RAPID COMMUNICATION

Does Hippocampus Associate Discontiguous Events? Evidence From Event-Related fMRI

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ABSTRACT: To examine the hypothesis that the hippocampus is necessary to overcome temporal or spatial "discontiguity" (Wallenstein et al., Trends Neurosci 1998; 21:317–323), subjects were imaged by functional magnetic resonance imaging (fMRI) when they were making judgments as to whether two words were semantically related. Two words were presented, either at the same time (the Simultaneous Presentation Condition) or one after the other with a short unfilled rest period (the Delayed Presentation Condition). The latter condition, relative to the former, was proposed to involve the process of "discontiguity association." Event-related fMRI results of eight subjects showed that, relative to the binding of simultaneously presented words, the binding of delay presented words was associated with left hippocampus activity. This result provided direct neuroimaging evidence for the role of the hippocampus in "discontiguity association." © 2004 Wiley-Liss, Inc.

KEY WORDS: associative processing; associations across time; episodic memory; hippocampus; event-related fMRI

INTRODUCTION

The function of medial temporal lobe (MTL), more specifically the function of hippocampus in episodic memory, is generally well accepted (Squire, 1992; Eichenbaum et al., 1994). Yet, the critical characteristics of hippocampal processing in episodic memory are unclear. It has been proposed that the hippocampus is necessary to overcome temporal or spatial "discontiguity" within an episode. That is, to overcome discontiguity one has to form new associations between stimuli that do not temporally or spatially overlap (Rawlins, 1985). This hypothesis was consistent not only with the experimental evidence on the function of hippocampus, but also with recent theoretical considerations. For example, in classic conditioning, when the presentation of conditioned stimulus (CS; tone) and the presentation of unconditioned stimulus (US; air-puff to eye) overlap in time, animals with hippocampal lesions and normal animals both learn the response equally well. However, when there is a brief delay period between the two stimuli, hippocampal-damaged animals show marked impairment in learning compared with normal animals (Thompson et al., 1982). Also, in maze learning, when visual stimuli used to guide performance are situated in close proximity to one another, forming a compound cue, both hippocampal-damaged rats and controls learn maze tasks equally well. However, when the same cues are distributed around the maze, requiring the capacity for forming associations among spatially disparate items to guide performance, hippocampal-damaged rats typically show significant impairment relative to controls (O'Keefe and Conway, 1980). Moreover, based on the confluence of experimental observations and computational modeling, recent computational work suggested the contribution of the hippocampus to learning and memory in the association of discontiguous events (Wallenstein et al., 1998).

However, there is still no functional neuroimaging research that directly investigates this important topic regarding hippocampal function. Episodic memory task includes the retention interval between encoding and testing, and so involves the process of "discontiguity association." However, episodic memory retrieval can be accomplished through recognition memory that does not essentially contain associative components and challenge hippocampus (Eichenbaum et al., 1994; Aggleton and Shaw, 1996; Vargha-Khadem et al., 1997; Aggleton and Brown, 1999). Possible for this reason, episodic memory retrieval tasks failed to show consistent hippocampal activation (Eldridge et al., 2000).

In the present study, the function of the hippocampus in associating discontiguous events was investigated in an event-related functional magnetic resonance imaging (fMRI) experiment, using a 3.0-tesla (T) MRI scanner. The 3.0-T machine has sufficient field strength to avoid localization biases toward draining veins and enables us to record the activation of hippocampus efficiently; event-related analysis methods permits us to detect the transient activity that occurred in the moment of contiguous or discontiguous events-bridging. The cognitive task was to make a subjective judgment as to whether the two words were semantically related (semantic relatedness judgment). Two words are presented at the same time (Simultaneous Presentation Condition), or one af-

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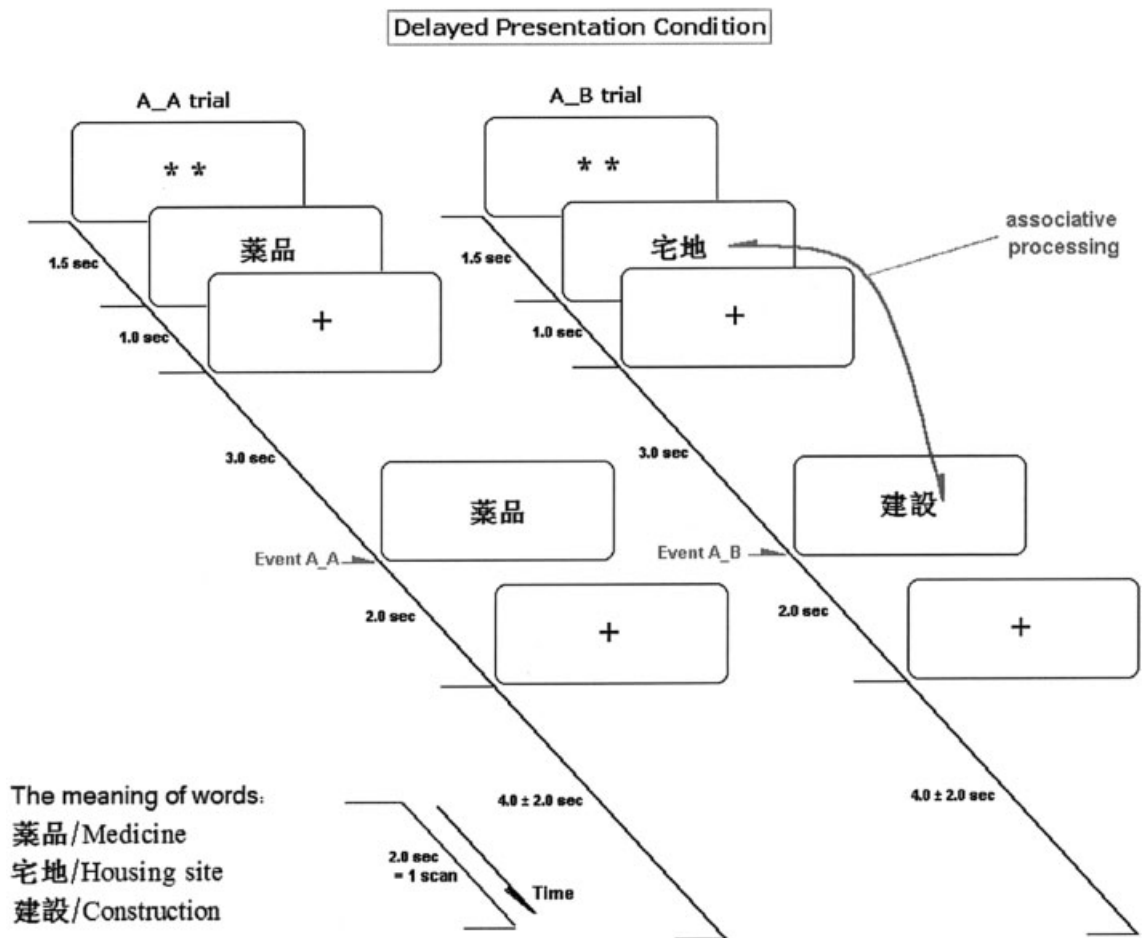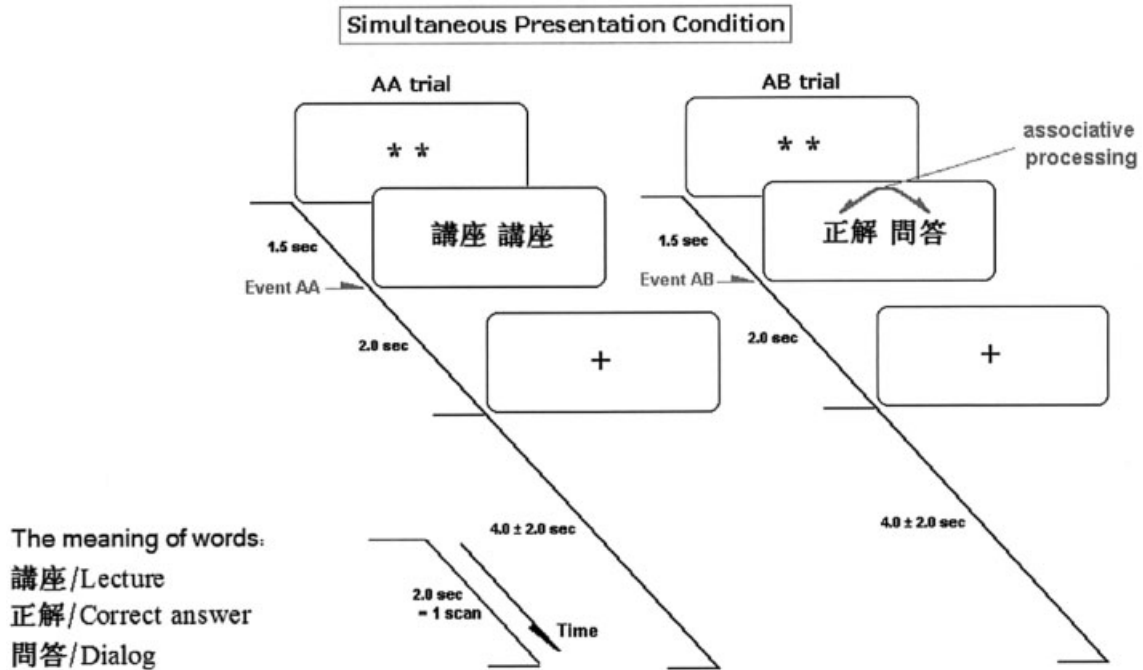
FIGURE 1.   Examples of the four types of trials in the experiment.

ter the other with a short rest period (Delayed Presentation Condition) (Fig. 1). By comparing the moment of associative processing in the Simultaneous Presentation Condition and in the Delayed Presentation Condition, we can evaluate the role of the hippocampus in associating discontiguous events. In contrast to the recognition memory that could be achieved through a familiarity heuristic, the semantic relatedness judgment can only be accomplished through an associative process (Henke et al., 1999; Lepage et al, 2000; Luo and Niki, 2002). Another advantage in using semantic-relatedness judgment is that it can provide a reasonable reference state for detecting hippocampus activity. It is now known that the non-memory conditions, which were usually taken as the reference state in the previous recognition memory task (Cabeza and Nyberg, 2000), could have caused the "baseline problem" that critically influenced the detection of hippocampus activity by neuroimaging method (Stark and Squire, 2001). However, our design avoids this baseline problem and enables us to precisely estimate the activity of hippocampus in "discontiguity-associating," because both the experimental condition and the control condition involve the same semantic relatedness judgment.

MATERIALS AND METHODS

Subjects

Eight healthy, right-handed volunteers (six female and two male, aged 21–33; mean = 27.13) participated in this experiment. They were interviewed 1 or 2 days before participating in the fMRI experiment and giving informed consent following the MRI ethics committee guidelines (Neuroscience Research Institute, AIST).

Cognitive Task

The cognitive task was to judge whether the two words, presented at the same time or one after the other with a short interval, were semantically related. In the Simultaneous Presentation Condition, two words were presented at the same time (AB trial). In the Delayed Presentation Condition, the two words were presented one after another with an inserted rest condition (in which subjects were required to simply fix their eyes on the cross-hair [+] presented in the center of the screen), subjects were required to keep the first word in their mind and to judge whether the first word was semantically related to the second one when it was presented (A_B trial). The presentation durations of each stimulus are given in Figure 1. To avoid confusion between trials, two small asterisk marks (**) were presented in the center of the screen for 1.5 s to mark the beginning of each trial. In the Simultaneous Presentation Condition, two words were presented simultaneously for 2.0 s, followed by a varied rest period (2.0–6.0 s; mean: 4.0 s). This varied rest period was adopted to increase "optimal statistical efficiency," i.e., the accuracy with which the event-related hemodynamic response to different stimuli can be estimated for a given amount of imaging time, in the study (Dale, 1999; Burock et al., 1998). Subjects were asked to press the left key of the button box (which was attached to their right leg) with the right index finger, if they thought the two words were semantically related, or to press

the right key with the right middle finger if they did not think the two words were semantically related (see AB trial in Fig. 1). In the Delayed Presentation Condition, the first word was shown for 1.0 s; then, after a 3.0-s rest period, the second word was presented for 2.0 s, and subjects were required to judge whether the first word was semantically related to the second word (yes: left key; no: right key). Again, the second word was followed by a varied rest period of 4.0 ± 2.0 s (see A_B trial in Fig. 1). In this study, 60 pairs of low-frequency, two-character Japanese Kanji words were used as materials. One-half of them were assigned to the Simultaneous Presentation Condition and one-half to the Delayed Presentation Condition. Word pairs were counterbalanced across subjects. To minimize judgment bias and maintain the subjects arousal, one-half of the pairs in each condition contained obvious semantic relation, and one-half of them not (Luo and Niki, 2002). Both conditions included reference trials in which two same words were presented simultaneously (see AA trial in Fig. 1), or one after another with an inserted 3-s rest period (see A_A trial in Fig. 1). In those trials, subjects were required to press the left key ("yes" judgment) and were told the reason that "a word is always related to itself." The pace of A_A trials was the same as that of A_B trial; the pace of AA trial was the same as AB trial. To familiarize the subjects with the procedure and pace of the task, they were trained with another set of similar materials in the same pace before the formal experiment.

Data Acquisition

All scanning was performed on a 3.0-T MRI scanner (GE 3T Signa) equipped with EPI capability. 18 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 = 2,000 ms, TE = 30 ms, FA = 70 degrees, FOV = 20 × 20 cm (64 × 64 mesh). To avoid head movement, they wore a neck brace and were asked not to talk or move during scanning. Motion correction was also performed by a standard realignment process in SPM99 (SPM, 1999).

Data Analysis

Images were first pre-processed (time slice adjusted, re-aligned, normalized, and smoothed) by SPM99. Then, the image data of eight subjects were analyzed by the Event-Related Analysis module of SPM99. The aim of this study is to investigate the transient brain activation in the moment of the associative processing or semantic-relatedness judgment. For AB trials, the associative processing occurred when the two words were simultaneously presented, whereas for A_B trials, the associative processing occurred when the second word was presented. Therefore, the association of discontiguous events was time-locked to the presentation of the second words in A_B trials (we called this event Event A_B), while the association of contiguous events was time-locked to the presentation of the two words in AB trials (called Event AB) (see Fig. 1). Similarly, Event A_A or AA was defined in the same way. Besides these four types of event, the presentation of the first words in A_A and A_B trials were also defined. Although the processing of the first words were not considered in this study (because during the

Mean Reaction Time (in sec) in Experiment 1

Event type	Event AA	Event AB	Event A_A	Event A_B
Mean (SD)	1.04 (0.33)	1.52 (0.28)	0.75 (0.19)	1.05 (0.15)

N = 8.

presentation of these words, subjects still did not know what kind of associative processing they would do), it was still necessary to define them in the estimation; otherwise, the brain responses evoked by these mental events might have a chance to be falsely attributed to other events. In sum, we defined five types of events in the estimation: Event AA and AB in the Simultaneous Presentation Condition, Event A_A, Event A_B, and the first word of the A_A and A_B trials in the Delayed Presentation Condition. All events were time-locked to the beginning of stimulus presentation and modeled with canonical hemodynamic response function (HRF). Conjunction analysis, which is used to make inferences about a population from a relatively small number of subjects (N < 12) (Friston et al., 1999), was adopted to examine the difference between conditions. The threshold of $P < 0.05$ (corrected) was taken to detect activation in cerebral cortices, and, a relatively loose threshold, $P < 0.001$ (uncorrected), was taken to detect the activation in hippocampus (this threshold is stringent enough for detecting the hippocampus activity that is predicted by previous hypothesis, because the signal-to-noise ratio in this area is generally known to be low) (Ojemann et al., 1997). Locations reported by SPM99 (SPM coordinates) were converted into Talairach coordinates (Talairach and Tournoux, 1988) by the transform specified in the mni2tal.m program (Brett, 1999). These coordinates were used to determine the nearest gray matter (region and corresponding Brodmann area), using Talairach Daemon program version 1.1 (Lancaster et al., 2000) with the maximum range of 11 mm.

RESULTS AND DISCUSSION

Behavior Results

The mean reaction time (RT) to different kinds of events is given in Table 1. RT of Event AB was significantly longer than that of Event A_B, t(7) = 7.22, $P < 0.001$. Different from the old/new recognition task, which has a standard criterion, the semantic-relatedness judgments are based on one's subjective "feeling" of the word pairs. Therefore, it is difficult to estimate subjects' response accuracy. But afterward, the subjects' reports indicated that they had no any difficulties or failures in memorizing and retrieving the first word in Delayed Presentation Condition.

Neuroimaging Results

Relative to their baselines, both Event AB and A_B were associated with activation in left ventrolateral prefrontal cortex (PFC)

and bilateral medial PFC. Relative to Event AA, Event AB was associated with activation in bilateral inferior frontal gyrus (BA47: x,y,z = −38,21,−11; x,y,z = −30,25,−11; x,y,z = 38,21,−16), left superior temporal gyrus (BA38: x,y,z = −32,18, −23), bilateral cingulate gyrus (BA32: x,y,z = 12,21,27; x,y,z = −4,17,30), and left parahippocampal gyrus (BA19: x,y,z = −16, −53,−4). Relative to Event A_A, Event A_B was associated with activation in left inferior frontal gyrus (BA47: x,y,z = −42,17, −14; x,y,z = −50,19,−4), left superior temporal gyrus (BA38: x,y,z = −28,18,−26), bilateral medial frontal gyrus (BA8: x,y,z = 2,25,41; BA6: x,y,z = 0,33,35), and bilateral superior frontal gyrus (BA8: x,y,z = 2,43,38; BA9: x,y,z = −4,52,25) (Table 2 and Fig. 2).

The direct contrast of Event A_B and AB showed that, relative to Event AB, Event A_B was associated with activation in left middle temporal gyrus (BA39: x,y,z = −42,−70,27), left middle occipital gyrus (BA19: x,y,z = −46,−72,−8), and left hippocampus (x,y,z = −30,−24,−9; x,y,z = −30,−11,−21; x,y,z = −34,−22,−17). Relative to Event A_B, Event AB was associated with activation in left cerebellum (x,y,z = −42,−71, −28) and right precuneus (BA19: x,y,z = 32,−66,40; x,y,z = 32, −70,33) (Table 2 and Fig. 3).

With the standard threshold ($P < 0.001$, uncorrected), we did not detect any hippocampus activation in the contrast of "Event A_B minus A_A" and "Event A_A minus AA." To estimate precisely whether there were tendencies of hippocampus activation in these contrasts, we checked each individual's data. Among a total number of eight subjects, three (thresholded at $P < 0.001$, uncorrected) or four (thresholded at $P < 0.005$, uncorrected) subjects showed hippocampus activation (that was located near the one highlighted in the critical contrast "Event A_B minus AB") in the contrast of "Event A_B minus A_A"; but there were only one (thresholded at $P < 0.001$, uncorrected) or two (thresholded at $P < 0.005$, uncorrected) of the subjects showed similar hippocampus activation in the contrast of "Event A_A minus AA."

DISCUSSION

Neuroimaging results showed that the general neural network subserving the associative processing included left ventrolateral PFC (together with left superior temporal gyrus) and medial PFC. The left ventrolateral PFC is known to mediate the active comparison of stimuli held in working memory (Petrides, 1994) and especially subserve the semantic selection (Thompson-Schill et al., 1997), whereas the medial PFC (including the anterior cingulate cortex) is involved in a wide range of cognitive activities that re-

TABLE 2. ▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬

Activation List Shown in the Contrasts

Contrasts	Cluster level K_E	Voxel level $P_{corrected}$	Z-value	$P_{uncorrected}$	Talairach coordinates (x,y,z)			Areas
Event AB > AA	164	0.000	7.81**	0.000	−38	21	−11	L inferior frontal gyrus, BA47
		0.000	7.40**	0.000	−30	25	−11	L inferior frontal gyrus, BA47
		0.000	6.76**	0.000	−32	18	−23	L superior temporal gyrus, BA38
	39	0.000	6.43**	0.000	38	21	−16	R inferior frontal gyrus, BA47
	23	0.001	5.89**	0.000	12	21	27	R cingulate gyrus, BA32
	8	0.003	5.68**	0.000	−4	17	30	L cingulate gyrus, BA32
	6	1.000	3.28*	0.001	−16	−53	−4	L parahippocampal gyrus, BA19
Event AA > AB	4	0.000	6.08**	0.000	50	−64	33	R angular gyrus, BA39
Event A_B > A_A	122	0.000	6.98**	0.000	−42	17	−14	L inferior frontal gyrus, BA 47
		0.000	6.79**	0.000	−50	19	−4	L inferior frontal gyrus, BA47
		0.000	6.17**	0.000	−28	18	−26	L superior temporal gyrus, BA38
	88	0.000	6.94**	0.000	2	25	41	R medial frontal gyrus, BA8
		0.000	6.65**	0.000	0	33	35	L medial frontal gyrus, BA6
		0.003	5.68**	0.000	2	43	38	R superior frontal gyrus, BA8
	15	0.000	6.60**	0.000	−4	52	25	L superior frontal gyrus, BA9
Event A_A > A_B	138	0.000	7.17**	0.000	6	−48	45	R precuneus, BA7
		0.000	7.16**	0.000	10	−35	39	R cingulate gyrus, BA31
		0.000	6.25**	0.000	6	−41	43	R cingulate gyrus, BA 31
	29	0.000	6.4**	0.000	48	−54	43	R inferior parietal lobule, BA40
		0.000	6.1**	0.000	50	−44	45	R inferior parietal lobule, BA40
	9	0.000	6.35**	0.000	16	−76	41	R precuneus, BA7
Event A_B > AB	105	0.000	6.69**	0.000	−42	−70	27	L middle temporal gyrus, BA39
		0.002	5.82**	0.000	−46	−72	−8	L middle occipital gyrus, BA19
	134	0.927	4.17*	0.000	−30	−24	−9	L hippocampus
		0.994	3.97*	0.000	−30	−11	−21	L hippocampus
		1.000	3.44*	0.000	−34	−22	−17	L hippocampus
Event AB > A_B	117	0.000	Inf**	0.000	−42	−71	−28	L cerebellum
	76	0.000	7.17**	0.000	32	−66	40	R precuneus, BA19
		0.000	7.11**	0.000	32	−70	33	R precuneus, BA19

L, left; R, right; BA, Brodmann area.
K_E, number of voxels contained in the cluster (voxel size: 2.0 * 2.0 * 2.0 mm); $P_{corrected}$, the P-value that was corrected for multiple comparisons; $P_{uncorrected}$, P-value that was uncorrected for multiple comparisons; P-value of 0.000 means it was less than 0.001; **significant at $P < 0.05$ (corrected) level; *significant at $P < 0.001$ (uncorrected) level.

quire the "executive function" (Vogt et al., 1992). The activity of left ventrolateral and bilateral medial PFC embodied the general processes of attentional control and semantic selection involved in associative processing.

Critically, our study showed that the mental events of binding discontiguous items (Event A_B), relative to that of binding contiguous items (Event AB), were associated with activities in the hippocampus and occipital-temporal regions. This result was consistent with the neuroimaging studies on the associative recognition memory task (e.g., Yonelinas et al., 2001). Yonelinas et al. (2001) proposed that occipital-temporal regions supported the processing of the individual aspects that made up a study event (e.g., object information), while the hippocampal and parahippocampal regions were involved in reconstructing the associations between aspects of the study event. In the present research, the to-be-associated words were presented in different temporal context in the A_B trial. Relative to the AB trial, the A_B trial might evoke more focused processing of the individual word and more

intensive bridging of discontiguous events, which were subserved by the occipital-temporal regions and hippocampus, respectively.

However, relative to the binding of discontiguous events (Event A_B), the binding of contiguous events (Event AB) was associated with activity in the right precuneus and left cerebellum. The precuneus was proposed to mediate the shifting of spatial attention between feature dimensions (Nagahama et al., 1999), locations (Culham et al., 1998), or multiple items that were maintained in working memory (Phillips and Niki, 2002). The right cerebellum was known to be involved more extensively in semantic associative processing when the difficulty of the task was increased (Xiang et al., 2003). Event AB might differ from Event A_B in two aspects. First, different from the A_B trails in which the encoding of the first word had already been finished in the initial stage, both of the to-be-evaluated words were encoded at the moment of semantic-relatedness judgment in AB trials. Therefore, the task complexity might be higher in Event AB than A_B (consistently, the RT of Event AB was significantly longer than that of Event A_B). Sec-
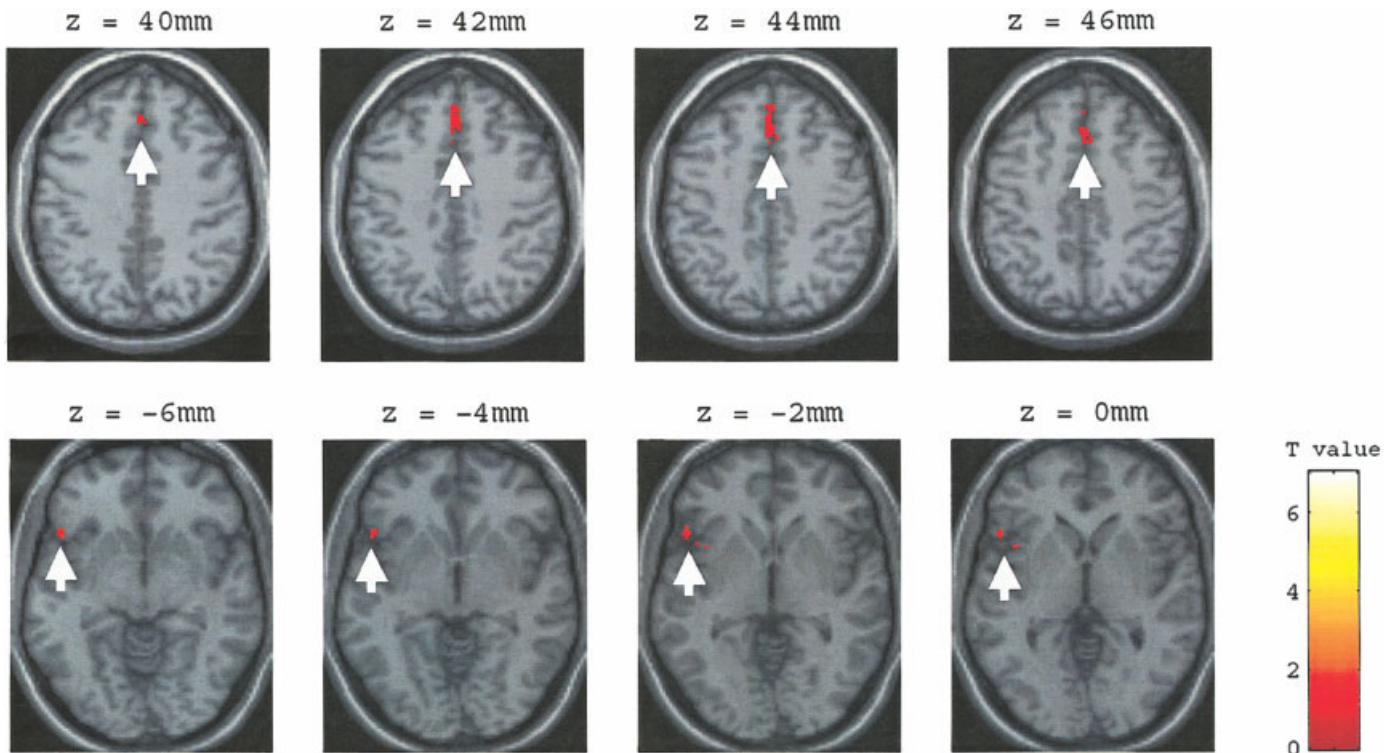
FIGURE 2. Activation in medial PFC (top) and left ventrolateral PFC (bottom) shown in the contrast of "Event A_B minus A_A" at the threshold of *P* < 0.05 (corrected). Talairach z-coordinates are shown at the top of each horizontal section.

ond, in making a relatedness judgment in Event AB, subjects might shift their attention more frequently between the to-be-evaluated items than they did in Event A_B. It was for this reason that Event AB relative to Event A_B showed elevated activation in the cerebellum and precuneus, which were the areas known to be involved in task complexity and attention shifting, respectively.

In summary, in the A_B trial, subjects processed the first word and kept the results of the semantic processing in their working memory. When the second word was presented, they processed the second one, matched the results with the information kept in working memory, and made a relatedness judgment. In the AB

trial, subjects had to alternatively process the two words and match their meaning till they were able to make a decision. For this reason, relative to Event AB, Event A_B might contain more components of memory retrieval and "discontiguity association." Relative to Event A_B, Event AB might involve more processes of semantic matching and attention shifting.

However, there were still distinctions between "discontiguity association" and working memory retrieval, and our findings could not be simply interpreted as a role of the hippocampus in working memory retrieval. In particular, working memory retrieval can be accomplished by the process of "discontiguity association" or/and
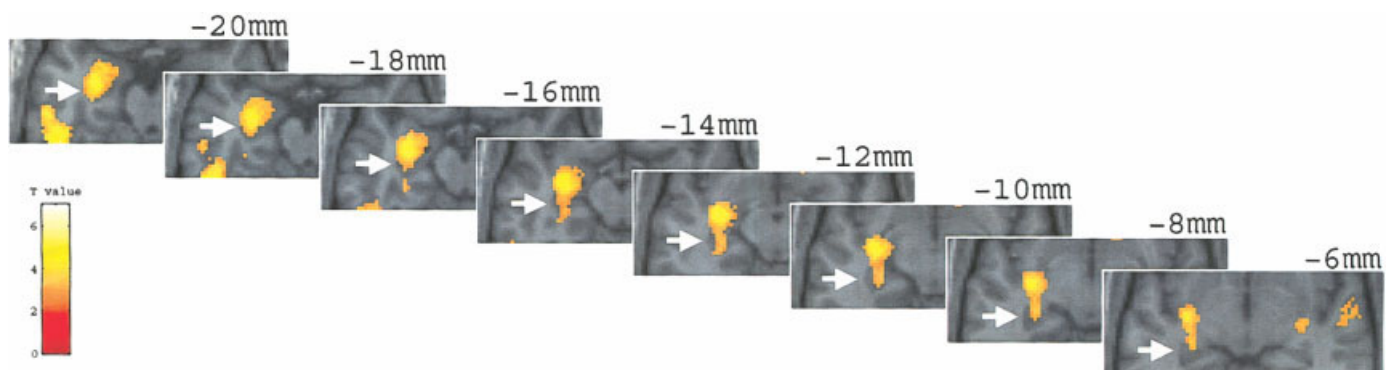

FIGURE 3. Hippocampus activation shown in the contrast of "Event A_B minus AB" at the threshold of *P* < 0.001 (uncorrected). Talairach z-coordinates are shown at the top of each horizontal section.

by the process of "familiarity heuristic." Generally speaking, working memory retrieval does not typically rely on the function of hippocampus unless when the delay period was long (6–15 s) and the stimulus was novel and complex (e.g., Aggleton et al., 1992; Buffalo et al., 1998; Holdstock et al., 1995; Owen et al., 1995; Squire et al., 1988; Ranganath and D'Esposito, 2001)—a possible reason for this was that the long delay period and the novelty and complexity of stimulus made the "familiarity heuristic" less efficient, and thus the working memory retrieval had to rely more on "discontiguity association" that was supported by hippocampus. Given the stimulus we used were very simple and highly familiar and the delay period were very short (3 s), we believe that the working memory component contained in the moment of associative processing in Event A_B was not dominant. Consistent with the view Event A_B only involved few working memory retrieval components, the prefrontal activation, which was typically reported in working memory retrieval, was not observed in the contrast of "Event A_B minus Event AB."

The effects of working memory retrieval on hippocampus can be estimated approximately by considering the situation in A_A trials in which the same word was presented twice, because the processing of the second word in Event A_A corresponded to working memory retrieval. The results, however, were inconsistent. On the one hand, compared with Event A_A, Event A_B did not show significant hippocampus activation. This might be caused by the fact that Event A_A also evoked a hippocampus activity tendency, and this tendency might eliminate the possible difference between Event A_B and A_A. In contrast, Event A_A relative to Event AA also did not show significant hippocampus activation. This observation excluded the possibility that the working memory retrieval alone challenged the hippocampus. In fact, only 1/8 or 1/4 of the subjects exhibited significant hippocampus activation in "Event A_A minus AA" (in contrast, 3/8 or 1/2 of the subjects exhibited such an activation in "Event A_B minus A_A"), this implied the contribution of working memory retrieval to the observed hippocampus activation in "discontiguity association" might be fairly limited if there were any.

Elliott and Dolan (1999) showed that the long delay was associated with more hippocampus activation than the short delay in delayed-match-to-sample (DMS) and delayed-non-match-to-sample (DNMS) task. This observation was consistent with the hypothesis of the role of the hippocampus in associating discontiguous events. However, Elliott and Dolan's study did not examine this hypothesis directly, given that both long and short delays could be regarded as "discontiguous" and that block designs did not reveal the time when the hippocampus was activated. Although the study carried out by Monk et al. (2002) showed the involvement of hippocampus in DMS and DNMS tasks by event-related fMRI, just as with other studies that used pictures, it remained unclear whether hippocampal activation could be attributed to sensory or mnemonic processes, especially given that there was also hippocampal activation during the encoding period (Phase 1). The present study directly compared the binding processes of "contiguous" (simultaneous) and discontiguous (delay) events by a event-related method and provided direct evidence for the role of the hippocampus in "discontiguity association."

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