembering associations between items compared to their ability to remember the individual items themselves (Turriziani et al. 2004; Giovanello, Verfaellie, and Keane 2003; Mayes et al. 2004). A human intracranial study demonstrated that hippocampal stimulation during encoding modulated memory performance in a task-dependent manner. Specifically, it enhanced associative memory while impairing item memory (Jun et al. 2020). Therefore, the HC is commonly described as a central hub for processing and linking information, being more involved in forming association between different elements of memory rather than encoding individual elements on their own (Squire and Zola 1998; Davachi 2006; Eichenbaum, Otto, and Cohen 1994).



Figure 1 A tentative taxonomy of long-term memory and associated brain structures. [Figure adapted from (Thompson and Kim 1996)]

The observation of postoperative changes in comprehensive neuropsychological tests in patients who underwent temporal lobe epilepsy surgery presents a valuable opportunity to explore the organization of the human memory system. Our knowledge of the neuroanatomy of memory has been greatly advanced by the study of the clinical outcomes of temporal lobe epilepsy surgery. Resective surgery for MTLE has a risk of memory decline after surgery. Approximately 30%-60% of patients experience postoperative verbal memory decline after left anterior temporal resection (Sherman et al. 2011). Also, patients after right-sided surgery have a risk of decline in nonverbal memory, although it is not as consistent as in verbal memory (Dulay et al. 2009; Vaz 2004).

However, there is still ongoing debate regarding the specific temporal subregions that are crucial for different aspects of episodic memory (Alpherts et al. 2008; Silbergeld 1997; Saling 2009; Yonelinas et al. 2005). In particular, studies that have examined the relationship between hippocampal resection and memory changes have found inconsistent results. Some studies have reported that larger hippocampal resection predicts a worse memory outcome, while others have reported that it does not (Helmstaedter et al. 2011; Jones-Gotman et al. 1997; Wyler, Hermann, and Somes 1995; Trenerry et al. 1993; Bonelli et al. 2010; Baxendale, Thompson, and Kitchen 2000). These controversies may be due to the limitation of groupwise comparison analyses, which have included neglect of individual differences in extent and in the exact locus of resection and usually comparisons of postoperative memory change according to the different surgical procedures. Therefore, to determine the contribution of the HC to memory function, an analysis that accounts for individual differences in resection is required.

1.2. Associative Memory beyond the MTL

1.2.1 Successful Memory Encoding and the Default Mode Network

Many studies of episodic memory have traditionally focused on the MTL; however, the HC does not work in isolation but rather functions together with cortical networks (Wang and Morris 2010). The HC is interconnected with other brain regions and plays a crucial role in processing and storing memories by linking related items (Mayes, Montaldi, and Migo 2007). During the encoding process, sensory information from the external environment is initially processed in the neocortex, which is responsible for higher-order cognitive functions. Subsequently, this processed information is relayed to the HC. The HC serves as a crucial hub for memory encoding and consolidation, integrating and associating different aspects of sensory information, such as context, emotions, and spatial relationships (Moscovitch et al. 2016).

Therefore, the interactions between large-scale networks and the HC influence the formation of associative memories (Kim and Voss 2019; Jeong, Chung, and Kim 2015). The most prominent large-scale memory network is known as the DMN (**Figure 2**). The DMN is mainly known as the a "task-negative" network, where regions show highly correlated activity at rest and are deactivated during goal-directed cognitive tasks (Raichle et al. 2001). Regions of the DMN include the dorsomedial prefrontal cortex (DMPFC), the posterior cingulate cortex (PCC), the angular gyrus (AG), the middle temporal gyrus (MTG), and the HC. Since successful encoding requires externally directed attention, activation in DMN

regions should be suppressed. Thus, deactivation of the DMN during encoding is known to reflect successful memory encoding (Anticevic et al. 2010; Chai et al. 2014; Raichle 2015; Sato and Mizuhara 2018), whereas activation of the DMN during encoding is known to be associated with subsequent forgetting (Kim 2011). On the other hand, previous research has demonstrated that distinct regions within the DMN can modulate both encoding success and failure. For instance, the medial prefrontal cortex, AG, and lateral temporal cortex were reported to mediate encoding success in a self-referential memory encoding task, whereas the posterior cingulate was reported to be related to both encoding failure and task unrelated thought (Maillet and Rajah 2014). DMN can also affect memory encoding in a variety of ways. The DMN assists the brain in freely associating and imagining. Free association and imagination help in generating new ideas and concepts and can aid in better understanding and encoding of information related to memory. During the construction of mental scenes based on memory, a specific subsystem of the DMN is preferentially engaged. This process involves the recruitment of the posterior cingulate, inferior parietal cortex, and lateral temporal cortex (Hassabis, Kumaran, and Maguire 2007). In summary, previous studies have demonstrated the involvement of various brain regions within the DMN in the success and failure of the memory encoding process.

The HC is widely recognized as the central hub of the DMN. It is known that the components of the DMN and MTL are not only strongly connected neuroanatomically (Clower et al. 2001; Lavenex, Suzuki, and Amaral 2002) but also neurofunctionally (Siapas, Lubenov, and Wilson 2005; Young and McNaughton 2009). There are several studies that have examined the relationship between the HC and other nodes within the DMN. Most functional connectivity studies in Alzheimer's disease and mild cognitive impairment have reported specific evidence of altered connectivity between the DMN and the MTL, which is associated with memory impairment (Celone et al. 2006; Greicius et al. 2004; Petrella et al. 2011; Rombouts et al. 2005). Moreover, the HC has been shown the decouple from the DMN to enable successful memory encoding (Herting and Nagel 2013; Vannini et al. 2011). On the other hand, stronger functional connectivity between the HC and DMN at rest has been associated with better memory performance (Wang et al. 2010; McCormick et al. 2013). To summarize, previous studies have shown that the connectivity between the HC and brain areas involved in the DMN may play an essential role in memory encoding.



Figure 2. Default Mode Network. (A) DMN regions show decreases in activity when subjects perform cognitive tasks performance. (B) BOLD resting state activity is strongly correlated within DMN regions. Here activity is shown for the seed region in posterior cingulate cortex (yellow arrow in A) and another region which shows a similar pattern of activity, in medial prefrontal cortex (orange arrow in A). (C) Functional connectivity across DMN regions defined by spatial coherence in resting state BOLD signal fluctuations across these areas. [Figure from (Raichle 2015)].

1.2.2 Subsequent memory effects

The subsequent memory paradigm is a classic technique in studying neural mechanisms underlying successful memory encoding (Figure 3). In this paradigm, neural activities in response to distinct stimuli are recorded in encoding the stimuli for an upcoming memory test. Afterward, the stimuli are classified based on whether they were remembered or forgotten. Differences in brain activity between subsequently remembered and forgotten trials at learning are often referred to as subsequent memory effects (SMEs) (Paller and Wagner 2002). There are two kinds of SMEs, the "positive subsequent memory effects" (positive SMEs) and the "negative subsequent memory effects" (negative SMEs). Positive SMEs refers to brain regions that demonstrate higher response during study items that were subsequently remembered than those subsequently forgotten. On the other hand, several regions demonstrate the opposite effect. That is a higher response during subsequently forgotten items than remembered, termed the negative SMEs.

There have been many studies that have investigated SMEs for associative memory formation. One study found that hippocampal activity during word-pair encoding predicted subsequent memory for inter-item associations (Jackson and Schacter 2004). In the meta-analysis of fMRI SMEs, verbal-associative memory SMEs were observed in the left posterior inferior frontal cortex/insula, bilateral fusiform cortex, and left HC. Pictorial-associative SMEs were observed in the HC, fusiform cortex, premotor cortex, left inferior frontal cortex, and right posterior parietal cortex (Kim 2011). In the aspect of brain oscillation, many studies demonstrated that successful memory formation is accompanied by changes in brain oscillatory activity. Furthermore, these studies found that the increases as well as decreases in activity at various frequencies have been related to memory formation [see (Hanslmayr and Staudigl 2014) for review]. For the associative memory, theta oscillations were reported to mediate item–context binding or associative memory formation (Summerfield and Mangels 2005; Kota, Rugg, and Lega 2020; Joensen et al. 2023).

As brain activity during encoding has a crucial effect on subsequent memory outcomes, it is plausible to use it to predict the success of subsequent memory outcomes. A number of studies have successfully established that brain oscillations in multiple EEG frequency bands during the encoding phase can predict subsequently remembered and forgotten trials (Hanslmayr and Staudigl 2014). In addition to SMEs during the encoding phase, previous studies also showed that prestimulus activities could predict subsequent memory outcomes, as anticipatory activity prior to stimulus presentation could play a critical role in how a stimulus will be processed (Otten et al. 2006; Guderian et al. 2009; Addante et al. 2011; Addante, de Chastelaine, and Rugg 2015; Burke et al. 2015; Cohen et al. 2015; Schneider and Rose 2016).

In this regard, there have been studies that predicted subsequent memory outcomes (i.e., remembered or forgotten) using single-trial EEG SMEs features of prestimulus and during the encoding phase. By combining the prestimulus and during encoding phase SMEs, a previous study achieved 59.6% classification accuracy (Noh et al. 2014), whereas another study achieved 72.1% classification accuracy (Sun et al. 2016). These studies have used the spectral power or eventrelated potential (ERP) of specific regions to predict subsequent memory outcomes. However, as the brain works collaboratively to process memory, other than features of local signal amplitude, a better option to predict subsequent memory outcomes could be to use the functional connectivity between multiple brain regions. Despite the importance of communication between the memory related networks and the HC, there have been no studies that have examined the ability to predict subsequent memory outcomes using the single-trial functional connectivity in prestimulus and during the encoding phases. Therefore, my objective was to investigate whether single-trial connectivity between the HC and the memory-related network could be utilized to predict memory success and failure.



Figure 3. The subsequent memory paradigm. In the encoding phase, brain activity is recorded while subjects attempt to remember stimuli. In the retrieval phase, memory tests are conducted to assess the participants' recall of these stimuli. The performance on these memory tests is then used to classify the stimuli presented during the encoding phase and their corresponding neural measures into two categories: subsequently remembered and subsequently forgotten. By comparing the neural activity associated with these two conditions, differences in neurophysiological responses can be computed based on subsequent memory performance.

1.3 Purpose of the present study

The hippocampus (HC) plays a critical and irreplaceable role in associative memory. However, it is important to note that the HC does not work in isolation to perform associative memory. Rather, it collaborates and interacts with different regions of the brain to facilitate memory processes.

To identify the specific contribution of the HC to associative memory, I examined the relationship between the resection of the HC and the postoperative memory changes on various memory tests in patients who underwent surgery for MTLE. I conducted a voxel-based analysis that accounts for individual differences in the location and extent of resection.

Expanding upon this understanding, I sought to investigate the role of hippocampal connectivity with memory-related networks in predicting memory success and failure. Among the various memory-related networks, I particularly focused on the DMN, the network involved in memory success and failure. Therefore, I aimed to determine whether the connectivity between the HC and the DMN could predict memory success and failure.

The aim of this study was to enhance our understanding of the role of the HC and its connectivity in associative memory by elucidating the effects of hippocampal resection on associative memory and highlighting the predictive power of the connectivity between the HC and the DMN for subsequent memory performance. My thesis emphasizes the importance of the large-scale memory network, rather than solely focusing on specific brain regions.

II. METHODS

2.1 Participants

2.1.1 Experiment 1. Medial Temporal Lobe Epilepsy Patients

I retrospectively included patients with MTLE who underwent resective surgery between 2005 and 2015 in the epilepsy clinic at the Seoul National University Hospital. Each patient's surgery was performed based on comprehensive preoperative tests, including history and neurological examination, seizure semiology, long-term video-EEG monitoring, structural MRI, PET, interictal and ictal SPECT, invasive monitoring if necessary, and/or magnetoencephalography. Inclusion criteria were intractable MTLE patients with histologically proven hippocampal sclerosis (Figure 4), whose postoperative highresolution MRI and pre- and postoperative neuropsychological test results were available. To control other confounding factors caused by differences in clinical practice, only patients who had surgery by a single neurosurgeon (C.K.C.) were included. Finally, I included 74 patients (60.8% female; 42 left-sided surgeries) in this study. All patients underwent either a temporal pole resection with an amygdalohippocampectomy (TPR+AH) or a selective amygdalohippocampectomy (SAH) (Figure 5 Left). The type of surgery was randomly assigned to the patients whose epileptogenic zone was located in the MTL determined by preoperative evaluation. In TPR+AH, the patients underwent a TPR (the average extent of the resection was 3.39 ± 0.78 cm from the temporal pole) with an AH (Helmstaedter et al. 2008). For SAH, all patients underwent a transsylvian approach (**Figure 5 Right**), entering the temporal horn of the lateral ventricle through the temporal stem. To determine seizure outcome, I used the Engel Epilepsy Surgery Outcome Scale (class I, free of disabling seizure; class II, rare disabling seizures; class III, worthwhile improvement; and class IV, no worthwhile improvement) (Engel 1993). All patients were in Engel classes I to III; no patient was in class IV. This study was approved by the institutional review board of the Seoul National University Hospital Clinical Research Institute. A summary of patient demographics is provided in **Table 1**.



Figure 4. hippocampal sclerosis. (A) T1 weighted acquisition showing an atrophic hippocampus (on right of image: arrow). (B) T2 weighted FLAIR image demonstrating increased T2 weighted signal within the sclerotic hippocampus [Figure adapted from (Cook and Kilpatrick 1994)].



Figure 5. A typical surgical resection for MTLE. (Left) Resection extent in selective amygdalohippocampectomy (SAH) and temporal pole resection (TPR+) on transverse MRI images (Right) Transsylvian, transcortical, and subtemporal approach in temporal lobe epilepsy. 1, gyrus temporalis superior, 2, gyrus temporalis inferior and -medius, 3, hippocampus. [Figures adapted from (Helmstaedter et al. 2008)].

	Lt MTLE $(n = 42)$	Rt MTLE (n = 32)
Sex, M/F	16:26	13:19
Handedness, n (%)		
Rt	37 (88.1)	30 (93.8)
Lt	4 (9.5)	1 (3.1)
Ambidextrous	1 (2.4)	1 (3.1)
Surgery type, n (%)		
SAH	14 (33.3)	8 (25.0)
TPR+AH	28 (66.7)	24 (75.0)
Mean age at seizure onset, yrs	15.8 (8.5)	18.3 (12.3)
Mean duration of illness, yrs	16.4 (9.5)	14.5 (10.1)
Mean age at surgery, yrs	32.3 (8.2)	32.8 (10.0)
Engel Class, n (%)		
Ι	39 (92.9)	29 (90.6)
II	2 (4.8)	1 (3.1)
III	1 (2.4)	2 (6.3)

Table 1. Demographics and clinical characteristics of patients

Mean values are presented as the mean (SD).

2.1.2 Experiment 2. EEG Study Participants

Twenty-nine right-handed healthy subjects without neurological or psychiatric abnormalities were recruited. The datasets of two participants were excluded from further analysis because of insufficient artifact-free trials. The final study group included 27 participants (11 females; mean age = 26.0 ± 2.1 years, range = 23-31 years; education level = 17.0 ± 1.2 years). As an effort to control the physiological condition of subjects, I instructed the subjects to get enough sleep the day before they participated in the experiment. This study was approved by the institutional review board (IRB) of the Seoul National University Hospital Clinical Research Institute (IRB number: H-1808-098-967).

2.2 Experimental Design

2.2.1 Experiment 1. Pre- and Post-Operative Memory Test

same comprehensive neuropsychological assessments The were conducted both before surgery (within 1 month) and after surgery as part of routine clinical practice (Shin et al. 2009). Verbal item memory was assessed using the verbal immediate and delayed recall subtests from the Korean version of the Rey Auditory Verbal Learning Test. This test requires immediate recall for a list of 15 words presented audibly at intervals of 1 second and repeated 5 times (verbal item immediate recall) and after 20 minutes requires recall for the list of words (verbal item delayed recall). Verbal associative memory was assessed using the verbal paired-associates subtest from the Wechsler Memory Scale-third edition, which requires patients to learn 14 pairs of words presented audibly, to then listen to the first word of each pair, and to recall immediately the other word in the pair (verbal associative immediate recall); after 30 minutes, the first word of the pair was presented and the patient was required to recall the other word in the pair (verbal associative delayed recall). Nonverbal memory was assessed using scores of the Korean version of the Rey Complex Figure Test, which requires patients to reproduce a complicated line drawing, first by copying it immediately (figural immediate recall) and then drawing it from memory after 20 minutes (figural delayed recall). In order to account for these individual differences in changes of memory functions, the postoperative memory change was calculated by subtracting the presurgical scores from the postsurgical scores of the patient.

2.2.2 Experiment 2. EEG Experimental Paradigm

I applied a subsequent memory paradigm that consisted of scene-word pairs in study and test blocks (Figure 6). Each study and test block had 75 trials. Scene stimuli consisted of 50% indoor images and 50% outdoor images. As word stimuli, concrete nouns of 50% nature objects and 50% manmade objects were used. During the study phase, subjects were instructed to remember scene-word pairs using a strategy that made an imaginary scene associated with the paired word for 3 s. In order to boost subjects' participation in the experiment, the subjects were instructed to press a button on whether or not the associative imaginary scene in the mind vividly appeared when a red fixation was presented on the screen. To eliminate the residual effect of the previous stimulus, boxes filled diagonally were presented for 1.5 s. The encoding phase of one experimental session lasted about 10 min. After the study block, subjects were instructed to answer as many simple arithmetic problems as possible in 2 min for a distracting task (e.g., alternately subtract 4 and 7 from 100). During the test phase, subjects were instructed to verbally recall the word cued by the scene previously learned at self-paced speed. There was a time limit of up to 20 s, and if exceeded, it was classified as forgotten. To maintain the attention of the participants, the next session went on when the subjects were fully prepared. One session consisted of a block of study, distraction, and test. Three sessions were conducted for each subject. Stimuli were presented using STIM2 presentation software (Compumedics Neuroscan, Australia).



Figure 6. Experimental Paradigm. (A) Study block. Subjects were instructed to remember scene–word pairs using a strategy that makes an imaginary associative scene. (B) Test block. Subjects were asked to verbally recall the word cued by the scene at self-paced speed.

2.3 Data Analysis

2.3.1 Experiment 1. MRI Image and Statistical Analysis

Image Analysis

T1-weighted MR images with a thickness of 1.0 mm were used. All patients were examined using a 1.5T (Signa Horizon, GE Healthcare; or Magnetom Avanto, Siemens) or a 3T (Signa Excite, GE Healthcare; or Magnetom Verio, Siemens) MRI system both before and after surgery. The mean follow-up for postoperative MRI was 1.10 ± 2.23 years. Lesions were manually delineated by one author (D.H.K.) on native T1-weighted images using MRIcron software (http://www.nitrc.org/projects/mricron/). Then, the T1-weighted images were segmented and normalized into the Montreal Neurological Institute (MNI) template by using the Clinical Toolbox (Brett et al. 2001; Rorden et al. 2012) for SPM12 (https://www.fil.ion.ucl.ac.uk/software/spm12/), which implements a unified nonlinear normalization and segmentation process. Normalization was conducted using lesion cost function masking (Brett et al. 2001; Rorden et al. 2012) to prevent image distortion, which is often observed in brain images with lesions. All manually delineated individual resection maps were overlapped on the MNI atlas for generating the resection frequency map in order to display individual differences in extent and locus of resection and for voxel-based statistical analysis (Figure 7) (Bonilha et al. 2007; Galovic et al. 2019; Kim et al. 2011).



Figure 7. Overlapped images of manually delineated individual resection maps. A: Frequency of the resected area in left-sided MTLE surgery. B: Frequency of the resected area in right-sided MTLE surgery. For each voxel, the frequency of patients who had the resection are represented by colors. As shown in the scale bar, red represents the area resected in most patients, and blue represents the area resected less frequently.

Voxel-Based Analysis

In this study, according to the material-specific memory model (Willment and Golby 2013), I analyzed verbal memory in the left MTLE group and nonverbal memory in the right MTLE group. For each voxel, patients were divided into two groups depending on whether the voxel was resected or not. The difference in postoperative memory score changes between the two groups was tested using the Mann-Whitney U-test. Finally, mapping was performed on voxels with a significantly small value of memory score change in the resected group compared with the nonresected group (p < 0.05, familywise error corrected; cluster extent threshold, 30 voxels). All voxel-based statistical analyses were performed using Matlab (version R2018a, MathWorks Corp.).

2.3.2 Experiment 2. EEG Connectivity Analysis for Memory Performance Prediction

EEG Data Acquisition and Preprocessing

EEG was recorded using a Neuroscan EEG recording system (Compumedics Neuroscan, United States) with 64-channel Quick caps (Compumedics Neuroscan, United States) in an electrically shielded cabin. EEG signals were digitized at a sampling frequency of 1,000 Hz with a SynAmps2 amplifier (Compumedics Neuroscan, United States). Preprocessing was conducted using EEGLAB open source toolbox (version 2019.11) and self-written MATLAB scripts (version R2019b; MathWorks Corp.). At the first preprocessing step, common average reference was applied. The data were segmented into epochs ranging from -1,000 to 2,000 ms relative to the stimulus onset. Trials that include high noise were manually discarded, and only the remaining artifact-free trials were used for further classification analysis.

Time-frequency analysis

For the time-frequency analysis, continuous wavelet transformation was applied. I focused on the theta (3–7 Hz), alpha (8–12 Hz), and beta (13–30 Hz) frequency bands. These power values were then normalized by the baseline activity before the stimulus onset of -1 to -0.8 s. EEG signals at -500 to 0 ms before the stimulus onset were used as a "prestimulus" phase, and EEG signals after the stimulus onset at 0 to 1,000 ms were used as an "encoding" phase for subsequent connectivity analysis.
Source Localization

For the source analysis, regions of interest (ROIs) were selected in regions that were representative of the DMN (Raichle 2015). The ROIs included the DMPFC, PCC, AG, MTG, and HC. **Table 2** shows the coordinates of the ROIs. Source activity was extracted using the built-in function of discrete model probing in BESA research 6.0 (GmbH, Germany).



Inverse problem: source imaging

Figure 8. Source localization [Figures adapted from (Becker et al. 2016)]

EEG source localization is the process of using EEG data to estimate the original location of activity occurring within the brain. The inverse problem refers to the problem of estimating the original source location backward from the measured data. A lead field matrix is a matrix that describes the relationship between a signal source and a sensor.

If I define X as EEG signals, the relation could be described as follows;

$$X = L \cdot S + n$$

where S represents source activities, n denotes the measurement noise, and L is a

lead field matrix. The inverse problem refers to finding S given known X. To calculate the source model, Equivalent Current Dipoles (ECD) algorithm was used. The current density at the j-th point, S_{j} is given by

$$S_j \!= W_j \cdot X$$

where $W_j = (L_j^T \cdot L_j)^{-1} \cdot L_j^T$

Right hippocampus

Region	Abbreviation	Х	У	Z
Dorsomedial prefrontal cortex	DMPFC	0	32	5
Posterior cingulate cortex	PCC	0	-51	23
Left angular gyrus	AG (L)	-44	-54	23
Right angular gyrus	AG(R)	44	-54	23
Left middle temporal gyrus	MTG (L)	-53	-2	-18
Right middle temporal gyrus	MTG (R)	53	-2	-18
Left hippocampus	HC (L)	-27	-11	-13

HC(R)

27

-11

-13

Table 2. Talairach coordinates of regions of interest

Connectivity Analysis

For the source connectivity analysis, I calculated the time–frequency cross-MI (Jeong, Gore, and Peterson 2001). After the continuous wavelet transform, the mean value of each frequency band (theta, alpha, and beta) was obtained. Then, cross-MI was calculated using samples from each time interval (prestimulus and encoding phase). MI is a measure of the amount of dependency between two signals. Compared to linear correlation, MI is a more general measurement, because it can measure non-linear dependency. The temporal series of averaged frequency band signals were used to compute the cross-MI between ROIs. MI values between two input signals X and Y can be calculated using the probability density function, as follows:

$$MI_{XY} = MI_{YX} = MI(X, Y) =$$
$$\sum p (X, Y) \log \frac{p(X, Y)}{p(X) \cdot p(Y)}$$

here, p(X, Y) is the joint probability distribution function of variables X and Y, and p(X) and p(Y) are the marginal probability distribution functions of X and Y, respectively.

Then, I investigated the differences in EEG connectivity between subsequently remembered and forgotten trials (during both the Prestimulus and Encoding phases).

Single Trial Classification

I used a linear support vector machine (SVM) in MATLAB for the classification of memory success. We used functional connectivity and normalized power as features to classify subsequent memory outcomes to compare the classification accuracy of each measurement. I utilized the Matlab algorithm "sequentialfs" on our training data for feature selection. This algorithm takes into account feature interactions and selects a subset of features by adding them one at a time. It keeps track of the misclassification rate and the corresponding feature indices. The algorithm stops when the minimum misclassification error is reached. By doing so, "sequentialfs" identifies the five most important features were selected for classification. The classification of individual EEG signals was assessed using a method called Five-fold cross-validation with 100 repetitions. In this approach, the total trials or samples are randomly divided into five blocks or subsets. Out of these, four blocks are used as training data to train the model, while the remaining one block is used as test data to evaluate the model's performance.

III. RESULTS

3.1 Experiment 1. Postoperative Memory Change Analysis Results

3.1.1 Neuropsychological Outcome

The mean interval between pre- and postoperative neuropsychological tests was 1.61 ± 1.18 years. Details of the neuropsychological memory scores are presented in **Table 3**. There were no significant differences in group-level comparison of pre- and postoperative memory by paired sample t-test. However, there were various differences in the individual level as shown in **Figure 9**.

Table 3. Results of preoperative and postoperative neuropsychologicalmemory testing

	Preop	Postop
Lt MTLE		
K-RAVLT $(n = 42)$		
Verbal item immediate recall	39.8 (8.7)	39.4 (10.6)
Verbal item delayed recall	5.9 (3.2)	6.8 (3.7)
WMS-III $(n = 36)$		
Verbal associative immediate recall	6.4 (3.1)	6.4 (3.4)
Verbal associative delayed recall	6.0 (3.1)	5.9 (3.5)
Rt MTLE		
K-RCFT (n = 32)		
Figural immediate recall	16.2 (7.6)	16.6 (5.7)
Figural delayed recall	15.1 (7.5)	16.0 (6.6)

K-RAVLT = Korean version of the Rey Auditory Verbal Learning Test; K-RCFT = Korean version of the Rey Complex Figure Test; WMS-III = Wechsler Memory Scale-third edition.Values are presented as the mean (SD).



Figure 9. Individual memory change. (A) Individual memory changes in verbal item memory, (B) verbal associative memory and (C) figural memory. Each line represents an individual patient. Red lines indicate postoperative improvement and blue lines represent postoperative decline.

3.1.2 Voxel-based Analysis

Voxel-Based Statistical Mapping of Verbal Memory

For verbal item memory, resection of the left lateral temporal area (superior, middle, inferior temporal, and fusiform) was significantly associated with the decline in immediate and delayed recall of a word list. For the verbal associative memory, resection of the anterior part of the left HC, left parahippocampal area, and left lateral temporal area (superior, middle, inferior temporal, and fusiform) was significantly related to a worse memory outcome in immediate recall of word pairs. Resection of the posterior part of the left HC, left parahippocampal area, and left lateral temporal area (superior, middle, inferior, and fusiform) was significantly related to a worse memory outcome in immediate recall of word pairs. Resection of the posterior part of the left HC, left parahippocampal area, and left lateral temporal area (superior, middle, inferior, and fusiform) was significantly related to a worse memory outcome in delayed recall of word pairs (Figure 10).



Figure 10. Voxel-based statistical mapping of verbal memory. Mapping was performed on voxels with a significantly small value of memory score change in the resected group compared with the nonresected group (p < 0.05, familywise error corrected; cluster extent threshold, 30 voxels). A: Voxel-based statistical mapping of verbal item memory. B: Voxel-based statistical mapping of verbal item memory.

Voxel-Based Statistical Mapping of Nonverbal Memory

In the nonverbal memory, resection of the anterior part of the right HC, right amygdala, right parahippocampal area, and medial part of the right superior temporal area was significantly associated with the decline of immediate recall of complex figures. Resection of the posterior part of the right HC and the right parahippocampal area was significantly associated with worse outcome in delayed recall for the same task (**Figure 11**).



Figure 11. Voxel-based statistical mapping of figural memory.

3.2 Experiment 2. Memory Performance Prediction Results

3.2.1 Behavioral Results

On average, participants correctly remembered $54.64\% \pm 18.26\%$ (mean \pm standard deviation) trials of the stimulus, indicating that they were able to efficiently encode materials and that I obtained enough trials for both remembered and forgotten conditions.

3.2.2 Differences in Connectivity Features

Figure 12 and **Table 4** presents the results of the t-test (uncorrected) for the difference between the remembered and forgotten condition. At the prestimulus and encoding phase, the subsequently remembered condition showed increased connectivity between the HC and the DMPFC in the alpha band, and increased connectivity between the HC and the AG in the beta band. On the other hand, the subsequent forgotten condition showed increased connectivity between the HC and the PCC in the theta and alpha bands at the prestimulus and encoding phase.

3.2.3 Classification Accuracy

Table 5 describes the individual classification accuracy using source activity for each phase and frequency band. The SVM binary classifier achieved the highest mean classification accuracy of 72.52 % \pm 11.46 % (mean \pm standard deviation) using the theta source activity at the encoding phase (chance level =

50%). On the other side, the SVM classifier achieved the highest mean classification accuracy of 91.38 % \pm 6.68 % using the beta connectivity features at the encoding phase (**Table 6**).



Figure 12. Results of the t-test for the difference in mutual information between the remembered and forgotten conditions (p < 0.05). The nodes selected in this study are the midline DMPFC, midline PCC, left and right ANG, right and left MTG, and right and left HC

Time	Band	R	t-value	
prestimulus	theta	MTG (R)	HC (R)	-1.760*
		HC (L)	HC (R)	-2.096 *
	alpha	DMPFC	HC (L)	2.941**
		PCC	HC (L)	-2.119*
		PCC	HC (R)	-2.271*
		AG(L)	HC (R)	-1.922*
		MTG (R)	HC (R)	-2.334*
	beta	AG(R)	HC (L)	2.624**
Encoding	theta	PCC	HC (R)	-1.807*
		HC (L)	HC (R)	-1.890*
	alpha	DMPFC	HC (L)	1.759*
		PCC	HC (R)	-1.879*
		MTG (R)	HC (R)	-2.728**
	beta	AG(R)	HC (L)	2.475*

 Table 4. Results of the t-test for the difference between the remembered and forgotten conditions.

*p < 0.05, **p < 0.01

	prestimulus (-500 to 0 ms)			Encoding (0-1,000ms) %		
subject	theta	alpha	beta	theta	alpha	beta
sub1	63.00	79.75	54.67	60.95	68.40	58.67
sub2	69.17	61.22	71.72	78.11	73.78	77.89
sub3	70.78	58.39	59.67	75.67	50.61	80.94
sub4	70.00	54.75	64.65	71.35	57.30	68.05
sub5	71.27	53.82	77.73	80.23	52.50	82.91
sub6	61.36	63.95	69.86	65.18	69.14	70.27
sub7	53.35	56.90	68.90	63.55	56.35	67.20
sub8	62.45	53.64	93.45	71.91	60.09	89.68
sub9	68.90	67.30	61.70	72.15	58.50	55.45
sub10	60.75	58.50	66.69	77.56	67.25	71.06
sub11	74.80	52.75	65.45	91.50	67.25	65.55
sub12	56.35	67.40	61.20	59.70	58.25	60.45
sub13	59.06	62.06	65.67	70.61	57.78	71.56
sub14	54.27	61.36	49.59	66.14	59.95	52.45
sub15	61.72	84.44	63.44	64.50	92.28	65.11
sub16	58.82	54.82	55.68	67.50	58.73	51.68
sub17	60.90	52.40	46.50	60.20	53.15	52.10
sub18	60.75	50.17	51.25	71.50	67.42	55.75
sub19	74.31	67.50	66.31	79.31	67.00	72.13
sub20	54.75	54.56	52.81	58.88	59.19	54.25
sub21	60.22	61.56	53.89	59.67	60.72	51.28
sub22	57.35	55.65	64.75	68.45	58.95	73.60
sub23	50.41	51.41	47.68	56.86	49.09	54.14
sub24	66.95	59.15	71.20	89.35	63.55	72.65
sub25	92.00	59.35	60.65	88.45	58.00	56.60
sub26	87.10	52.00	62.25	89.00	70.20	55.85
sub27	99.33	91.78	64.33	99.72	90.67	61.11
Average	65.93	60.98	62.66	72.52	63.19	64.75
SD	11.73	10.20	9.94	11.46	10.24	10.71

 Table 5. Individual classification accuracy (DMN regions source activity)

	$\mathbf{r}_{\text{restimulus}}$ (500 to 0 ms) Encoding (0.1.000ms)				ma) 04	
	presum	10105 (-300 to	1	Encoding (0-1,000ms) %		
subject	theta	alpha	beta	theta	alpha	beta
sub1	73.78	82.28	89.14	78.60	87.35	81.60
sub2	69.97	93.61	97.75	84.72	93.78	97.56
sub3	64.34	62.55	86.05	81.83	71.72	86.17
sub4	85.05	96.55	95.55	90.55	96.75	95.40
sub5	74.48	96.55	98.00	74.59	87.95	98.95
sub6	90.57	84.59	95.07	95.68	88.77	96.27
sub7	49.70	85.15	93.55	53.80	75.10	93.80
sub8	73.98	78.30	97.27	85.45	84.41	98.63
sub9	83.35	72.03	97.38	83.75	82.20	95.80
sub10	83.81	90.88	80.69	80.75	87.50	85.69
sub11	66.17	91.52	88.21	94.75	93.05	81.25
sub12	74.11	87.58	93.76	80.20	85.85	95.05
sub13	92.63	95.87	94.29	95.89	95.44	96.28
sub14	70.82	77.25	94.59	78.86	86.86	99.05
sub15	61.22	77.56	76.75	64.33	84.5	81.83
sub16	65.80	56.52	85.09	74.82	67.95	88.77
sub17	55.18	66.95	65.95	65.95	74.40	71.90
sub18	58.25	73.38	85.33	66.92	81.00	90.92
sub19	96.34	72.50	91.56	89.75	76.38	92.06
sub20	60.88	80.97	86.71	68.31	88.19	88.31
sub21	71.45	64.53	79.61	82.56	70.22	88.78
sub22	77.36	77.98	97.48	68.45	78.25	98.67
sub23	57.75	54.57	82.95	68.86	65.77	92.86
sub24	92.03	73.00	92.24	91.75	85.00	89.85
sub25	88.18	71.29	87.47	80.90	72.30	90.40
sub26	82.95	92.36	92.43	87.40	95.05	94.55
sub27	95.92	91.83	96.16	97.44	95.56	96.83
Average	74.67	79.56	89.67	80.25	83.38	91.38
SD	13.24	12.18	7.69	11.18	9.10	6.68

Table 6. Individual classification accuracy (functional connectivity betweenHC and other DMN regions)

IV. Discussion

4.1 Summary

The main objective of this thesis was to enhance our understanding of the role of the HC and its connectivity in associative memory. In the first part of my thesis, I sought to shed light on the actual significance of the HC in associative memory. To achieve this, I conducted an investigation of postoperative changes in memory function in patients who underwent surgery for MTLE. Using a voxel-based analysis that accounts for the individual differences in the resection, I found that resection of the HC was associated with a decline in associative memory rather than item memory. In both verbal and visual memory, resection of the anterior part of the HC was associated with immediate recall, and resection of the posterior part of the HC was associated with delayed recall.

The second part of my thesis aimed to investigate whether successful associative memory performance depends on the functional connectivity between the HC and the memory-related network. Among the various memory-related networks, I specifically focused on the DMN. I utilized single-trial EEG connectivity between the HC and DMN to investigate its potential in predicting the success and failure of associative memory. By using the functional connectivity between these regions, I achieved a significantly higher accuracy in predicting memory outcomes compared to solely considering activity in specific regional sources.

4.2. Experiment 1. Associative Memory and Hippocampal Resection

Verbal Associative Memory and the Hippocampal Resection

From voxel-based analysis, I found that resection of the left lateral temporal area was related to worse outcome of postoperative verbal item memory, and resection of the left HC, left parahippocampal area, and left lateral temporal area was related to postoperative verbal associative memory decline. That is, there was no statistical significance in the extent of resection of the HC when observed with the item memory task, but there was a significant relationship between the resection of the HC and postoperative memory change in the task requiring associative memory.

From the task-specific perspective in verbal memory, several previous studies reported dissociation of item and associative memory. In a bilateral hippocampal lesion study, patients did worse on the associative memory task than on the item memory tasks (Gold, Hopkins, and Squire 2006). In the study involving individuals with amnestic mild cognitive impairment, it was observed that the impairment in learning ability was more pronounced in associative memory compared to item memory (Wang et al. 2013). In a functional MRI study, the HC was more activated in memory for the associations between informational elements than in memory for individual elements (Giovanello, Schnyer, and Verfaellie 2004). In a brain stimulation study, direct electrical stimulation of the HC enhances verbal associative memory but not verbal item memory (Jun et al. 2020).

Nonverbal Memory and the Hippocampal Resection

In the figural memory task, it requires the analysis and reproduction of the spatial relationship between individual elements. In other words, this task requires the ability to associate individual elements into a single figure. I found that resection of the anterior part of the right HC, right amygdala, right parahippocampal area, and medial part of the right superior temporal area was related to the decline in immediate recall of complex figures. On the other hand, the decline in the figural delayed recall was related to the resection of the posterior part of the right HC and right parahippocampal area.

From a task-specific perspective in visual memory, a non-invasive stimulation study has shown that hippocampal-targeted theta-burst stimulation enhances object-location associative memory formation, while item memory remains unaffected (Tambini, Nee, and D'Esposito 2018). Several nonhuman primate studies reported that the hippocampal lesion impaired visual paired comparison tasks (i.e., visual associative memory task) but not visual item memory tasks (Nemanic, Alvarado, and Bachevalier 2004; Pascalis and Bachevalier 1999). However, there is no study in humans that has clarified the task specificity of nonverbal memory decline in patients who underwent temporal resection. Therefore, future study is warranted to test the task specificity in the nonverbal memory by using various figural memory tests after resection of the right temporal area in humans.

Long axis specialization of the human hippocampus

Interestingly, both in verbal associative memory and figural memory, resection of the anterior part of the HC was associated with worse immediate recall outcome, whereas resection of the posterior part of the HC was associated with worse delayed recall outcome. Considering these results, the locus of hippocampal resection may affect immediate and delayed recall differently. There are many studies about the functional differentiation along the anteroposterior axis of the HC. The anterior and posterior regions of the HC have different anatomical connections and support different behavioral functions (Grady 2020). In line with our findings, a nonhuman primate study reported that posterior hippocampal neurons were predominantly activated compared with anterior hippocampal neurons in a delayed spatial memory task (Colombo et al. 1998). Similarly, in a functional MRI study in humans, anterior hippocampal activity decreased over the retention interval; however, posterior hippocampal activity did not decline over time (Dandolo and Schwabe 2018). In addition, my results align with a study indicating stronger anterior hippocampal activity for recent memories than for remote memories (Gilboa et al. 2004). In this sense, I speculate that the anterior part of the HC might play an important role for immediate recall, and the posterior part of the HC has an important role for delayed recall.

4.3 Experiment 2. Prediction of Associative Memory Performance Using Hippocampal Connectivity

Subsequent Memory Effects of Hippocampal Functional Connectivity

I examined the connectivity between the HC and other regions within the DMN to predict the success or failure of associative memory performance. Using prestimulus beta band connectivity, I achieved 89.67% average classification accuracy, and using encoding beta band connectivity, I achieved 91.38% prediction accuracy. Meanwhile, using prestimulus theta source activity, I achieved 65.93% average classification accuracy, and using encoding theta source activity, I achieved 72.52% prediction accuracy. That is, by using hippocampal functional connectivity features, I achieved a higher classification accuracy compared to using local brain activities.

Conventional studies have investigated the role of local brain activities in relation to the formation of human memories. Previous studies have consistently reported that successful memory encoding is related to the activation of specific brain regions. In particular, successful memory encoding is related to the MTL and prefrontal cortex (Wagner et al. 1998; Paller and Wagner 2002; Reber et al. 2002; Kim 2011), whereas the failure of memory encoding is related to PCC and temporoparietal junction (Otten and Rugg 2001; Kim 2011). In addition to encoding SMEs, as anticipatory activity prior to stimulus presentation could play a critical role in how a stimulus will be processed, many studies have also investigated prestimulus SMEs (Otten et al. 2006; Guderian et al. 2009; Addante et al. 2011; Addante, de Chastelaine, and Rugg 2015; Burke et al. 2015; Cohen et al.

2015; Schneider and Rose 2016). However, recent studies have suggested the involvement of the more widely distributed cortical network and the importance of its collaborative roles in episodic encoding (Jeong, Chung, and Kim 2015).

Previous studies have predicted subsequent memory outcomes based on regional activity. By combining prestimulus and encoding SMEs, one study achieved 59.6% classification accuracy (Noh et al. 2014), whereas another study achieved 72.1% (Sun et al. 2016). They used brain activity in specific areas (e.g., spectral power or ERP of specific regions) as a feature. On the other hand, our results showed that subsequent memory outcomes could be better predicted using hippocampal functional connectivity compared to the local brain activity. Because multiple brain regions work together to process memory, using functional connectivity within memory-related brain networks may be a better option than using local brain activity to predict subsequent memory performance. Furthermore, because EEG brain activity is highly variable over time, random fluctuations and temporal dynamics can be artifacts in predicting memory performance. In contrast, functional connectivity between brain regions is synchronized in time, making it more robust to artifacts and temporal dynamics. For these reasons, functional connectivity may be more accurate in predicting memory than using localized brain activity.

Based on previously published research results (Kim et al. 2020), I achieved accuracy of up to 72.45% in the prestimulus phase and up to 80.83% accuracy in the encoding phase by using the connectivity between all DMN regions as features. Whereas, in this study, by solely utilizing the connectivity between the HC and other DMN regions, I achieved up to 89.67% accuracy in the prestimulus

phase and up to 91.38% accuracy in the encoding phase. These findings indicate that using only the connectivity between the HC and other DMN regions yields superior accuracy compared to using connectivity across all DMN regions. These results suggest the crucial role of hippocampal connectivity in predicting subsequent memory, which aligns with the well-established fact that episodic memory critically depends on the MTL and its functional connections to the cortex (Jeong, Chung, and Kim 2015; Wang et al. 2006).

The Frequency Characteristics of Subsequent Memory Effects

In the prediction results using source activity, both in the prestimulus and the encoding phases, the theta band source activity feature exhibited the highest classification accuracy. Numerous studies have investigated the relationship between theta band oscillations and successful memory performance. Theta oscillations have been found to play a role in learning and memory [see (Herweg, Solomon, and Kahana 2020) for review]. In a previous study combining EEG and fMRI, the results of EEG source localization showed that increased theta band activity in the MTL is associated with the binding of items to their spatiotemporal context (Hanslmayr et al. 2011). Another study combining EEG and fMRI demonstrated that theta power during encoding predicts subsequent memory performance and deactivation of DMN (White et al. 2013). For the prestimulus activity, successful memory performance involves an increase in theta oscillations [see (Cohen et al. 2015) for review]. In the MEG study, amplitudes of theta oscillations shortly preceding the onsets of the stimulus were higher for later-recalled than for later-forgotten stimuli (Guderian et al. 2009). Thus, it may be

reasonable to conclude that theta activity is a reliable predictor of successful memory encoding.

For the connectivity features, beta band connectivity revealed the highest classification accuracy. Increased ongoing prestimulus beta is reported to reflect a memory-promoting state (Scholz, Schneider, and Rose 2017). Candidate mechanisms for memory-promoting states in beta-band connectivity are attentional (Egner and Gruzelier 2004) or inhibitory processes (Waldhauser, Johansson, and Hanslmayr 2012). Also, beta band oscillation is known to serve as a communication mechanism between distant cortical areas (Wang et al. 2017). Therefore, it can be speculated that the communication within the DMN network during the prestimulus and encoding phases, which is associated with memory performance, is facilitated through large-scale coupling of beta band neural oscillations.

Hippocampal Connecitivty Characteristics of Successful Associative Memory

The activation and connectivity within large-scale brain networks prior to task onset influence performance levels (Kamp et al. 2018). In the prestimulus phase, preparation for successful encoding requires maintaining top-down attention to the task and suppressing task-irrelevant thoughts before the stimulus onset. Therefore, the ongoing neural activity that occurs before stimulus onset may play an important role in preparing the brain for a successful memory outcome (Otten et al. 2006; Guderian et al. 2009; Addante et al. 2011; Addante, de Chastelaine, and Rugg 2015; Burke et al. 2015; Cohen et al. 2015; Schneider and Rose 2016). During the encoding phase, in the results, most of the functional connectivity patterns of the prestimulus phase were maintained in the encoding phase. It is speculated that successful memory encoding requires a sustained state of memory promoting state between prestimulus and encoding. Presumably, attention or intention to encode during the prestimulus phase will affect subsequent memory performance (Schneider and Rose 2016; Galli, Gebert, and Otten 2013).

Although it is generally known that the DMN regions are involved in encoding failure (Kim 2011), I found encoding success effects in the connectivity of DMN regions, including between the HC and the DMPFC, AG. The connectivity between HC and DMPFC in the alpha band and the connectivity between HC and AG in the beta band were related to the subsequently remembered condition, and the connectivity between HC and PCC in the theta and alpha bands appeared in the forgotten condition. Similarly, previous research has demonstrated that distinct regions within the DMN can modulate both encoding success and failure. The medial prefrontal cortex, AG, and lateral temporal cortex were reported to mediate encoding success in a self-referential memory encoding task, whereas the posterior cingulate was reported to be related to both encoding failure and task unrelated thought (Maillet and Rajah 2014). The connectivity of the DMPFC has been reported to be associated with maintaining top-down attention and focus on the task for successful encoding (Miller and Cohen 2001). Also, the interplay between HC and medial PFC is known to play an important role in memory encoding (Preston and Eichenbaum 2013; Simons and Spiers 2003). The connectivity between the HC and the AG may be related to semantic processing. Semantic processing is the most consistent function that activates the AG (Seghier 2013). Semantic processing can enhance memory encoding by providing a more meaningful and elaborate

representation of the information being encoded. On the other hand, the connectivity between the HC and the PCC appeared in the forgotten condition. In many studies, the PCC showed more activity for subsequently forgotten items than for the subsequently remembered items (Otten and Rugg 2001; Wagner and Davachi 2001; Daselaar, Prince, and Cabeza 2004; Daselaar et al. 2009; Miller et al. 2008; Duverne, Motamedinia, and Rugg 2009).

4.4 Conclusion

The HC plays an important role in associative memory, but this function is accomplished through communication between the HC and other areas of the brain. In the first part of this thesis, by observing postoperative memory changes in patients with MTLE, I found that the HC was involved in associative memory rather than item memory. Building on this finding, the second part of this thesis focused on examining the connectivity between the HC and other regions within the DMN to predict subsequent memory performance. Using single-trial EEG connectivity features, I achieved an average accuracy of over 90% in predicting of subsequent memory performance. This level of accuracy was notably higher compared to using brain activity in specific regions.

These findings suggest that associative memory function is supported not only by the HC but also by the cooperative interaction between the HC and distributed memory-related networks. My thesis highlights the importance of understanding the role of the large-scale memory network, not just the role of specific brain regions. In the future, these results could be very useful in building a closed-loop brain stimulation system for memory enhancement, which could provide stimulation only when a subsequent memory outcome is predicted to be forgotten (Ezzyat et al. 2018).

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국문 초록

연합기억에서의 해마의 역할: 절제 연구와 뇌파 연결성 연구로부터의 통찰

김다혜

연합 기억은 서로 관련없는 항목들의 관계에 대한 기억으로 정의됩니다. 해마는 연합기억에서 대체할 수 없는 중요한 역할을 하는 것으로 알려져 있습니다. 그러나, 해마가 단독으로 작용하여 연합 기억을 수행하는 것은 아니라는 점에 유의하는 것은 중요합니다. 연합 기억은 뇌의 여러 영역이 상호 작용하여 작동합니다. 따라서 연합 기억을 수행할 때 단순히 특정 영역이 활성화 되는 것 보다 해마와 기억 관련 네트워크 간의 기능적 연결이 더 중요할 수 있습니다.

먼저 해마가 연합 기억에 어떤 기여를 하는지 알아보기 위해 내측 측두엽 뇌전증으로 수술을 받은 환자를 대상으로 해마의 절제 여부와 수술 후 다양한 기억력 검사에서 나타난 기억력 변화 사이의 관계를 조사했습니다. 절제 영역과 위치의 개인차를 반영하는 복셀 기반 분석을 통해 해마의 절제가 항목 기억보다는 연합 기억의 저하와 관련이 있음을 발견했습니다.

이러한 이해를 바탕으로 저는 기억의 성공과 실패를 예측하기 위해 해마와 기억 관련 대뇌 피질 네트워크 영역 사이의 단일 시행 뇌파 연결성을 활용했습니다. 그 결과, 기억의 수행도를 예측할 때 평균 90% 이상의 정확도를 달성했습니다. 이 정확도는 특정 영역의 뇌 활동만을 예측에 사용하는 것과 비교했을 때 현저히 높은 수치입니다. 요약하자면, 이 논문은 연합 기억에서 해마와 해마의 연결성의 중요한 역할을 강조합니다. 이 연구는 연합 기억 과정을 이해하는 데 있어 특정 뇌 영역에만 초점을 맞추는 것이 아니라 대규모 기억 네트워크의 역할을 이해하는 것이 중요하다는 점을 강조합니다.