

Exploring the contextual factors of episodic memory: dissociating distinct social, behavioral, and intentional episodic encoding from spatio-temporal contexts based on medial temporal lobe-cortical networks*

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Episodic memory consists of a core event and the associated contexts. Although the role of the hippocampus and its neighboring regions in contextual representations during encoding has become increasingly evident, it remains unclear how these regions handle various context-specific information other than spatio-temporal contexts. Using high-resolution functional MRI, we explored the patterns of the medial temporal lobe (MTL) and cortical regions' involvement during the encoding of various types of contextual information (i.e., journalism principle 5W1H): “Who did it?,” “Why did it happen?,” “What happened?,” “When did it happen?,” “Where did it happen?,” and “How did it happen?” Participants answered six different contextual questions while looking at simple experimental events consisting of two faces with one object on the screen. The MTL was divided to sub-regions by hierarchical clustering from resting-state data. General linear model analyses revealed a stronger activation of MTL sub-regions, the prefrontal lobe (PFC), and the inferior parietal lobule (IPL) during social (Who), behavioral (How), and intentional (Why) contextual processing when compared with spatio-temporal (Where/When) contextual processing. To further investigate the functional networks involved in contextual encoding dissociation, a multivariate pattern analysis was conducted with features selected as the task-based connectivity links between the hippocampal subfields and PFC/IPL. Each social, behavioral, and intentional contextual processing was individually and successfully classified from spatio-temporal contextual processing, respectively. Thus, specific contexts in episodic memory, namely social, behavior, and intention, involve distinct functional connectivity patterns that are distinct from those for spatio-temporal contextual memory.

Key words : Contextual Memory, Hippocampus, High-resolution fMRI, Functional Connectivity Pattern Analysis

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Introduction

Episodic memory consists of a core event and its associated contexts. Episodic context refers to various environmental information, such as temporal, spatial or any other details of past experiences, in which items or events were previously encountered. There has been broad consensus among researchers that the Hippocampus is the region mainly responsible for the binding and association of encoding contextual information (Manns & Eichenbaum, 2006; Yonelinas et al., 2019). There has also been research showing that the prefrontal cortex and parahippocampal regions are responsible for context memory relative to item memory. (Rugg et al., 2012; Zhang et al., 2018). Although the role of the hippocampus and its neighboring regions in forming the spatio-temporal contextual representation during encoding has become increasingly evident, it remains unclear how these regions handle various context-specific information other than spatio-temporal contexts. For example, a study by Kvavilashvili (1987) suggests that remembering behavioral action regarding an item or event, which is the goal of mnemonic behavior, can be dissociated from remembering the contents of the event itself.

There may be several reasons why neuroscientific research regarding contextual memory encoding has not been studied outside the realm of spatio-temporal contexts and has not branched out to investigate other various encoding neural representations. First, for research that emphasizes memory performance (i.e., retrieval success), context is represented as mnemonic information merely used as a supplementary tool for successful memory retrieval, and is thought of as a process that could be incidentally or passively encoded, and not as an intentional process. (see Smith and Vela, 2001, for review and meta-analysis). Second, due to the nature of neurobiological animal research, which comprises the majority of associative memory, main research paradigms focused on the spatial and temporal information in which the event was experienced rather than declarative context for facts, semantic information, action, event-related tasks. Therefore, the encoding and retrieval of spatio-temporal contextual factors in episodic memory have been investigated in a broad range of comparative studies in humans and animals, and the medial temporal lobe (MTL) has been highlighted for its crucial contribution to both spatial learning and temporal processing (Colombo et al., 1998; Squire et al., 2004; Forwood et al., 2005; Smith & Mizumori, 2006; Aminoff et al., 2007; Eichenbaum, 2013; Nadel et al., 2013; Hsieh et al., 2014; Davachi & DuBrow, 2015).

In addition to spatio-temporal information, however, episodic context is a wide term applied to the other details of an event beyond spatio-temporal information. For example, in a memory of a

social interaction, *who* was involved, how the social partner was engaged in the event, and why the behaviors were made during the event (i.e., intention-in-action) are all specified types of contextual information, which should be considered significant and further scrutinized. We explored a variety of contextual factors by encoding five different episodic contexts using the “5W1H” journalism principle of writing depicting a subject (Who), in a certain time (when) and place (Where), expressing physical or psychological action (How) and representing intention and valuation (Why) toward a certain object/event (what): (i.e., “When did it happen?,” “Where did it happen?,” “Who did it?,” “Why did it happen?,” “What happened?,” and “How did it happen?”) (Hsieh et al., 2014). The advantage of this principle is that it can clearly assort complex episodic contexts into six categories to help context-aware. The “When” and “Where” represent the traditionally investigated temporal and spatial context, respectively. The “Who,” “How,” and “Why” reflect social, behavioral, and intentional contexts, respectively.

Previous behavioral and neurophysiological research emphasized neural representation and mechanisms for various contexts as mnemonic information that supports episodic encoding. For instance, the social context of whether the person was a friend or foe was manipulated during encoding, and a face recognition task was subsequently performed (Vrtička et al., 2009). Several brain regions, including posterior cingulate cortex, amygdala, and caudate, showed increased activation while remembering the face of a foe rather than a friend. Thus, the social context during the encoding phase results in a difference in brain activation during face retrieval. Behavioral (or action) context was studied by observing the motor representation in the brain during the perception of tool objects (Grèzes & Decety, 2002). The motor imagery task activated the dorsal precentral gyrus, superior parietal lobule, and temporo-parietal junction. This experiment showed how the brain processes the behavioral use of tools apart from object recognition. Furthermore, Kvavilashvili (1987) studied the memory of an intention of an action compared to a memory of the “contents” of the event. In the course of the experiments, the variables of remembering the intention and remembering the contents did not correlate with each other. The existence of memories of intention was verified. These prior studies raise the possibility that the social, behavioral, and intentional factors may be distinctly processed from the spatio-temporal contextual factors of an event. However, whether the dissociable neural substrates and networks exhibit differential representation for various episodic contexts remains unclear.

The present study sought to provide a new perspective on how the human brain differentially processes contextual information. We suggest that new contexts in episodic memory, including social, action, and intention, require neural representation that are distinct from spatio-temporal contextual

memory. To our knowledge, there has been no prior fMRI study simultaneously comparing multiple context neural representation in a within-subject design. There is especially limited research that looks at whole brain dynamics, rather than the MTL as the sole contributor for contextual encoding representation, analyzed by multivariate pattern analysis (MVPA) employing machine learning algorithms, and network theory.

In the present study, we employed functional connectivity multivariate pattern analyses to determine the discriminative components of networks for contextual encoding based on task-based interactions (i.e., correlations) between the medial temporal lobe (MTL) and cortical nodes. MVPA using functional connectivity can be more sensitive than mass-univariate analysis only focusing on the amplitude of specific regions; thus, this method can provide additional insight into how distributed regions and cross-interaction across regions encode mnemonic information (Weaverdyck et al., 2020).

Given the increasing evidence for the interactive involvement of cortical regions, such as the prefrontal cortex and parietal lobe, in contextual memory, we developed near whole-brain high-resolution fMRI techniques centered on the MTL to acquire the whole brain connectivity network patterns used for encoding different contextual factors (Burgess et al., 2001; Hutchinson et al., 2009; Kirchoff et al., 2000; Simons & Spiers, 2003; Dobbins & Han, 2006; Duarte et al., 2010). Our study assessed which fronto-temporal or temporo-parietal connections differentiate the various representations of contextual processes. Multivariate classification analyses were conducted using functional connectivity patterns as classifying features in a machine learning algorithm (Pantazatos et al., 2012). In addition, we explored the optimal composition of the links that are most informative by plotting and calculating network index (i.e., degree centrality) estimated from the MVPA results. We sought to confirm if newly defined contexts (Who, How, and Why) could be distinguished from spatio-temporal contexts and if the connectivity patterns from the MTL to cortical regions show critical differences from the pattern for spatio-temporal context.

Materials and Methods

Participants

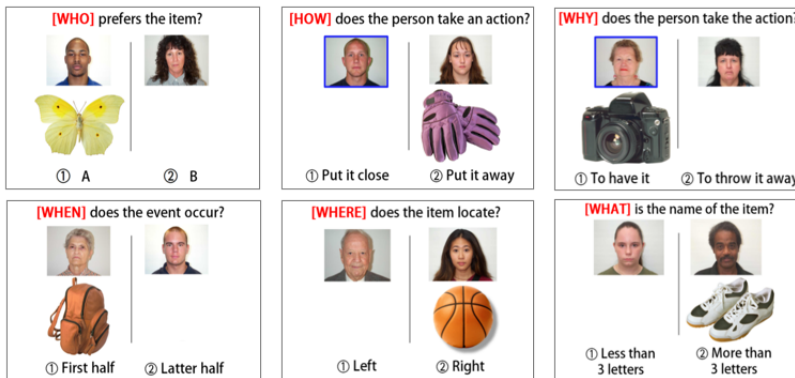
A total of 22 (seven women; mean age = 23.81 years, SD = 2.70) right-handed healthy volunteers with normal vision were recruited. Before MRI scanning, a written informed consent was

obtained from all participants, and the study was approved by the Institutional Review Board of OOOO University. Participants also completed a screening form to declare any significant medical conditions they might have. The subsequent analyses were conducted in 19 participants. Two participants dropped out of the study due to physical discomfort during scanning, and one participant was excluded due to scanner malfunction and image data distortion.

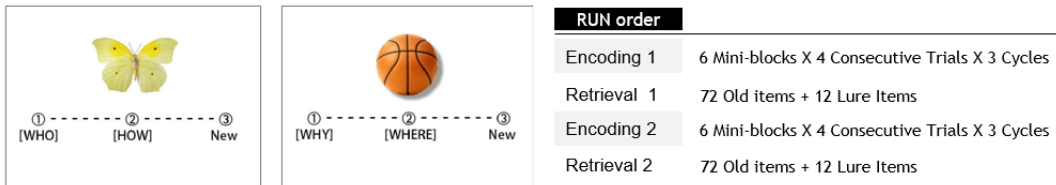
Contextual encoding task and experimental procedure

The task sessions consisted of four consecutive sessions with alternating encoding and retrieval tasks. The encoding task run consisted of mini-blocks, each of which contained six different types of contextual questions. Each question used the 5W1H principle: “Who prefers the item?,” “When does the event occur?,” “Where is the item located?,” “What is the name of the item?,” “Why

A. Encoding



B. Retrieval



(Figure 1). Schematic of experimental paradigm and stimuli example. (A) Example trials from the encoding sessions. Contextual questions (5s each) based on the 5W1H principle were asked one by one in mini-blocks over four consecutive trials. (B) Example trials from the retrieval sessions. Participants had to determine within 5 seconds if the given item was old or new and relay their source memory of the type of contextual question asked during the encoding for an old item.

does the person act?,” and “How does the person take action?” (Figure 1A). During the encoding tasks, the screen maintained the same format: two faces and an object that required participants to give binary responses (Minear & Park, 2004). Contextual questions based on these 5W1H principle were asked one by one in mini-blocks over four consecutive trials. Participants were required to answer the question within the fixed duration of 5 seconds in each trial (20s total in each mini-block). During the encoding run, the six mini-blocks alternated three times (6 mini-blocks X 4 trials X 3 cycles = total 72 trials).

When the question changes, participants can also switch their attention from one type of contextual information to another while looking at the same formatted event (two stimuli and binary judgment response). The question of “Who would most prefer the given item?” was asked while participants focused on two presented faces. There was no fixed answer, rather the response was the participant’s immediate and subjective judgment of the faces. For the When question, participants judged when the event (or a given trial) had occurred during the four-trial mini-block. The participants had two available answers: “first half,” which referred to the first or second trial of the mini-block or “latter half,” which referred to the third or fourth trial of the mini-block. The Where question simply asked the location of the item: left or right. The How question asked about the action of an event. The person marked by a blue rectangle on the screen was set to be the agent of an action. If the item was closer to the agent, participants were instructed to think that the agent placed the item close to him or her. If the item was far from the agent, it was assumed that the agent moved the item away. The Why question asked the participant to judge the intention of the action. If the agent placed the item close to him or her, it was because he or she wanted the item and vice versa. The What condition required the simple identification of the item by counting syllable of the objects name.

During the retrieval session, a source memory judgment task was performed. Here the participants recalled the type of contextual judgment made during the encoding session with the given item (Figure 1B). Specifically, the item was shown on the middle of the screen for 5 seconds with three response choices located beneath the image, including the old-correct source (i.e., Who), old-incorrect source (i.e., How), and a new-incorrect response. Each retrieval session tested 72 old items from the encoding session, and 12 lure items were added. After the task sessions, resting-state fMRI data were collected for the ROI segmentation procedure. Participants were instructed to close their eyes, remain awake, and not think of anything in particular.

fMRI Data Acquisition and General Linear Model Analyses

The neuroimaging data was collected with a 3T GE Healthcare Discovery MR750 instrument using a 32-channel radiofrequency head coil. Functional images were acquired with a T2*-weighted gradient-echo echoplanar imaging (EPI) sequence ($1.5 \times 1.5 \times 3.0$ mm voxels; TR = 2500 msec; TE = 22 msec; FOV = 20×20 cm; matrix size = $128 \times 128 \times 38$; flip angle = 90° ; 38 axial slices, interleaved collection). In previous research investigating the MTL with high-resolution fMRI, mainly in sagittal slices, the MRI protocol parameters came at a cost of losing coverage of the prefrontal and parietal cortices (Olman et al., 2009). With our aforementioned parameters, we obtained near whole-brain coverage with only minor loss of the superior parietal lobe and skull. The initial five volumes were discarded to allow for magnetization equilibrium. For each encoding and retrieval session, 198 and 168 volumes were collected, respectively. The subsequent resting-state MRI data were collected as 204 volumes. The responses were received with a magnet-compatible button box placed under the participant's right hand. T1-weighted structural images ($1 \times 1 \times 1$ mm resolution) were acquired for data co-registration during preprocessing.

Functional MRI data were preprocessed and analyzed using SPM8 (Wellcome Department of Cognitive Neurology, London, U.K.). The slice acquisition timing was corrected by resampling all slices relative to the middle slice (i.e., 19th slice) in temporal order. Functional images were realigned to correct for head movement and coregistered with each participant's anatomical scan. After the segmentation of coregistered images, the functional images were spatially normalized to the Montreal Neurological Institute template provided in SPM8, followed by spatial smoothing with a 4-mm full width at half maximum (FWHM) isotropic Gaussian kernel.

Our main interest was to disentangle how distinct neural networks are involved in the processing of different contexts; thus, the subsequent analyses focused on the encoding sessions. For the initial general linear model (GLM) analysis, the volumes were treated as a temporally correlated time-series and modeled by convolving a canonical hemodynamic response function (HRF) and its temporal derivative. The resulting hemodynamic functions were used as covariates in a GLM along with a base set of cosine functions that were used to high-pass filter the data and a covariate representing session effects. Least-squares estimates of the best-fitting synthetic HRF for each condition of interest were used in pairwise contrasts and stored as a separate image for each participant. These images were then tested against the null hypothesis of no difference between contrast conditions using one-tailed *t*-tests to determine if the effects were random at each group level. All GLMs treated each trial as an event with zero duration. Two encoding sessions were concatenated into a single

run from which the nuisance covariate of the run effect was regressed out to minimize any effects of run concatenation. For the first-level analysis, imaging data were modeled to the onset of the seven different experimental conditions: When, Where, Who, How, Why, What and Fixation. For group-level analysis, clusters of five or more contiguous voxels at the threshold of $p < 0.001$ were considered to be reliable.

For ROI analyses, the clusters identified from the GLM were made into masks using the MarsBar toolbox (ROI definition: Get SPM cluster(s); [Brett et al., 2002]). The parameter estimates of the ROI were extracted condition-wise. For the MTL, the entire mask of the hippocampus (HC) and parahippocampal cortex (PHC) were measured instead of sub-clusters. The pairwise t -tests were performed between the contrasts of interest (social/behavioral/intention versus spatial/temporal contexts) to identify potential clusters for ROIs analyses: Who vs. When, Who vs. Where, How vs. When, How vs. Where, Why vs. When, and Why vs. Where.

Resting-State Data Preprocessing and Hierarchical Clustering Analysis

Preprocessing of resting-state data was conducted using a Data Processing Assistant for Resting-State fMRI (DPARSF) ((Yan & Zang., 2010), <http://www.restfmri.net>). This procedure was developed based on SPM8 and the Resting-State fMRI Data Analysis Toolkit (REST) ((Song et al., 2011); <http://www.restfmri.net>). Slice-timing correction, realignment, spatial normalization, and smoothing processes for resting-state data followed the same protocols used in the preprocessing of functional data described above. Following these processes, data were detrended and temporally filtered with a low-pass band filter (0.01-0.08 Hz). The nuisance covariates, including 6 head motion parameters of global mean signals, white matter signals, and cerebrospinal fluid signals, were regressed out. The 4-dimensional (4D) image of resting-state data was acquired for each participant.

To examine fine grained connections between the MTL and cortical regions, we used the intrinsic connectivity profiles from the preprocessed resting-state data of voxels within MTL regions to create six regions of interests (ROIs) (anterior/middle/posterior hippocampus, parahippocampal cortex, and anterior/posterior perirhinal cortex) based on a hierarchical clustering algorithm [Wang et al., 2016]. Specifically, the overall boundaries of the HC and PHC masks were generated from Automated Anatomical Labeling (AAL) using the WFU pickatlas tool (Tzourio-Mazoyer et al., 2002; Maldjian et al., 2003). The time-series of entire voxels in the HC and PHC were extracted from the 4D brain images and then averaged across participants. These mean time-series of voxels in coronal slices along the longitudinal axis of the HC and PHC were correlated in pair-wise

manner to create a group-level connectivity maps: $2,544 \times 2,544$ and $2,736 \times 2,736$ connectivity similarity (r) matrix, respectively, in each hemisphere. Next, the connectivity distance was calculated as one minus connectivity ($1 - r$) which was entered into the hierarchical clustering algorithm UPGMA (Unweighted Pair Group Method with Arithmetic Mean), a built-in function in MATLAB. To view the segmented structures in 3D images, we used the open-source software ITK-SNAP 3.4.0 (Yushkevich et al., 2006).

Functional Connectivity Multivariate Pattern Analyses (fcMVPA)

Node definition and beta series functional connectivity

Six ROIs from the MTL were previously defined by resting-state analyses. Additionally, seven regions previously implicated as working with the MTL in contextual memory were confirmed to be engaged in the Who/How/Why contextual processing in the present GLM analyses and thus were added as ROIs: ventromedial prefrontal cortex (vmPFC; BA 47, BA 11), dorsolateral prefrontal cortex (dlPFC; BA 8, BA 9, BA 46), ventrolateral prefrontal cortex (vlPFC; BA44, BA45), frontopolar cortex (FPC; BA 10), angular gyrus, supramarginal gyrus, and amygdala (Vrtička et al., 2009; Schedlbauer et al., 2014). The prefrontal cortices coverage were picked from the templates defined by Brodmann areas, and the masks for the remaining regions were obtained from the AAL atlas using the WFU pickatlas tool.

To begin the multivariate pattern analysis, we adopted beta series correlation analyses in which each trial was modeled separately and treated as an individual event of interest (Rissman et al., 2004). Specifically, one regressor for the trial of interest and another regressor for the remaining $n - 1$ trials were modeled and iterated for all trials (Mumford et al., 2012). The beta series of ROIs were extracted and sorted by study condition. There were 24 trials for the six conditions; i.e., When, Where, Who, How, Why, and What, thus each beta series of an ROI contained 24 beta-estimates. Next, the correlation between ROI pairs was calculated for every condition. This procedure generated a total of 234 links per participant. The correlations within 28 functional ROIs were not included because we were only interested in links containing at least one MTL node.

Pattern classification of large-scale functional connectivity to discriminate contextual conditions

A multivariate pattern analysis was conducted using functional connectivity links as a classifying

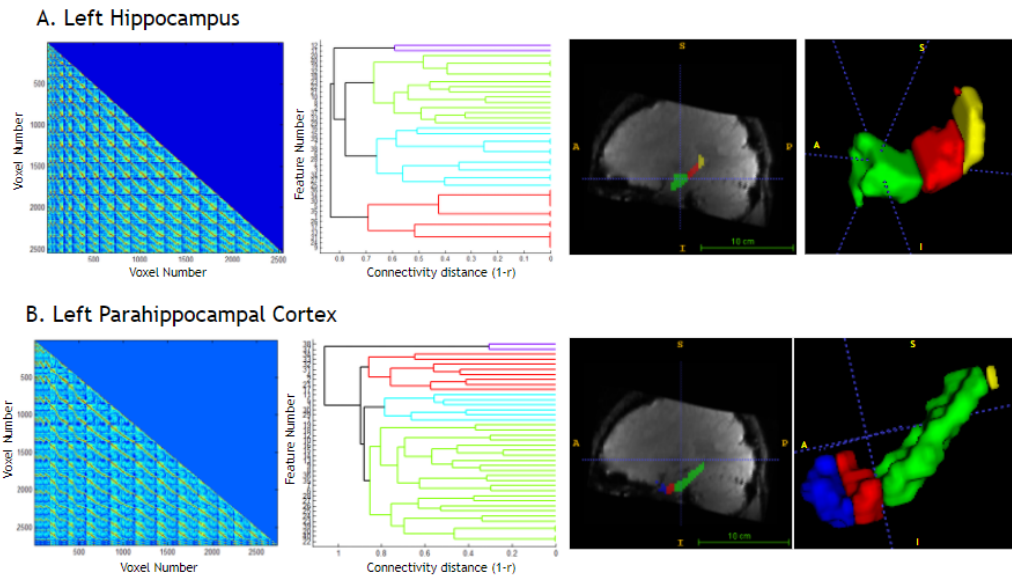
feature. The purpose of this analysis was to investigate if the network pattern of link strengths between nodes can effectively distinguish social and behavioral-intention contexts (Who, How and Why) from the spatio-temporal (When and Where) contextual processing and to explore which nodes and links are potentially informative. There were six pairwise contrasts of interest (Social/Behavioral/Intentional X Temporal/Spatial): Who vs. When, Who vs. Where, How vs. When, How vs. Where, Why vs. When, and Why vs. Where. The pattern analysis procedure described below was independently conducted on each contrast.

For proper feature selection, the paired *t*-test of correlation coefficients between two conditions was performed and the links were sorted by the absolute *t*-score. Pattern classification was conducted using a support vector machine (SVM) and Spider v1.71 MATLAB toolbox (<http://people.kyb.tuebingen.mpg.de/spider/>) with default parameters (linear kernel SVM, regularization parameter $C = 1$). The leave-one-out cross validation (LOOCV) method was applied so that one participant's link was subtracted from the training set and used as the test data. This method was repeated based on the number of participants. There were 38 total samples, thus 38 classification accuracies were generated from 38 rounds of LOOCV iterations, which were then averaged to obtain a single representative accuracy. Given that including complete features for SVM classification may induce noise during training and testing, features were cumulatively added in the order of *t*-score rank in each round of cross-validation. That is, the N^{th} SVM classification accuracy was obtained using the top N features whose *t*-score values are from the highest to N^{th} , and the $(N+1)^{\text{th}}$ accuracy was calculated by adding the feature that had the next highest *t*-score value. This process was iterated until the classification used the complete set of features, i.e., from the top feature to the last feature with the least *t*-score value. Thus, this method resulted in a total of 234 accuracies. We explored the optimal composition of the links that are most informative (i.e., peak accuracy) to discriminate behavioral-intention context versus spatio-temporal contextual processing. To test if the pattern classification accuracies were significantly above chance level, permutation tests were conducted. The class label (e.g., Who or When) was randomly assigned to classifying features, and the pattern classification was performed using LOOCV. This process was repeated 1,000 times and generated the chance accuracy null-distribution. The network analysis was performed using open source Gephi 0.8.2 software (Maldjian et al., 2003). The plot of the network estimated from the MVPA results was illustrated, and the index of degree centrality was calculated.

Results

Behavioral results

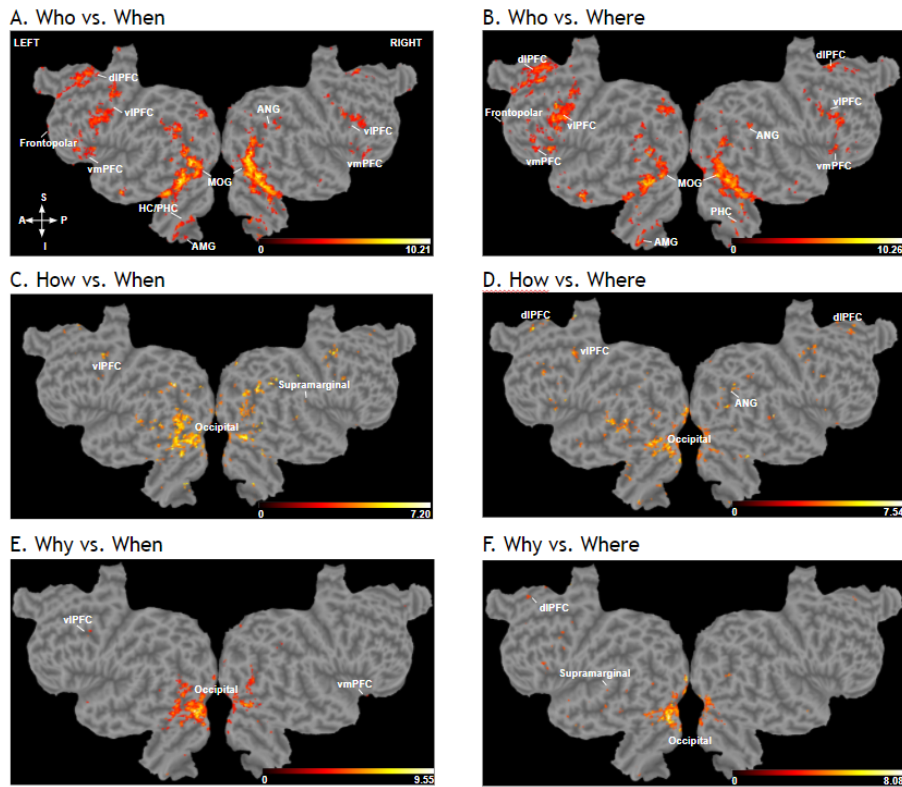
The recognition memory performance at judging whether the item is old or new regardless of source judgment correctness showed an overall accuracy of 74.81%. When, Where, Who, How, Why, and What was 55.76% (stdev = 19.75), 61.90% (16.64), 61.84% (15.33), 52.14% (21.89), 60.91 (19.21), and 76.64% (10.87), respectively. False alarm response for lure items was 58.72%. The source memory performance, which judged the question type associated the item, showed an overall accuracy of 47.7%. Specifically, the source memory accuracy of When, Where, Who, How, Why, and What was 37.56% (stdev = 21.88), 46.44% (17.69), 52.69% (18.03), 37.39% (18.97), 43.31% (18.77), and 68.86% (14.95), respectively.



(Figure 2). The procedure for hierarchical clustering and the results of segmentation. (A) The 2,544 x 2,544 connectivity homogeneity matrix, dendrogram, and images of the segmented left hippocampus are shown. The y axis of dendrogram suggests the features included in clustering, which represents the 2,544 voxels of hippocampus. Only 40 representative voxels are shown in y axis for the effective displaying. (B) The 2,736 x 2,736 connectivity homogeneity matrix, dendrogram, and images of the segmented left parahippocampal cortex are shown.

MTL sub-region segmentation from hierarchical clustering results

Based on the dendrogram created from the connectivity distance matrix, a maximum of four clusters were constructed using distance as a criterion for both HC and PHC. Figure 2A shows the sample procedure of segmentation on the left HC. The connectivity between entire voxels in the left HC created a $2,544 \times 2,544$ connectivity homogeneity matrix. The dendrogram depicts the 40 representative nodes out of total 2,544 nodes, and the four clusters formed at a distance threshold of 0.7 ($1 - r$). Three of these significant clusters were used as ROIs in subsequent analyses: anterior, middle, and posterior HC. Figure 2A shows the overlaid brain image and a zoomed 3D image of the clusters. Similarly, the left PHC consisted of a 2736×2736 connectivity homogeneity matrix and four clusters at a distance threshold of 0.8 ($1 - r$). Three significant clusters were used



(Figure 3). Contrast results of contextual conditions: (A) Who versus When, (B) Who versus Where, (C) How versus When, (D) How versus Where, (E) Why versus When, and (F) Why versus Where. Abbreviations: AMG - amygdala, MOG - medial occipital gyrus, ANG - angular gyrus, HC - hippocampus, PHC - parahippocampal cortex.

as ROIs: PHC and anterior and posterior perirhinal cortex (PRC). The clusters were used as nodes in multivariate pattern analyses.

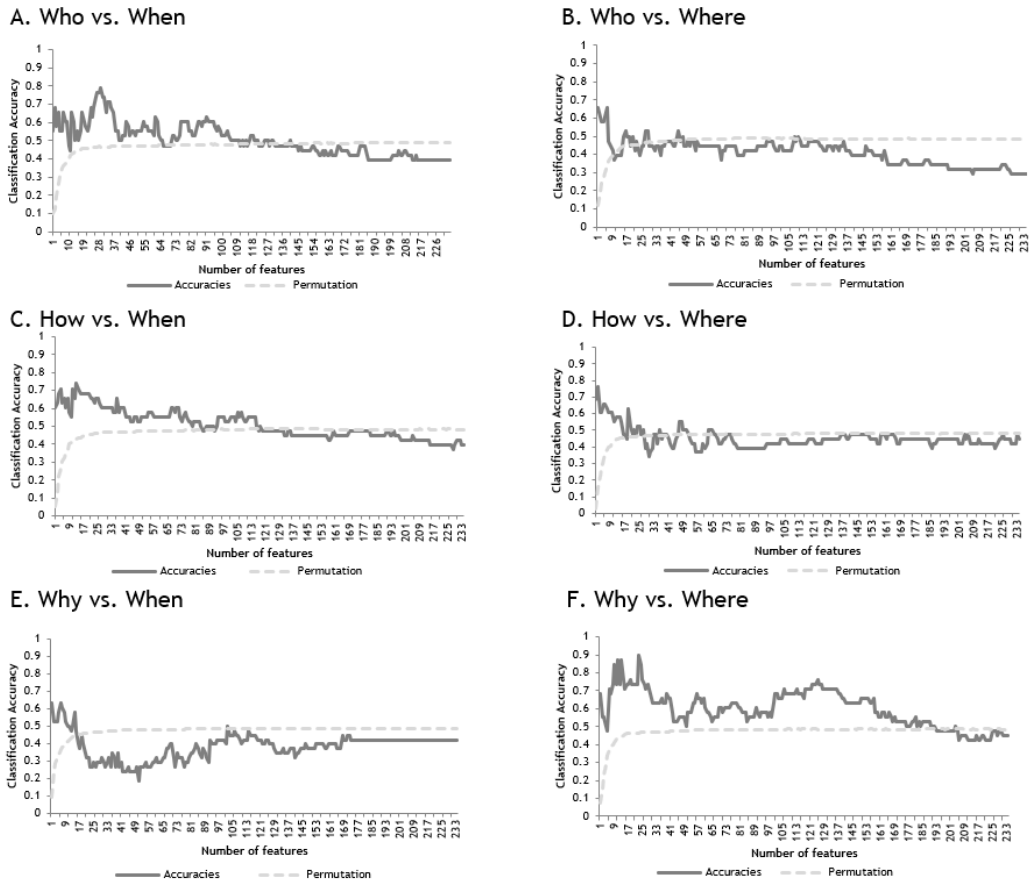
Exploratory Whole-brain Univariate Analyses

To define all the potential ROIs clusters involved in the contextual encoding as functional nodes for subsequent connectivity pattern analyses, we explored the different neural substrates involved in Who/How/Why vs. When/Where contextual processing, six contrasts were investigated (Who vs. When, Who vs. Where, How vs. When, How vs. Where, Why vs. When, and Why vs. Where). Significant activation was identified in the MTL, ventromedial prefrontal cortex (vmPFC; BA 47, BA 11), dorsolateral prefrontal cortex (dlPFC; BA 8, BA 9, BA 46), ventrolateral prefrontal cortex (vlPFC; BA44, BA45), frontopolar cortex (FPC; BA 10), angular gyrus, supramarginal gyrus, and amygdala (See Figure 3 and Table 1 available in the Figshare repository DOI:10.6084/m9.figshare.19289510 for detailed information).

These results clearly demonstrate the involvement of the MTL in social, behavioral, and intentional contextual processing (see the detailed patterns of engagement of MTL sub-regions in the next section). These findings demonstrate a consistent involvement of the PFC in social contextual processing. Social decision-making procedures in the PFC were actively recruited during social contextual processing rather than spatio-temporal contextual processing (Koenigs et al., 2007; Heekeren et al., 2003). In addition, behavioral context processing recruited the right vmPFC, which may be explained by the action representation function of the PFC (Eskenazi et al., 2009). The involvement of the inferior parietal lobule (IPL) in social, behavioral, and intentional contextual processing suggests that empathic functions may have been recruited during social cues and the speculation of the cause and effect of the event. These results confirm the engagement of the nodal ROIs during the encoding of Who, How, and Why contextual processing.

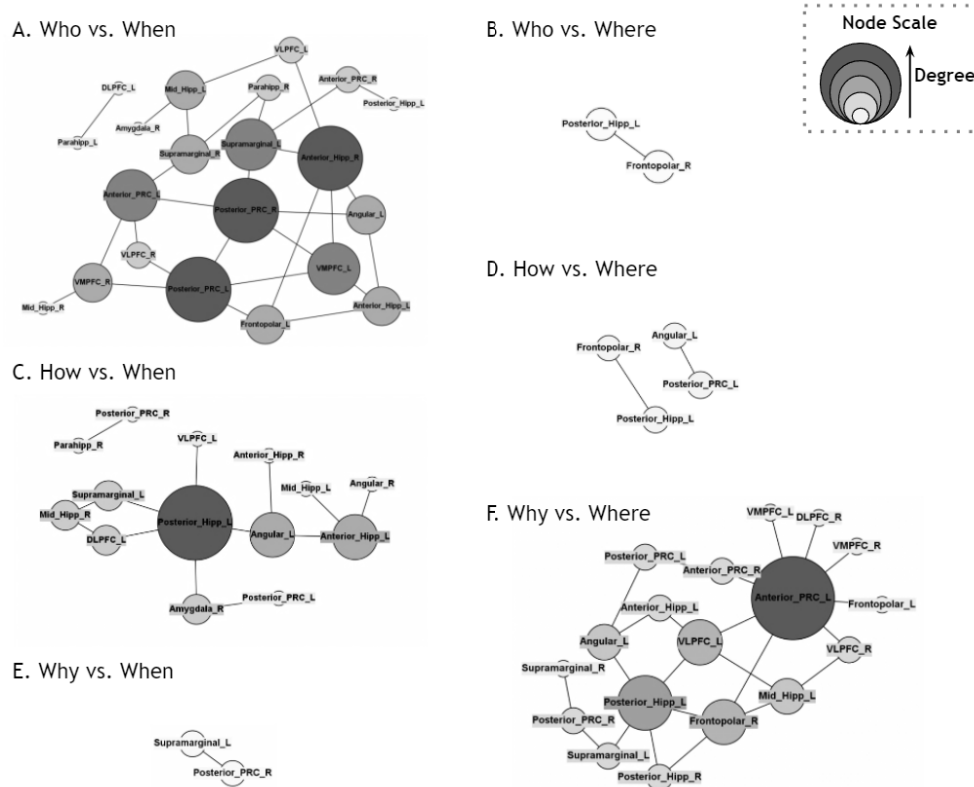
Functional connectivity Multivariate Pattern Analyses

We conducted functional connectivity multivariate pattern analyses (fcMVPA) to examine how the defined MTL and other cortical regions are differentially linked to dissociate each type of contextual encoding from spatio-temporal contextual processing. Specifically, the beta series of predefined bilateral ROIs in the clustered MTL and GLM results (total of 26 ROIs) were extracted and correlated within the conditions. Next, the structured patterns of condition-specific functional



(Figure 4). Classification results of functional connectivity multivariate pattern analyses. The dark gray lines represent the discrimination accuracies of the SVM classifier of each contrast: (A) Who vs. When, (B) Who vs. Where, (C) How vs. When, (D) How vs. Where, (E) Why vs. When, and (F) Why vs. Where. The peak accuracies of 78.9%, 65.8%, 73.6%, 76.3%, 63.1%, and 89.5% were obtained when 29, 1, 13, 2, 1, and 23 features were included for classification, respectively. The dashed light gray lines represent the permutation test results.

connectivity that sensitively categorize the dynamic of Who/How/Why processing from When/Where processing were investigated from the perspective of classification based on a machine learning algorithm. The classification accuracy results are shown in Figure 4. For Who vs. When discrimination, the peak accuracy was 78.9% with the inclusion of 29 links. The accuracy gradually decreased to 39% with the inclusion of all 234 links. Thus, the inclusion of irrelevant features caused a drop in classification performance. Likewise, the classification of Who vs. Where showed an



(Figure 5). The network that best discriminates each contextual contrast: (A) Who vs. When, (B) Who vs. Where, (C) How vs. When, (D) How vs. Where, (E) Why vs. When, and (F) Why vs. Where. The nodes have different colors and sizes. The color becomes darker and the size becomes bigger as the degree increases. The scale for color and size is shown on the upper right side of the figure. Notably, the scale is not applicable to a single-edge network, i.e., (B), (D), and (E), because there is no difference in network degree.

accuracy of 65.8% with a single link. The classification of How vs. When and How vs. Where showed an accuracy of 73.6% and 76.3% with 13 and two links, respectively. The peak accuracy of classifying Why vs. When was 63.1% with a single link and 89.5% for Why vs. Where with 23 links.

The results of the network analyses are plotted in Figure 5. The color (i.e., darkness) and size of the node represents the degree and number of connections. To identify the important nodes in each network, degree centrality was calculated for each node. In the Who vs. When discrimination, the bilateral posterior PRC was identified as the main node of the network, and both the left and right

posterior PRC had five edges with 0.25 degree centrality. A smaller network separated from main network between the left PHC and left DLPFC was identified. The PRC has a crucial role in associative memory, which is also essential for social contextual memory, i.e., combining the social context with the object (Staresina & Davachi, 2008; Feinberg et al., 2012). The perirhinal links made with the IPL suggest the cooperation of social decision-making and associative visual memory. The network discriminating Who and Where processing had only one link; thus, the centrality was one in the left posterior HC and right frontopolar cortex, which shared a single edge. The posterior HC is well-known for its contribution to spatial learning (Poppenk et al., 2013). Here, the stronger connection with the frontopolar cortex during Where tasks allowed for its distinction from Who tasks.

The classification between “How” vs. “When” resulted in a hub node in the left posterior HC, with five connections and degree centrality of 0.38. The left angular gyrus and left anterior HC represented two informative nodes with three edges and 0.23 degree centrality. The connectivity between the right posterior PRC and right PHC comprised a small network for “How” and “When” contextual discrimination that was detached from the main network of the posterior HC-hub. The hippocampal connectivity with the IPL was essential for differentiating behavioral contextual processing from temporal contextual processing. In other words, the judgment on actions made during an event requires the empathic ability of the IPL. In contrast, the detached small network of the PHC and posterior PRC was stronger in temporal contextual processing, thus, replicating the consistent temporal contextual representation within the MTL. The “How” vs. “Where” classification was comprised of two separate networks with a centrality of 0.33, including one from the left posterior HC to the right frontopolar cortex and another from the left posterior PRC to the left angular gyrus. Both links were stronger in spatial contextual processing: the posterior was recruited during spatial learning, and the angular gyrus was engaged during spatiovisual abilities, such as mental rotation (Grabner et al., 2009).

The “Why” vs. “When” network had one link between the right posterior PRC to the left supramarginal gyrus with a centrality of one. The link strength was greater in “Why” than “When” contextual processing, which suggests that the speculation of underlying intention actively recruited the empathic function of the supramarginal gyrus combined with the memory function of the PRC. The discrimination of “Why” vs. “Where” revealed a single large network with the hub in the left anterior PRC, eight edges, and a 0.47 degree centrality. The left posterior HC, right frontopolar cortex, and left vIPFC were the next three important nodes each having five, four, and four links and a 0.29, 0.24, and 0.24 degree centrality, respectively. Not surprisingly, spatial

learning actively recruited the posterior HC and PRC in conjunction with sub-regions of the PFC.

Discussion

The current study provides a novel insight into how encoding contextual memory representation varies with distinct neural network connectivity patterns. Specifically, each social, behavioral, and intentional contextual encoding conditions were hypothesized to be distinctively classified from spatio-temporal contexts, respectively, using a machine learning classification algorithm with functional connectivity patterns as feature inputs. By acquiring near whole-brain coverage of high-resolution MRI data, we were able to better understand the engagement of brain regions connected with the MTL during contextual encoding. Recognizing the crucial role of the MTL in contextual memory, the present study targeted MTL as the foremost seed region (Squire et al., 2004; Eichenbaum, 2013; Nadel et al., 2013). Recent studies emphasized the functional network among the MTL and other brain regions for spatio-temporal contextual memory. For instance, during the retrieval of spatio-temporal contexts, the network with a hub in the MTL was recruited with different interaction patterns for each context type. A synchronized activation of the IPL and hippocampus was demonstrated during spatio-temporal contextual retrieval. Our study showed that the regions implicated in past studies that cooperate with MTL in contextual encoding processing, including the PFC, IPL, and amygdala, were also confirmed to be involved in social, behavioral, and intentional contextual encoding by univariate GLM analyses (Vrtička et al., 2009; Burgess et al., 2001; Kirchoff et al., 2000). More importantly, we aimed to reveal the discriminative contextual functional connectivity network using a multivariate connectivity pattern analysis with features classified as task-based interactions between pre-defined nodes during contextual encoding. MVPA using functional connectivity could provide more sensitive and additional insight into how distributed regions and cross-interaction across regions encode contextual mnemonic information.

The task-related connectivity-based pattern classification resulted in networks that discriminated social, behavioral, and intentional contextual encoding from spatio-temporal contexts. The interpretation of each network was based on the hub node with the highest degree centrality. The discrimination of social and temporal context (Who vs. When) revealed the bilateral posterior PRC as the hub node of the network, which was linked with the vmPFC, vlPFC, frontopolar cortex, angular gyrus, and supramarginal gyrus (Figure 5A). Among the sub-clusters of the MTL, the PRC was strongly connected with the PFC and IPL during social contextual encoding rather than

temporal contextual encoding. Thus, social contextual encoding requires the association between stimuli in the PRC. The binding of face and object was actively processed, whereas temporal contexts did not have a tangible stimulus to bind with the given object. The involvement of the PRC during associative memory was reviewed by Mayes et al. (2007). The activation of the PFC and IPL was consistently reported in studies of social decision-making (Lee, 2008). The cooperation of the PRC, PFC, and IPL demonstrates the contribution of associative memory during social decision-making procedures. The small detached network of the left dlPFC and PHC showed stronger connectivity during temporal contextual encoding. This network appeared again in the classification of behavioral and temporal contexts (“How” vs. “When”), thus representing the temporal aspect of the encoding. The network discriminating social and spatial contextual processing (“Who” vs. “Where”) consisted of a single link between the posterior HC and frontopolar cortex. This link was stronger in spatial contexts than social contexts, reflecting the function of spatial learning in the posterior hippocampus (Poppenk et al., 2013). Next, the classification between behavioral and temporal contextual encoding revealed a network of HC components connected with the IPL (Table 2 data available in Figshare repository DOI 10.6084/m9.figshare.19289537). The IPL is noted for its engagement during empathic ability. For instance, Shamay-Tsoory (2011) discovered the neural basis for empathy. Emotional empathy is recruited by the IPL and other regions, whereas cognitive empathy is recruited by the network of the PFC and MTL. Our study required the both emotional and cognitive empathy, i.e., the link between the IPL and MTL, during the “How” task. In other words, judging the action made by others demanded the comprehensive empathic interpretation of the events about action and intention. As previously mentioned, the PHC link was engaged in temporal contextual processing, thus replicating the temporal contextual representation of the MTL. The network classifying behavioral and spatial contextual encoding (“How” vs. “Where”) consisted of two separated links with a stronger link for spatial encoding (Figure 5D). The spatial learning involving the posterior HC was replicated with a connection to the frontopolar cortex. The PRC to angular gyrus link was the second identified link. The visual perceptive function of the PRC was linked with spatial cognitive function, such as mental rotation, of the angular gyrus (Grabner et al., 2009; Lee, 2008). Next, the classification of intentional and temporal contextual encoding revealed a single link network between the PRC and supramarginal gyrus that showed higher connectivity in behavioral contexts (Figure 5E). The intentional context is closely related to the behavioral context based on the underlying mechanism of empathy. To understand the intention of another person’s action, empathic function in supramarginal gyrus is required. This emotional empathy in the IPL was linked with the cognitive empathy in the MTL. The network classifying

intentional and spatial contextual processing (“Why” vs. “Where”) was slightly complicated (Table 2). Many links between the PRC and PFC were detected, which were stronger during spatial contextual encoding when compared with intentional contextual encoding. The visuospatial function in the PRC was actively synchronized with the spatial contextual processing of the PFC. In contrast, there were two links that were stronger during intentional contexts: the bilateral posterior HC and PRC to the supramarginal gyrus. Thus, empathic function was again recruited by internal speculation about the intention of others.

Nevertheless, these networks do not represent single contextual processing. The networks were investigated based on pattern classification; thus, a discriminative network must effectively classify two contexts. The current study successfully addressed if the social and behavioral-intentional contexts could be differentiated from spatio-temporal contexts. However, the neural mechanisms for each contextual encoding require further investigation. In addition, the network edges do not provide information on the direction between two contexts. When interpreting Figure 5, we cannot simply say that the edges are stronger in either context because some links are stronger in one context while some were stronger during other contextual processing. Table 2 is required to identify the direction of connectivity. In addition to contextual encoding, we directly measured item memory by asking “What” questions. Future studies will compare item memory with social and behavioral-intentional context.

Although we used the framework of 5W1H, there is a possibility that this may not fully capture the characteristics of the different encoding contexts. For example, the questions about How and Why may also contain information about Who. Besides, the difference in task difficulty, semantic salience, or complexity during each contextual encoding may limit the interpretation of the findings. However, there are portions of the questions that are more limited than the 5W1H principle conditions in an effort to unify the perceptual elements as much as possible. We therefore need to evaluate direct comparison and to focus on the multivariate consideration through the use of fcMVPA (even with information that is not univariate). Although the overall conditions may lack typical representativeness of contextual encoding tasks as a whole, the present study was able to see through the actual MVPA feature results that multivariate contributions were present during various contextual memory encoding. Thus, it is necessary for future studies to implement other experimental paradigms and contextual conditions to see whether similar experimental results can be obtained.

Notwithstanding its limitations, by employing neural connectivity-based MVPA, our results provide a new perspective on how the human brain differentially processes contextual information.

The MTL works as a hub serving an overall context-setting, and the connectivity between the MTL and other regions represent the different types of contextual processing. Thus, we suggest that new contexts in episodic memory, including social, action, and intention, require neural mechanisms that are distinct from spatio-temporal contextual memory. These three context types can be explored in countless ways during future research on episodic memory.

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(요약)

일화기억을 구성하는 맥락 요소에 대한 탐구: 시공간적 맥락과 구분되는 사회적, 행동적, 의도적 맥락의 내측두엽-대뇌피질 네트워크 특징을 중심으로*

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일화기억은 핵심 이벤트와 그에 연합된 맥락으로 구성된다. 해마와 해마 주변 영역이 일화기억의 부호화에서 맥락을 표상하는 역할에 관해 연구되어왔지만, 시공간적 맥락 외에 다양한 맥락-특이적 정보들에 대한 표상에 관한 연구는 많지 않다. 본 연구에서는 고해상도 자기기능공명기법을 이용하여 여러 맥락정보(예, 육하원칙 - 누가, 왜, 무엇을 언제, 어디서, 어떻게)의 부호화에 관여하는 내측두엽 및 대뇌피질 신경연결성의 특징을 탐색하였다. 참가자들은 두 명의 얼굴과 하나의 사물로 구성된 실험 이벤트를 보면서 여섯 가지 맥락 부호화 과제를 수행하였다. 휴지기 기능적 자기공명영상 정보를 활용해 내측두엽의 세부 영역을 기능적으로 구분하였고 맥락 기억 과제별 기능적 신경연결성 네트워크를 탐색하였다. 일반선형화 모델 분석을 통해 시공간적 맥락정보를 처리할 때보다 사회적, 행동적, 의도 맥락을 연합할 때 내측두엽의 세부영역, 전전두엽, 하부두정엽 영역이 유의미하게 증가한 활성화를 보이며 관여함을 확인하였다. 나아가 이 영역들과 내측두엽 영역이 맥락조건간 차이에 관여하는 기능적 연결성 특징을 탐색하기 위하여 맥락부호화 과제를 수행하는 동안의 해마세부영역들과 전전두엽, 하부두정엽 등 간의 과제기반 기능적 연결성 정보들을 다변량 패턴분석의 주요입력변수로 선정하였고, 기계학습을 통해 맥락 조건 간 연결성 패턴분류를 시도하였다. 네트워크 패턴분류에서도 시공간 맥락 조건과 각 사회적, 행동적, 의도 맥락처리 조건 간에는 기능적 연결성의 차이가 두드러졌다. 본 연구결과를 통해 일화기억에서 특정 맥락을 처리하는 신경학적 기제의 특성과 맥락 조건 간 차이를 제시하였다.

주제어 : 출처지역, 해마, 고해상도 fMRI, 기능적 연결성 패턴 분석