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Functional characterization of memory-encoding networks after medial temporal lobe resection

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ABSTRACT

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Considering the central position of the hippocampus as a densely interconnected hub in brain networks and its role in episodic memory, medial temporal lobe resection, including the hippocampus, should modify recruitment and strength of connectivity of functional memory network. However, functional memory encoding network in patients with medial temporal lobe resection has not been well characterized, which could provide a clue for new therapeutic targets for people with memory impairment. The aim of present study is to understand how brain supports normal episodic memory function without unilateral medial temporal lobe structures in a new perspective of functional interactions of brain network. Thirty-seven patients who underwent unilateral medial temporal lobe resection for the treatment of

medically intractable temporal lobe epilepsy (17 left, 20 right; median age 34 years) and 24 healthy controls (median age 32 years) were studied. To understand stable and an effective memory network, patients who underwent resective surgery at least 1 year before fMRI scanning and who have normal range of postoperative memory capacity were recruited. All subjects performed functional MRI memory encoding paradigm of words and figures. Hippocampal regions of interest analysis revealed that greater activation of hippocampus contralateral to the resection was related to higher memory scores in both patient groups. Whole-brain functional activation analysis revealed that well-known task-negative areas including the medial prefrontal cortex were less deactivated in patient groups than healthy controls. Task-based functional connectivity analysis revealed that the right medial prefrontal cortex showed stronger interactions with widespread brain areas including hippocampus contralateral to the resection during successful word encoding in left surgery group and during successful figure encoding in right surgery group. Furthermore, the strengths of right medial prefrontal cortex functional connectivity predict individual memory capacity of patients. The results of present study suggest that hyper-connectivity of medial prefrontal cortex may play a pivotal role in episodic memory function with the absence of functional connections of medial temporal lobe. These results, therefore, further implicated in the studies of brain stimulation toward enhancing memory for people who suffer from medial temporal lobe-dysfunction-related memory disturbances by providing possible new target area of medial prefrontal cortex.

Key words: Episodic memory, Temporal lobe epilepsy, Medial temporal lobe resection, Functional MRI, Functional connectivity, Medial prefrontal cortex

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LIST OF ABBREVIATIONS

AD, Alzheimer’s disease

AEDs, antiepileptic drugs

AFNI, analysis of functional neuroimage

AH, amygdalohippocampectomy

aMCI, amnestic mild cognitive impairment

ATL, anterior temporal lobectomy

ATN, anterior temporal network

ATWR, anterior temporal wedge resection

BOLD, blood-oxygen level dependent

CA, Cornu Ammonis

DBS, deep brain stimulation

DLPFC, dorsolateral prefrontal cortex

DMN, default mode network

DNET, dysembryoplastic neuroepithelial tumors

ERC, entorhinal cortex

FC, functional connectivity

FCD, focal cortical dysplasia

FG, fusiform gyrus

FLAIR, fluid attenuated inversion recovery

fMRI, functional magnetic resonance imaging

gPPI, generalized psychophysiological interaction

HC, healthy control

HIP, hippocampus

HIP*ant*, anterior hippocampus

HIP*pst*, posterior hippocampus

HS, hippocampal sclerosis

HRF, hemodynamic response function

IEDs, interictal epileptiform discharges

IFG*orb*, inferior frontal gyrus orbital part

IFG*tri*, inferior frontal gyrus triangular part

KAVLT, Korean version of Rey auditory verbal learning test

KCFT, Korean version of Rey complex figure test

KWAIS, Korean Wechsler Adult Intelligence Scale

LMTLR, left medial temporal lobe resection

MCC, middle cingulate cortex

MFG, middle frontal gyrus

mPFC, medial prefrontal cortex

MQ, memory quotient

MRI, magnetic resonance imaging

MTG, middle temporal gyrus

MTLE, medial temporal lobe epilepsy

MTLR, medial temporal lobe resection

OrbG, orbital gyrus

PCC, posterior cingulate cortex

PCUN, precuneus

PFC, prefrontal cortex

PHC, parahippocampal cortex

PMC, posteromedial cortices

PoCG, postcentral gyrus

PPI, psychophysiological interaction

PRC, perirhinal cortex

PreCG, precentral gyrus

PUT, putamen

RMTLR, right medial temporal lobe resection

ROIs, regions of interest

RSC, retrosplenial cortex

SAH, selective amygdalo-hippocampectomy

SMG, supramarginal gyrus

tDCS, transcranial direct current stimulation

THAL, thalamus

TLE, temporal lobe epilepsy

TMS, transcranial magnetic stimulation

SECTION I. INTRODUCTION

Chapter 1: Memory and Medial Temporal Lobe

1.1. Human Memory System

Henry Gustav Molaison widely known as H.M. (1926-2008), was an important case study for neurological research in the twentieth century. In 1953, at the age of 27, he underwent experimental surgery called a bilateral medial temporal lobe resection (MTLR) to control his epileptic seizures. The resection region includes amygdala, entorhinal cortex (ERC), perirhinal cortex (PRC), and two-thirds of his hippocampal region (dentate gyrus, hippocampus, and subicular complex) (**Fig. 1-1**) (Scoville and Milner, 1957). The surgery successfully alleviated his epileptic seizures; however, he developed a severe memory deficit in the absence of any general intellectual loss or perceptual disturbances. In particular, he could not form new memories about anything going on around him or in the world, called "episodic memory." But he was able to learn simple sensorimotor skills and to hold information for very short periods of time. These findings showed that MTL structures are uniquely specialized to establish and maintain episodic memory, which is memory of personal experiences [see (Dickerson and Eichenbaum, 2010) for review].

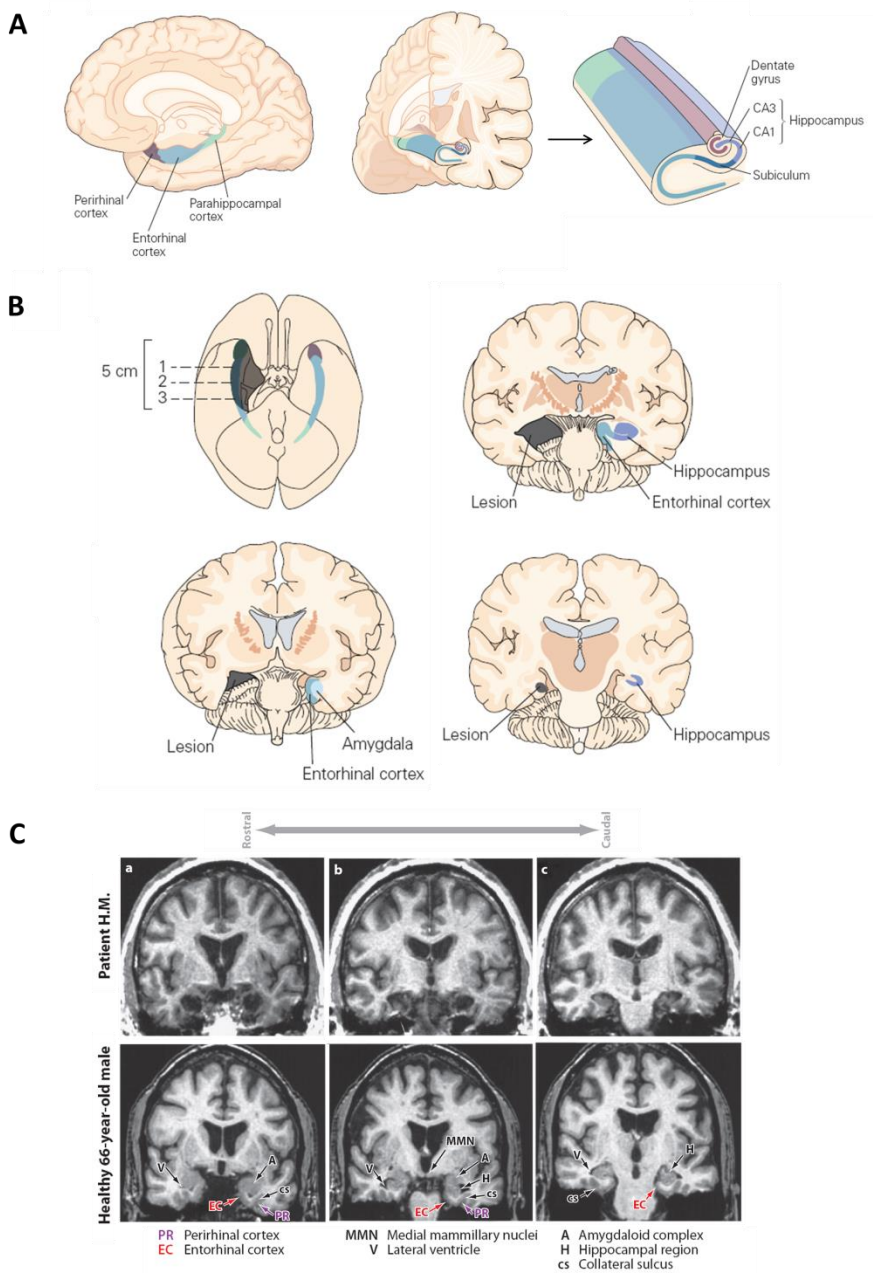

Figure 1-1. Medial temporal lobe and H.M.'s brain. (A) The key components of the MTL. (B) Surgically resected areas (gray shading) of patient H.M. (C) MRI of patient H.M. [Figure adapted from (Kandel et al., 2012; Squire and Wixted, 2011)]

1.2. Structures and Connections of the MTL

The MTL structures encompass the hippocampus (HIP) and amygdala, as well as the neocortical regions of ERC, PRC, and parahippocampal cortex (PHC) (**Fig. 1-1A**). The HIP is a curved structure situated on the medial aspect of the temporal lobe. Three regions can be defined based on morphology and relationship to the brainstem, the hippocampal head, body, and tail. The head is located at the anterior aspect of the brainstem and can be identified by digitations that resemble toes of the feet. The body is a cylindrically shaped structure situated adjacent to the brainstem. The tail narrows rapidly as it sweeps upward behind the brainstem. The HIP includes fields Cornu Ammonis (CA)1–CA3 of the HIP proper, the dentate gyrus and the subicular complex.

The MTL has connections within MTL structures as well as with more distant connections (Simons and Spiers, 2003). There are large cortico-cortical direct reciprocal connections between the MTL and the prefrontal cortex (PFC), passing through the uncinated fasciculus, anterior temporal stem and anterior corpus callosum. The orbitofrontal and dorsolateral cortices have strong reciprocal connections with the PRC and ERC. There are more connections from the PFC to the PRC than vice versa. Unidirectional projections exist from the CA1 field to the caudal region of medial PFC (mPFC). The subicular complex and neocortical MTL have reciprocal

connections with caudal mPFC. In addition, the MTL receives information from a range of unimodal and polymodal sensory association areas. This information predominantly enters through the PRC and PHC, which project back to these regions. The PFC has reciprocal connections with sensory association cortices including temporal and parietal regions and many subcortical structures.

1.3. MTL-dysfunction-related Memory Deficits

1.3.1. MTL Lesion Studies

Ever since the study of H.M., memory research has primarily focused on teasing apart the contributions of different regions within the MTL (Henson, 2005). To find out the specific roles of different MTL structures on memory process, early focal lesion studies with non-human primates strategically damaged different MTL structures. These studies have shown that the structures of MTL, such as the HIP, PRC, and PHC, have qualitatively distinct roles in memory (Alvarado and Bachevalier, 2005; Suzuki et al., 1993). Similar to non-human primate lesion studies, human lesion studies have also focused on the different roles of MTL structures in the memory process; however, the precise contributions of the MTL sub-regions in episodic memory are still controversial [see (Jeong et al., 2015) for review].

In another stream of research, studies have been focused on the

hemispheric contributions of MTL structures to episodic memory. One of the most influential frameworks describes the hemispheric specialization of memory based on verbal and non-verbal characteristics. Early lesion studies indicate that left and right MTL structures are essential for verbal and visuospatial memory, respectively (Helmstaedter et al., 1994; Milner, 1972). Concordantly, patients with dominant (usually left) medial temporal sclerosis have abnormalities of verbal memory, whereas those with nondominant foci may have deficits of visuospatial memory, although this is less well established [see (Bell et al., 2011; Willment and Golby, 2013) for review]. Based on the foundation of material-specific memory deficits, our understanding of hemispheric lateralization of memory function has expanded over time. A number of neuropsychological and neuroimaging studies have demonstrated a relationship between material-specific memory impairment and lateralized MTL dysfunction.

1.3.2. Memory Deficits in Neurological Disorders

Episodic memory is severely compromised in various neurological disorders including temporal lobe epilepsy (TLE), amnestic mild cognitive impairment (aMCI), and Alzheimer's disease (AD). Episodic memory impairment has long been regarded as the chief neuropsychological issue in TLE, which is characterized by recurring seizures that stem from the medial or lateral temporal lobes of the brain [see (Bell et al., 2011) for review]. The

characteristics of TLE will be discussed in detail in Chapter 2.

MTL-dysfunction-related memory disturbance is also well documented in patients with aMCI or AD. The aMCI is a syndrome associated with faster memory decline than normal aging and frequently represents the prodromal phase of AD. AD is a progressive neurodegenerative disease that is the most common cause of dementia and may contribute to 60-70% of cases (World Health Organization, 2016). Disruptions to the episodic memory system are the earliest and most prominent symptoms of AD (Gold and Budson, 2008). In addition, the episodic memory loss in AD is regarded as a result of encoding failure rather than result from forgetting information (Carlesimo and Oscar-Berman, 1992; Degenszajn et al., 2001; Dick et al., 1989). The earliest sites of tau deposition and MRI-based atrophic changes typically lie along the perforant hippocampal pathway, consistent with early memory deficits (Frisoni et al., 2010). Accordingly, the degree of atrophy of MTL structures such as the HIP is a diagnostic marker for AD at the MCI stage. The example of AD brain is presented in **Fig. 1-2**. Currently, there is no treatment available to cure dementia or halt its progressive course; therefore, numerous new treatments are being investigated in various stages of clinical trials.

Interestingly, similar structural and neurophysiological characteristics underlying memory decline in TLE, aMCI, and AD have been addressed in recent studies (Höller and Trinka, 2014; Palop and Mucke, 2009).

Both TLE and AD showed similar hypometabolism in the basal temporal region, atrophy in mesial and lateral temporal regions, alteration of the functional network, and pathologic changes including amyloid deposition and phosphorylated tau overexpression (Horváth et al., 2016). Regardless of these similarities, a considerable number of TLE patients exhibited comparable memory performances with healthy subjects while patients with aMCI and AD always displayed disturbances of memory function (Baxendale et al., 2006; Baxendale et al., 2008; Baxendale et al., 2013).

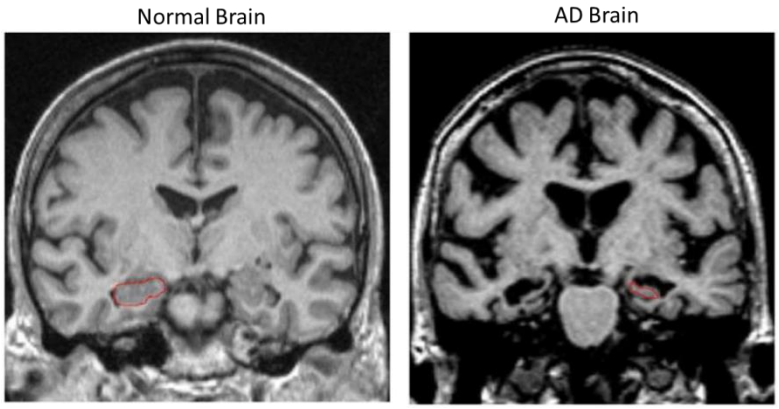

Figure 1-2. Hippocampal atrophy in Alzheimer's disease. The HIP has severe atrophy in both hemispheres in AD. [Figure from (Shen et al., 2011)]

Chapter 2: Epilepsy and Epilepsy Surgery

2.1. Definition of Epilepsy

The prevalence of epilepsy worldwide is estimated to be around 10 per 1,000 people (Banerjee et al., 2009), and approximately 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally (World Health Organization, 2017). Epilepsy is a neurological disorder characterized by recurrent seizures, which are a result of abnormal excessive or synchronous electrical discharges in a group of brain cells (Fisher et al., 2014). Different parts of the brain can be the site of such discharges. The outward effect can vary from uncontrolled jerking movement (tonic-clonic seizure) to as subtle as a momentary loss of awareness (absence seizure).

There are many types of seizures and different forms of epilepsy. An epileptic disorder is defined as either being generalized, partial (focal) or undetermined (Scheffer et al., 2017). Primary generalized seizures start as a disturbance in both hemispheres synchronously without evidence of a localized onset. Partial forms of epilepsy start in a focal area of the brain and may remain localized without alteration of consciousness. According to the location of seizure onset, focal epilepsies can be divided into TLE, frontal lobe epilepsy, parietal lobe epilepsy, and occipital lobe epilepsy. Partial

seizures most often arise from the limbic structures of the temporal lobe and are often quite refractory to medical therapy alone.

In up to 70% of people with epilepsy, seizures are well controlled with antiepileptic drugs (AEDs); however one out of three patients cannot control seizures solely by using available medications (Laxer et al., 2014; Mohanraj and Brodie, 2006; Sander, 2003). Drug resistant (often used interchangeably with ‘‘medically refractory/intractable”) epilepsy is defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules to achieve sustained seizure freedom (Kwan et al., 2010). Apart from the burden of continued seizures, patients with refractory epilepsy have a significantly increased risk of death, as well as psychiatric and somatic comorbidities (de Boer et al., 2008; Schmidt and Schachter, 2014). For these drug resistant epilepsy patients, surgery is the most important treatment option with a realistic hope of seizure freedom (McIntosh et al., 2004). In general, patients with partial seizure disorders are the most amenable to surgical intervention.

2.2. Temporal Lobe Epilepsy

TLE is the most common form of partial or localization-related epilepsy in adults, accounting for approximately 60 – 70 % of cases (Hauser et al., 1991; Spencer and Spencer, 1985). There are two types of TLE; one involves the

medial or internal structures of the temporal lobe (medial TLE, MTLE), while the second, called neocortical TLE, involves the outer portion of the temporal lobe. Seizures arising from the temporal neocortex are relatively rare in relation to mesial temporal lobe seizures. Patients with TLE typically have a signature deficit in episodic memory and often poorly controlled with medications. MTLE is one of the most intractable partial epilepsies achieving seizure control with medical therapy in only 25 – 40% of patients (Spencer, 2002).

TLE can be associated with a magnetic resonance imaging (MRI) lesion or be non-lesional. The main causes of lesional TLE are hippocampal sclerosis (HS, sclerosis means hardening), benign tumors, vascular malformations, cortical development malformations (e.g. focal cortical dysplasia, FCD), and post-traumatic or post-infectious gliosis [see (Ladino et al., 2014) for review]. HS is the most common cause of TLE, representing greater than 80% of cases (Tatum, 2012). The most common low-grade tumors are gangliogliomas, low-grade gliomas, and dysembryoplastic neuroepithelial tumors (DNET) (Woermann and Vollmar, 2009).

2.3. Epilepsy Surgery

2.3.1. Aims of Surgery

The main aim of most epilepsy surgery is to accurately localize and then completely excise the epileptogenic zone without causing any significant impairment on eloquent function such as vision, language, memory, and sensory and motor functions. The epileptogenic zone refers to the minimum amount of cortex to produce seizure freedom, consists of five conceptual cortical abnormal 'zones': symptomatogenic, irritative, seizure-onset, structurally abnormal (epileptogenic lesion) and functional deficit. An important determinant of the risk of surgery is the relationship of the epileptogenic zone to functionally important or "eloquent" brain regions because injury to these "eloquent" areas can cause irreversible neurological impairment.

Surgical treatment of refractory partial epilepsy is gaining ground (Chung et al., 2005). There are different kinds of epilepsy surgery. One kind of surgery involves removing a specific area of the brain which is thought to be causing the seizures (resective surgery). Another kind involves separating the part of the brain that is causing seizures from the rest of the brain (palliative surgery). The most common epilepsy surgery procedure is resective surgery for temporal lobe. The safety and efficacy of surgery for TLE was well established in randomized clinical trials (Wiebe, 2004; Wiebe et al.,

2001).

2.3.2. Resective Surgery for TLE

The techniques for removing temporal lobe tissue vary from resection of large amounts of tissue, including lateral temporal cortex along with medial structures, to more restricted anterior temporal lobe resection to more restricted removal of only the medial structures (selective amygdalo-hippocampectomy, SAH). The most common surgical procedures for TLE are standard anterior temporal lobectomy (ATL) and SAH (**Fig. 2-1**).

The standard ATL involves resection of the anterior portion of the lateral neocortex. Neocortical resection extends from the temporal pole along the superior temporal gyrus to the level of the central sulcus and precentral sulcus in non-dominant and dominant resections respectively. The anterior HIP is resected, at the junction of the body and tail of the HIP. The anterior PHG, the uncus, and 4/5 of the amygdala are also removed (Ojemann and Park, 2008). Since almost 80% of temporal lobe seizures originate in the medial structures, several operative approaches have been designed to reduce the amount of temporal neocortex removed but still resect the amygdala and HIP. In this surgical procedure of SAH, the anterior 2/3 of the HIP, a major portion of the amygdala, the uncus, and the anterior PHG were resected, leaving the lateral temporal neocortex intact (Yasargil et al., 1985).

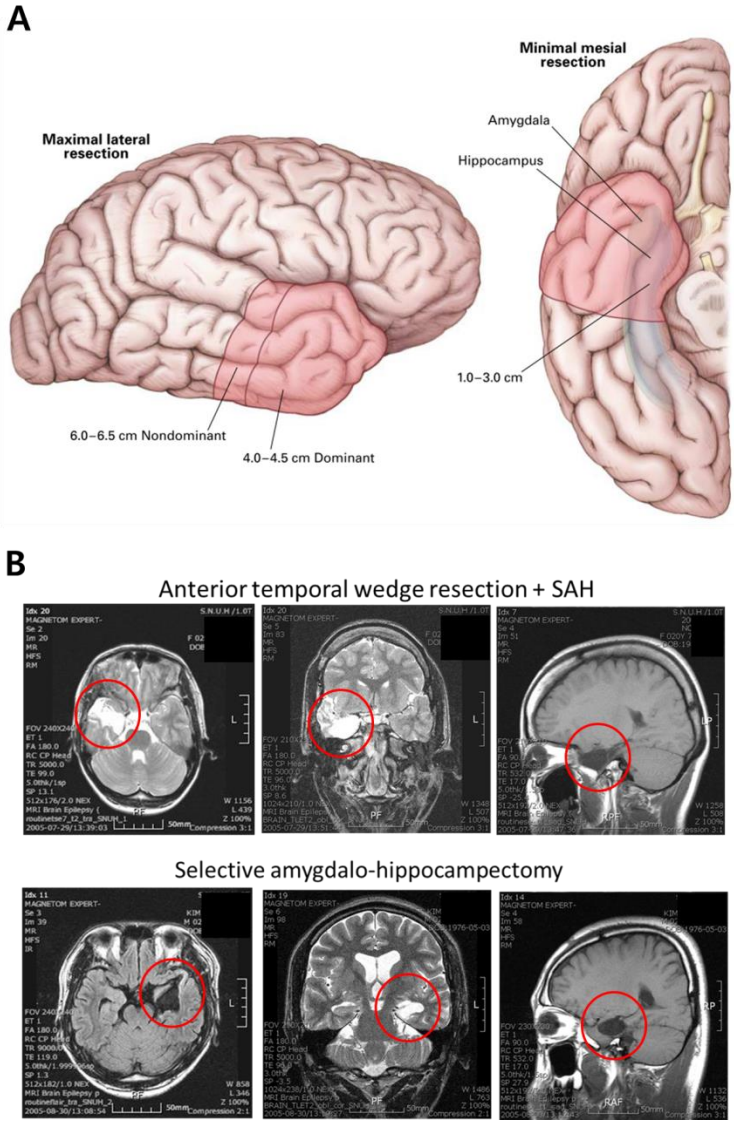

Figure 2-1. A typical surgical resection for TLE. Resection for this condition may include resection of up to 6.5 cm of the anterior lateral nondominant temporal lobe and 4.5 cm of the dominant temporal lobe. The mesial resection encompasses the amygdala and a minimum of 1.0 to 3.0 cm of the HIP. The extent of the lateral resection may be guided by functional mapping of this area. Wedge resection is a surgical procedure to remove a triangle-shaped slice of tissue. [Figure adapted from (Wiebe et al., 2001)]

2.4. Consequence of Medial Temporal Lobe Resection

2.4.1. Seizure Outcome

Surgical treatment is a highly effective intervention in selected patients with medically refractory epilepsy. Previous studies demonstrated that surgical outcome depends on several factors including the types of pathology, presence of MRI visible lesion, and/or types of surgical procedures (Berkovic et al., 1995; Chung et al., 2005; Schramm, 2008; Yun et al., 2006). To classify postoperative outcomes for epilepsy surgery, Engel's classification has been widely used for decades (**Table 2-1**). About ~60-90% of patients with TLE achieve seizure-free outcome following resective surgery (Engel, 1996; Foldvary et al., 2000; Salanova et al., 1999).

Table 2-1. Engel epilepsy surgery outcome scale (Engel, 1993)

Class I: Free of disabling seizures

A. Completely seizure free since surgery
B. Non disabling simple partial seizures only since surgery
C. Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
D. Generalized convulsions with AED discontinuation only

Class II: Rare disabling seizures ("almost seizure free")

A. Initially free of disabling seizures but has rare seizures now
B. Rare disabling seizures since surgery
C. More than rare disabling seizures since surgery, but rare seizures for the last 2 years
D. Nocturnal seizures only

Class III: Worthwhile improvement

A. Worthwhile seizure reduction
B. Prolonged seizure-free intervals amounting to more than half the follow-up period, but not less than 2 years

Class IV: No worthwhile improvement

A. Significant seizure reduction
B. No appreciable change
C. Seizures worse

2.4.2. Cognitive Outcome

Despite the effectiveness and safety of TLE surgery, it carries risks of impairment in one or more cognitive domains; including memory, language, attention, motor function, and visuoconstruction (Elger et al., 2004; Helmstaedter, 2004; Helmstaedter and Kockelmann, 2006; Helmstaedter and Witt, 2012). Cognitive impairment in TLE was clearly dominated by memory impairment (40-70%), followed by problems in language function, such as naming difficulties.

For the postoperative memory function, material-specific decline has been consistently reported (Chelune et al., 1991; Lee et al., 2002). On average, verbal memory outcome is worse after left ATL (dominant hemisphere) than after right ATL [see (Bell et al., 2011) for review]. By contrast, visual memory outcome is worse after right ATL than after left ATL, although this effect is much less robust. Despite this trend, there is a great deal of variability in memory outcome following surgery (**Fig. 2-2**). Many patients who undergo epilepsy surgery show no change or might even show postoperative improvement in memory (Helmstaedter et al., 2016; Lee et al., 2002). Moreover, recent studies reported that the long-term outcome of epilepsy surgery is mostly characterized by a stable or even improved cognitive status [see (Witt and Helmstaedter, 2017) for review].

There is controversy about the effect of surgery type on cognitive outcome, especially memory outcome [see (Schramm, 2008) for review].

Until now no convincing studies exist that show that more selective mesial resections are correlated with better neuropsychological outcomes, although this has been claimed and might be the case. It is likely that the more selective surgery (SAH) causes less memory problem than standard two-thirds ATL (Clusmann et al., 2002; Wieser et al., 2003). However, other researchers argued that potential collateral cortical damage due to the SAH approach must be considered a potential source of additional memory impairment.

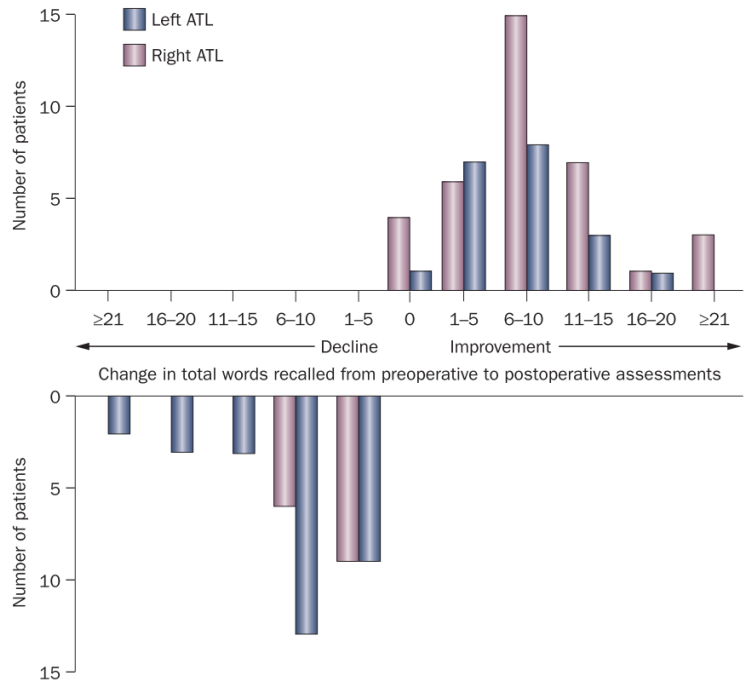

Figure 2-2. Variability in verbal memory change following anterior temporal lobectomy. Preoperative to postoperative changes in verbal learning performance (total words recalled on California Verbal Learning Test) in 100 patients who underwent left or right anterior temporal lobectomy (ATL). The dependent variable is the number of words recalled from a 16-item word list across five learning trials. [Figure from (Bell et al., 2011)]

Chapter 3: Functional Neuroimaging Studies of Episodic Memory

3.1. Introduction of fMRI Memory Studies

The neuroanatomical basis of memory has also been suggested by studies that have recorded neural activity while subjects performed various memory tasks in an MRI scanner. Functional MRI (fMRI) was developed in the early 1990s and measures brain activity by detecting changes associated with blood flow (Ogawa et al., 1990a; Ogawa et al., 1990b). This technique relies on the fact that cerebral blood flow (hemodynamic response) and neuronal activation are coupled. When an area of the brain is in use, blood flow to that region also increases. The primary form of fMRI uses the blood-oxygen-level dependent (BOLD) changes associated with physiological and pathological processes in the brain.

Similar to lesion studies, early fMRI studies have also investigated the roles of MTL structures in human memory function. Subsequently, conventional whole brain analysis of fMRI memory studies revealed the involvement of widely distributed cortical regions beyond the MTL. More recent fMRI studies have begun to investigate the brain regional interactions that subserved the large-scale memory network. Either normal aging or pathologic neurodegeneration which demonstrate significant deterioration on

memory function is associated with alteration of functional interactions between distributed brain regions. The understandings of large-scale brain mechanisms in the episodic memory process have started to be used in the treatment of memory disorders in clinical settings.

3.2. MTL Regions of Interest

3.2.1. MTL Activations in Healthy Controls

Previous fMRI studies with healthy subjects have consistently shown MTL activation in episodic memory tasks [see (Cabeza and Nyberg, 2000; Schacter and Wagner, 1999) for review]. In one early fMRI study, researchers compared encoding activity in the anterior MTL depending on subsequent word associative recognition (Jackson III and Schacter, 2004). They found that the encoding activity in the bilateral anterior MTL regions was greater for successfully bound pairs than for all other pairs. Another study reported similar findings that the anterior MTL showed increased activation for subsequently remembered associations compared with pairs that were forgotten (Chua et al., 2007). These results provide evidence that the anterior MTLs support the successful encoding of memory. Material-specific lateralization of verbal and non-verbal memory is also supported in fMRI studies of healthy subjects (Golby et al., 2001; Kelley et al., 1998). Previous studies confirmed that left MTL was activated during word encoding while

right MTL was activated during visual encoding.

3.2.2. MTL Activations in Patients with TLE and MTLR

Functional neuroimaging studies focused on memory function of the MTL regions were also performed with preoperative patients with TLE and postoperative patients with MTLR. Previous preoperative TLE fMRI studies have consistently shown atypical material-specific involvement of the MTL in episodic memory encoding of TLE patients. Reorganization of verbal and visual memory encoding to both the contralateral MTL (Golby et al., 2002; Powell et al., 2007; Richardson et al., 2003) and the ipsilateral posterior MTL (Bonelli et al., 2010) in TLE patients have been described. In early fMRI study demonstrated not only ipsilateral reduction in MTL activations but also greater activation in the MTL contralateral to the seizure focus in MTLE patients (Golby et al., 2002). Specifically, verbal encoding engaged the right MTL in the left MTLE group, whereas in the right MTLE group, nonverbal encoding engaged the left MTL. In contrast, other study reported that better verbal memory correlated with left sided activations in left TLE patients whilst right sided activations correlated with better visual memory in right TLE patients (Bonelli et al., 2010).

The neural mechanism supporting memory function after resection of anterior temporal lobe has only investigated in a few studies (Bonelli et al., 2013; Cheung et al., 2009). In unilateral TLE patients, the postoperative

memory performance was significantly associated with postoperative functional activation of MTL contralateral to the side of the resection (Cheung et al., 2009). The authors suggested that the function of the contralateral MTL might play an important role in supporting memory performance after temporal lobe resection. Other study with unilateral TLE patients suggested that the posterior remnant of the ipsilateral HIP rather than the functionally reserved contralateral HIP is important for maintaining memory function after the ATL (Bonelli et al., 2013). Researchers found that better verbal memory outcomes were related to the greater pre- than postoperative activation in the ipsilateral posterior MTL, whereas, worse post-operative memory was related to the greater post- than preoperative activation in the same area.

3.3. Large-scale Memory Network

3.3.1. Episodic Memory-related Whole-brain Regions

Although the MTL is thought to be the essential system for episodic memory, the roles of large-scale neural networks in memory have suggested from functional neuroimaging studies. The regions beyond the MTL have been regarded as having a secondary role in memory processing through effects on attention, organization, and motivation (Uncapher and Wagner, 2009). However, some researchers have suggested that different cortical regions, such as subregions of the frontal and parietal lobes, have a primary role in

episodic memory function [see (Dickerson and Eichenbaum, 2010) for review].

The meta-analysis of fMRI studies on episodic memory encoding in healthy subjects reported five most consistent brain regions including left inferior frontal cortex (IFC), bilateral fusiform gyrus, bilateral hippocampus, bilateral premotor cortex, and bilateral posterior parietal cortex (Kim, 2011) (**Fig. 3-1**). Regarding whole-brain episodic memory network without MTL structures, until today, only one study has been conducted in TLE patients with MTLR (Sidhu et al., 2016). The authors reported that both MTL and neocortical areas showed postoperative activational changes after MTLR. These results confirm that large-scale memory network rather than only MTL structures is important in episodic memory function.

Notably, whole-brain fMRI studies on episodic memory encoding consistently reported that not only activations of distributed brain areas but also deactivation patterns in the set of brain areas are observed during memory encoding tasks (Dickerson and Eichenbaum, 2010; Kim et al., 2010) (**Fig. 3-1C**). Deactivation refers to a relatively lower signal in one condition over another. The set of brain areas which showed deactivation during cognitively demanding tasks as well as memory encoding task compared with activation during relaxed non-task states called "default mode network (DMN)" (Raichle, 2015; Raichle et al., 2001) (**Fig. 3-2**). Ever since the discovery of the DMN, extensive studies have been conducted regarding

whole-brain episodic memory network and most researchers in this field agreed that memory function is subserved by a set of distributed networks, DMN in particular. The regions of DMN include the anteromedial PFC, the posterior cingulate cortex (PCC), the precuneus (PCUN), angular gyrus, and the MTL.

By definition, one condition has to be compared to another condition to observe deactivation patterns of the brain. To reveal fluctuations of brain activity in one condition without comparison to another condition, researchers adopted functional connectivity (FC) analysis in neuroimaging data and found that DMN regions highly correlated with each other during non-task resting state (Greicius et al., 2003). Detailed methods for FC analysis will be explained in the following section. Given that the pivotal role of DMN in episodic memory and strongly connected features of DMN areas, perspective of coherent fluctuations of large-scale memory network rather than focusing on static MTL structures is necessary for better understanding of the neural mechanisms underlying episodic memory.

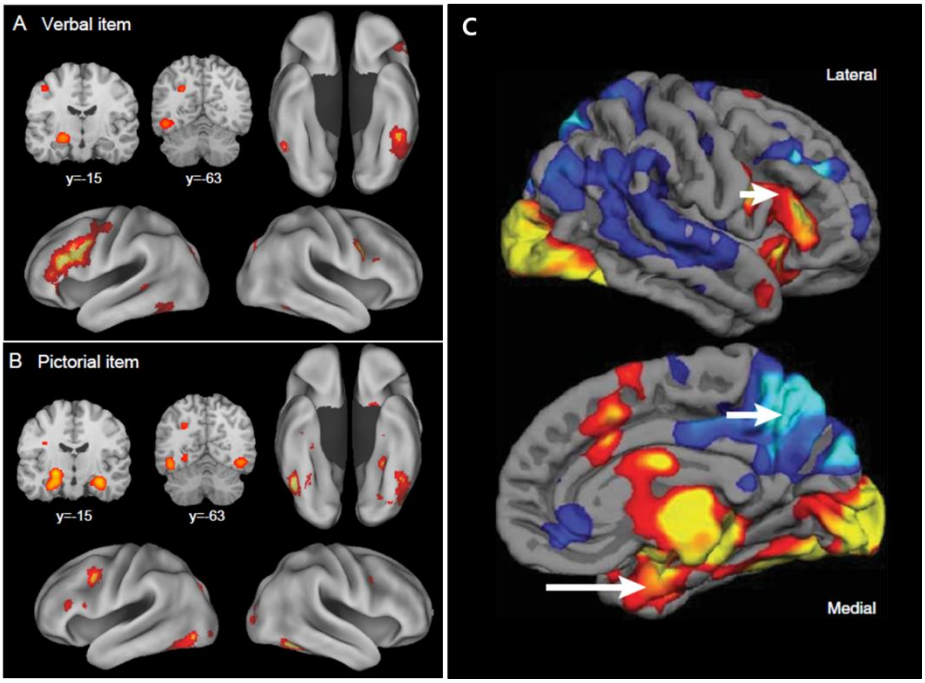

Figure 3-1. Brain regions associated with subsequent memory effects. (A, B) fMRI results from meta-analysis of verbal-item (A), pictorial-item (B). (C) fMRI of a group of young human subjects during the encoding of novel pictures that are subsequently recalled, showing cortical regions involved in the large-scale episodic memory network. Red/yellow regions are activated during the encoding, whereas blue regions are deactivated below baseline. [Figure adapted from (Dickerson and Eichenbaum, 2010; Kim, 2011)]

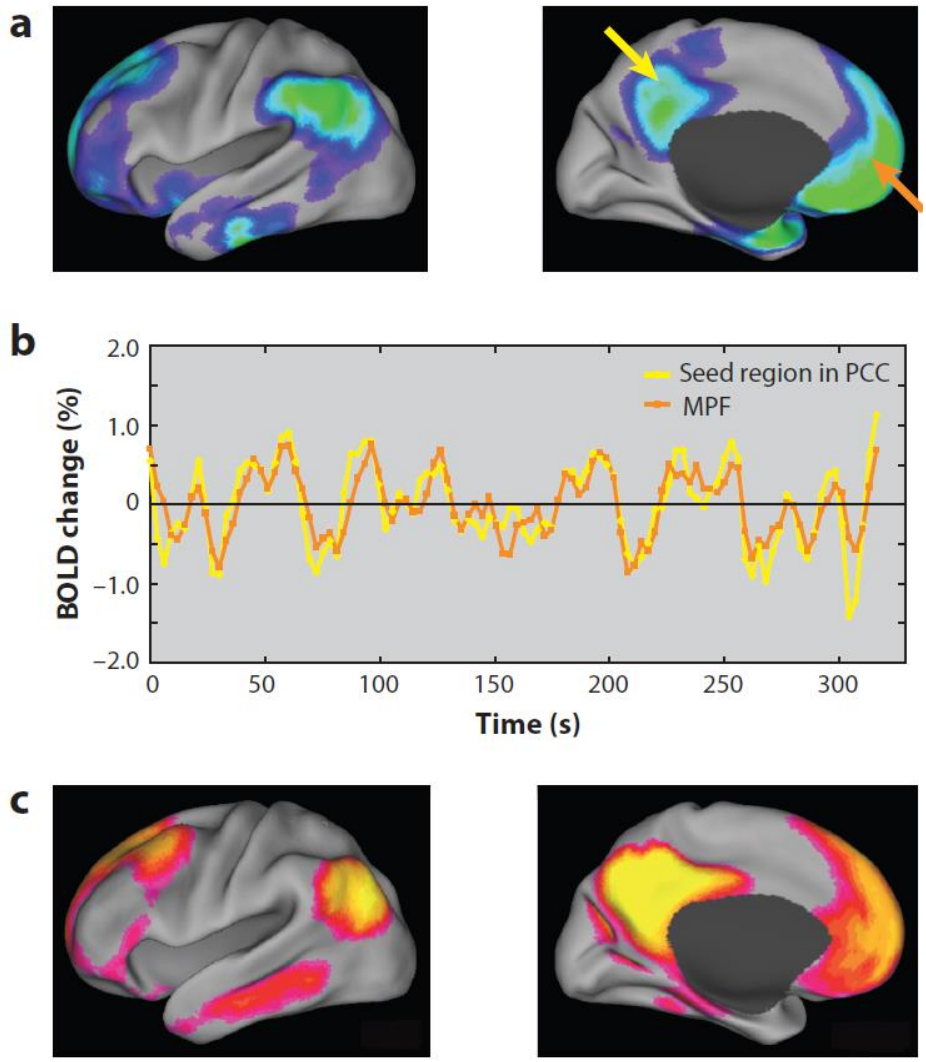

Figure 3-2. Default mode network. (A) Views of the DMN from the perspective of activity decreases during task performance. (B, C) Resting-state coherence patterns in the DMN elicited by placing a region of interest in either the posterior cingulate cortex (PCC, yellow arrow) or the ventral medial prefrontal cortex (MPF, orange arrow). The resulting time-activity curves (B) reflected a coherence pattern within the entire DMN (C). [Figure from (Raichle, 2015)]

3.3.2. Introduction to Functional Connectivity of fMRI

Generally, FC has been defined as the correlation between activities in the regions of interest (ROIs) and activities in the rest of the brain, measured by neuroimaging. To reveal the relationship among the brain regions related to memory function, an examination of the correlation between low frequency fMRI signal fluctuations in the HIP and those in all other brain regions was performed in several studies. Since DMN areas showed strong connections with each other during resting-state, resting-state intrinsic network has been extensively studied in relation with episodic memory capacity.

Meanwhile, to directly examine the network properties during performing memory task, the psychophysiological interaction (PPI) model has been developed and adopted in neuroimaging data (Friston et al., 1997). This approach allows investigators to examine FC in the context of specific cognitive processes. The PPI model identifies voxels whose FC with predefined seed ROIs were significantly modulated by the interaction of task condition. More recently, generalized PPI (gPPI) analysis has been developed (McLaren et al., 2012) (**Fig. 3-3**). While standard PPI analysis includes only a single PPI regressor in each general linear model (GLM), gPPI analysis enables more comprehensive modeling of the entire task. A gPPI analysis has shown to more accurately fit the data, which led to improvements in sensitivity and specificity of findings (Cisler et al., 2014).

More recently, new analytic methods from network science have

been applied in brain science which enables the investigation of functional integration of the brain [see (Sporns, 2014) for review]. Of various network science methodologies, graph theoretical analysis has been widely used in cognitive network studies [see (Medaglia et al., 2015) for review]. This method is often used to describe functional relationships across all of the nodes (regions) of the brain. Using the graph theoretical analysis of brain, previous study demonstrate that brain hubs form a so-called “rich club,” characterized by a tendency for high-degree nodes to be more densely connected among themselves than nodes of a lower degree (Sporns, 2014; van den Heuvel and Sporns, 2011). The authors suggested that one plausible hypothesis for the rich-club connectivity might be the tendency of the brain to provide a certain level of resilience to its core, in case of malfunction of one of its key hubs, regardless of a higher cost of the needed white matter wiring. Interestingly, they found that rich club members include bilateral HIP. Regarding the importance of HIP in episodic memory function, therefore, FC approaches could enlighten our understandings of the distributed process supporting effective memory performance. Recent studies have begun to show the interactions between brain regions that make up the large-scale episodic memory network.

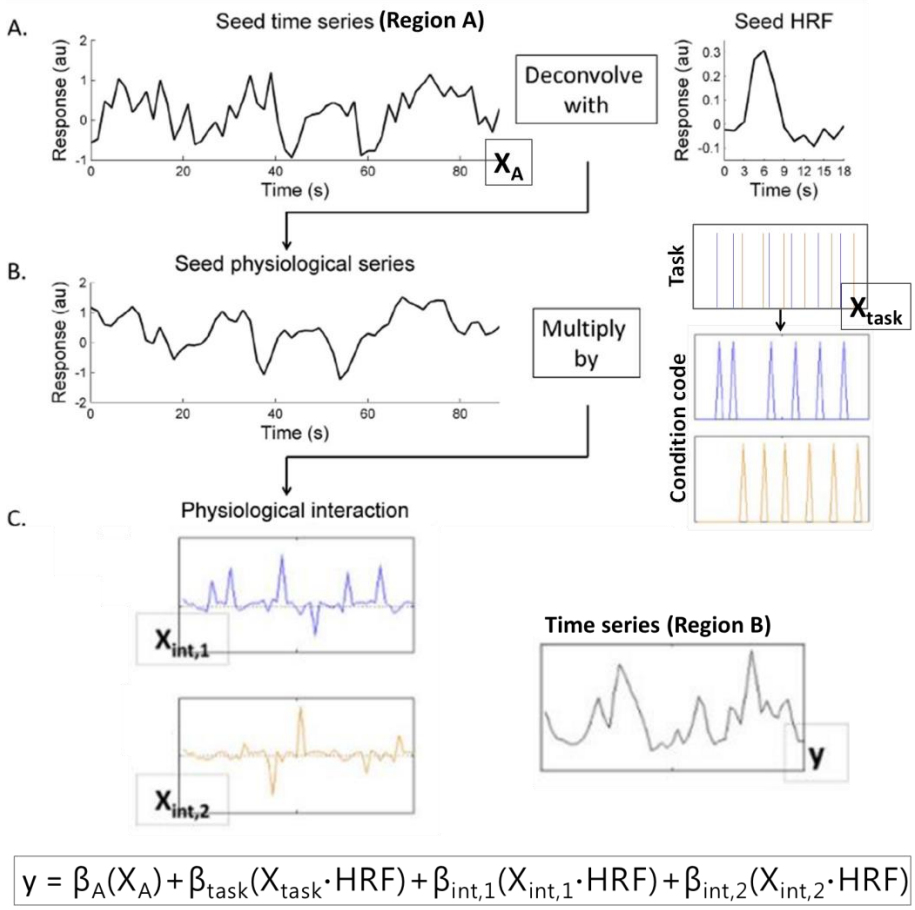

Figure 3-3. Generalized psychophysiological interaction. (A) The seed time series were first deconvolved based on the estimated hemodynamic response function (HRF) to obtain physiological responses. (B) Multiplied the seed physiological series by the condition code from each condition separately. (C) The resulting model contains two interaction terms, $\beta_{int,1}$, and $\beta_{int,2}$, representing the functional connectivity for each stimulus condition. The interaction term, X_{int}, is then convolved with the HRF and used as a predictor of region B's BOLD activity in a multiple regression model that also includes the direct effect of the task, X_{task}, and of region A, X_A. [Figure adapted from (Cisler et al., 2014; Qiu et al., 2016)]

3.3.3. Resting-state Network and Memory

Spontaneous fluctuations in the BOLD signal, as measured by fMRI at rest, showed a temporally correlated activity regarded as reflection of functionally related networks. A number of investigators have measured FC with resting-state fMRI in studies on memory. Some of these studies focused on FC within MTL structures, while others focused on the FC of DMN-related regions in groups of healthy subjects and in memory-impaired patients.

Intra-MTL resting-state functional connectivity

One previous study investigated FC within MTL structures in patient with MTLE (Bettus et al., 2009). Resting-state fMRI signals extracted from the anterior temporal network (ATN) consisted of the temporal pole, the amygdala, the ERC, the anterior HIP (HIP*ant*), and the posterior HIP (HIP*pst*). FC analysis revealed that the left MTLE group showed decreased FC of the ipsilesional left HIP*ant* - HIP*pst* link compared to healthy controls. They also found a trend of increased FC of the contralateral right HIP*ant* - HIP*pst* link. Moreover, this increased FC was positively correlated to memory performance of patients. The authors interpreted contralateral increased FC as compensatory mechanisms that occur in response to early pathological insult.

Default-mode network in relation to memory

Altered integrity of the DMN in relation to episodic memory task

performance was reported in several fMRI studies with memory-impaired patient groups of MCI, at genetic risk for AD, and AD [see (Sperling et al., 2010) for review]. Generally, the HIP featured as a prominent node within the DMN and showed reduced FC with other DMN regions in AD [see (Broyd et al., 2009) for review]. Decreased resting-state connectivity patterns in PCC, PCUN, and PFC which are the important parts of DMN was most consistently observed in individuals at risk for AD [see (Li and Wahlund, 2011) for review]. More recent meta-analysis also found decreases in connectivity within the DMN in MCI and AD patients, which increases with disease progression (Jacobs et al., 2013). A progressive decrease of FC within DMN as the disease progresses was also reported in another study with AD (Damoiseaux et al., 2012).

Not only investigating patterns of FC in specific patient groups, some previous studies also investigated the relationship between the strength of FC and memory capacity. The posteromedial cortices (PMC), specific regions of the DMN including the PCUN and the PCC, have functional connection to the MTL and thought to play a central role in memory process (Daselaar et al., 2009; Kim et al., 2010). One study found that stronger resting-state FC between the HIP and PMC predicts better episodic memory performance in cognitively intact older individuals (Wang et al., 2010). Interestingly, this FC was only related to episodic memory, but not related to the performance in non-memory domains. A more recent study that examined

DMN connectivity across aging revealed that within older participants, reduced DMN connectivity was associated with deficits in memory performance (Ward et al., 2014).

The strength of resting-state FC in association with memory capacity was also found in TLE patients (McCormick et al., 2014; Voets et al., 2014). In one study with MTLE, the authors investigated both pre- and postoperative resting-state network in relation with memory (McCormick et al., 2014). Preoperatively, greater FC between ipsilateral HIP and PCC was associated better preoperative episodic memory capacity. Following MTLR, greater FC between contralateral HIP and PCC was associated with better postoperative memory performance. Another study with an MTLE patients observed the similar results (Voets et al., 2014). They showed that aberrant resting FC within anterior and posterior hippocampal-cortical networks distinguishes memory-intact from memory-impaired patients. Reduced FC between the contralateral HIP*pst* and PCC was significantly more pronounced in memory-impaired patients than in patients with intact memory performance.

Taken together, the greater decreases of FC between DMN regions were mostly seen in patients with the greater memory impairments. Conversely, stronger FC of those DMN regions predicts better episodic memory capacity. A close dialogue between both MTLs and the DMN seems essential to maintain episodic memory function. A summary of the DMN studies on memory is presented in **Table 3-1**.

Table 3-1. Summary of memory-related resting-state network studies

Study	Group	Main Findings
Increased Functional Connectivity		
Bettus et al. (2009)	MTLE, HC	Increased FC between contra-lesional HIPant-HIPpst link in MTLE was positively correlated with memory capacity.
Wang et al. (2010)	HC	Stronger FC between HIP-PMC (PCC/PCUN) in cognitively intact older individuals was positively correlated with memory capacity.
McCormick et al., (2014)	MTLE, HC	Increased FC between ipsilateral HIP and PCC in preoperative MTLE and increased FC between contralateral HIP and PCC in postoperative MTLE were positively correlated with pre- and postoperative memory capacity, respectively.
Decreased Functional Connectivity		
Ward et al. (2014)	HC	Reduced FC of DMN was associated with deficits in memory performance.
Voet et al. (2014)	MTLE, HC	Reduced FC between the contralateral posterior HIP and PCC was more pronounced in memory-impaired patients than patients with intact memory function.

3.3.4. Task-related Memory Network

Some previous studies adopted a task-related FC analysis to more directly examine the patterns of functional interactions between brain regions that related to episodic memory process. In early study, researchers used PPI analysis to examine age-related FC changes of MTL areas during episodic memory encoding (Menon et al., 2005). This analysis showed that MTL connectivity with the left dorsolateral PFC (DLPFC) increases with age even when controlled the individual differences of memory performance.

Altered FC during memory encoding was also reported in several studies with AD-related patients (Harrison et al., 2016; Oh and Jagust, 2013). The β-amyloid (Aβ) deposition was measured using positron emission tomography amyloid imaging in addition to fMRI in one previous study (Oh and Jagust, 2013). Accumulation of Aβ, a histopathological finding in AD, is associated with neural alterations and episodic memory decline. Cognitively intact older adults without Aβ deposition showed reduced regional brain activation with stronger FC between the PHC and PFC than young adults and older adults with Aβ deposition during memory encoding (**Fig. 3-4**). In addition, stronger connectivity is associated with better recognition performance. In contrast, no such increased task-related FC was observed in individuals with Aβ deposition. The authors interpreted those results as compensative roles of FC for reduced regional activity during successful memory encoding. Altered memory-related FC of MTL was also reported in

recent study with healthy older adults at increased genetic risk for AD (APOEε4 carriers) (Harrison et al., 2016). By applying gPPI analysis, the authors found that context-dependent FC of HIP during memory encoding in APOEε4 carriers had lower FC between HIP*ant* and right PCUN, anterior insular and cingulate cortex than non-carriers.

In summary, memory studies that applying context-dependent FC analysis revealed that FC during memory task can be differ according to the subject groups (e.g. different age groups) even when their memory capacity was similar between groups. Moreover, previous studies showed that increased task-related FC was related to better memory performance in patient groups which is believed to reflect compensation.

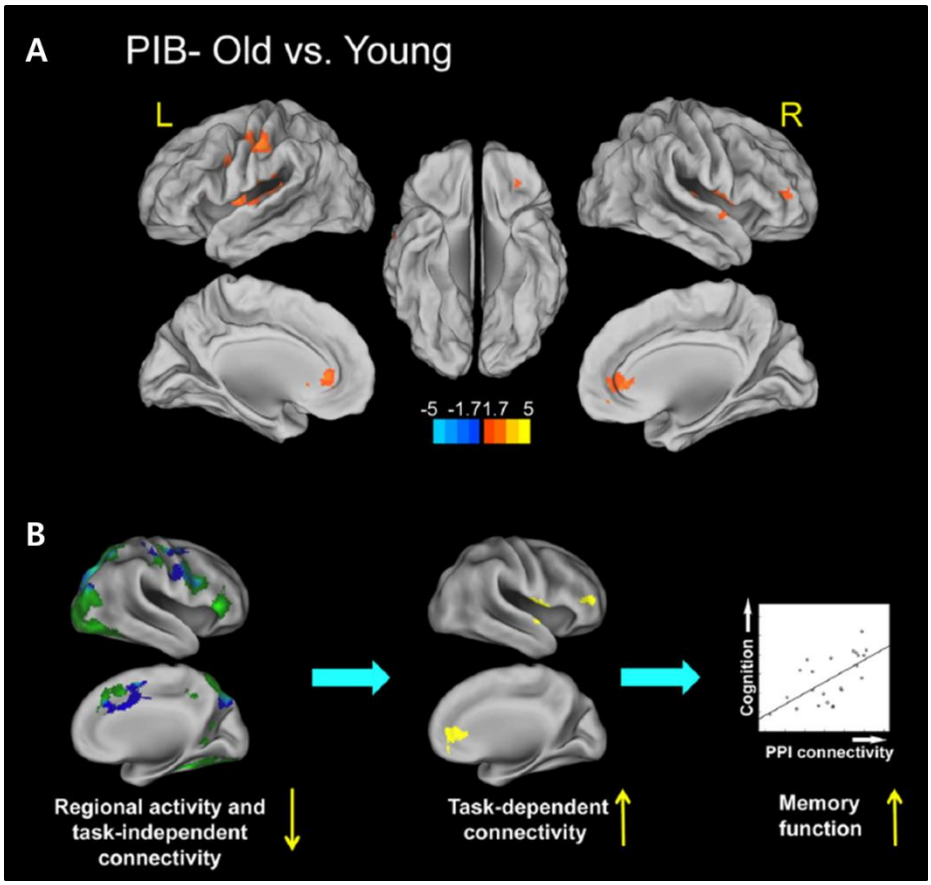

Figure 3-4. Relationships between age, brain function, and memory. (A) Stronger FC between PHG and PFC in older adults without Aβ deposition (PIB- OLD) than YOUNG during successful memory encoding (HIT vs MISS). No region shows significantly stronger connectivity with the PHG seed region in YOUNG compared with PIB- OLD adults. (B) Age-related changes in regional activity and MTL-seeded connectivity during episodic encoding. Age (in the absence of Aβ) is associated with failure to engage brain regions crucial to encoding new information, such as MTL structures, and also with reduced task-independent FC across brain regions. These changes are accompanied by increased task-dependent FC contributing to preserved episodic memory performance in older adults. [Figure adapted from (Oh and Jagust, 2013)]

3.3.4. Findings from Brain Stimulation Studies

From the long history of studies on various aspects of episodic memory, we now start to have understandings of large-scale brain mechanisms in the episodic memory process. These understandings have started to be used in the treatment of memory disorders in clinical settings. Deep brain stimulation (DBS) has been used to successfully treat movement disorders such as Parkinson's disease and dystonia. More recently, it has also been used in experimental treatments of memory disorders (Hansen, 2014; Okun, 2014; Suthana and Fried, 2014). The implications of such enhancement for patients affected by disorders of memory may be of great significance.

Most DBS studies with the aim to enhance memory function selected MTL structures for the stimulation target area because they are known to be clearly related to episodic memory function. DBS of the ERC can enhance the encoding of new information through hippocampal theta phase resetting (Suthana et al., 2012). It is likely that stimulation of the ERC may enhance hippocampal dependent memory because of the close proximity of the electrodes to the perforant pathway. Interestingly, direct electrical stimulation of the HIP proper generally shows disruptions in memory (Lacruz et al., 2010). DBS targeting the brain regions beyond the MTL which have afferent and efferent connections to the HIP, including the anterior nucleus of the thalamus, hypothalamus, and septal nucleus, has been shown to enhance memory (Clark et al., 1999; Hamani et al., 2008; Hamani et al., 2011; Laxton

et al., 2010; Lee et al., 2013; Oh et al., 2012).

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been widely used for non-invasive neuro-modulation of memory [see (Manenti et al., 2012) for review]. Currently, stimulation of the MTL structures is difficult with TMS and tDCS, since both non-invasive methods stimulate large surface cortical areas. Accordingly, these non-invasive stimulation studies have mostly targeted cortical areas such as the DLPFC and parietal lobe during memory tasks. Regarding the distributed network features of episodic memory brain mechanisms, targeting cortical areas seems quite feasible in modulation of memory function.

FC changes in the resting-state networks, which is measured by fMRI, prefrontal-hippocampal network, and task-specific activations after the noninvasive prefrontal stimulation, have been reported (Bilek et al., 2013; Keeser et al., 2011; Vidal-Piñeiro et al., 2014). After tDCS of the left DLPFC, significant changes of regional brain connectivity were found in distinct functional networks of the DMN and the bilateral frontal-parietal networks in healthy subjects (Keeser et al., 2011). In repetitive TMS study, the left inferior frontal gyrus (IFG) was targeted during episodic memory task (Vidal-Piñeiro et al., 2014). Pre- and post-stimulation scanning of fMRI revealed that TMS-related activity increases in the left PFC and cerebellum-occipital areas during memory encoding. Additionally, authors found that task-related connectivity between the left IFG, stimulation target area, and cerebellum-occipital areas

were changed which is correlated with the TMS effects. Another study also found that targeted repetitive TMS of the lateral parietal cortex improved episodic memory performance in healthy subjects, and enhanced information flow between the HIP and a number of other brain regions were observed (Wang et al., 2014).

In summary, in order to modulate memory function, direct or indirect electrical stimulations of specific networks of brain structures are delivered via DBS and non-invasive TMS tDCS methods. Most previous brain stimulation studies on memory enhancement, however, are not conclusive, because the results vary across studies depending on their stimulation target areas and parameters [see (Lee et al., 2013; Suthana and Fried, 2014) for review]. The memory enhancing mechanisms through either invasive or non-invasive brain stimulation certainly needs much more study; nonetheless, recent studies have shown that stimulation may impact memory through modulating functional networks of the brain. In this sense, brain stimulation targeting modulation of functional memory network could be a novel interventional therapy for individuals with memory impairment in the future.

Chapter 4: Purpose of the Present Study

Medial temporal lobe resection (MTLR) for treating medically intractable TLE is commonly associated with complications of episodic memory impairment (Bell et al., 2011; Shin et al., 2009; Shin et al., 2012). MTL dysfunction-related memory disturbance is also well-documented in patients with MCI or AD (Frisoni et al., 2010). Indeed, recent studies have addressed similar structural and neurophysiologic characteristics underlying memory decline among TLE, MCI, and AD [see (Höller and Trinka, 2014) for review]. However, while patients with MCI and AD have always displayed memory impairment, two-thirds of patients with TLE maintained stable intact memory function following MTLR (Baxendale et al., 2008). In this sense, studies investigating MTLR patients who are free from underlying disease and have intact memory function could provide a clue for new therapeutic targets for patients with MTL dysfunction-related memory impairment, specifically MCI or AD.

Most of previous studies that investigated the neural mechanism supporting memory function after unilateral MTLR have restricted their analysis to regions of interest (ROIs) in MTL structures (Bonelli et al., 2013; Cheung et al., 2009), which tended to emphasize contralateral hippocampus (HIP) for maintaining postoperative episodic memory function [see (Bell et al.,

2011) for review]. Although episodic memory was traditionally regarded as mostly relying on MTL structures, recent studies have suggested involvement of a more widely distributed cortical network and the importance of its interactive roles in the memory process [see (Jeong et al., 2015) for review]. One previous study investigated postoperative episodic memory network in the whole-brain level, and reported that both MTL and neocortical areas showed postoperative activational changes after MTLR (Sidhu et al., 2016). It is of note that those previous studies recruited heterogeneous patients in their memory capacity and none of previous studies recruited homogeneous patients who have comparable memory function with healthy controls to investigate normal intact memory network following MTLR.

To better understand the widespread memory network, researchers adopted functional connectivity (FC) analysis in neuroimaging data. Considering HIP's central position as a densely interconnected hub in brain networks (van den Heuvel and Sporns, 2011), MTLR, including parts of the HIP, can affect FC of HIP as well as widely distributed neocortical regions. Therefore, analyzing functional interactions during performing memory task can enable direct investigation of functional memory network in MTLR patients at whole-brain level. However, memory-related FC patterns in patients with MTLR are still poorly understood.

The aim of present study is to understand effective episodic memory encoding network in patients with MTLR in a new perspective of FC on the

premise that HIP does not operate as individual entity but in a strongly interlinked fashion. Therefore, whole-brain memory encoding network in terms of both functional activation and FC was investigated. In addition, the activation patterns in ROIs of bilateral HIP were compared with memory performances in order to confirm the findings of previous studies that investigated MTL ROIs. To understand an effective memory network, patients who have normal range of postoperative memory function were recruited.

SECTION II. EXPERIMENTAL STUDY

Chapter 5: Materials and Methods

5.1. Subjects

Patients who underwent unilateral MTLR for treating medically intractable epilepsy at Seoul National University Hospital were retrospectively recruited. Including criteria were as follows: 1) underwent unilateral MTLR by a single surgeon (CKC), 2) general intelligence score over 70 at most recent standard neuropsychological test of Korean Wechsler Adult Intelligence Scale (KWAIS), 3) age at the time of recruiting between 19 and 50 years. 4) underwent unilateral MTLR at least 1 year before recruiting. Final criterion was added to ensure stable brain network after surgery since previous study showed dynamic brain activational changes throughout the 3- and 12-month follow-ups after surgery (Sidhu et al., 2016). Forty-three patients agreed to participate in this study. Three patients were excluded due to severe dental metallic artifacts, and another 3 patients were excluded for their low memory capacity evaluated by postoperative standard neuropsychological test (2 borderline, 1 impairment). Finally, 37 patients were included in this study (17 left [9 females]; median age 34 years, range 23-46; 20 right [10 females];

median age 33 years, range 23-45). Demographics of patients were presented in **Table 5-1**. There were no statistically significant differences between the patient groups in their seizure-onset age (p=0.935), age at the time of surgery (p=0.513), duration of illness (p=0.712), and follow-up duration (p=0.985). Mean interval between surgery and participation of the present study was 6.45±2.75 years on average.

All patients underwent either selective amygdalohippocampectomy (SAH) or anterior temporal wedge resection (ATWR) with amygdalohippocampectomy (AH). A previous report has described surgical procedures (Chung et al., 2005). In short, HIP, parahippocampal gyrus, and amygdala were resected in all patients; neocortical temporal lobe was also surgically removed in patients with ATWR plus AH. Since the number of patients in each group was not enough for fMRI analysis, the memory encoding network according to the surgery types was not compared; 6 of 17 in left MTLR (LMTLR) and 3 of 20 in right MTLR (RMTLR) underwent SAH. Moreover, memory outcome was not different according to the surgery types (Mann-Whitney U test). Therefore, memory network differences due to different surgical procedures can be minimized in this study. Surgical outcome was classified according to the Engel's classification (Engel, 1993). The majority of patients (84%, LMTLR=15, RMTLR=16) were seizure-free after surgery. Eight LMTLR (47%) and 12 RMTLR patients (60%) stopped antiepileptic drugs (AEDs) after surgery, and remaining patients took 1 or 2

AEDs. No patients changed or increased AEDs after surgery. Pathology was reviewed in all patients who underwent resection. Pathologies were diverse, including hippocampal sclerosis, focal cortical dysplasia, and tumor.

Age and education year and matched 24 healthy controls (HC) were also recruited (13 females; median age 32 years, range 23-45). There were no significant differences in age (p=0.526) and education years (p=0.060) among groups. All subjects were right-handed except 1 LMTLR and 1 RMTLR patient (bilateral handedness). All subjects were native Korean speakers. Detailed demographics for HC and patients were presented in **Table 5-1** and **Table 6-1**. All subjects provided informed consent. This study was approved by the institutional review board of Seoul National University Hospital (IRB No.H1411-075-626).

Table 5-1. Demographics of patients * (year)

#	*Age	Sex	*Education/ handedness		*Seizure onset age	*Follow -up	Engel class	# AEDs	Surgery	Pathology
LMTLR group										
1	23	F	14	R	12	7.50	1	0	SAH	HS
2	29	M	16	Bi	19	2.33	1	0	ATWR	FCD IIIA (HS)
3	26	F	16	R	15	6.17	1	0	SAH	FCD IIIA (HS)
4	29	M	18	R	2	7.50	1	0	ATWR	HS
5	35	F	16	R	28	3.75	1	0	SAH	FCD IIIA (HS)
6	43	F	15	R	18	9.67	1	0	SAH	HS
7	31	M	14	R	1	8.50	2	1	ATWR	HS
8	38	M	12	R	2	10.00	1	2	ATWR	HS
9	45	M	12	R	33	10.50	1	1	ATWR	Astrocytoma
10	41	M	16	R	18	9.33	1	1	SAH	HS
11	34	F	12	R	22	7.25	1	0	ATWR	Ganglioglioma
12	32	F	16	R	16	5.50	1	0	ATWR	FCD IIIA (HS)
13	31	M	13	R	1	5.25	1	1	ATWR	HS
14	33	M	12	R	30	1.25	1	1	ATWR	FCDIA
15	37	F	16	R	12	6.67	1	2	ATWR	FCD IIIA (HS)
16	34	F	14	R	9	3.33	1	1	SAH	HS
17	46	F	12	R	12	5.00	2	1	ATWR	FCD IIIA (HS)
RMTLR group										
1	32	F	14	Bi	15	3.67	1	0	ATWR	FCDIIIC
2	35	F	15	R	2	8.08	1	0	SAH	HS
3	30	M	16	R	22	2.83	1	0	SAH	FCDIIIA (HS)
4	44	M	16	R	31	7.83	1	0	ATWR	FCDIIIA (HS)
5	42	M	12	R	31	5.50	1	0	ATWR	FCDIA
6	42	F	16	R	30	10.83	1	0	ATWR	HS
7	31	F	12	R	3	5.25	1	1	ATWR	FCDIIIA (HS)
8	34	F	13	R	14	7.00	3	2	ATWR	FCDIA
9	22	F	12	R	19	2.58	1	0	ATWR	FCDIIIA (HS)
10	45	M	14	R	12	9.42	1	1	ATWR	FCDIIIA (HS)
11	24	F	15	R	1	4.67	2	2	ATWR	FCDIA
12	23	M	15	R	6	6.92	1	0	ATWR	FCDIA, Astrocytoma
13	34	M	12	R	28	2.92	1	0	ATWR	FCDIIIC
14	33	M	19	R	18	2.50	1	0	ATWR	FCDIIIC
15	29	F	14	R	4	4.83	1	1	SAH	HS
16	24	M	14	R	5	5.25	1	0	ATWR	FCDIIIB
17	45	F	12	R	15	10.92	3	2	ATWR	HS
18	27	F	13	R	16	9.17	1	0	ATWR	HS
19	32	M	15	R	19	9.25	1	1	ATWR	DNET
20	42	M	14	R	7	9.75	2	1	ATWR	HS

5.2. Neuropsychological Tests

All subjects underwent standardized neuropsychological examination to ensure all subjects have normal range of cognitive ability, including general intelligence and memory performance at the time of fMRI scanning. Neuropsychological tests were performed on a separate day within 1 month apart with the day of fMRI scanning. KWAIS was administered in a standardized way to assess general intelligence (Yum et al., 1992). The Korean version of the Rey–Kim memory test was also administered (Kim, 1999). In the Rey-Kim memory test, verbal memory performance is assessed by the Korean version of the Rey Auditory Verbal Learning Test (KAVLT), and nonverbal visual memory performance is assessed by the Korean version of the Rey Complex Figure Test (KCFT). The KAVLT requires serial learning of a list of 15 unrelated words over 5 consecutive trials, each trial followed by immediate recall. After a delay period of 20 min, the patient is again required to recall the 15 words and then choose the 15 words from a list of 50 words. The KCFT is essentially identical to a standard version of the Rey Complex Figure Test. The following four MQ subtest scores were used in this study: the KAVLT immediate recall (sum of trials 1–5), the KAVLT delayed recall, the KCFT immediate recall, and the KCFT delayed recall. Age-adjusted scores were used for these four measures.

All statistics of behavioral data in the present study were calculated

using SPSS 19.0 software (IBM, Armonk, NY, USA) with the significance levels at 0.05 and application of a Bonferroni correction for multiple testing to subgroups. The one-way ANOVA, paired-sample t test, or Pearson correlation analysis were applied, where appropriate.

5.3. Magnetic Resonance Data Acquisition

All patients were examined before surgery by using either a GE 1.5 or 3 T MRI unit (GE Horizon Echospeed) or a Siemens 1.5 T scanner (Siemens Avento system, Erlangen, Germany). The standard structural MRI protocol included T1-weighted, T2, fluid attenuated inversion recovery (FLAIR) axial, T2 and FLAIR oblique coronal, fast inversion recovery with myelin suppression, and three-dimensional (3D) gradient echo coronal T1 imaging with whole-brain coverage. In the present study, preoperative MRI was compared with postoperative MRI in order to confirm surgically resected areas of each patient.

The MR images of HC and postoperative patients were acquired on a research-dedicated 3T MAGNETOM Trio Tim Syngo (Siemens, Erlangen, Germany) using a 32-channel head coil. A series of high-resolution anatomic T1-weighted images were obtained with 3D TFL sequence (TR = 1670 ms, TE = 1.89 ms, field of view = 250 × 250 mm, flip angle = 9°, voxel size = 1.0 × 1.0 × 1.0 mm^3) before the functional scans. Functional data were acquired

using a T2*-weighted gradient echo planar imaging sequence (36 axial slices, slice thickness = 3.4 mm (no gap), TR = 2750 ms, TE = 30 ms, field of view = 220 x 220 mm, flip angel = 80°, voxel size = 3.4 x 3.4 x 3.4 mm^3, and interleaved). The field of view covered the temporal and frontal lobes with slices aligned with the long axis of the HIP.

5.4. Memory Task Paradigm

For memory task, similar procedures from the previous studies that investigated memory encoding network of patients with TLE were adopted (Sidhu et al., 2013; Sidhu et al., 2016). Since it is generally known that left MTL lesion causes abnormalities mainly in verbal memory domain while right MTL lesion causes reductions in nonverbal visual memory domain (Bell et al., 2011), two different material types were used to assess material-specific differences according to the hemisphere of surgical intervention. Two material types, verbal stimuli (words) and visual stimuli (figures), were visually presented on a MR-compatible screen viewed through a mirror. All stimuli were presented using the E-prime software (Version 2.0, Psychology Software Tools Inc., Pittsburgh, PA, USA).

For words, single concrete nouns were presented in white font on a black background. The word stimuli were selected from a previous study that reported word imagery using a 7-point Likert scale (Park, 2004). All word

stimuli consisted of two syllables and had larger than 3-point imagery values. Word frequencies were matched across the blocks based on the criteria obtained by National Institute of Korean Language (National Institute of Korean Language, 2005). Emotionally adverse words were excluded. Finally, 170 words that consisted of 17 sets of 10 words were selected. Each block of words contained 50% artificial and 50% natural words. Mean imagery values and word frequency were 5.95 (SD=0.57, IQR=5.69-6.34) and 126.62 (SD=197.96, IQR=28-148), respectively.

For figures, black and white unnamable abstract figures were used as stimuli. Figures were selected from previous studies (Jung and Cha, 2012; Lee et al., 2011). In these previous studies, the authors collected 800 fractal images from the Internet and rated their beauty using a 9-point Likert scale and reported that high level of beautiful figures boost incidental and intentional memory encoding. Therefore, 170 high and middle level beautiful figures were selected for stimuli for boosting memory encoding.

Each item was presented for 3 s in 60 s blocks. In order to introduce jitter and ensure random sampling, a different interstimulus interval (3 s) from the repetition time of 2.75 s was used. The same protocol was used in previous studies (Sidhu et al., 2013; Sidhu et al., 2016; Sidhu et al., 2015). Each block consisted of 10 words and 10 figures followed by 15 s of cross-hair fixation (**Fig. 5-1**). Ten blocks (100 words and 100 figures) were presented in 2 separate scanning runs. All stimuli were counterbalanced

across subjects. Participants were explicitly instructed to memorize items for subsequent out-of-scanner recognition. A deep encoding task, which involved a subjective decision on whether each stimulus was pleasant or unpleasant, using a magnetic compatible button box, was performed.

About 30 minutes after encoding, word and figure recognition was tested separately in an out-of-scanner recognition task. In each recognition task, subjects were shown the same 100 items intermixed with an additional 50 novel words/figures in random order at the same speed as items were displayed within the scanner. Patients used a keyboard to indicate whether items were remembered (old), familiar, or novel. These responses were used to sort each item shown in the scanner to items remembered, familiar, and forgotten. Recognition accuracy (%) was calculated for both words and figures as: hit rate (stimuli correctly remembered) - false alarm rate (novel stimuli incorrectly tagged as remembered).

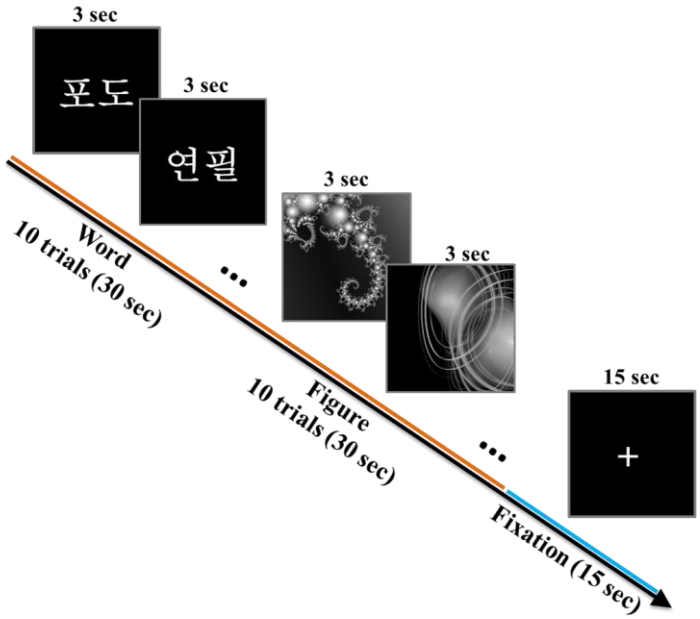

Figure 5-1. Examples of memory task stimuli. Two-syllable concrete nouns for verbal memory encoding and figures for nonverbal visual memory encoding were used for stimuli. The examples Korean word stimuli '포도' means 'grape' and '연필' means 'pencil'.

5.5. Data Analysis

5.5.1. Preprocessing

The functional imaging data were analyzed using Analysis of Functional Neuroimage (AFNI) software (https://afni.nimh.nih.gov/afni/). The first two TRs at the beginning of each run were discarded for T1 stabilization. Motion correction and slice timing correction were performed for all slices within a volume. After correcting for differences in slice acquisition time and head motion, the functional images were coregistered to the T1-weighted image.

Spatial normalization of the coregistered images was performed to transform data into the Talairach space using the Montreal Neurological Institute avg152T1 template provided by the AFNI. All voxels were resampled as 2 × 2 × 2 mm size by linear interpolation. Mean-based intensity normalization was done after spatial smoothing using a Gaussian filter with 8 mm full-width at half-maximum.

5.5.2. Event-related Analysis

Event-related analysis on a block-designed experiment has been performed in memory studies (Sidhu et al., 2013; Sidhu et al., 2016). In the present study, event-related analysis was used to explore brain activations for subsequently remembered stimuli. For the whole-brain analysis, only subsequently remembered trials were used, which has been previously reported better than subtraction contrast (remembered minus forgotten) in revealing whole-brain activation patterns during a memory task (Sidhu et al., 2015). A two-level event-related random-effects analysis was employed. In first-level analysis, hemodynamic response starting from the stimulus onset to 13.75 s using cubic spline basis functions (AFNI's 3dDeconvolve with 'CSPLINzero' option) were estimated, separately for words remembered, words familiar, words forgotten, figures remembered, figures familiar, and figures forgotten. To correct motion-related artifacts, six motion parameters were also included in the first-level GLMs and censored TRs as outlier volume based on a threshold

of framewise displacement >0.9 from the GLMs. Contrast images were created by averaging beta from the second to fifth points (2.75 s - 11 s) of estimated response for each subject for word encoding and figure encoding.

In the second-level analysis, one-sample t-test was used to examine the group effect of each contrast in each group. A two-sample t-test was performed to examine group differences between HC and MTLR groups, separately for LMTLR and RMTLR. To examine only the task-related effects without influence of baseline differences of individual general cognitive ability, individual IQ and MQ differences were controlled by using them as covariates in the second-level analyses. Significance thresholding for group analyses was carried out using 3dClustSim available in the AFNI software suite. The 3dClustSim creates a table with cluster-extent estimates at different voxel-wise *p* values and cluster-wise alpha values. In the present study, results were thresholded to reveal clusters significant at $p<0.01$ with a voxel-wise threshold of $p<0.005$ unless otherwise stated. Using this method and these thresholds, the significant cluster size minimum was 155 contiguous voxels for whole brain. For activations within the HIP, the10 mm diameter sphere was used instead of the entire brain to create a thresholding table. A voxel-wise threshold of $p<0.01$ within a cluster extent threshold of 21 voxels was used for the HIP, which corresponds to the corrected $p<0.05$.

5.5.3. Hippocampal ROIs

The bilateral HIP for all HCs and patients were manually segmented in each subject's high- resolution structural space (**Fig. 6-2A**). The manual segmentation was conducted because automatic segmentation did not accurately detect the posterior remnant parts of HIP in some of patients. Determination of the anatomic boundaries of hippocampal formation was based on previously developed protocols (Jack, 1994). Two LMTLR patients had no remaining posterior HIP due to atrophic changes after surgery. The mean percent signal changes of activated voxels in the HIP ROIs during encoding of subsequently remembered stimuli compared with subsequently forgotten or familiar stimuli were calculated in all subjects. Left and right HIP activations were then correlated with clinical variables using Pearson correlation coefficient.

5.5.4. Task-based Functional Connectivity

To examine FC in the context of memory process, a generalized psychophysiological interaction (gPPI) model was employed (McLaren et al., 2012). Using this analysis, brain regions whose FC with predefined seed ROIs were significantly modulated by the interaction of subsequent remembered stimuli were isolated. Seed ROIs were created from the surviving clusters in the group analysis. The bilateral HIP were also selected as seed ROIs.

Firstly, the mean time series of voxels within the ROIs were extracted and deconvolved into estimates of neural events. Next, the interaction terms between the neural estimates and each column of the task design were calculated, which are then convolved with a canonical hemodynamic response function. A GLM that includes these interaction regressors, the task regressors, and a regressor for the average time series of the seed ROI was used to analyze FC between the seed ROI and whole brain during memory task for each participant. Task-based FC maps of each seed ROI for word and figure encoding were obtained. Two-sample t-test was performed with each FC map for each seed ROI to compare group difference between the MTLR and HC. To correct for multiple comparisons, a corrected $p<0.01$ using cluster-level thresholding were maintained, in which a significant cluster is defined as a minimum of 155 contiguous voxels that survive uncorrected threshold of $p<0.005$.

Chapter 6: Results

6.1. Neuropsychological Performance

General intelligence (IQ) was not statistically different between the two patient groups of LMTLR and RMTLR (p=0.361) (**Table 6-1**). HC showed significantly higher IQ than RMTLR (p<0.05) without significant difference compared with LMTLR (p=0.080).

For the memory performance, full-scale memory quotient (MQ) was significantly higher in HC than both patient groups of LMTLR (p<0.001) and RMTLR (p<0.05); two patient groups did not show differences. Regarding MQ subtests, both verbal immediate and delayed recall scores were significantly lower in LMTLR group than both HC (p<0.05) and RMTLR groups (p<0.05). In contrast, both visual immediate and delayed recall scores were significantly lower in RMTLR group than HC (p<0.001) and LMTLR groups (p<0.05). Both visual memory sub-test scores were also lower in LMTLR than HC (p<0.05). Regardless of the differences among groups, both IQ and MQ scores of all subjects were at a high-average to low-average range, which proves the intact cognitive function of subjects at the time of study participation.

Table 6-1. Subjects demographics and neuropsychological results

	HC (n=24)	LMTLR (n=17)	RMTLR (n=20)
Age (years)	32.8 (6.53)	34.53 (6.49)	33.50 (7.62)
Sex (M/F)	11/13	8/9	10/10
Education (years)	15.29 (1.46)	14.35 (1.93)	14.15 (1.81)
Seizure onset (years)	-	14.71 (9.98)	14.90 (9.95)
Duration of illness (years)	-	13.24 (9.40)	12.00 (8.74)
Age at surgery (years)	-	27.94 (6.11)	26.90 (6.54)
Follow up (years)	-	6.44 (2.74)	6.46 (2.83)
IQ [b]	117.92 (9.49)	109.53 (13.82)	105.60 (11.99)
MQ [aa, b]	113.08 (10.55)	98.12 (11.61)	104.60 (9.64)
Verbal immediate recall [a, b]	11.75 (1.87)	9.76 (2.02)	12.30 (2.03)
Verbal delayed recall [a, b]	11.88 (1.96)	8.47 (4.65)	11.50 (2.33)
Visual immediate recall [a, bb, c]	13.50 (1.89)	12.00 (1.87)	9.95 (1.64)
Visual delayed recall [a, bb, c]	13.54 (1.96)	11.47 (2.70)	9.75 (2.29)

Data presented as mean (SD).

[a] HC vs. LMTLR significant differences ($p<0.05$).

[aa] HC vs. LMTLR significant differences ($p<0.001$).

[b] HC vs. RMTLR significant differences ($p<0.05$).

[bb] HC vs. RMTLR significant differences ($p<0.001$).

[c] LMTLR vs. RMTLR significant differences ($p<0.05$).

6.2. Behavioral Results

There were no statistically significant differences on word recognition performances among subject groups (mean accuracy %, HC=62.70±23.15, LMTLR=48.75±22.99, RMTLR=54.30±18.55, p=0.137) (**Fig. 6-1**). For the figure recognition, HC showed higher performance (33.33±15.10) than both patient groups (LMTLR=18.35±14.19, p<0.05; RMTLR=15.00±13.48, p<0.001). There were no significant figure recognition differences between the two patient groups. Regardless of performance differences, the results confirm that all subjects understood and performed the memory task well.

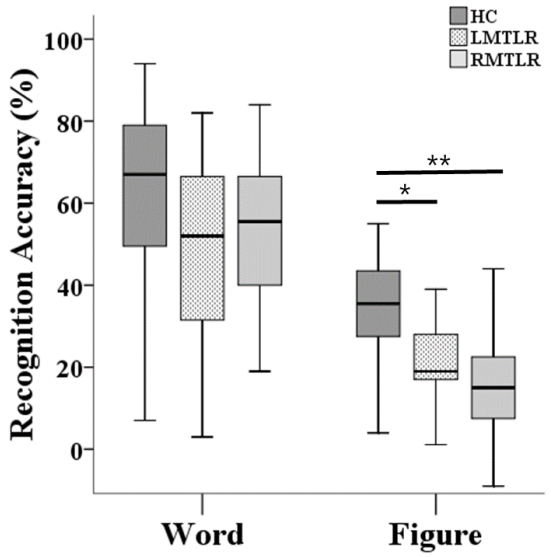

Figure 6-1. Behavioral results. Box plots showing mean percentage recognition accuracy for word and figure recognition across all groups. Bars represent standard deviation of the mean. HC=healthy controls, LMTLR=patients with left medial temporal lobe resection, RMTLR=patients with right medial temporal lobe resection. *p<0.05, **p<0.001.

6.3. Hippocampal ROI Activations

In LMTLR patients, activations in the contralateral right HIP during word encoding were positively correlated with verbal immediate recall scores (r=0.498, p<0.05, **Fig. 6-2B**). In RMTLR patients, activations in the contralateral left HIP during figure encoding were positively correlated with visual delayed recall scores (r=0.447, p<0.05, **Fig. 6-2C**). No significant correlations were identified during figure encoding in LMTLR and during word encoding in RMTLR patients.

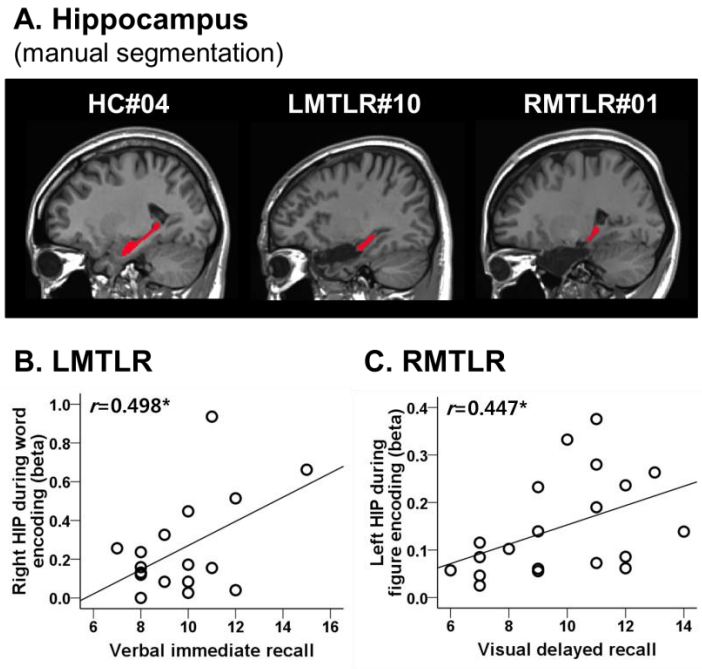

Figure 6-2. Hippocampal ROI activations. (A) Examples of manually drawn hippocampal ROIs. (B-C) HIP activations in relation to memory scores in LMTLR (B) and RMTLR (C).

6.4. Whole-brain Activations during Memory Encoding

The activated areas during both successful word and figure encoding of each group are presented in **Table 6-2** and **Fig. 6-3**. At whole-brain level, the in-scanner memory encoding paradigm reliably activated well-known episodic memory related MTL and neocortical brain areas (Jeong et al., 2015; Kim, 2011; Sidhu et al., 2013). To investigate group differences, brain activities of each patient group with HC for each modality (word or figure) were compared (**Table 6-3, Fig. 6-4**). In addition, *post hoc* analysis of ROIs that showed significant group differences was also performed to show patterns of activation (activation or deactivation) in each group.

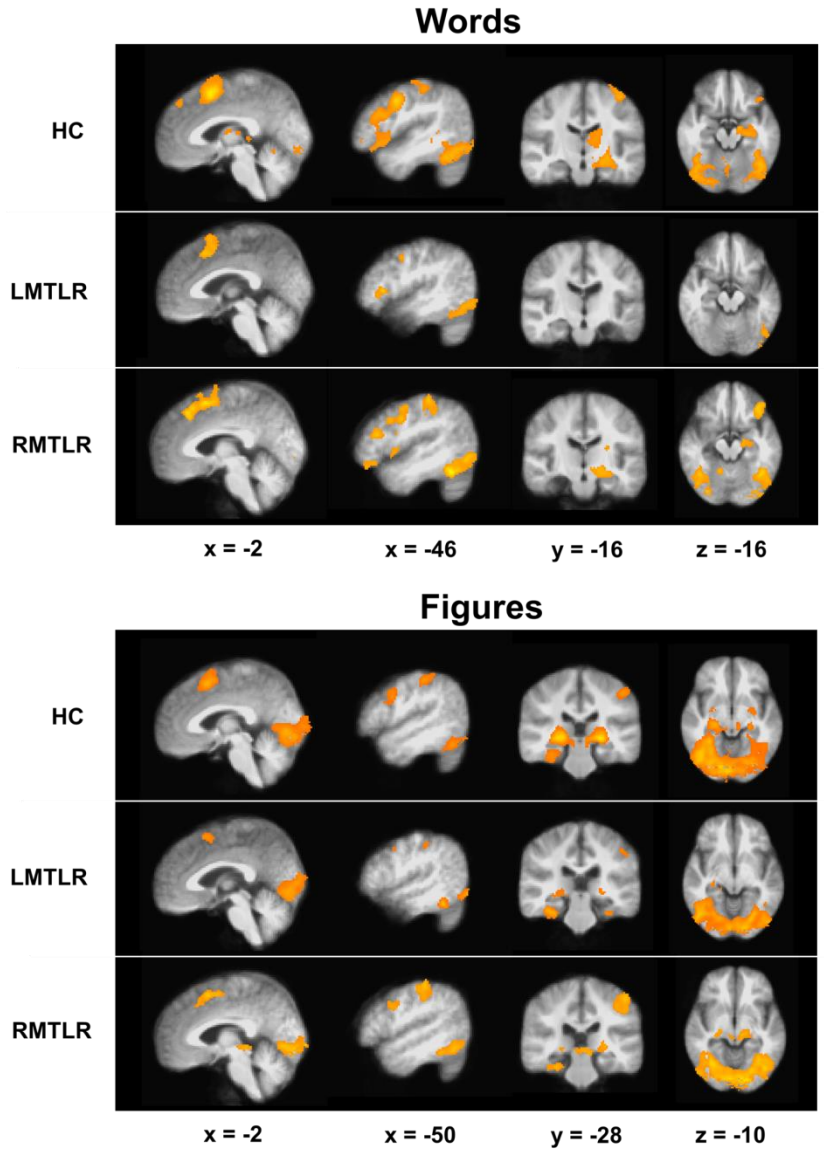

Figure 6-3. Whole-brain activation maps during successful word and figure encoding. Significant regions are superimposed onto averaged normalized mean T1 images from each group. Similar brain areas were activated across three subject groups. L=left, R=right. $p_{corrected}$<0.01 ($p_{uncorrected}$<0.00001, voxels >22).

Table 6-2. Main effects for encoding words and figures

	HC (n=24)	**LMTLR (n=17)**	**RMTLR (n=20)**
Lobe	Regions *(x, y, z/voxels/T max)*	Regions *(x, y, z/voxels/T max)*	Regions *(x, y, z/voxels/T max)*
Subsequently remembered word encoding			
F	L PreCG/ L IFG*oper,tri,orb* *(-46, 2, 40/2352/10.96)*	L SMA *(0, 18, 48/639/9.96)*	L SMA *(-6, 10, 56/1500/11.97)*
		L IFG*tri* *(-46, 22, 6/101/11.78)*	L IFG*oper,tri* *(-58, 10, 28/986/9.88)*
	L SMA *(-2, 10, 54/1216/13.00)*	L PreCG *(-46, 2, 42/43/7.84)*	L IFG*orb* *(-38, 32, -14/385/9.91)*
	L SFG *(-16, 42, 48/650/8.47)*	L SFG *(-8, 56, 32/32/8.02)*	L SFG *(-12, 60, 24/66/7.84)*
	L PreCG/ L PoCG *(-40, -16, 60/551/8.50)*		L PreCG *(-32, -6, 64/58/7.80)*
P			L PoCG *(-48, -28, 58/428/8.97)*
T/O	R MOG *(22, -92, 2/4383/14.70)*	R MOG *(20, -92, -2/1189/14.67)*	R MOG *(44, -66, -10/2407/11.09)*
	L FG *(-40, -68, -10/3435/12.15)*	L MOG/FG *(-38, -78, -6/1069/10.62)*	L FG *(-38, -82, -10/2373/13.21)*
	L HIP*ant*/ L PUT *(-22, -28, -4/2072/12.34)*		L HIP*ant* *(-16, -12, -8/389/10.37)*
	L MTG *(-48, -42, 4/66/6.59)*	L PUT *(-24, 2, 6/31/7.35)*	R INS *(30, 24, 6/198/7.71)*
	R THAL *(30, -30, 0/44/7.12)*		L PUT *(-18, -4, 10/107/7.11)*
	R CN *(16, 2, 24/41/6.49)*		L INS *(-32, 4, 10/80/8.01)*
Subsequently remembered figure encoding			
F	L SMA *(-2, 12, 52/640/11.55)*	R SMA *(8, 8, 54/227/9.82)*	L SMA *(-6, 12, 54/487/11.10)*
	R IFG*oper* (48, 10, 32/395/10.36)	R IFG*oper* *(50, 12, 28/66/8.03)*	L IFG*oper* *(-56, 10, 32/166/8.20)*
	L IFG*oper* *(-42, 6, 32/352/8.68)*	L IFG*oper* *(-44, 4, 32/25/6.99)*	R IFG*oper* *(52, 10, 32/66/8.13)*
	R IFG*tri* *(44, 36, 18/168/7.92)*		L IFG*orb* *(-34, 24, -16/47/7.32)*
	L PreCG *(-32, -16, 72/36/6.03)*		
	L IFG*tri* *(-42, 32, 16/27/6.29)*		
P	L PoCG *(-48, -30, 50/292/9.05)*	L PoCG *(-48, -32, 46/63/7.87)*	L PoCG *(-48, -30, 56/788/10.05)*
	L SPL *(-26, -56, 50/23/6.00)*	L SPL *(-28, -60, 54/24/7.78)*	L SPL *(-22, -66, 54/32/7.28)*
T/O	R IOG/R HIP*pst* *(44, -62, -14/19379/19.37)*	L MOG/Bi FG *(-26, -88, 12/11644/19.98)*	L FG/Bi MOG *(-30, -52, -14/11994/13.80)*
	L PUT *(-20, 6, 10/76/7.44)*	R HIP*pst* *(24, -32, 0/126/9.00)*	L THAL *(-8, -24, -6/809/8.94)*
	R AMYG *(32, -4, -16/59/7.11)*	L THAL *(-22, -30, -2/40/8.20)*	R HIP*pst* *(26, -16, -10/85/7.55)*
	R FG *(34, -4, -34/31/7.35)*		L INS *(-32, 22, 4/29/6.73)*
			R INS *(32, 20, 6/25/7.27)*

AMYG, amygdala; Bi, bilateral; CN, caudate nucleus; F, frontal lobe; FG, fusiform gyrus; HIP*ant*, anterior hippocampus; HIP*pst*, posterior Hippocampus; IFG*oper*, inferior frontal gyrus opercular part; IFG*tri*, IFG triangular part; IFG*orb*, IFG orbital part; INS, insular lobe; IOG, inferior occipital gyrus; L, left; MOG, middle occipital gyrus; MTG, middle temporal gyrus; O, occipital lobe; P, parietal lobe; PoCG, postcentral gyrus; PreCG, precentral gyrus; PUT, putamen; R, right; SFG, superior frontal gyrus; SMA, supplementary motor area; SPL, superior parietal lobule; T, temporal lobe; THAL, thalamus.

$p_{corrected}<0.01$ ($p_{uncorrected}<0.00001$, voxels >22).

6.4.1. Less Activation in MTLR than in HC

During successful memory encoding, only limited areas of the MTL and frontal areas showed less activation in MTLR groups than in HC. In word encoding, LMTLR group showed significantly less activation in the left inferior frontal gyrus triangular part (IFG*tri*), IFG orbital part (IFG*orb*), and anterior HIP (HIP*ant*) compared with HC. The *post hoc* analysis of left IFG*tri* and IFG*orb* revealed that both areas showed significantly lower activations in LMTLR than both HC ($p<0.001$) and RMTLR groups ($p<0.05$). No areas showed group differences during word encoding compared with RMTLR and HC group. In figure encoding, LMTLR showed less activation in the left middle frontal gyrus (MFG) and HIP*ant* compared with HC. Again, *post hoc* analysis showed significantly less activation of the left MFG in LMTLR than both HC ($p<0.001$) and RMTLR ($p<0.05$) groups during figure encoding. When comparing HC and RMTLR groups, RMTLR showed less activation limited to the MTL areas, including the right thalamus (THAL) and posterior HIP (HIP*pst*). The *post hoc* analysis of right THAL showed less activation in RMTLR than HC ($p<0.001$).

6.4.2. Greater Activation in MTLR than HC

During successful word encoding, no areas showed significantly greater activation in both patient groups than HC. In figure encoding, the right medial prefrontal cortex (mPFC) showed greater activations in LMTLR than HC. The *post hoc* analysis of the right mPFC displayed a deactivation pattern in all subject groups, and LMTLR ($p<0.001$) and RMTLR ($p<0.001$) groups showed less deactivation than HC. In contrast, RMTLR group showed greater activation in widespread brain areas than HC. Areas include right middle temporal gyrus (MTG), medial areas of middle cingulate cortex (MCC), postcentral gyrus (PoCG), superior parietal lobule, mPFC, and left supramarginal gyrus (SMG). Interestingly, all these areas deactivated in HC group, while RMTLR showed significantly less deactivation or even activation patterns ($p<0.001$ for all).

Taken together, the right mPFC was the common area that showed greater activation (less deactivation) in both LMTLR and RMTLR groups than HC during successful figure encoding. It is of note that, although the cluster survived at lower threshold (voxels > 90), the right mPFC showed similar activation patterns during successful word encoding (**Table 6-3, Fig. 6-4**).

Table 6-3. Group differences during successful word and figure encoding

Regions	*(x, y, z/voxels/T max)*	Regions	*(x, y, z/voxels/T max)*
Word Encoding			
HC > LMTLR		**LMTLR > HC**	
L IFG*tri*	*(-42, 22 28/378/4.09)*	R mPFC*	*(6, 52, 4/93/3.52)*
L IFG*orb*	*(-48, 44, -2/184/4.44)*		
L MTG*	*(-56, -30, 4/146/4.59)*		
L HIP*ant*†	*(-14, -10, -14/29/3.30)*		
HC > RMTLR		**RMTLR > HC**	
n.s.		R PoCG*	*(42, -36, 60/130/3.87)*
		R IFG*orb**	*(48, 50, -12/113/4.99)*
		R RSC*	*(6, -50, 14/105/3.71)*
Figure Encoding			
HC > LMTLR		**LMTLR > HC**	
L MFG/IFG*tri*	*(-48, 24, 38/505/4.65)*	R mPFC	*(6, 48, 14/244/4.30)*
L HIP*ant*†	*(-16, -10, -24/22/3.05)*		
HC > RMTLR		**RMTLR > HC**	
R THAL/ HIP*pst*	*(22, -30, 2/169/4.62)*	R MTG	*(62, -14, -8/2816/5.44)*
R ITG*	*(34, 2, -40/133/5.19)*	R MCC	*(2, -24, 44/417/4.92)*
		R PoCG/SPL	*(22, -44, 62/377/4.49)*
		R mPFC	*(2, 48, 16/245/4.35)*
		L SMG	*(-56, -18, 14/242/4.82)*
		L PoCG*	*(-22, -40, 46/126/3.92)*
		R IFG*orb**	*(48, 38, -8/106/3.96)*
		L IFG*orb**	*(-36, 48, -12/101/3.65)*

ITG, inferior temporal gyrus; MCC, middle cingulate cortex; MFG, middle frontal gyrus; mPFC, medial prefrontal cortex; PCUN, precuneus; PoCG, postcentral gyrus; RSC, retrosplenial cortex; SMG, supramarginal gyrus

$p_{corrected}<0.01$,*$p_{uncorrected}<0.005$ (voxels>90), †$p_{corrected}<0.05$ (small volume corrections for HIP).

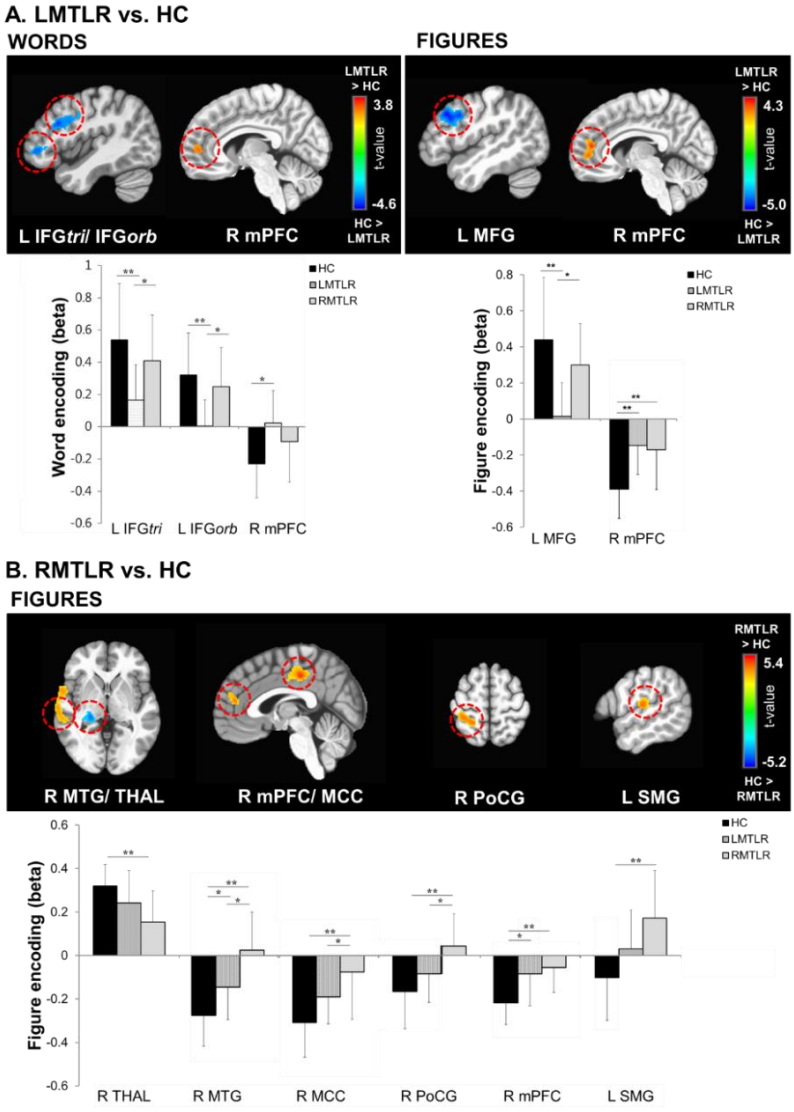

Figure 6-4. Location and activation patterns of brain areas that showed group difference. Survived areas in multiple comparison corrections were superimposed onto MNI152 T1 template. Although not survived in multiple comparison correction, the right mPFC of word condition in 'LMTLR vs. HC' contrast was included for the display purpose of seed ROIs of functional connectivity analysis. No areas showed group differences during word encoding in 'RMTLR vs. HC' contrast. L=left, R=right. *p<0.05, **p<0.001

6.5. Task-based Functional Connectivity

To investigate FC between brain regions during episodic memory encoding, seeds derived from the group differences of task-related activation between HC and MTLR patients were used (**Table 6-3, Fig. 6-4**). For the bilateral HIP ROIs, the areas showing group differences were not always available in patient groups due to the surgical resection; therefore, manually segmented HIP instead of using the areas from group comparisons were used. For analysis of left HIP seed, two LMTLR patients were excluded because no remnant HIP was found in these patients. For the FC analysis during word encoding, the left IFG*tri*, IFG*orb*, right mPFC, and bilateral HIP were selected for seed ROIs. Although the right mPFC during word encoding survived only at lower cluster size, this area was also included as a seed ROI for FC during word encoding since the mPFC is a well-known memory encoding-related area. For the FC analysis during figure encoding, the bilateral HIP, left MFG, right mPFC, THAL, MTG, MCC, PoCG, and left SMG were selected for seed ROIs. FC of LMTLR and RMTLR groups were compared with HC separately for both word and figure memory encoding conditions. Regions exhibiting significant interactions with the seed ROIs during subsequently remembered word and figure encoding are presented in **Table 6-4** (word), **Table 6-5** (figure) and **Fig. 6-5**. ROIs that showed no significant group differences in FC analysis are not shown in the Table.

During memory encoding, FC between seed ROIs and many different brain areas were mostly stronger in both patient groups than HC. During successful word encoding, the seed of right mPFC exhibited significantly stronger interactions with many different memory encoding-related brain areas, including the left SMG, retrosplenial cortex (RSC), SMA, MFG, bilateral PoCG, and right HIP*ant* in LMTLR patients than in HC group. In addition, FC between right mPFC – left MFG was positively correlated with verbal delayed recall scores (r=0.487, p<0.05) in LMTLR group (**Fig. 6-6**). In contrast to widespread changes in LMTLR group, RMTLR patients showed significantly stronger FC in only one connection of the left HIP seed and right mPFC than HC. Interestingly, weaker FC in patient groups than in HC was found in only one connection of the right HIP seed and left orbital gyrus (OrbG) in RMTLR group during word encoding. No other weaker FC in both MTLR groups than HC was found during both word and figure encoding.

During successful figure encoding, FC between the left MFG – right mPFC was stronger in LMTLR than HC group although activation of the left MFG was weaker in LMTLR than HC group. Meanwhile, more widespread brain areas exhibited significantly stronger interactions with seed ROIs in RMTLR than HC group. Similar to stronger FC in LMTLR during word encoding, the right mPFC seed showed stronger interactions with many different parts of brain areas in RMTLR during figure encoding. The right

mPFC seed showed stronger interactions with left HIP*ant*, right PreCG, and right putamen (PUT) in RMTLR group. Moreover, FC between the right mPFC – left HIP*ant* and right PreCG during successful figure encoding were positively correlated with visual immediate recall scores in RMTLR group (r=0.475, p<0.05; r=0.520, p<0.05) (**Fig. 6-6**). The reverse direction of the left HIP – right mPFC also showed stronger FC in RMTLR group. Other seed ROIs of the right MTG and MCC also showed significantly stronger interactions with many different brain areas in RMTLR patients than HC (right MCC – right PUT, and FG; right MTG – right FG, PCUN, SMG, left anterior cingulate cortex, and PoCG). Interestingly, although FC values were higher in RMTLR, FC between the right MTG – right FG was positively correlated with visual immediate (r=0.584, p<0.05) and visual delayed recall scores (r=0.483, p<0.05) in HC.

In summary, HC showed stronger task-based FC between the right HIP and left OrbG than RMTLR group during word encoding. No other significantly stronger FC was observed in HC even though HC showed greater activations in the left frontal areas than patient groups during both word and figure memory encoding. In contrast, LMTLR group showed stronger interactions with widespread brain areas during word encoding, while only one stronger FC was found during figure encoding. The opposite patterns of FC were observed in patients with RMTLR; only one stronger connection during word encoding was found, while more widespread stronger

connections were observed during figure encoding. Furthermore, the strength of right mPFC FC predicts verbal memory scores in LMTLR patients and visual memory scores in RMTLR patients.

Table 6-4. Regions exhibiting significant interactions with the seed ROIs during subsequently remembered word encoding

Contrast	Regions/include	x, y, z	Voxels	T max	gPPI values					
					[1)] HC	[2)] LMTLR	[3)] RMTLR	Sig. (ANOVA *post-hoc*) [1)] vs. [2)]	[1)] vs. [3)]	[2)] vs. [3)]
Functional connectivity during WORD encoding										
LMTLR vs. HC										
R mPFC-seed										
	L SMG/RSC	-34, -26, 4	1687	5.54	-0.14 (0.14)	**0.21 (0.15)**	-0.04 (0.20)	***		***
	R PoCG	54, -6 , 32	616	5.22	-0.18 (0.17)	**0.12 (0.20)**	0.02 (0.29)	***	*	
	L PoCG	-20, -40, 46	576	5.31	-0.10 (0.13)	**0.17 (0.16)**	0.00 (0.21)	***		*
	L SMA	-2, 0, 68	431	5.05	-0.22 (0.29)	**0.30 (0.40)**	0.07 (0.87)	*		
	L MFG	-46, 50, 12	165	4.79	-0.16 (0.31)	**0.47 (0.61)**	0.24 (0.62)	***	*	
	R HP*ant*†	36, -20, -12	45	3.80	-0.13 (0.22)	**0.16 (0.27)**	-0.03 (0.31)	**		
RMTLR vs. HC										
L HIP-seed										
	R mPFC	16, 44, 22	186	5.06	-0.05 (0.23)	0.03 (0.18)	**0.26 (0.22)**		***	**
R HIP-seed										
	L OrbG	-14, 40, -10	225	-4.82	**0.63 (0.97)**	-0.04 (1.20)	-0.76 (0.95)		***	

Table 6-5. Regions exhibiting significant interactions with the seed ROIs during subsequently remembered figure encoding

Contrast	Regions/include	x, y, z	Voxels	T max	gPPI values			Sig. (ANOVA *post-hoc*)		
					1) HC	2) LMTLR	3) RMTLR	1) vs. 2)	1) vs. 3)	2) vs. 3)
Functional connectivity during FIGURE encoding										
LMTLR vs. HC										
L MFG-seed										
	R mPFC	18, 48, 22	162	4.83	-0.10 (0.24)	**0.24 (0.23)**	0.05 (0.26)	***		
RMTLR vs. HC										
L HIP-seed										
	R mPFC	16, 44, 22	186	5.06	-0.11 (0.31)	0.01 (0.16)	**0.29 (0.30)**		***	*
R MTG-seed										
	R CB/FG	30, -40, -26	841	5.18	-0.57 (0.47)	-0.28 (0.51)	**0.35 (0.38)**		***	***
	R SPL/PCUN	24, -72, 46	400	4.05	-0.34 (0.44)	-0.20 (0.44)	**0.25 (0.40)**		***	**
	R IPL/SMG	34, -42, 46	292	4.15	-0.22 (0.23)	-0.11 (0.20)	**0.15 (0.28)**		***	**
	L ACC	-14, 40, 6	286	4.92	-0.31 (0.48)	-0.02 (0.12)	**0.35 (0.45)**		***	
	L PoCG	-24, -34, 42	264	5.25	-0.23 (0.22)	0.03 (0.26)	**0.15 (0.18)**	***	***	
R MCC-seed										
	R PUT	22, 8, -4	279	5.524	-0.32 (0.34)	-0.25 (0.29)	**0.19 (0.35)**		***	***
	R LING/FG	28, -54, 0	258	4.5035	-0.11 (0.38)	-0.23 (0.43)	**0.45 (0.37)**		***	***
R mPFC-seed										
	R PUT	34, 0, 4	341	4.3288	-0.21 (0.16)	-0.10 (0.26)	**0.11 (0.26)**		***	*
	R PreCG	48, -2, 28	171	4.3894	-0.18 (0.19)	0.03 (0.26)	**0.12 (0.28)**	*	***	
	L HIP*ant*†	-32, -26, -14	47	3.9863	-0.12 (0.23)	-0.00 (0.30)	**0.18 (0.28)**		***	

ACC, anterior cingulate cortex; CB, cerebellum; LING, lingual gyrus; OrbG, orbital gyrus.

*p<0.05, **p<0.01, ***p<0.001. $p_{corrected}$<0.01, †$p_{corrected}$<0.05 (small volume corrections for HIP).

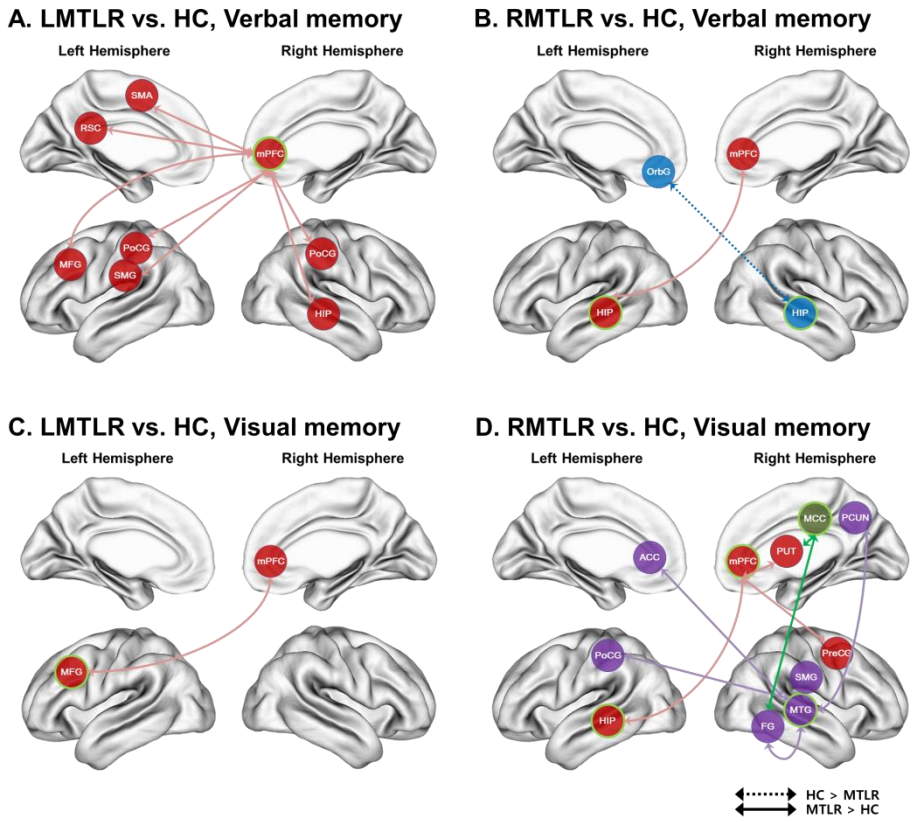

Figure 6-5. Functional connectivity during successful memory encoding. Boundaries with a green color indicate seed ROIs. Solid line indicates greater FC in MTLR patients than HC, and dotted line indicates less FC in MTLR patients than HC. All except one connection showed increased FC in MTLR groups than HC. Note that the right mPFC displayed increased FC with widespread brain areas, including contralateral HIP. Material-specific FC changes were observed; more widespread changes of FC in verbal memory encoding for LMTLR and visual memory encoding for RMTLR. See **Table 6-4** and **Table 6-5** for more details.

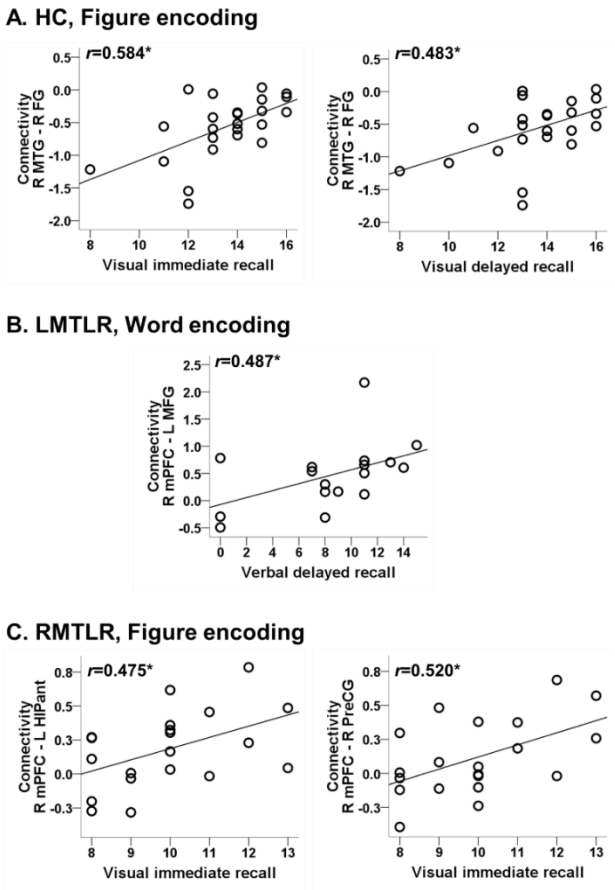

Figure 6-6. Clinical correlation of functional connectivity during successful memory encoding. *$p<0.05$

SECTION III. DISCUSSION AND CONCLUSION

Chapter 7: Discussion

The purpose of present study was to understand how brain supports normal episodic memory function without unilateral MTL structures in a new perspective of functional interactions of brain network. By using a whole-brain fMRI, effective episodic memory encoding network was investigated in patients who had normal range of memory function following MTLR.

7.1. Behavioral Results

Regarding out-scanner word-recognition performance, the result of no group differences regardless of lower neuropsychological verbal memory scores in LMTLR group may be due to a relatively simple recognition task with three alternative choices (old, familiar, new), which makes it difficult to reveal the performance differences among groups that have a normal range of verbal memory capacity. Moreover, all verbal items consisted of common nouns, and no subjects reported any unknown or unfamiliar words during the encoding and recognition. In contrast, figural memory seemed more difficult, since

most of the figure items were not only unfamiliar to subjects but also difficult to name. However, regardless of performance differences, the behavioral results prove that all subjects understood and performed the memory task well. Moreover, since only successful encoding (subsequently remembered) trials were included for functional imaging analyses, the possible effects of behavioral performance differences on functional memory network could be minimized in the present study.

7.2. Hippocampal ROI Activities

Only a few studies investigated patterns of postoperative memory-related brain activation (Cheung et al., 2009; Sidhu et al., 2016). Those studies found that individual memory performance was positively associated with functional activation of HIP on the side contralateral to the resection. The results of present study are in line with previous studies. It is notable that mean interval between MTLR and participation of the present study was 6.45 years (range=1.25-10.92), while it was at most 1 year after surgery in previous studies. Therefore, the present study firstly provide evidence that engagement of the contralateral intact HIP after unilateral MTLR is persisted long after surgery, and it represents effective compensatory network in both patient groups. However, the mechanism of how contralateral HIP substitutes for the role of ipsilateral HIP has not been clearly elucidated at whole-brain level. I

will discuss the possible mechanism in the later section of “Functional interactions during memory encoding”.

7.3. Whole-brain Activations during Memory Encoding

In the whole-brain group comparisons of activation, the results of less activated areas in patient groups are mostly explained by pathologic changes due to underlying disease. Since the left HIP*ant* was included in surgically removed areas, it is not surprising to see the absence of left HIP*ant* activity during memory encoding in LMTLR group. Regarding direct connection between HIP and THAL and the important role of right HIP*pst* in visual memory encoding (Stern et al., 1996), lower activation levels in these areas during figure encoding in RMTLR group could be the results of deafferentation changes following the right HIP lesion before surgery and/or RMTLR. For the frontal activations, reduced frontal activity during both verbal and visual memory encoding in patients with LMTLR was also reported in the previous postoperative memory encoding study (Sidhu et al., 2016).

The brain areas that exhibited greater activation in MTLR groups were deactivated from the baseline in HC while MTLR patients showed less deactivation or activation patterns during successful memory encoding. The areas that showed deactivation in HC group coincide well with the areas

previously known as default mode network (DMN), which showed deactivation during cognitive tasks as well as memory encoding tasks compared with activation during relaxed non-task states (Raichle et al., 2001). Previous studies reported that the greater task-induced deactivation of the DMN predict better memory performance in HC, while patients with cognitive impairment show failure of DMN suppression [see (Anticevic et al., 2012; Cataldi et al., 2013) for review]. However, given that memory performance differences were controlled by using MQ as a covariate and using only successful encoding trials for functional analysis, it is highly unlike that less suppression in the present study reflects poor performance. Indeed, several previous studies reported that mPFC, one well-known DMN area, failure of deactivation remained evident after controlling the task performance differences in patients with schizophrenia (Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009) and bipolar disorder (Pomarol-Clotet et al., 2012). It is also notable that all patients except two RMTLR patients achieved a favorable seizure outcome; therefore, less deactivation cannot be attributed to the pathologic states of patients as well.

It has been questioned whether observed altered patterns of task-related brain activations reflect compensatory activation or a marker of network disruption, as performance levels do not always equate between HC and patients [see (Willment and Golby, 2013) for review]. In the present study, the possibilities of continuing pathologic condition as well as differences in

baseline cognitive differences could be excluded. Therefore, it seems possible that an altered pattern may not reflect network disruption, yet to be sure how less deactivation could effectively compensate failure of resected MTL recruitment during memory encoding. Previous studies showed that stronger FC could exist without stronger brain activation (Braakman et al., 2013). Since brain areas showed less deactivation in the present study, especially the mPFC, are well-known hubs of DMN, FC differences during successful memory encoding could in part explain compensatory mechanism.

7.4. Functional Interactions during Memory Encoding

The task-based FC analysis revealed that the right mPFC showed stronger connections with many different parts of brain areas—DMN in particular—in both patient groups with more widespread changes during verbal encoding in LMTLR and during visual encoding in RMTLR groups. Moreover, strength of mPFC FC predicts individual memory capacity of patients. Meanwhile, only one connection showed stronger FC in HC. One previous study with TLE reported that, although disturbed FC was observed between MTL and DMN areas, functional and structural connectivity between mPFC and other nodes of DMN were preserved (Liao et al., 2011). Therefore, speculation is that this preservation continued or was even strengthened due to the plastic changes after surgical intervention and that the FC of mPFC possibly partly takes the

role of resected MTL in patients. Since verbal memory is known to activate more lateralized left MTL areas while visual memory involves bilateral MTLs (Kim, 2011), different effects of the left and right MTLR on memory modality in the present study is understandable.

Interestingly, stronger FC between the right mPFC and HIP contralateral to resection was observed in both patient groups. Previous studies which investigated patterns of postoperative memory-related brain activation reported that individual memory performance is positively associated with functional activation of HIP contralateral to the resection (Cheung et al., 2009; Sidhu et al., 2016). Despite the emphasis of compensatory role of contralateral HIP, the mechanism of how contralateral HIP substitutes the role of ipsilateral HIP has not been clearly elucidated. Given that HIP's central position as a densely interconnected hub in brain networks (van den Heuvel and Sporns, 2011), it seems logical to consider FC as a possible mechanism of contralateral HIP action. Similar to the results of present study, one previous study which investigated preoperative resting-state also found that the FC between the contralateral nonpathologic MTL and the mPFC was positively correlated with the memory performances in TLE (Doucet et al., 2013). It has also been reported that interaction between mPFC and HIP is important in episodic memory of healthy subjects (Preston and Eichenbaum, 2013). Therefore, the results of present study suggest that contralateral HIP's compensatory role in episodic memory encoding could be

achieved by its connections with the right mPFC in MTLR patients.

It is also notable that stronger FC between the right FG and MTG predicts better visual memory capacity in HC, although RMTLR showed stronger FC of that connection than HC. It suggests that alterations of FC in RMTLR resemble effective FC in HC to compensate the loss of FC in the ipsilateral right HIP that is generally known to be related to visual memory encoding. Altogether, the observation of hyper-connectivity of the right mPFC strongly suggests a potential adaptive compensatory mechanism to preserve episodic memory function for the loss of possible FC in surgically removed MTLs.

7.5. Implications of the Present Study

To date, no known treatments halt the progression of memory impairments; therefore, a novel nonpharmacologic approach of brain stimulation is currently considered an alternative treatment of memory impairments [see (Jeong et al., 2015; Kim et al., 2016) for review]. Network-based brain stimulation, which involves targeting modulation of interactions between multiple memory-related brain areas rather than considering individual brain regions in isolation, has been proven effective for memory modulation in many previous studies. Previous studies also showed that brain stimulation modulates memory function through changes of memory task-related FC.

Most previous brain stimulation studies that aimed to enhance memory function, however, selected HIP or areas that have afferent or efferent connections to the HIP for the stimulation target. Although targeting the cortical-hippocampal network seems promising for memory enhancement, we should note that patients with memory deficits such as MCI or AD often showed an altered cortical-hippocampal network due to the MTL dysfunction. Therefore, it seems questionable whether targeting the hippocampal network in patients with hippocampal damage would be effective in treating memory disturbance.

In the present study, the right mPFC showed strong connections with many parts of memory-related brain areas during successful memory encoding in MTLR patients with intact memory function; therefore, the mPFC could be a novel target for the brain stimulation for people with MTL-dysfunction-related memory disturbance. One recent animal study revealed that after chronic deep brain stimulation of mPFC, both short- and long-term memories were robustly improved compared to sham (Liu et al., 2015). In human, one recent study reported memory modulation by mPFC stimulation (Berkers et al., 2017). Since they did not aim to improve memory, the authors perturbed mPFC function but they still found a memory modulation effect by mPFC stimulation, which resulted in reduction of false memories. These previous studies support the possibility that mPFC stimulation may serve as a novel effective therapeutic target for memory disorders. However, for being a

therapeutic target, more research is required to determine whether mPFC stimulation could actually enhance memory function and modulate FC of the memory encoding network in human subjects.

7.6. Methodologic Considerations and Future Directions

The results of present study could be limited by possible effect of remaining epileptic activities of non-seizure-free patients (Engel II=4, III=2) on functional brain imaging results. However, the impact of interictal epileptiform discharges (IEDs) on neural signal is still inconclusive (Centeno and Carmichael, 2014). Moreover, four of six patients showed no IEDs in the clinical EEG follow-up; only 2 patients showed a few sharp waves in temporal lobe of resected hemisphere. Therefore, the effect of epileptic activities should be minimal in the present study.

Increased FC in MTLR patients could also be observed preoperatively. Due to the pathologic HIP before surgery, functional brain reorganization could have already occurred effectively. Since it was beyond the scope of the present study, the preoperative data was not compared with postoperative data. Future preoperative study could investigate whether the patients with normal memory function show the brain network similar to the findings of present study. Further longitudinal study could also investigate whether the patients who showed similar brain network to findings of the

present study preoperatively maintained stable intact memory function after MTLR.

Functional network of memory consolidation in MTLR patients can be another interesting topic for future work. The importance of cortical interactions during post-encoding resting in later memory performances has been demonstrated in a previous study with HC (Tambini et al., 2010). However, no study has investigated the FC during post-encoding resting that corresponded to memory consolidation process in MTLR patients. Investigating functional network of memory consolidation in MTLR could broaden our understanding of human episodic memory network in the future.

Chapter 8: Conclusion

The present study adopted a new perspective of functionally connected brain entities in understanding episodic memory encoding networks of patients with MTLR. The present study identified that the right mPFC acts as a hub for effective memory encoding network in the absence of medial temporal area. The results also suggested that a compensatory role of HIP contralateral to the resection is achieved by its functional link with the right mPFC. Finally, the possibility of the mPFC as a new brain stimulation target area toward enhancing memory for people who suffer from MTL-dysfunction-related memory disturbances was suggested.

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국문초록

내측 측두엽 절제 후 기억기능에 관여하는 뇌의 네트워크 규명 연구

정 우 림

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협동과정 뇌과학 전공

해마 (hippocampus)는 일화기억에 중심 역할을 담당할 뿐만 아니라, 기능적으로 연결된 뇌 연결망에서 주요한 허브에 해당된다. 해마를 포함하는 내측 측두영역에 대한 수술적 절제는 기억기능을 담당하는 영역뿐만 아니라, 기억과 관련된 뇌 영역들 사이의 기능적 연결성의 강도도 변화시킬 것이다. 본 연구는 한쪽 반구의 내측 측두영역이 절제되었는데도 정상적인 기억 기능을 유지하는 환자들을 대상으로 기능적 연결성이라는 관점에서 그 기전을 밝히고자 하였다. 난치성 뇌전증의 치료적 목적으로 내측 측두영역 (medial temporal lobe)의 앞쪽 일부를 절제한 후에도

정상적인 기억능력을 유지하고 있는 환자 37명 (좌반구 절제환자 17명, 우반구 절제환자 20명; 연령 중앙값 34세)과 통제집단으로 건강한 성인 24명을 모집하였다. 안정되고 효율적인 기억 연결망을 관찰하기 위하여, 수술을 받은 지 1년 이상이 되는 환자들을 모집하였다. 환자집단과 통제집단에게 언어자극 (단어)과 시각자극 (그림)을 제시하고 학습하게 한 후 재인검사를 실시하였다. 과제를 수행하는 동안의 뇌 활동을 기능적 자기공영상 기법을 통해 측정하여 분석하였다. 해마 영역을 관심영역 (ROI)으로 활성화 강도를 분석한 결과, 수술 영역의 대측 반구 해마의 활성화 수준이 높을수록 수술 후 기억능력이 높았다. 특히, 좌반구 측두엽절제 환자들은 언어기억에서, 우반구 측두엽절제 환자들은 시각기억에서 뇌의 활성화 수준과 기억기능 간에 상관이 나타났다. 전체 뇌 영역에 대한 활성화 분석 결과, 인지 과제를 수행하는 동안 부적 활성화를 보인다고 알려진 영역들의 부적 활성화 정도가 환자군에게는 약하게 나타나는 것으로 나타났다. 성공적인 과제수행에서의 기능적 뇌 연결성 분석 결과, 환자군에서 수술 대측 반구 해마를 포함한 기억 관련 뇌 영역들과 우반구 내측 전전두영역 (right medial prefrontal area) 간의 기능적 연결성의 강도가 높게 나타났다. 특히, 좌측두엽 수술 환자의 경우는 언어기억 과제에서, 우측두엽 수술 환자의 경우는 시각기억 과제에서 뇌 영역 간의 기능적 연결성이 정상인에 비해 그 강도가 높았다. 기능적 연결성의 강도는 좌측두엽절제 환자들의 언어기억

점수 및 우측두엽절제 환자들의 시각기억 점수를 예측해 주었다. 본 연구의 결과는 내측 전전두영역의 강화된 기능적 연결성이 내측 측두영역이 절제된 경우에도 성공적인 기억기능을 수행하는데 중요한 역할을 수행하고 있음을 시사한다. 본 연구의 결과는 내측두영역의 손상과 관련된 기억장애를 겪는 다른 질환군의 치료에 적용될 수 있을 것으로 기대된다.

주요어: 일화기억, 측두엽 뇌전증, 내측 측두엽 절제술, 기능적 자기공명영상, 기능적 뇌 연결성, 내측 전전두 피질

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