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Characterization of brain network supporting episodic memory in the absence of one medial temporal lobe

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Abstract

How the brain supports normal episodic memory function without medial temporal lobe (MTL) structures has not been well characterized, which could provide clues for new therapeutic targets for people with MTL dysfunction-related memory impairment. To characterize brain network supporting effective episodic memory function in the absence of unilateral MTL, we investigated the whole-brain cortical interactions during functional magnetic resonance imaging memory encoding paradigms of words and figures in patients who showed a normal range of memory capacity following unilateral MTL resection and healthy controls (HC). Compared to the HC, the patients showed less activation in the left inferior frontal areas and right thalamus together with greater activation in the many cortical areas including the medial prefrontal cortex (mPFC). Task-based functional connectivity (FC) analysis revealed that the mPFC showed stronger interactions with widespread brain areas in both patient groups, including the hippocampus contralateral to the resection. Moreover, the strength of the mPFC FC predicts the individual memory capacity of the patients. Our data suggest that hyperconnectivity of distributed brain areas, especially the mPFC, is a neural mechanism for memory function in the absence of one MTL.

KEYWORDS

episodic memory, functional connectivity, functional MRI, medial prefrontal cortex, medial temporal lobe resection

1 | INTRODUCTION

Since medial temporal lobe (MTL) structures are uniquely specialized to establish and maintain episodic memories (Dickerson & Eichenbaum, 2010), MTL resection (MTLR) for treating medically intractable temporal lobe epilepsy (TLE) is commonly associated with postresection episodic memory impairment (Bell, Lin, Seidenberg, & Hermann, 2011; Shin et al., 2009). Therefore, much effort has been made to develop clinically applicable memory outcome prediction methods which still remain a challenge (Bonnici, Sidhu, Chadwick, Duncan, & Maguire, 2013; Haag & Bonelli, 2013; Sidhu et al., 2015). Although considerable studies have investigated the neural basis of episodic memory in the preoperative TLE brain hoping to develop better prediction models of memory outcome, much less attention has been given to characterizing the neural basis of

memory function in postoperative brain. Given that two-thirds of patients with TLE maintained stable normal memory function following MTLR (Baxendale, Thompson, & Duncan, 2008), understanding the neural characteristics underlying normal memory function in the MTLR brain could not only provide a deeper understanding of the human memory system in general but also provide significant insights for developing better prediction models of memory outcome after MTLR. Moreover, considering that patients with mild cognitive impairment (MCI) or Alzheimer's disease (AD) share similar structural and neurophysiological characteristics underlying the memory decline with TLE (Frisoni, Fox, Jack Jr., Scheltens, & Thompson, 2010; Holler & Trinka, 2014), studying the memory network in MTLR patients who have a normal range of memory capacity and who are free from an underlying epileptic condition could also provide a clue for new therapeutic targets for patients with MCI or AD. However, little is known about how the brain supports normal episodic memory function in patients with MTLR.

Woorim Jeong and Hyeongrae Lee contributed equally to this study.

Only a few studies investigated the neural mechanism supporting episodic memory function in patients with unilateral MTLR (Bonelli et al., 2013; Cheung, Chan, Lam, & Chan, 2009; Jeong, Lee, Kim, & Chung, in press; Sidhu et al., 2016). However, none of those previous studies, except our own previous study (Jeong et al., in press), recruited homogeneous patients who have a normal memory function but instead recruited heterogeneous patients by their memory capacity, which complicates the capturing of the neural characteristics of effective memory in the MTLR brain. Moreover, although it is well-known that the engagement and interactions of widely distributed cortical areas, including areas belonging to the default mode network (DMN), ventrolateral prefrontal cortex, premotor cortex, and sensory-related areas support successful episodic memory formation in healthy adults (Dickerson & Eichenbaum, 2010; Jeong, Chung, & Kim, 2015; Kim, 2011), most previous studies have restricted their analysis only to regions of interest (ROIs) in the MTL structures (Bonelli et al., 2013; Cheung et al., 2009; Jeong et al., in press). Therefore, although those previous studies emphasized the compensatory role of the hippocampus (HIP) contralateral to the resection, the whole-brain mechanism underlying effective memory function in patients with MTLR has not been clearly elucidated.

Considering the central position of the HIP as a densely interconnected hub in brain networks (van den Heuvel & Sporns, 2011), investigation of cortical interactions at the whole-brain level could extend our understanding of the memory network that supports episodic memory function in the absence of parts of the unilateral MTL structures including the HIP. For the purpose of better understanding the cortical interactions during cognitive task performance, task-based functional connectivity (FC) analysis has been widely adopted in neuroimaging data (McLaren, Ries, Xu, & Johnson, 2012). Therefore, an investigation of the whole-brain FC during memory task performance can provide a more comprehensive understanding of the effective memory network by means of characterizing how other cortical areas interact with the HIP contralateral to the resection and/or how other cortical areas might interact with each other for supporting memory function in the absence of one HIP. Indeed, MTLR is an excellent

model for studying whole-brain functional interactions associated with the memory process excluding the effects of the epileptic HIP.

To characterize brain network underpinning normal episodic memory function in patients with MTLR, we adopted task-based FC analysis of functional magnetic resonance imaging (fMRI) data at the whole-brain level on the premise that the HIP does not operate as an individual entity but in a strongly interlinked fashion. Here, we investigated the episodic memory network in MTLR patients who had an average range of memory function at the time of the study participation and who achieved a good seizure outcome. The whole-brain patterns of neural activity and the FC while patients performed a verbal and visual memory encoding task were analyzed and compared with age- and education-matched healthy controls (HC). The strength of the FC was also compared with the memory capacity evaluated by a standard neuropsychological test.

2 | MATERIALS AND METHODS

2.1 | Subjects

In the present study, we used the same patients' data set from our previous study (Jeong et al., in press). All patients underwent unilateral MTLR for treating medically intractable TLE at Seoul National University Hospital at least 1 year before recruitment (mean follow-up = 6.31 ± 2.72 years) and were between 19 and 50 years of age at the time of the recruitment (median age = 33 years). We only included patients who showed at least a low average or a higher level (scores >80) of memory capacity and general intelligence evaluated by the postoperative standard neuropsychological test of the Rey–Kim memory test and Korean Wechsler Adult Intelligence Scale, respectively. Excluded were patients who achieved a poor surgical outcome (Engel Class III or IV) (Engel, 1993) and who showed severe dental metallic artifacts. Finally, 35 patients were included in this study (17 left and 18 right; Table 1). All included patients underwent either standard selective amygdalohippocampectomy or anterior temporal wedge resection with amygdalohippocampectomy, which both include removal of the anterior two-thirds of the HIP (Table S1). Only two left MTLR (LMTLR) patients had no remaining posterior HIP (HIPpst) due to atrophic changes after surgery. Examples of the resection area are shown in Figure 1. The majority of the patients (89%, LMTLR = 15, right MTLR [RMTLR] = 16) was seizure-free after surgery. Then, 8 LMTLR (47%) and 12 RMTLR (67%) patients stopped antiepileptic drugs (AEDs) after surgery, and the remaining patients took one or two AEDs. None of the patients changed or increased their AEDs after surgery. Neuropsychological memory scores were not significantly different between the patients who stopped and the patients who continued taking AEDs after surgery ($p < 0.05$). Detailed demographics of the patients are shown in Table S1.

We recruited 24 age- and education-year-matched HC (median age = 32 years). There were no significant differences in age ($p = 0.528$) and education years ($p = 0.106$) among the groups. For cognitive capacity, the HC showed a significantly higher intelligence quotient (IQ) than that of the RMTLR ($p < 0.05$) and a significantly higher memory quotient (MQ) than that of the LMTLR ($p < 0.001$)

TABLE 1 Subjects demographics

	HC (n = 24)	LMTLR (n = 17)	RMTLR (n = 18)
Age (years)	32.8 (6.53)	34.53 (6.49)	32.83 (7.52)
Sex (M/F)	11/13	8/9	10/8
Education (years)	15.29 (1.46)	14.35 (1.93)	14.33 (1.81)
Seizure onset (years)	–	14.71 (9.98)	14.94 (10.52)
Duration of illness (years)	–	13.24 (9.40)	11.56 (9.07)
Age at surgery (years)	–	27.94 (6.11)	26.50 (6.68)
Follow-up (years)	–	6.44 (2.74)	6.18 (2.78)
IQ[a]	117.92 (9.49)	109.53 (13.82)	106.16 (11.90)
MQ[b]	113.08 (10.55)	98.12 (11.61)	105.05 (9.83)

Data presented as mean (SD). HC = healthy controls; IQ = intelligence quotient; LMTLR = left medial temporal lobe resection; MQ = memory quotient; RMTLR = right medial temporal resection.
[a] HC versus RMTLR significant differences ($p < 0.05$).
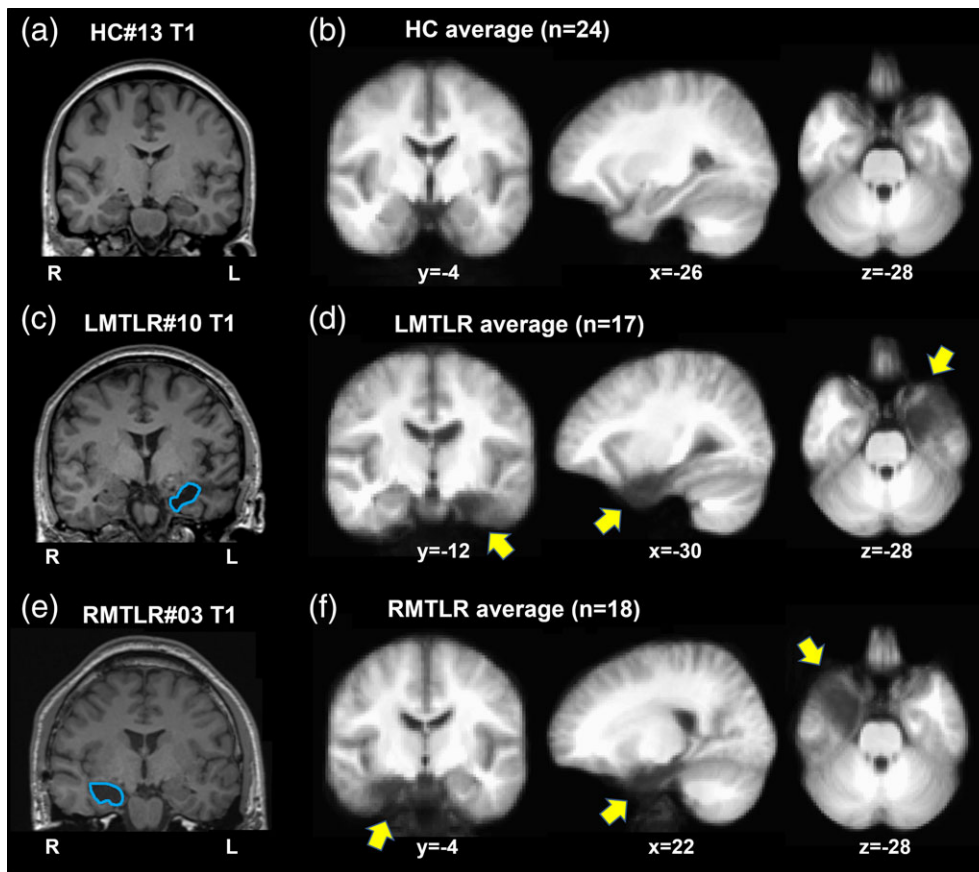[b] HC versus LMTLR significant differences ($p < 0.001$).

FIGURE 1 Examples of resection area. (a, c, e) Coronal section of T1 MRI. Blue line indicates the resection margin of the patients. (b, d, f) Group-averaged normalized T1 images. Arrow indicates the resection areas of each patient group [Color figure can be viewed at wileyonlinelibrary.com]

(Table 1). We should note that regardless of these group differences, both the MQ and IQ scores of all subjects were in the high-average to low-average ranges, which proves the normal range of cognitive function in our subjects at the time of the study participation. All subjects were native Korean speakers and provided a written informed consent. This study was approved by the Seoul National University Hospital Institutional Review Board (IRB H1411-075-626).

2.2 | Neuropsychological memory test

All subjects underwent a standardized neuropsychological examination on a separate day within 1 month of the fMRI scanning. Verbal memory performance was assessed by the Korean version of the Rey Auditory Verbal Learning Test (KAVLT), and nonverbal visual memory performance was assessed by the Korean version of the Rey Complex Figure Test (KCFT) (Kim, 1999). For the purpose of revealing the relationship between individual memory capacity and the neural signals of memory fMRI, the age-adjusted scores for the following four Rey-Kim memory subtests were used in this study: KAVLT immediate and delayed recall; and KCFT immediate and delayed recall.

2.3 | Experimental design

For the memory task, two material types, verbal stimuli (words) and visual stimuli (figures), were visually presented on an MR-compatible screen viewed through a mirror. In short, single concrete nouns in

white font on a black background and black and white unnamable abstract figures were used as the stimuli. Cross-hair fixation was presented for 15 s every time after the presentation of 20 items (10 words and 10 figures; 1 item for 3 s). We presented a total of 100 words and 100 figures in two separate scanning runs. All stimuli were counterbalanced across the subjects. Subjects were explicitly instructed to memorize items for the subsequent out-of-scanner recognition task. A deep encoding task, which involved a subjective decision on whether each stimulus was pleasant or unpleasant, was performed using a magnetic compatible button box. All stimuli were presented using the E-prime software (Version 2.0; Psychology Software Tools Inc., Pittsburgh, PA).

About 30 min after encoding, the word and figure recognitions were tested separately in an out-of-scanner recognition task. In each recognition task, subjects were shown the same 100 items randomly intermixed with an additional 50 novel words/figures. Subjects used a keyboard to indicate whether the items were old, familiar, or novel. These responses were used to sort each item shown in the scanner to items remembered, familiar, and forgotten. Recognition accuracy (d') was quantified for both the words and figures using conventional d' calculations based on the Z-transformed hit rate (old stimuli correctly remembered, old responses to old stimuli) and false alarm rate (novel stimuli incorrectly tagged as remembered, old responses to novel stimuli). All statistics for the behavioral data were calculated using the SPSS 19.0 software (IBM, Armonk, NY) with significance levels at

0.05. We used the one-way analysis of variance and the application of Bonferroni correction for multiple testing to subgroups.

2.4 | Magnetic resonance data acquisition and preprocessing

The MR images 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 the 3D TFL sequence (TR = 1,670 ms, TE = 1.89 ms, field of view = 250 × 250 mm^2, 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 (EPI) sequence (36 axial slices, slice thickness = 3.4 mm [no gap], TR = 2,750 ms, TE = 30 ms, field of view = 220 × 220 mm^2, flip angel = 80°, voxel size = 3.4 × 3.4 × 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.

The functional imaging data were analyzed using the Analysis of Functional Neuroimage (AFNI) software (https://afni.nimh.nih.gov/afni/, version: AFNI_16.0.00). The first two TRs of the EPI time series at the beginning of each run were discarded for magnetization stabilization. Motion correction was performed by rigid body registration of the EPI images to the first truncated EPI volume, and slice timing correction was performed for all slices within a volume for correcting the slice-time acquisition. The high-resolution anatomical T1 was aligned to the mean EPI volume of the EPI time series via an affine transformation. To reduce the error imposed by the surgical cavity, we used the local Pearson correlation cost function, which had been shown to be superior for this purpose than the more general multimodal cost functions (Saad et al., 2009; Zaca, Nickerson, Deib, & Pillai, 2012). After co-registration to the T1-weighted images, spatial normalization was performed to affine transform data into the Montreal Neurological Institute (MNI) stereotactic space using the MNI avg152T1 template provided by AFNI. All voxels were resampled as a 2 × 2 × 2 mm^2 size by linear interpolation. The quality of the co-registration and spatial normalization of each patient was visually inspected and confirmed that all processes were successfully performed for all patients. Mean-based intensity normalization was performed after spatial smoothing using a Gaussian filter with 6 mm full-width at half-maximum.

2.5 | Statistical analysis

2.5.1 | Functional MRI analysis

Event-related analysis on the experimental design of memory encoding similar to the present study was performed in previous studies (Sidhu et al., 2013; Sidhu et al., 2016). For event-related analysis, we used only subsequently remembered trials, which was previously reported to be better than the subtraction method (remembered–forgotten) in revealing whole-brain activation patterns during a memory task (Sidhu et al., 2015). We employed a two-level event-related random-effects analysis. In the first-level analysis, we estimated the hemodynamic response starting from the stimulus onset to 13.75 s using cubic spline basis functions (AFNI's 3dDeconvolve with "CSPLINzero" option) separately for words remembered and figures

remembered. To correct for motion-related artifacts, we included six motion parameters in the first-level general linear models (GLMs) and censored TRs as an outlier volume based on a framewise displacement threshold >0.9 mm from the GLMs. Contrast images were created by averaging beta from the second to fifth points (2.75–11 s) of an estimated response for each subject for the word 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 the HC and MTLR. To examine only the task-related effects without the influence of baseline differences of individual general cognitive ability, we controlled for the individual IQ and MQ scores by using them as covariates. Significance thresholding for the group analyses was carried out using 3dClustSim available in the AFNI software suite. The 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 the whole brain.

2.5.2 | Task-based FC

To examine the FC in the context of the memory process, we employed the generalized psychophysiological interaction model (McLaren et al., 2012). Using this analysis, we isolated brain regions whose FC with seed ROIs were significantly modulated by the interaction of subsequently remembered stimuli. Seed ROIs were created from the surviving clusters in the group analysis (Table 2). Although the right medial prefrontal cortex (mPFC) during word encoding in the LMTLR versus HC condition survived only at a lower cluster size, we also included this area as a seed ROI for FC during the word encoding because the mPFC is a well-known memory-related brain area (Jeong et al., 2015). For the FC analysis, we first extracted the mean time series of voxels within the ROIs and deconvolved the time series into estimates of neural events. Next, we calculated the interaction terms between the neural estimates and each column of the task design, which were then convolved with a canonical hemodynamic response function. A GLM, which includes interaction regressors, task regressors, and a regressor for the average time series of the seed ROI, was used to analyze the FC between the seed ROI and the whole brain during the memory task for each subject. We obtained task-based FC maps of each seed ROI for successful word encoding and successful figure encoding. A two-sample t test was performed with each FC map for each seed ROI in order to compare the group difference between MTLR and HC. FC values in areas that showed group differences were then compared with neuropsychological memory scores by using the Spearman correlation analysis. The data of two subjects (one HC and one LMTLR) were only used for the figure memory analysis because their behavioral responses to the word recognition task were not recorded due to technical problems.

For statistical thresholding of the FC analysis, we used both whole-brain family-wise error (FWE) cluster correction (3dClustSim) and Bonferroni correction for the number of seed ROIs ($n = 16$). The cluster-extent thresholds corresponding to the statistical probability $\alpha < 0.05$ at a predefined voxel-wise threshold of $p < 0.005$ were used to report results of the FC analysis. Using this method and these

TABLE 2 Group differences during successful word and figure encoding

Regions/included	x, y, z	Voxels	T_{max}	Regions/included	x, y, z	Voxels	T_{max}
Word encoding							
HC > LMTLR				LMTLR > HC			
L IFGtri	−42, 22, 28	378	4.09	R mPFC*	6, 52, 4	93	3.52
L IFGorb	−48, 44, −2	184	4.44				
L MTG*	−56, −30, 4	146	4.59				
HC > RMTLR				RMTLR > HC			
n.s.				R IFGorb*	46, 52, −12	108	4.66
Figure encoding							
HC > LMTLR				LMTLR > HC			
L MFG/IFGtri	−48, 24, 38	505	4.65	R mPFC	6, 48, 14	244	4.30
HC > RMTLR				RMTLR > HC			
R THAL/HIPpst	22, −30, 2	243	4.97	R MTG	62, −14, −8	2071	5.01
				R PoCG/SPL	34, −38, 60	303	4.44
				L ACC/R mPFC	−8, 32, 16	226	4.08
				R IFGorb	48, 40, −10	185	3.88
				L SMG/PoCG	−56, −18, 14	184	4.33
				R MCC	2, −24, 44	176	4.57
				L PoCG*	−42, −38, 52	133	4.62
				L IFGorb*	−38, 44, −14	95	3.61

$p_{corrected} < 0.01$, *$p_{uncorrected} < 0.005$ (voxels>90). ACC = anterior cingulate cortex; HIPpst = posterior hippocampus; IFGtri = inferior frontal gyrus triangular part; IFGorb = IFG orbital part; LMTLR = left medial temporal lobe resection; MCC = middle cingulate cortex; MFG = middle frontal gyrus; mPFC = medial prefrontal cortex; MTG = middle temporal gyrus; PoCG = postcentral gyrus; RMTLR = right medial temporal resection; SMG = supramarginal gyrus; SPL = superior parietal lobule; THAL = thalamus.

thresholds, the significant cluster size minimum was 173 contiguous voxels at $p_{FWE} < 0.0031$ (0.05/16 = 0.0031) for the whole brain. For the HIP, the bilateral HIP mask from the AAL atlas was used instead of the whole brain in order to create a thresholding table. The resected brain regions were excluded from the HIP mask. We used a voxel-wise threshold of $p < 0.005$ within a cluster extent threshold of 18 voxels, which corresponds to the small volume corrected $p < 0.05$ for the HIP. After applying Bonferroni correction, the cluster extend thresholds were 43 voxels at $p_{FWE} < 0.0031$ (0.05/16 = 0.0031) for the HIP. Given that the HIP is one of the key brain areas involved in the memory process, and considering the special condition in which our patients had no anterior HIP (HIPant) in one hemisphere, we reported the FC results of the HIP under both a strict statistical threshold of Bonferroni correction for the number of seed ROIs in addition to small volume cluster correction, and also for clusters which survived only after applying a small volume cluster correction.

3 | RESULTS

3.1 | Behavioral results

There were no statistically significant differences in the word recognition performances among the subject groups (mean $d' \pm SD$, HC = 2.08 ± 0.93, LMTLR = 1.52 ± 0.83, RMTLR = 1.76 ± 0.65; $F_{(2, 54)} = 2.256$, $p = 0.115$). For the figure recognition performances, there were statistically significant differences among the subject groups (mean $d' \pm SD$, HC = 0.93 ± 0.44, LMTLR = 0.49 ± 0.89, RMTLR = 0.43 ± 0.41; $F_{(2, 56)} = 9.304$, $p < 0.001$).

Post hoc comparisons using the Bonferroni correction revealed that the HC had a higher performance than both patient groups (LMTLR, $p < 0.05$; RMTLR, $p < 0.05$). Because only correct (subsequently remembered) trials were selected for the fMRI analysis, we could minimize the effect of the performance difference in the figure recognition on the neural signals. Figural memory seemed more difficult because most of the figure items were not only unfamiliar to our subjects but also difficult to name. Of the 100 trials, the average number of subsequently remembered trials was 83.49 ± 12.17 for words (HC = 85.21 ± 11.63; LMTLR = 81.37 ± 14.29; RMTLR = 85.67 ± 8.57) and 59.21 ± 14.01 for Figures (HC = 62.83 ± 13.37; LMTLR = 58.47 ± 10.16; RMTLR = 58.33 ± 14.25).

3.2 | Whole-brain activations during memory encoding

To investigate the group differences, we compared brain activities of each patient group with the HC for each modality (word or figure). Compared to the LMTLR group, the HC showed a significantly greater activation in the inferior frontal areas during both successful word and figure encoding (Table 2). Compared to the RMTLR group, the HC showed a greater activation in the right thalamus (THAL) and right HIPpst during figure encoding.

For the areas that showed a greater activation in the patients than in the HC, the right mPFC showed greater activations in both the LMTLR and RMTLR groups during figure encoding. Of note, although the cluster survived at a lower threshold (voxels >90), the right mPFC also showed a greater activation during successful word encoding in

the LMTLR than in the HC. In addition to the mPFC, there was a greater activation in widespread brain areas in the RMTLR group than in the HC during figure encoding (Table 2).

3.3 | Task-based FC

There was a stronger FC across widespread brain areas in the MTLR groups than in the HC (Figure 2 and Table 3). In contrast, no stronger FC was observed in the HC compared to the MTLR groups. In the LMTLR patients, when compared to the HC, the right mPFC seed exhibited significantly stronger interactions with many different memory encoding-related brain areas during the word encoding. Of note, when compared to the HC, the mPFC showed stronger connections with the HIP contralateral to the resection in the LMTLR group, and the strength of the FC between the right mPFC and right HIP*ant* showed a positive correlation with the verbal immediate recall scores ($r = 0.523$, $p < 0.05$) in the LMTLR group (Figure 3a). The other seed of the left inferior frontal gyrus orbital part (IFG*orb*) also showed a stronger FC with the left mPFC, and the strength of the FC between these areas was positively correlated with the verbal immediate recall

scores in the LMTLR group ($r = 0.530$, $p < 0.05$). In contrast to the widespread changes in the LMTLR group, the RMTLR group showed no significant FC differences with the HC during word encoding.

During figure encoding, the FC between the left MFG/IFG*tri* and right mPFC was stronger in the LMTLR than in the HC group. Meanwhile, more widespread brain areas exhibited significantly stronger interactions with the seed ROIs in the RMTLR than in the HC group. Similar to the stronger FC in the LMTLR during word encoding, the right mPFC seed showed stronger interactions with many different parts of the brain areas which include the HIP contralateral to the resection in the RMTLR during figure encoding. Moreover, the strength of the mPFC FC was positively correlated with the visual memory scores of the RMTLR patients (Figure 3b). Specifically, the strength of the FC between the right mPFC and the left retrosplenial cortex (RSC) was positively correlated with the visual immediate and delayed recall scores ($r = 0.664$, $p < 0.05$; $r = 0.618$, $p < 0.05$), and the FC between the right mPFC and left HIP*ant* was positively correlated with the visual immediate recall scores ($r = 0.479$, $p < 0.05$). In contrast, the FC of the right mPFC and left HIP*ant* was negatively correlated with the visual immediate and delayed recall scores in the HC ($r = -0.426$,
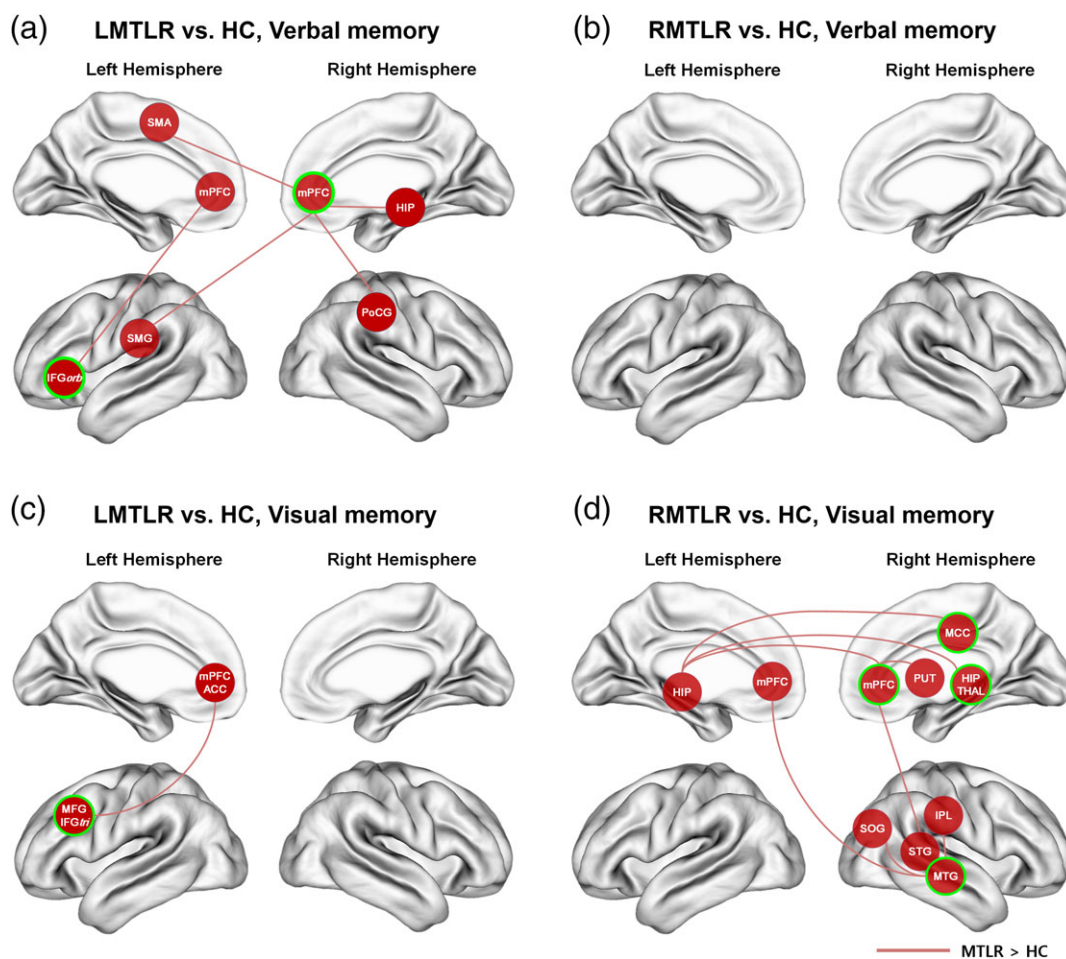

FIGURE 2 Functional connectivity during successful memory encoding. Boundaries with green color indicate seed regions of interest. All connections showed an increased FC in the medial temporal lobe resection (MTLR) groups compared to the healthy controls (HC). Because many connections survived in the "right MTLR (RMTLR) versus HC" contrast for visual memory (d), except for the HIP, only areas that have more than 300 voxels were shown for display purposes. Note that the right mPFC showed an increased FC with widespread brain areas, including the HIP contralateral to the resection. More widespread areas showed a stronger FC in the verbal memory encoding for left medial temporal lobe resection and in the visual memory encoding for the RMTLR. See Table 3 for details [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Regions exhibiting significant interactions with the seed ROIs

Contrast	Regions/included	x, y, z	Voxels	T_{max}	gPPI values	
					HC	MTLR
FC during WORD encoding						
LMTLR versus HC						
R mPFC-seed						
L SMG		−34, −26, 4	801	5.48	−0.17 (0.14)	0.16 (0.15)
R PoCG		54, −6, 26	651	5.61	−0.18 (0.13)	0.12 (0.20)
R SMA		4, 0, 66	415	5.05	−0.27 (0.29)	0.27 (0.41)
R HIP*ant**		36, −20, −12	28	3.92	−0.18 (0.22)	0.15 (0.32)
L IFG*orb*-seed						
L mPFC		−14, 50, 18	212	4.20	−0.18 (0.23)	0.15 (0.20)
FC during FIGURE encoding						
LMTLR versus HC						
L MFG/IFG*tri*-seed						
L mPFC/ACC		−20, 44, 2	197	4.38	−0.93 (0.24)	0.24 (0.23)
RMTLR versus HC						
R MTG-seed						
R IPL/SMG		32, −42, 46	585	4.16	−0.34 (0.39)	0.19 (0.34)
L mPFC		−14, 40, 6	383	4.74	−0.29 (0.48)	0.38 (0.46)
R SOG		28, −66, 22	346	4.20	−0.31 (0.43)	0.24 (0.32)
L PoCG		−26, −36, 42	285	5.31	−0.23 (0.19)	0.15 (0.18)
R PCUN		18, −46, 8	229	4.48	−0.19 (0.46)	0.40 (0.28)
R mPFC-seed						
R STG		52, −20, 4	770	4.64	−0.20 (0.18)	0.18 (0.28)
R PUT		34, 0, 4	303	4.20	−0.23 (0.14)	0.14 (0.24)
R MTG		40, −60, 12	267	4.26	−0.18 (0.21)	0.14 (0.28)
L MTG		−46, −48, 10	231	5.22	−0.13 (0.23)	0.27 (0.29)
L RSC		−2, −60, 14	187	4.51	−0.26 (0.33)	0.24 (0.41)
L HIP*ant**		−32, −26, −14	22	4.03	−0.13 (0.24)	0.18 (0.25)
R MCC-seed						
R PUT		20, 8, −6	222	5.44	−0.33 (0.36)	0.20 (0.37)
R MTG		54, −4, −18	177	5.51	−0.13 (0.23)	0.29 (0.27)
L HIP*ant**		−28, −6, −22	46	3.97	−0.16 (0.35)	0.28 (0.31)
R THAL/HIP*pst*-seed						
L HIP*pst**		−26, −36, −2	55	4.10	−0.27 (0.27)	0.18 (0.38)

$p_{corrected} < 0.05$, *$p_{svc} < 0.05$ (small volume correction for HIP). ACC = anterior cingulate cortex; FC = functional connectivity; HC = healthy controls; HIP*ant* = anterior hippocampus; HIP*pst* = posterior hippocampus; IFG*orb* = inferior frontal gyrus orbital part; IFG*tri* = IFG triangular part; IPL = inferior parietal lobule; LMTLR = left medial temporal lobe resection; MCC = middle cingulate cortex; MFG = middle frontal gyrus; mPFC = medial prefrontal cortex; MTG = middle temporal gyrus; PCUN = precuneus; PoCG = postcentral gyrus; PUT = putamen; RMTLR = right medial temporal resection; ROIs = regions of interest; RSC = retrosplenial cortex; SMA = supplementary motor area; SMG = supramarginal gyrus; SOG = superior occipital gyrus; STG = superior temporal gyrus.

$p < 0.05$; $r = −0.440$, $p < 0.05$). The other seed ROIs of the right middle temporal gyrus (MTG), middle cingulate cortex (MCC), and THAL also showed significantly stronger interactions with many different brain areas in the RMTLR patients than in the HC (Table 3). Of note, many areas including the right mPFC, MCC, and THAL/HIP*pst* showed significantly stronger connections with the left HIP contralateral to the resection in the RMTLR patients than in the HC.

4 | DISCUSSION

The aim of this study was to understand how the brain supports normal episodic memory function without unilateral MTL structures from

a new perspective of functional interactions of the brain network. By using whole-brain fMRI, the effective episodic memory encoding network was investigated in patients who had a normal range of memory function in the absence of one MTL structures.

4.1 | Brain activations during memory encoding

Our in-scanner verbal and nonverbal memory task reliably activated the well-known episodic memory-related brain areas in all the subject groups (Table S2 and Figure S1) (Jeong et al., 2015; Kim, 2011). In the group comparisons, only a few areas of the left lateral prefrontal areas and right HIP*pst*/THAL showed a greater activation in the HC than in the patient groups. Meanwhile, several more areas showed a greater
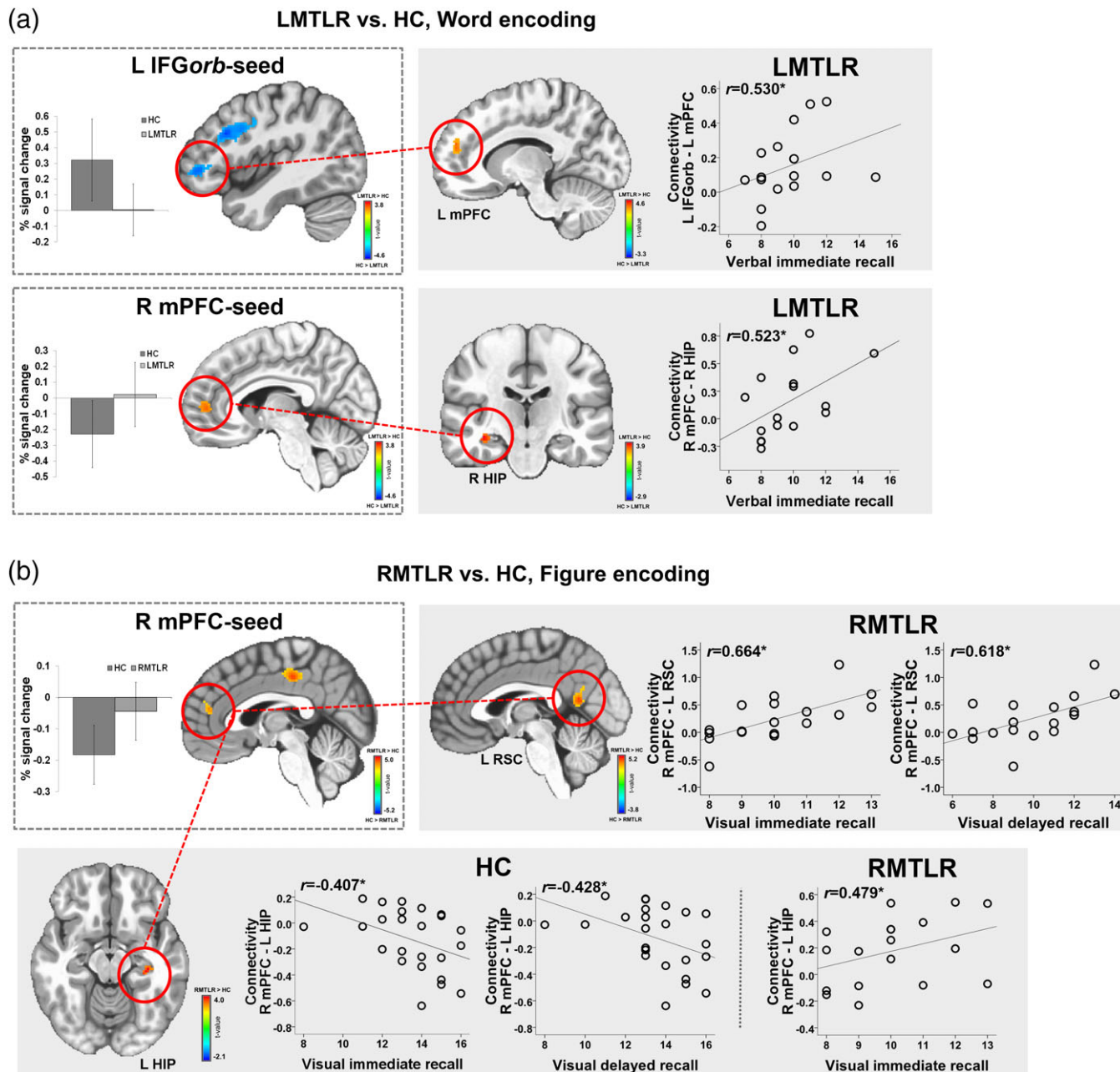
FIGURE 3 Clinical correlation of functional connectivity during successful memory encoding. The box with the dotted line shows the location and activation patterns of the seed regions of interest (Table 2). Results of the group analysis were superimposed onto the MNI152 T1 template. The gray box shows the brain regions that showed significant FC differences between the healthy controls and medial temporal lobe resection groups and clinical correlation between the strength of the FC and memory scores. *p < 0.05, L = left, R = right [Color figure can be viewed at wileyonlinelibrary.com]

activation in the MTLR than in the HC group. Some of these areas that showed a greater activation in our MTLR groups, including the mPFC and lateral temporal cortex, coincide well with the areas previously known as the DMN, which showed deactivation during cognitive tasks as well as memory encoding tasks compared with activation during relaxed nontask states (Raichle, 2015; Raichle et al., 2001). We also found deactivation patterns (activation below baseline) in these areas during successful memory encoding in our HC group (Figure S2). In contrast, our MTLR patients showed reduced deactivation or even a lack of deactivation patterns in these areas. An additional post hoc analysis according to the subsequent memory analysis confirmed that

these different levels of brain engagement between the MTLR and HC groups truly reflect the different neural responses to a successful memory encoding process between the groups. We did not find significant group differences during the subsequently forgotten trials in most areas that showed group differences during the successfully remembered trials (Figure S2).

Previously, altered task-related activation in the DMN areas as well as other cortical areas that support episodic memory function in healthy adults including the lateral PFC were also reported in TLE patients with a MTL lesion and/or resection similar to our results (Maccotta, Buckner, Gilliam, & Ojemann, 2007; Sidhu et al., 2016).

However, because memory capacity was not controlled for between HC and patients in previous studies, it is difficult to conclude whether the altered task-related brain activation pattern is a neural characteristic of effective or impaired memory function. To the best of our knowledge, this is the first study that controlled the level of the memory capacity of the MTLR patients to that of the HC. Considering that our patients had a normal range of memory function and that we also controlled for individual cognitive ability by using IQ and MQ as covariates for the fMRI analysis, we assert that the altered regional activation pattern in the present study is not a reflection of a network disruption related to impaired memory function in MTLR patients. In addition, we should mention that the MQ scores of our patients were not dropped after surgery, but rather increased in both LMTLR and RMTLR groups in comparison to the preoperative baseline scores, which also support our assertion. Detailed preoperative memory scores were presented in our previous study (Jeong et al., in press).

Although our data showed that the altered activation does not reflect an impaired-memory-related network disruption in the MTLR brain, whether it reflects effective modulation of the memory network that typically is recruited in the HC or simply reflects the secondary damage from MTL-related pathology still needs to be clarified. At the functional level, cognitive preservation after brain damage was regarded as based on either additional recruitment of the same network with the HC and/or compensatory recruitment of the alternative network that was not used in the HC (Stern, 2002). However, we did not find any regions that showed either more activation or deactivation in our MTLR groups than in the HC, which suggests that it is not a supporting mechanism for memory function in the absence of MTL structures. In previous studies, structural abnormalities in widespread brain areas other than the damaged MTL were consistently reported in patients with TLE and/or MTLR (Bell et al., 2011), which shows the possibility that altered activation might reflect pathologic degeneration. Moreover, irrespective of the episodic memory reserve, altered activation patterns similar to our findings were also observed in patients with diverse diseases for which all are known to have structural abnormalities in the MTL areas. Specifically, failure of DMN suppression, that is, greater activation in the mPFC, was reported not only in patients with bipolar disorder and schizophrenia after controlling the memory performance levels of the patients to that of the HC (Pomarol-Clotet et al., 2008; Pomarol-Clotet et al., 2012) but also frequently reported in patients with cognitive impairment such as MCI and AD (Anticevic et al., 2012). Along with TLE, patients with above diseases also reported to have structural abnormalities in the MTL areas (Harrison, 2004; Otten & Meeter, 2015). It is also of note that although it is generally known that patients with cognitive impairment often show failure of DMN suppression during memory tasks, failure of DMN suppression does not always indicate cognitive impairment, but rather, it seems to reflect neuronal changes due to brain pathology.

Taken together, albeit the possibility that reduced, but not additional, recruitment of the brain network could be another form of effective neural adaption supporting memory function, it seems likely that our observation of an altered regional activation pattern in the MTLR brain possibly reflect MTL-related pathologic degeneration. Importantly, although the exact mechanism of the altered activation in the effective memory process remains to be answered, because we investigated MTLR patients in the present study, we could for the first time demonstrate how the brain works for effective memory encoding without one MTL structure regardless of its possible remaining function.

4.2 | Functional interactions during memory encoding

For the purpose of characterizing the patterns of cortical interactions during successful memory encoding in the absence of one MTL structure, we adopted the FC analysis of the task fMRI data. Our task-based FC analysis revealed that, compared to the HC, the MTLR groups showed a stronger FC across widespread brain areas which mostly belong to the areas that previously are known to support successful memory function in healthy adults (Jeong et al., 2015; Kim, 2011). In contrast, no stronger FC was observed in the HC compared to the MTLR groups. Notably, a stronger FC in more widespread areas was observed during the verbal rather than the visual memory encoding in the LMTLR group and during the visual rather than the verbal memory encoding in the RMTLR group. Moreover, the strength of the FC predicts the individual verbal memory capacity in the LMTLR and the visual memory capacity in RMTLR patients. Since verbal memory is known to activate more lateralized left MTL areas while visual memory involves bilateral MTLs (Kim, 2011), it seems that material-specific compensation occurred in the absence of either a left or right MTL in our patients.

Interestingly, we also found that, compared to the HC group, the contralateral HIP showed stronger connections with many cortical areas, including the mPFC, during verbal memory encoding in the LMTLR group and during visual memory encoding in the RMTLR group. Moreover, the strength of the FC between the contra-resected HIP and mPFC predicts the individual verbal memory capacity of the LMTLR patients and the visual memory capacity of the RMTLR patients. Of note, while a stronger FC between the left HIP and the right mPFC during successful figure encoding predicts a better visual memory capacity in the RMTLR patients, the same connection predicts a worse visual memory capacity in the HC. In another aspect, while the patients with a better memory capacity had a stronger positive correlation of neural signals between these areas, the HC with a better memory capacity had a stronger negative correlation between the same areas. It seems that patients without one HIP recruit the alternative network to support effective memory function which is not used in people who have an intact bilateral HIP.

Previous TLE studies, which investigated the patterns of postoperative memory-related brain activation, consistently reported that individual memory performance is positively associated with functional activation of the HIP contralateral to the resection (Cheung et al., 2009; Sidhu et al., 2016). Our previous study with the same patients in the present study also found similar results (Jeong et al., in press). Although the compensatory role of the HIP contralateral to the resection is relatively well-known, since those previous studies only investigated MTL ROIs, the question how other cortical areas interact with the HIP contralateral to the resection and/or how other cortical areas might interact with each other for supporting the memory function in the absence of a resected HIP has not been clearly answered.

In healthy subjects, the functional interactions between the HIP and the mPFC have well-established roles in episodic memory function (Preston & Eichenbaum, 2013; Schlichting & Preston, 2015). Therefore, we suggest that the compensatory role of the contralateral HIP in episodic memory encoding is aided by its functional connections with other cortical areas, especially the mPFC, in MTLR patients. Of note, activation per se was not different between the patient and HC groups during both the verbal and visual memory encoding in the HIP contralateral to the resection in the present study.

It is also worth to note that, in addition to the contra-resected HIP, the mPFC showed stronger connections with widespread memory-related brain areas, some of which belong to the DMN such as the RSC and lateral temporal cortex, in both patient groups of left or right MTLR. One previous study reported that, although a disturbed FC was observed between the MTL and DMN areas, functional and structural connectivity between the mPFC and other nodes of the DMN were preserved in preoperative TLE patients with a MTL lesion (Liao et al., 2011). Another study conducted by the same research group demonstrated that the resting-state FC between the mPFC and other DMN areas was increased after MTLR in patients with a seizure-free outcome but not in the nonseizure free group (Liao et al., 2016). Taken together with our findings, it seems that the mPFC plays an important role in brain resilience to network perturbations caused by a MTL lesion and/or resection. Given that, compared to the HC, our MTLR patients with a good seizure outcome showed a stronger mPFC FC during the effective memory process to multiple brain areas (e.g., areas that are previously known to be involved in the memory encoding process of healthy adults and the HIP contralateral to the re-section which is known to have a compensatory role in the memory function of patients), we could speculate that this brain resilience with the mPFC as a functional hub may have a pivotal role in the compensatory network of memory function in the MTLR brain. In the present study, we also found that the strength of the mPFC FC to other cortical areas, including the IFG, RSC, and contra-resected HIP, predicts the individual memory capacity of patients. Again, episodic memory capacity was only predicted by the mPFC FC. This clinical correlation additionally supports our interpretation that the mPFC may act as a compensatory hub for effective memory function. Altogether, our observation of the mPFC hyperconnectivity during successful memory encoding in MTLR patients with a normal range of memory ability strongly suggests a potential neural compensatory mechanism to preserve episodic memory function in the absence of functional connections with surgically removed MTL and the presence of an altered regional activation by means of strengthening its connections with other memory-related cortical areas.

4.3 | Implications for future clinical applications

Our findings may help to develop better prediction models of postsurgical memory outcome of TLE by exploiting the memory-task-related FC of the mPFC. Although we could not directly prove that a similar memory network would be observed well before surgery in patients with a postoperative normal range of memory function, previous preoperative and postoperative studies provide some evidence that it might be present preoperatively. In preoperative TLE patients with hippocampal

damage, one previous study reported that the FC between the mPFC and contralateral nonpathologic MTL was positively correlated with memory performance (Doucet, Osipowicz, Sharan, Sperling, & Tracy, 2013), and other studies proved that the mPFC FC was preserved before surgery (Liao et al., 2011) and strengthened but not reduced after surgery (Liao et al., 2016). Those previous studies together with our results suggest that, regardless of a possible FC increase after surgery, a strong mPFC FC might support both a pre- and post-operative normal range of memory function. The fact that most of the patients (89%) in the present study had a normal range of preoperative MQ (MQ > 90, average level = 17; 80 < MQ < 89, low average level = 14) also supports our suggestion. Prediction of postsurgical memory outcome using resting-state FC has been previously proposed (Doucet et al., 2015; McCormick, Quraan, Cohn, Valiante, & McAndrews, 2013). However, because the altered resting-state network in an epileptic brain can be interpreted in many different ways, such as a reflection of the epileptic pathophysiology and a disabling psychiatric manifestation (Cataldi, Avoli, & de Villers-Sidani, 2013), task-related FC can be used for more reliable indicators of postsurgical memory function. Although comparisons with preoperative data in patients with postoperative normal memory function should be warranted, we first suggest that the task-related FC of the mPFC can probably be a reliable indicator of a normal range of memory function after MTLR. Further investigation on whether task-based whole-brain FC analysis can be used to predict postsurgical memory change (either improvement or decline) should also be warranted for clinical application.

Our results also could provide significant therapeutic insights for patients with MTL-dysfunction-related memory disturbance. Since there are no known treatments that halt the progression of memory impairments, a novel nonpharmacologic approach of brain stimulation is currently considered as an alternative treatment for memory impairments (Jeong et al., 2015; Kim, Ekstrom, & Tandon, 2016). Network-based brain stimulation, which targets the modulation of interactions between multiple brain areas rather than considering individual brain regions in isolation, has been suggested to be effective for modulating memory function in previous studies (for review, see Kim et al., 2016). Considering the strong functional connections between the mPFC and other multiple memory-related brain areas in our MTLR patients with a normal memory function, we suggest that the mPFC could be a novel target for brain stimulation in people with MTL-dysfunction-related memory disturbance. Recent studies that have reported on the memory modulation effect after applying mPFC stimulation in animals (Liu, Jain, Vyas, & Lim, 2015) and humans (Berkers et al., 2017) partly support the feasibility of our suggestion.

4.4 | Limitations

Our results could be limited by the possible effect of remaining epileptic activities in nonseizure-free patients (Engel II, n = 4) on the functional brain imaging results. However, the impact of interictal epileptiform discharges (IEDs) on an fMRI signal is still inconclusive (Centeno & Carmichael, 2014). Moreover, all patients reported no seizure event for more than 6 months before study participation and showed no IEDs in a clinical EEG follow-up. Therefore, although we cannot rule out the possible impact of IEDs on our fMRI results, the

effect of epileptic activities should be minimal in the present study. Another limitation of the present study is that we could not stipend the exact time at which the FC in the MTLR patients increased. The increased FC in the MTLR patients might have developed preoperatively. Because of the presence of the pathologic MTL before surgery, functional brain reorganization may have already occurred effectively. In this regard, we could not estimate the additive effect on the FC by the removal of the MTL. A future longitudinal study could investigate when reorganization occurs and how much the MTLR affects the reorganization, perhaps by using our findings as a standard for effective memory network against a MTL attack.

5 | CONCLUSIONS

In the present study, we questioned how brain supports normal episodic memory function in the absence of one of the MTL structures. The whole-brain memory network in MTLR patients who have a normal range of memory ability was characterized by altered patterns of regional activation together with enhanced functional interactions across widespread cortical areas. We first suggest that the hyperconnectivity of distributed brain areas, especially the mPFC, is a compensatory neural mechanism for effective memory function against the absence of one of the MTL structures. These findings may help to develop a better postsurgical memory outcome prediction model and also provide possible new therapeutic targets for patients with MTL-dysfunction-related memory disturbance.

CONFLICT OF INTERESTS

None.

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