Hippocampus's role in forming "task-related" associations: Flashing to the things you are looking for

ZHANG XiuLing[1], NIKI Kazuhisa[2,3], LUO Jing[1†]

[1] Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China;
[2] Neuroscience Research Institute, National Institute of Advanced Industrial Science and Technology, Tokyo, Japan;
[3] Brainscience and Education, RISTEX, JST, Tokyo, Japan

Eichenbaum and colleagues observed that the same place did or did not activate the "goal-approach" cells in hippocampus depending on whether the place was the way for rats to approach specific goal. Parallel with this, the present neuroimage study revealed that, the same type of items could activate the hippocampus more when it was related to the task at hand than when it not. Participants were scanned by fMRI while they made judgments on the type of relationships contained in the word-pairs (e.g., Does the word pair, "furniture-table", contain a "category-exemplar" relationship?). Event-related analysis revealed that the forming of "task-related" association activated hippocampus more than that of "task-unrelated", even if it was the same type of items, and, this hippocampal difference was not caused by the different judgment requirements, nor by the effects of "yes" response. Consistently, the post-judgment cued-recall test exhibited a better retrieval performance for "task-related" associations than for the same type but "task-unrelated" associations. Results also showed that, the semantic relatedness between the to-be-associated individual words (e.g., the related word pair "healthy-hospital" versus the unrelated word pair "price-way") was not enough to activate the hippocampus when it was "task-unrelated". Generally, we proposed that, through participating in forming of "task-related" associations and consolidating of episodic memory, hippocampus enabled the organism to keep the information that owned great survival values in mind for future usage.

Eichenbaum et al.[1] recorded "goal-approach" cells in hippocampus that fired selectively during specific orientation or locomotor movements, such as approach to the port or to the reward cup. There were several lines of evidence showing that the "goal-approach" cells did not simply reflect current animal location. First, the place-field distribution was far from homogeneous in the parts of the arena well sampled, as would have been predicted by the place-map theory. Second, unit activity in "goal-approach" cells was usually better correlated with a location-to-be-occupied (as much as 2 s in advance) than the current location. Third, time-locking to onset of movement often revealed better synchronization of unit activity in "goal-approach" cells than arrival in the place-field. Fourth, specific "goal-approach" cells

could be activated by specific place-field only when that place was the way to specific goal (i.e., reward cap). When that place was not the way to the goal, the "goal-approach" cells would not fired even if the same place was passed. And finally, the "goal-approach" cells for the reward cup ("cup-approach cells") fired vigorously only when the rat approached the cup for reward consumption, and not upon place-field entry on non-reinforced trials.

In current neuroimage research, we tried to show that this kind of regulation from the goals or tasks on the activation of hippocampus was not limited to the navigation behavior. Higher-level cognitive functions in human beings, such as semantic processing, could also be mediated by a similar hippocampal mechanism.

Neuroimaging research has proved the role of medial temporal lobe (MTL) including hippocampus in semantic processing[2−5]. Recently, Henke et al.[6] showed that there were more hippocampal activations when subjects were required to decide whether the two presented words (e.g., "level" and "need") fit together in meaning than when they were required to decide whether each of the two presented words was pleasant or unpleasant. Based on this, they proposed that it was the formation of the new semantic associations between two unrelated words, rather than deep semantic processing of each of the single word, that led to activation of the hippocampus[6]. However, in the follow-up research[7], we adopted the triple semantic judgment task and asked the participants to judge which one of the two bottom words was more semantically fit to the top target word. The number of bottom word that is semantically related to the top word was varied as 0, 1 or 2, e.g., the word on the top: "land", the words on the bottom: "clock", "music" (0); the top: "land", the bottom: "building", "music" (1); or the top: "land", the bottom: "building", "farm" (2). By doing this, we could disassociate MTL's involvement in associating the semantically related items (e.g. "land" and "building") from that in associating the semantically unrelated items (e.g. "land" and "music"). Contrary to the common understanding on MTL's role in forming novel associations (i.e., semantically unrelated items), our results showed MTL was more involved in associating the semantically related items. How could MTL be more activated in binding the semantically related words than in binding the semantically unrelated words? We thought all of the concepts (e.g. "land", "building", and "music") are familiar old (established) concepts, the "longer" semantic "distance" between "land" and "music", relative to the "distance" between "land" and "building", made in fact no difference. Critically, in this meaning-fitting judgment situation, to bind "land" with "building" was more consistent with or related to the goal or task at hand than to bind "land" with "music". It was the forming of the "task-related" associations, rather than forming of the "novel" associations, that really activated the hippocampus.

This hypothesis is consistent with Eichenbaum et al.[1]'s observation on "goal-approach" cells, and also consistent with the general framework that proposed a subsystem of "reference frame" that is goal or task-dependent[8,9]. The activation of hippocampus is not simply regulated by the external circumstances, but by the interactions between organism's internal goal and their external circumstances.

However, in the triple semantic judgment research[7], the process of forming "task-related" associations was confounded with the process of semantic relatedness. That is, the more words on the bottom that were semantically related to the word on the top (as 0, 1 or 2), the more activities of forming "task-related" associations, and at the same time, the more activities of semantic relatedness, were involved. Given that semantic relatedness among the to-be-associated individual items, through subserving the associative encoding, could also activate MTL[10], we still could not claim that it was the forming of "task-related" associations, or the semantic relatedness among the to-be-associated individual items that activated the MTL.

In the present research, to dissociate the effects of forming "task-related" associations from that of semantic relatedness among the to-be-associated individual items on MTL, the semantic judgment orientations in different blocks were different so that the same kind of semantic relatedness could be "task-related" in one task block and "task-unrelated" in another. The whole session consisted of three blocks in which participants were required to make different kinds of judgment on the presented word pairs. The first block was a control block in which participants were required to judge if the presented word pair satisfied a "category-exemplar relationship" (the C-E Block). In this block, besides the word pairs that contained a category-exemplar relationship (e.g., "furniture-table", abbreviated to CE[InC-E]), there were also word pairs that contained the "opposite-relationship" (e.g., "awake-asleep", abbreviated to OP[InC-E]), the "related-relationship" (the relationships other than "category-exemplar" or "opposite", e.g., "chair-table", abbreviated to RL[InC-E]), and the "unrelated-relationship" (e.g., "elephant-tea", abbreviated to UR[InC-E]). The OP[InC-E] trials in C-E Block would serve as the "task-unrelated" reference baseline for their corresponding items that would appear in the next judgment

block where participants were required to judge if the presented word pair satisfied the "opposite relationship" (the O-P Block). In this block, besides the word pairs that contained this relationship (abbreviated to $OP_{[InO-P]}$), there were also other word pairs that contained the "related-relationship" (abbreviated to $RL_{[InO-P]}$), and the "unrelated-relationship" (abbreviated to $UR_{[InO-P]}$). We also have a third judgment block in which participants were required to judge if each side of the word pair shared a same syllable (the trials of $SS_{[InSyllable]}$) or not (the trials of $DS_{[InSyllable]}$) (the Syllable Block). See Figure 1.

By contrasting the opposite word pairs in the O-P Block with those in the C-E Block (the contrast of "$OP_{[InO-P]}$ vs. $OP_{[InC-E]}$"), we can examine the effects of forming "task-related" association on MTL (that is, $OP_{[InO-P]}$ was "task-related", while $OP_{[InC-E]}$ was "task-unrelated"). The effects of semantic relatedness between the to-be-associated individual items on MTL can be examined by contrasting the related word-pairs with unrelated word-pairs within the same judgment block (i.e., the contrast of "$RL_{[InO-P]}$ vs. $UR_{[InO-P]}$"). The brain state difference caused by different semantic judgment tasks can be estimated by contrasting the same type of word pairs from the different blocks (i.e., the contrasts of "$RL_{[InC-E]}$ vs. $RL_{[InO-P]}$" or "$UR_{[InC-E]}$ vs. $UR_{[InO-P]}$"). The effects of "positive target" or "yes" response can be estimated by contrasting the "yes" items with "no" items in the Syllable Block (i.e., "$SS_{[InSyllable]}$ vs. $DS_{[InSyllable]}$"). See Figure 1, for demonstrations. In order to avoid the interferences, the category-exemplar word pairs in the C-E Block did not appear in other judgment blocks. After scanning, participants were presented with the words appearing on the left side of each word pairs injudgement blocks as cues and were asked to recall the words on the right side. We predicted the formation of "task-related" associations would (a) activate hippocampus more, and (b) be better kept in episodic memory. From the view of forming "task-related"
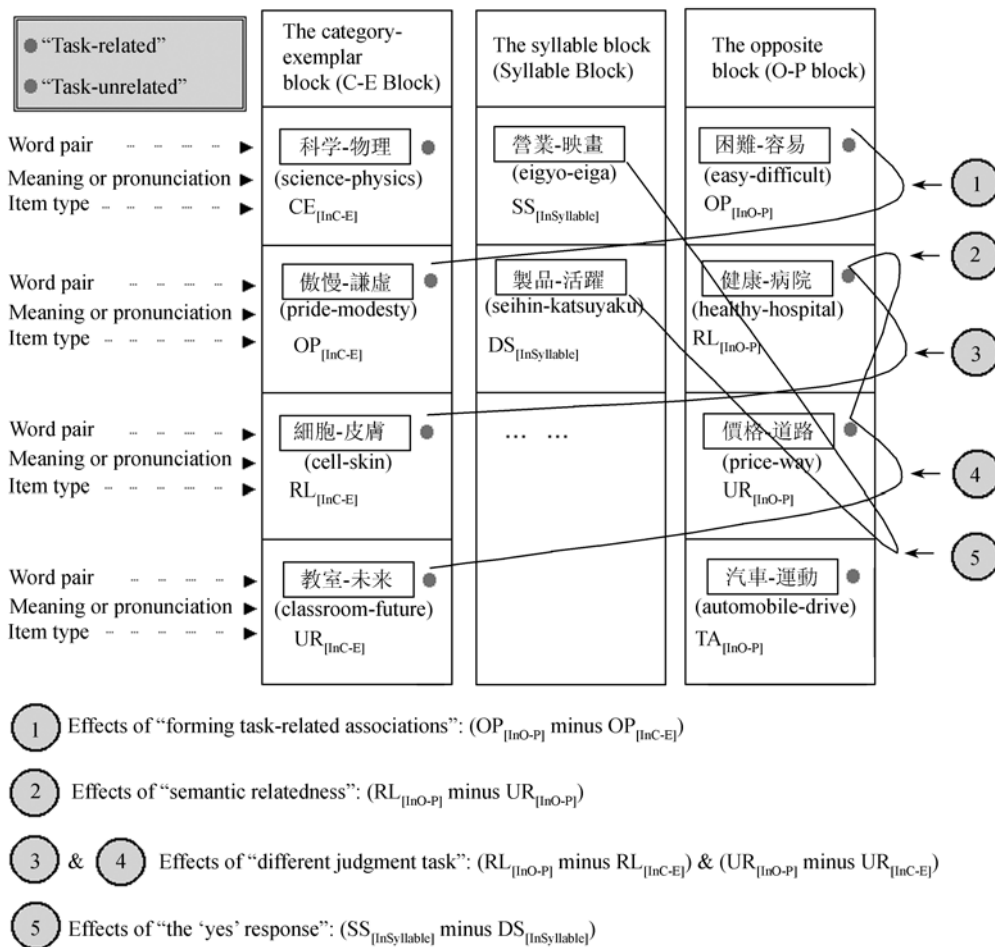

Figure 1 Demonstration of the cognitive task. The 5 critical contrasts were connected by lines.

associations, hippocampus's role in episodic memory can be regarded as keeping the "task-related" or "meaningful" information in mind to enlarge organism's chance to survival[7].

1 Methods

1.1 Participants

Seven healthy, right-handed volunteers (4 female and 3 male), aged from 20 to 22, recruited from the undergraduates of University of Tsukuba, participated in this experiment. They were interviewed 1 or 2 d before they attended the fMRI experiment and given informed consent that followed the MRI ethics committee in Neuroscience Research Institute, AIST. Participants were excluded if they had any medical, neurological, or psychiatric illness, or, if they did not feel well when in the MRI Machine.

1.2 Procedure

Participants were scanned by fMRI when they performed the following 3 judgment blocks sequentially: (i) the category-exemplar relationship judgment block (C-E Block); (ii) the syllable judgment block (Syllable Block); and (iii) the opposite relationship judgment block (O-P Block). Each block was started with the judgment instruction, e.g., the hint of "category-exemplar" in the C-E Block; the hint of "same syllable" in the Syllable Block; and the hint of "opposite" in the O-P Block. Before scanning, participants were instructed to understand the meaning of these hints very well. The hint was presented for 5000 ms followed by a 5000-ms unfilled delay, and then, the task items were presented. The first three items in each block were treated as fillers and not included in the critical analysis. Two of the three fillers required a "yes" response and one required a "no" response, to make the participants to be fully aware of the judgment requirement. Each word pairs were presented for 2700 ms and followed by a varied cross-viewing delay (from 3100 ms to 4900 ms with a mean of 4000 ms). The short SOA was chosen to maximize the sensitivity to difference in the BOLD response to different event-types. During the presentation of word pairs, participants were asked to press the left key on the button box, which was attached on their right leg, by the right index finger, if they thought the presented word pair fit the required condition (i.e., an $CE_{[InC-E]}$ item in the C-E Block, a $SS_{[InSyllable]}$ item in the Syllable Block, or an $OP_{[InO-P]}$ item in the O-P Block), or to press the right key by right middle finger if they did not think the presented word pair fit the required condition. To familiarize the participants with the procedure and pace of this task, participants were trained with another set of similar materials in the same procedure before the formal experiment.

The verbal materials used in the present researches were pairs of two-character Japanese kanji words[7], (Figure 1, for examples), the word pairs that contained different kinds of relationship were taken from specific verbal pools and were re-evaluated by our stuff majored in Japanese language. There were 5 kinds of items in the C-E Block: word pairs that contained a category-exemplar relationship ($CE_{[InC-E]}$); word pairs that contained an opposite relationship ($OP_{[InC-E]}$); word pairs that contained a related-relationship other than "category-exemplar" or "opposite" ($RL_{[InC-E]}$); word pairs that contained a unrelated-relationship ($UR_{[InC-E]}$); and a null event that contained no words (a cross hair was presented in these events). The trials of null event were inserted as rest events to increase the reliability and sensitivity of the event-related analysis in SPM. There were three kinds of events in the Syllable Block: word pairs in which the two words shared a same syllable ($SS_{[InSyllable]}$); word pairs in which the two words did not share a same syllable ($DS_{[InSyllable]}$), and the null event. All of the word pairs in the Syllable Block were semantically unrelated. There were five kinds of events in the O-P Block: word pairs that contained an opposite relationship ($OP_{[InO-P]}$); word pairs that contained a related-relationship other than "category-exemplar" or "opposite" (abbreviated to $RL_{[InO-P]}$); word pairs that contained a unrelated-relationship ($UR_{[InO-P]}$); word pairs that contained a object action relationship (e.g., "automobile-drive", abbreviated to $OA_{[InO-P]}$. This kind of word pairs was inserted in the O-P Block to make it have a comparable "yes" response ratio and item-structure with that in C-E Block); and the null event. Apart from the null event, there were 12 items (not including those that served as filler) in each kind of events. There were four items of null event in each of the three blocks and so there were 12 in the whole scanning session. In each block, the items belonging to different kinds of events were presented in a randomized order. Item lists were counterbalanced across subject such that a specific word pair that contained an opposite relationship was presented as $OP_{[InC-E]}$ for one subject and as $OP_{[InO-P]}$ for another. So they were

for the items in $RL_{[InC-E]}$ and $RL_{[InO-P]}$, or $UR_{[InC-E]}$ and $UR_{[InO-P]}$. After participants went out of the MRI machine (seven min after the relationship judgment task), they were asked to do an incidental cued-recall test. They were not informed that there would be such a retrieval test when they took the relationship judgment task. The words on the right side of the word pairs were presented as the cues in a randomized order relative to the judgment phase, and participants were required to write down the words that had been paired with the cues.

1.3 Data acquisition

All scanning was performed on a 3.0-T MRI Scanner (GE 3T Signa) equipped with EPI capability. Eighteen axial slices (5.3 mm thick, interleaved) were prescribed to cover the whole brain. A T2* weighted gradient echo EPI was employed. The imaging parameters were TR = 2 s, TE = 33 ms, FA = 70°, FOV = 20 cm × 20 cm (64 × 64 mesh). 3.0-Tesla had sufficient field strength to avoid localization biases toward draining veins. To reduce the susceptibility noise artifact (especially the EPI distortion) in the lower part of the brain including the anteromedial temporal lobes, we adopted wider bandwidth (130 kHz) and set the participants' chin down. To avoid head movement, they wore a neck brace and were asked not to talk or move during scanning. Motion correction was also performed in a standard realign process in SPM99.

1.4 Data analysis

Images were pre-processed (timeslice adjusted, realigned, normalized and smoothed) by SPM99. Then, image data of seven subjects were estimated to establish a fixed-effect model by the Event Related Analysis module of SPM99. 13 types of events were defined: $OP_{[InC-E]}$, $CE_{[InC-E]}$, $RL_{[InC-E]}$, $UR_{[InC-E]}$, $SS_{[InSyllable]}$, $DS_{[InSyllable]}$, $OP_{[InO-P]}$, $RL_{[InO-P]}$, $UR_{[InO-P]}$, $OA_{[InO-P]}$, the hints of judgment orientation, the fillers and items to which participants made unsuitable judgment (e.g., a "yes" response to a $RL_{[InC-E]}$ item), and the trial failures. Only the events that provided more than ten trials in each participant were considered; they were: $OP_{[InC-E]}$, $CE_{[InC-E]}$, $RL_{[InC-E]}$, $UR_{[InC-E]}$, $SS_{[InSyllable]}$, $DS_{[InSyllable]}$, $OP_{[InO-P]}$, $RL_{[InO-P]}$, $UR_{[InO-P]}$, and $OA_{[InO-P]}$. The threshold was set at $P < 0.001$ (uncorrected for multiple comparisons) and ten or more contiguous voxels. We set this uncorrected threshold given the analysis was conducted to testify the hypothesis (on the function of MTL) based on our previous studies[7] by using the same set of mate-

rials (but with some modifications), similar semantic judgment task, and the same data acquisition technology. The SPM coordinates for standard brain from Montreal Neurological Institute (MNI) were converted to Talairach coordinates by a non-linear transform method (Image Homepage, http://www.mrc-cbu.cam.uk/Imaging/mnispace.html).

2 Results

Several critical contrasts were conducted among various kinds of events. The contrast of "$OP_{[InO-P]}$ vs. $OP_{[InC-E]}$" was calculated to estimate the effects of forming "task-related" associations on the activity of hippocampus and on the performance of cued-recall. The contrast of "$RL_{[In O-P]}$ vs. $UR_{[In O-P]}$" was calculated to estimate the effects of semantic relatedness (but not the "task-related") among the to-be-associated items on the activity of hippocampus and on the performance of cued-recall. The contrasts of "$RL_{[In O-P]}$ vs. $RL_{[InC-E]}$" and "$UR_{[In O-P]}$ vs. $UR_{[In C-E]}$" were calculated to estimate the effects of different task block (category-exemplar relationship block and opposite-relationship block) on the activity of hippocampus and on the performance of cued-recall. The contrast of "$SS_{[InSyllable]}$ vs. $DS_{[InSyllable]}$" was calculated to estimate the effects of "yes" response in a perceptual (but not semantic) level task on the activity of hippocampus and on the performance of cued-recall. Neuroimage and behavior results are summarized in Table 1.

2.1 Behavior results

The cued-recall performance of $OP_{[InO-P]}$ was significantly higher than that of $OP_{[InC-E]}$ ($t_{(6)} = 3.39$, $P = 0.015$, Figure 2). Also, $OP_{[InO-P]}$ was recalled better than $RL_{[InO-P]}$ ($t_{(6)} = 3.82$, $P = 0.009$) and $UR_{[InO-P]}$ ($t_{(6)} = 4.74$, $P = 0.003$), respectively. $RL_{[InO-P]}$ was recalled better than $UR_{[InO-P]}$ ($t_{(6)} = 6.37$, $P = 0.001$). No difference in cued-recall performance was observed between $RL_{[InO-P]}$ and $RL_{[InC-E]}$, between $UR_{[InO-P]}$ and $UR_{[InC-E]}$, or between $SS_{[InSyllable]}$ and $DS_{[InSyllable]}$. However, considering that the cued-recall performance were fairly low in RL[In O-P] (Mean = 0.18, SD = 0.089) and RL[InC-E] (Mean = 0.20, SD = 0.18), and extremely low in UR[In O-P] (Mean = 0.01, SD = 0.03), $UR_{[InC-E]}$ (Mean = 0.01, SD = 0.03), $SS_{[InSyllable]}$ (Mean = 0), and $DS_{[InSyllable]}$ (Mean = 0), the observed no-difference could be caused by "floor effects" of retrieval.

Table 1 Activations in MTL, performance in cued-recall test, and the theoretical goal of analysis in the 5 pairs of critical contrasts

| Contrast	Goal of estimation	MTL activation	Cued-recall
$OP_{[InO-P]} - OP_{[InC-E]}$	effects of forming "task-related" associations	yes.	$OP_{[InO-P]} > OP_{[InC-E]}$
$OP_{[InC-E]} - OP_{[InO-P]}$	(revise contrast)	no.	
$RL_{[InO-P]} - UR_{[InO-P]}$	effects of semantic relatedness	no.	$RL_{[InO-P]} > UR_{[InO-P]}$
$UR_{[InO-P]} - RL_{[InO-P]}$	(revise contrast)	no.	
$RL_{[InO-P]} - RL_{[InC-E]}$	effects of judgment task	no.	no.
$RL_{[InC-E]} - RL_{[InO-P]}$	(revise contrast)	no.	
$UR_{[InO-P]} - UR_{[InC-E]}$	effects of judgment task	no.	no.
$UR_{[InC-E]} - UR_{[InO-P]}$	(revise contrast)	no.	
$SS_{[InSyllable]} - DS_{[InSyllable]}$	effects of "yes" response	no.	no.
$DS_{[InSyllable]} - SS_{[InSyllable]}$	(revise contrast)	no.	
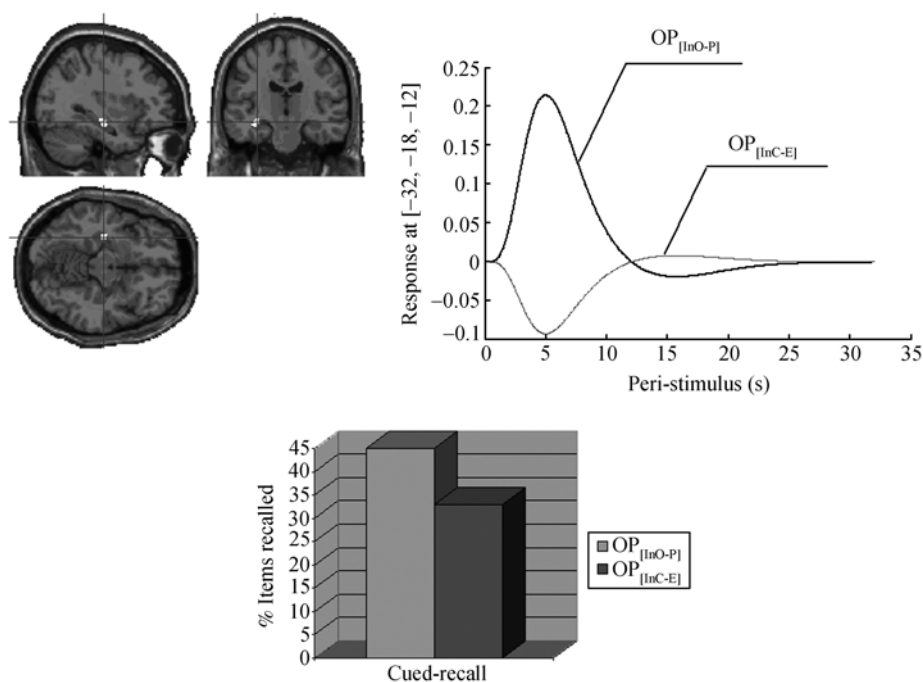
Figure 2 The comparison of hippocampal activation (the panel on the top) and cued-recall (the panel on the bottom) between $OP_{[InC-E]}$ and $OP_{[InO-P]}$. The panel on the top shows left hippocampal activations exhibited in the contrasts of "$OP_{[InO-P]}$-$OP_{[InC-E]}$". As the results of seven subjects normalized into Talairach space and imposed on a universal brain, the midsagittal, axial, and coronal sections showed territories of the hippocampal activation (top left) and the event-related plots showed the averaged signal change (%) of the best-fitting canonical hemodynamic response function from the peak voxel (as marked by the cross in the sections and located in the x, y, z coordinates of Talairach space beside the plots) that has the maximal value in the contrast (top right). Thresholded at $P < 0.001$ (uncorrected for multiple comparisons). The panel on the bottom showed cued-recall performance of $OP_{[InC-E]}$ and $OP_{[InO-P]}$. This is the average result of seven subjects.

2.2 Image results

On the effects of forming "task-related" associations, relative to $OP_{[InC-E]}$, $OP_{[InO-P]}$ was associated with positive activations in left middle frontal gyrus, left hippocampus, bilateral superior and right middle temporal gyrus (Figure 2 and Table 2), and was associated with negative activations in bilateral superior frontal gyrus, right medial frontal gyrus, right anterior cingulate, right middle and superior temporal gyrus, right caudate, left cuneus, and left lingual gyrus. On the effects of semantic relatedness between to-be-associated individual items,

relative to $UR_{[InO-P]}$, $RL_{[InO-P]}$ was associated with positive activations in bilateral superior frontal gyrus, bilateral precentral gyrus, left precuneus, left superior parietal lobule, and left middle occipital gyrus, and was associated with negative activations in bilateral superior, medial, middle, and inferior frontal gyrus, left precentral gyrus, right superior parietal lobule, left middle temporal gyrus, left lingual gyrus, and right cuneus (Table 2, the complete list of activations revealed in other contrasts can be required by contacting with the authors). The contrast of "$OP_{[InO-P]}$ minus $UR_{[InO-P]}$" and "$OP_{[InO-P]}$

Table 2 Activation in the contrasts of "OP$_{[InO-P]}$ vs. OP$_{[InC-E]}$" and "RL$_{[InO-P]}$ vs. UR$_{[InO-P]}$"

	T	x	y	z	Area
OP$_{[InO-P]}$ - OP$_{[InC-E]}$					
	3.66	−50	−52	10	Left Superior Temporal Gyrus, Brodmann area 39
	3.57	−32	−18	−12	Left Hippocampus
	3.56	−36	56	−6	Left Middle Frontal Gyrus, Brodmann area 10
	3.49	58	−56	4	Right Middle Temporal Gyrus, Brodmann area 21
	3.29	44	−48	14	Right Superior Temporal Gyrus, Brodmann area 39
OP$_{[InC-E]}$ - OP$_{[InO-P]}$					
	4.16	−14	−54	0	Left Lingual Gyrus, Brodmann area 19
	3.69	24	48	12	Right Medial Frontal Gyrus, Brodmann area 10
	3.68	22	40	10	Right Anterior Cingulate Brodmann area 32
	3.58	26	50	2	Right Superior Frontal Gyrus
	3.68	52	10	−34	Right Middle Temporal Gyrus, Brodmann area 21
	3.62	12	60	6	Right Medial Frontal Gyrus, Brodmann area 10
	3.38	6	56	10	Right Medial Frontal Gyrus, Brodmann area 10
	3.47	60	10	−4	Right Superior Temporal Gyrus, Brodmann area 22
	3.31	−2	−98	8	Left Cuneus, Brodmann area 18
	3.27	−26	54	12	Left Superior Frontal Gyrus, Brodmann area 10
	3.2	18	18	16	Right Caudate
RL$_{[InO-P]}$- UR$_{[InO-P]}$					
	4.43	8	58	40	Right Superior Frontal Gyrus, Brodmann area 9
	3.9	6	66	24	Right Superior Frontal Gyrus, Brodmann area 10
	3.65	−8	60	38	Left Superior Frontal Gyrus, Brodmann area 9
	4.21	−42	−84	4	Left Middle Occipital Gyrus, Brodmann area 19
	4.19	−62	−2	18	Left Precentral Gyrus, Brodmann area 6
	3.96	−60	−8	26	Left Precentral Gyrus, Brodmann area 4
	3.97	54	−8	34	Right Precentral Gyrus, Brodmann area 6
	3.88	66	−4	16	Right Precentral Gyrus, Brodmann area 4
	3.79	−32	−74	52	Left Superior Parietal Lobule, Brodmann area 7
	3.44	−44	−70	44	Left Precuneus, Brodmann area 19
	3.4	4	42	56	Right Superior Frontal Gyrus, Brodmann area 8
UR$_{[InO-P]}$- RL$_{[InO-P]}$					
	5.99	2	−96	16	Right Cuneus, Brodmann area 18
	5.7	−12	−92	−4	Left Lingual Gyrus, Brodmann area 17
	5.28	8	−82	16	Right Cuneus, Brodmann area 18
	4.66	−4	20	44	Left Medial Frontal Gyrus, Brodmann area 8
	4.58	4	26	40	Right Medial Frontal Gyrus, Brodmann area 8
	4.57	−30	26	−4	Left Inferior Frontal Gyrus, Brodmann area 47
	4.23	−10	8	70	Left Superior Frontal Gyrus, Brodmann area 6
	4.16	28	28	−14	Right Inferior Frontal Gyrus, Brodmann area 47
	4.13	30	28	−4	Right Inferior Frontal Gyrus, Brodmann area 47
	4.08	24	58	−2	Right Superior Frontal Gyrus, Brodmann area 10
	3.96	−38	2	52	Left Middle Frontal Gyrus, Brodmann area 6
	3.87	46	54	2	Right Inferior Frontal Gyrus, Brodmann area 10
	3.82	38	4	52	Right Middle Frontal Gyrus, Brodmann area 6
	3.66	34	8	58	Right Middle Frontal Gyrus, Brodmann area 6
	3.74	14	−58	62	Right Superior Parietal Lobule, Brodmann area 7
	3.62	−42	38	2	Left Inferior Frontal Gyrus, Brodmann area 46
	3.57	42	42	28	Right Superior Frontal Gyrus, Brodmann area 9
	3.47	−32	−14	58	Left Precentral Gyrus, Brodmann area 6
	3.36	−34	54	14	Left Superior Frontal Gyrus, Brodmann area 10
	3.24	−50	−38	0	Left Middle Temporal Gyrus, Brodmann area 22

minus RL$_{[InO-P]}$" revealed fairly significant difference in right hippocampal area: for "OP$_{[InO-P]}$ minus UR$_{[InO-P]}$", it peaked in $x, y, z = 34, -16, -14$ with a T-value of 3.77 ($P < 0.001$, uncorrected); for "OP$_{[InO-P]}$ minus RL$_{[InO-P]}$", it peaked in $x, y, z = 33, -16, -16$ with a T-value of 3.09 ($P = 0.001$, uncorrected).

Given the number of subjects is relatively small in this study ($n = 7$), we conducted two additional analyses to examine the key result (i.e., the hippocampus activation observed in the contrast of "OP$_{[InC-E]}$-OP$_{[InO-P]}$"). One is the conjunction analysis, which was proposed to be able to make an effective inference about quantitative differences of a regionally specific nature when the number of subjects is relatively small[11]. The other is the SVC (small volume correction) that search for the sphere at the observed hippocampus region ($x, y, z = -32, -18, -12$) with the radius of spherical VOI is 6 mm. Both analysis showed positive results and proved the key observation of this study were reliable:

(i) Results of conjunction analysis for the contrast of "OP$_{[InC-E]}$-OP$_{[InO-P]}$". $x, y, z = -32, -18, -12$ (peak voxel); $T = 0.43$, $Z = 3.31$; Pcorrected = 1.000, Puncorrected < 0.001, Number of voxels [KE] = 7.

(ii) Results of SVC for the contrast of "OP$_{[InC-E]}$ - OP$_{[InO-P]}$". [Sphere at ($x, y, z = -32, -18, 12$), radius of spherical VOI {mm} = 6]. Cluster-level: Number of voxels [KE] = 40, Puncorrected = 0.031, Pcorrected < 0.001. Voxel-level: $x, y, z = -32, -18, -12$ (peak voxel), $T = 3.57$, $Z = 3.57$ (Puncorrected < 0.001, Pcorrected = 0.003).

3 Discussion

3.1 Hippocampus and forming of "task-related" associations

The contrast of "OP$_{[InO-P]}$ minus OP$_{[InC-E]}$" highlighted the left hippocampus. This implied the role of hippocampus in forming "task-related" associations: the same type of items could activate the hippocampus more when it was related to the task at hand than when it not. This was parallel with Eichenbaum et al.'s[1] observation that the "goal-approach" cells in hippocampus were selectively activated by the specific place only when it was the way to the goal; when that place was not the way to the goal, the cells would not be activated even if the animal passed that place. Further analysis showed two additional points. First, the extra hippocampal activation exhibited in the contrast of "OP$_{[InO-P]}$ minus OP$_{[InC-E]}$"

was not caused by the mental state difference between the O-P Block and the C-E Block. The same type of task-unrelated relationship (the related word pairs or the unrelated word pairs) from these two task blocks did not show similar difference in MTL area. That is, neither the contrast of "RL$_{[InO-P]}$ minus RL$_{[InC-E]}$" nor the contrast of "UR$_{[InO-P]}$ minus UR$_{[InC-E]}$" revealed activation difference in hippocampus and other MTL areas. Second, the extra hippocampal activation exhibited in the contrast of "OP$_{[InO-P]}$ minus OP$_{[InC-E]}$" was not caused by the effects of the "yes" response. OP$_{[InO-P]}$ elicited "yes" responses in O-P Block, whereas OP$_{[InC-E]}$ elicited "no" responses in C-E Block. Was it possible that the "yes" response led to more hippocampal activation? The answer was "no", given that the "yes" responses (SS$_{[InSyllable]}$) were not associated with extra hippocampal activation relative to the "no" response (DS$_{[InSyllable]}$) in the Syllable Block. This observation also implied that hippocampus might only participate in forming the semantic level "task-related" associations. The perceptual (phonological) level associations did not activate the hippocampus.

3.2 Hippocampus and semantic relatedness among the to-be-associated individual items

Hippocampus is most critically supposed to subserve the learning in which the temporal or/and spatial positional discontinuous items, e.g., two individual items that appeared in different time or local point, have to be associated[12]. As to hippocampus's role in associating simultaneously presented individual items, a majority of neuroimage researches revealed that hippocampus was involved in associative encoding[10]. But this study showed more specified situations: although the semantically related word pairs (i.e., RL$_{[InO-P]}$) revealed better cued-recall performance than the semantically unrelated word pairs (i.e., UR$_{[InO-P]}$), they were not associated with more hippocampal activations relative to the latter; whereas the task-related associating (i.e., OP$_{[InO-P]}$) revealed both memory priority and extra hippocampal activation over the task-unrelated associating (i.e., UR$_{[InO-P]}$ and RL$_{[InO-P]}$). That implied that the semantic relatedness between to-be-associated individual items itself was not enough to activate the hippocampus when the associating was unrelated to the task at hand. In Lepage et al[10]'s research, one category name was presented on the top and participants were required to judge how many of the two words on bottom (semantic exemplars) were

semantically related to the category on top. They found that both the activity in MTL area and the cued-recall performance increased with the number of words (0, 1, or 2) that belonged to the category (top word), whereas our results only showed the same memory retrieval difference but no MTL activity difference in the contrast of "$RL_{[InO-P]}$ versus $UR_{[InO-P]}$". The retrieval priority of semantically related word pairs over the unrelated both in our research, and in Lepage et al's[10] research can be attributed to the efficiency of the retrieval cues. The cues from related word pairs were more efficient in evoking the corresponding retrieval targets than the cues from the unrelated word pairs. Similarly, the category names, which acted as the retrieval cues, were more efficient in evoking the items belonging to the categories than in evoking those not. In Lepage et al's[10] research, the cognitive task was to judge how many of the bottom words belonged to the top category. For this reason, the more exemplars, the more "task-related" associations formed. It was the forming of "task-related" associations to be formed that activated the MTL, and it was the efficiency of the retrieval cues that led to different retrieval performance in their research.

3.3 Forming of "task-related" associations and episodic memory

Consistent with the hippocampal activity difference in the contrast of "$OP_{[InO-P]}$ minus $OP_{[InC-E]}$", the cued-recall performance revealed that the $OP_{[InO-P]}$ items were better recalled than the $OP_{[InC-E]}$ items, although they were the same type of word pairs. To examine the possibility that the better retrieval performance of $OP_{[InO-P]}$ items was caused by the "recent effects" (that is, O-P Block came later in the experimental session than the C-E Block, and therefore was nearer or more recent to the final cued-recall test), the recall performance of the same type of task-unrelated word pairs from the two task blocks were compared. There was no significant difference between the semantically related word pairs in the O-P Block ($RL_{[InO-P]}$) and in the C-E Block ($RL_{[InC-E]}$). Also, no significant cued-recall difference was observed between the unrelated word pairs in the O-P Block ($UR_{[InO-P]}$) and in the C-E Block ($UR_{[InC-E]}$) (but this result could be caused by the "floor effects" given the percentage of cued-recall were very low). For this reason, it was unlikely that $OP_{[InO-P]}$ items were recalled better simply because they were more recent to the final retrieval test.

Neuroimage researches have shown that the items that would be better remembered in later episodic retrieval were associated with MTL activation in the incidental-encoding task than these not[2,13]. The predictive function of MTL activation on later memory retrieval performance does not mean that, of course, the MTL contains a small "prophet" who knows which item will be well remembered and which item will be forgotten in the future. Rather, it is reasonable to propose a common process underlying the "incidental" encoding and the episodic retrieval. One possibility is the "novelty". It is known that the novelty of stimulus will activate MTL[14−17], and, it is also known that the low frequency (and so the relatively novel) words will be recognized better than the high frequency words[18,19]. The predictive accuracy of MTL activation on later memory retrieval performance might be mediated by the novelty of the items. However, given the word frequency was controlled in these studies[2,13], it was unlikely that the novelty can lead to these differences. Here, we proposed the possibility of forming "task-related" associations. That is, some of the items in the learning list might have fitted the internal interest of the individual better (or, seems more idiosyncratic to them) than the others, and so, there were more "task-related" associations formed on these items. This might be plausible given that the critical items were selected based on participants' post-encoding performance (memory retrieval).

To sum up, the function of hippocampus has been supposed to subserve the forming of associations[20−23]. Not only the neuroimaging studies[24], but also animal neuroscience[11,22] and network model of hippocampus functions[25,26] pointed to MTL's role in associative encoding. The question is: what kind of associations the hippocampus (and its adjacent other MTL areas) forms? Different from previous studies in which the "task context" (i.e., the requirements of judgment) was always kept unchanged, the present research critically altered the "task contexts" so that the same type of word pairs could be associated as "task-related" associations in one "task context" and "task-unrelated" in another. The results implied that, it is the "task-related" associations, rather than the "novel" associations ("semantically unrelated") or "semantically related" associations, that were formed by the hippocampus and well kept by episodic memory. To regard hippocampus's function as forming of "task-related" associations can provide a general understanding

on its function in episodic memory. Memory is not for memory itself; memory is for survival. The forming of "task-related" associations is the kinds of mental events that own great survival values. Through participating in forming of "task-related" associations and consolidating them into episodic memory, hippocampus enabled the organism to keep the information that owned great survival values in mind for future usage[7].

1   Eichenbaum H, Kuperstein M, Fagan A, et al. Cue-sampling and goal-approach correlates of hippocampal unit activity in rats performing an odor-discrimination task. J Neurosci, 1987, 7: 716－732

2   Wagner A D, Schacter D L, Rotte M, et al. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science, 1998, 281: 1188－1191

3   Brasted P J. Role of the hippocampal system in associative learning beyond the spatial domain. Brain, 2003, 126: 1202－1223

4   Prince S E, Daselaar S M, Cabeza R. Neural correlates of relational memory: Successful encoding and retrieval of semantic and perceptual associations. J Neurosci, 2005, 25: 1203

5   Ross R S, Slotnick S D. The Hippocampus is preferentially associated with memory for spatial context. J Neurosci, 2008, 20: 432－446

6   Henke K, Weber B, Kneifel S, et al. Human hippocampus associates information in memory. Proc Natl Acad Sci USA, 1999, 96: 5884－5889

7   Luo J, Niki K. "Role of medial temporal lobe in extensive retrieval of task-related knowledge." Hippocampus, 2002, 12(4): 487－494

8   Redish A D. The hippocampal debate: are we asking the right questions? Behav Brain Res, 2001, 127: 81－98

9   Redish A D, Touretzky D S. Cognitive maps beyond the hippocampus. Hippocampus, 1997, 7: 15－35

10 Lepage M, Habib R, Cormier H, et al. Neural correlates of semantic associative encoding in episodic memory. Brain Res Cogn Brain Res, 2000, 9: 271－280

11 Friston K J, Holmes A P, Worsley K J. How many subjects constitute a study? Neuroimage, 1999, 10: 1－5

12 Wallenstein G V, Eichenbaum H, Hasselmo M E. The hippocampus as an associator of discontiguous events. Trends Neurosci, 1998, 21: 317－323

13 Brewer J B, Zhao Z, Desmond J E, et al. Making memories: Brain activity that predicts how well visual experience will be remembered. Science, 1998, 281: 1185－1187

14 Tulving E, Markowitsch H J, Kapur S, et al. Novelty encoding networks in the human brain: Positron emission tomography data. Neuroreport, 1994, 5: 2525－2528

15 Knight R. Contribution of human hippocampal region to novelty detection. Nature, 1996, 383: 256－259

16 Tulving E, Markowitsch H J, Craik F E, et al. Novelty and familiarity activations in PET studies of memory encoding and retrieval. Cereb Cortex, 1996, 6: 71－79

17 Grunwald T, Lehnertz K, Heinze H J, et al. Verbal novelty detection within the human hippocampus proper. Proc Natl Acad Sci USA, 1998, 95: 3193－3197

18 Gorman A N. Recognition memory for names as a function of abstractness and frequency. J Exp Psychol, 1961, 61: 23－29

19 Schulman A I, Lovelace E A. Recognition memory for words presented at slow or rapid rate. Psychonomic Science, 1970, 21: 99－100

20 Moscovitch M. Recovered consciousness: a hypothesis concerning modularity and episodic memory. J Clin Exp Neuropsychol, 1995, 17: 276－290

21 Squire L R, Zola-Morgan S. The medial temporal lobe memory system. Science, 1991, 253: 1380－1386

22 Squire L R. Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. Psychol Rev, 1992, 99: 195－231

23 Eichenbaum H, Otto T, Cohen N J. Two functional components of the hippocampal memory system. Behav Brain Sci, 1994, 17: 499－518

24 Cohen N J, Ryan J, Hunt C, et al. Hippocampal system and declarative (relational) memory: Summarizing the data from functional neuroimaging studies. Hippocampus, 1999, 9: 83－98

25 McClelland J L, McNaughton B L, O'Reilly R C. Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. Psychol Rev, 1995, 102: 419－457

26 Rolls E T. A theory of hippocampal function in memory. Hippocampus, 1996, 6: 601－620