

# Frontoparietal Network Involved in Successful Retrieval from Episodic Memory. Spatial and Temporal Analyses Using fMRI and ERP

Tetsuya Iidaka<sup>1</sup>, Atsushi Matsumoto<sup>1</sup>, Junpei Nogawa<sup>1</sup>, Yukiko Yamamoto<sup>2</sup> and Norihiro Sadato<sup>2</sup>

<sup>1</sup>Department of Psychology, Nagoya University, Graduate School of Environmental Studies, Nagoya, Japan and

<sup>2</sup>Department of Cerebral Research, National Institute for Physiological Sciences, Okazaki, Japan

**The neural basis for successful recognition of previously studied items, referred to as “retrieval success,” has been investigated using either neuroimaging or brain potentials; however, few studies have used both modalities. Our study combined event-related functional magnetic resonance imaging (fMRI) and event-related potential (ERP) in separate groups of subjects. The neural responses were measured while the subjects performed an old/new recognition task with pictures that had been previously studied in either a deep- or shallow-encoding condition. The fMRI experiment showed that among the frontoparietal regions involved in retrieval success, the inferior frontal gyrus and intraparietal sulcus were crucial to conscious recollection because the activity of these regions was influenced by the depth of memory at encoding. The activity of the right parietal region in response to a repeated item was modulated by the repetition lag, indicating that this area would be critical to familiarity-based judgment. The results of structural equation modeling revealed that the functional connectivity among the regions in the left hemisphere was more significant than that in the right hemisphere. The results of the ERP experiment and independent component analysis paralleled those of the fMRI experiment and demonstrated that the repeated item produced an earlier peak than the hit item by approximately 50 ms.**

**Keywords:** independent component analysis, picture, recognition, structural equation modeling

## Introduction

Using functional neuroimaging, numerous attempts have been made to elucidate the neural correlates involved when a normal subject successfully recognizes a previously learned item as “old” (Buckner and Wheeler 2001). Event-related functional magnetic resonance imaging (fMRI) has revealed that the parietal region of the brain is predominantly activated during the memory process termed “retrieval success.” This region plays a crucial role in conscious recollection from a past episode (Konishi and others 2000; Leveroni and others 2000; McDermott and others 2000; Donaldson and others 2001; Cansino and others 2002; Shannon and Buckner 2004; Achim and Lepage 2005; Wagner and others 2005). However, parietal activity has also been observed in subjects who encountered a repeated item during a task in which judgment was based more on familiarity than recollection (Koutstaal and others 2001; Henson and others 2002). In the present study, in order to disentangle the neural basis of these 2 processes, we included target and repeated items in a study-test cycle and asked subjects to judge the items as being either old or new. The repeated items were identical to the distractor items and were presented with either no intervening items or 2 intervening items after the presentation of distractor items. Because familiarity decreases more rapidly than recollection (Yonelinas 2002; Yonelinas and Levy

2002), we hypothesized that a significant difference in the activation of the parietal region between the 2 repetition conditions would be more likely to be observed in the case of familiarity than recollection.

Several fMRI studies have examined the effect of task manipulation during item encoding on the neural activity that is related to retrieval success (Kensinger and others 2003; Velanova and others 2003; Wheeler and Buckner 2003; Kahn and others 2004; Shannon and Buckner 2004). Experimental procedures such as the levels of processing (LOPs) (Craik and Lockhart 1972), division of attention, and repeated encoding are thought to affect recollection-based processes to a greater extent than familiarity-based processes (Yonelinas 2002). We employed the LOP procedure during encoding in order to test whether retrieval activity in the cortical and subcortical structures was affected by the depth of processing during memory encoding. We predicted that successful retrieval in the deep-encoding condition would involve recollective processes; therefore, the frontoparietal region would be activated to a greater degree than it would in the shallow-encoding condition. Finally, structural equation modeling (SEM) was performed on the fMRI data in order to examine the effective connectivity among these brain regions.

In addition to the fMRI experiment, using an identical task paradigm, we conducted an event-related potential (ERP) experiment on a separate group of subjects in order to obtain temporal information concerning these memory processes. Successful retrieval of studied items elicits the centroparietal positivity referred to as the “parietal old/new effect” (Rugg and Allan 2000). The positive deflection in parietal sites has also been observed to be larger at the second presentation of an item than at the first presentation (Rugg and Allan 2000; Kim and others 2001). Therefore, we expected the results of the ERP experiment to parallel those of the fMRI experiment and to contribute to the elucidation of the brain mechanisms involved in these retrieval-related operations. To enhance the superior time resolution of ERP, we employed independent component analysis (ICA) (Delorme and Makeig 2004) to decompose the large positive deflection of the waveform associated with retrieval success into several temporally segregated components. It was predicted that the repetition condition would elicit earlier brain responses than the hit condition and that the temporal difference between these conditions would be revealed by measuring the peak activity of the brain potentials.

## Materials and Methods

### Subjects

Thirty-two right-handed healthy subjects (16 males and 16 females; mean age  $\pm$  standard deviation [SD], 22.5  $\pm$  3.5 years) participated in the

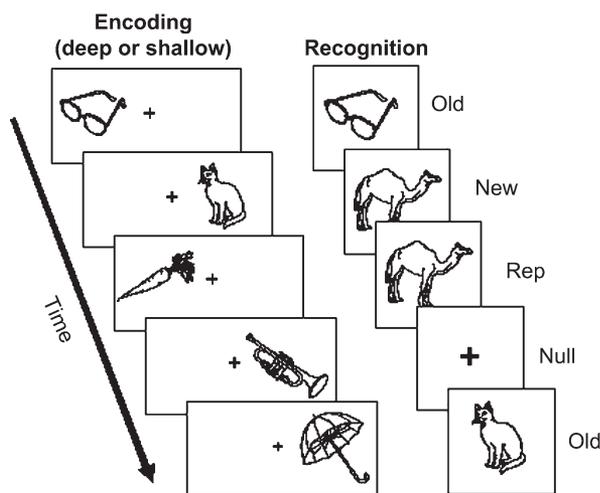
study after providing written informed consent. Sixteen subjects (8 males and 8 females) participated in the fMRI experiment, and the remaining 16 subjects (8 males and 8 females) participated in the ERP experiment. These 2 groups did not differ in terms of their mean age ( $F = 1.89, P = 0.18$ ). This study was approved by the ethics committee at the National Institute for Physiological Sciences.

### Experimental Stimuli

Digitalized black and white pictures of a concrete object that were developed by Snodgrass and Vanderwart (1980) were used as the experimental stimuli. Before the experiment, the complexity of each of the 192 pictures was rated by a separate group of subjects ( $n = 10$ ). The familiarity of a word that corresponded to the meaning of each picture was determined by using a Japanese database (Amano and Kondo 1999). Subsequently, 16 lists were created; each of these lists comprised 12 different pictures. The lists were equalized for complexity and familiarity. In each list, 5 items were natural objects (e.g., cat, carrot, horse), and the 7 remaining items were man-made objects (e.g., eyeglass, trumpet, umbrella). Eight of the 16 lists were used as target lists (i.e., "old" items), whereas the other 8 were used as distractor lists (i.e., "new" items). Target and distractor lists were assigned to each subject in a random and counterbalanced manner.

### Experimental Procedure

During encoding, the items on the target list were presented one at a time, and in random order, to either the left or right of a fixation point that was shown at the center of the screen (Fig. 1). The 2 encoding conditions, namely, "deep" and "shallow," were manipulated within each subject. In the deep-encoding condition, an item was presented for a duration of 1000 ms, and the interstimulus interval (ISI) was 4000 ms. The subject was required to judge whether the item was natural or man-made and to press the corresponding button. In the shallow-encoding condition, the presentation duration of each item was 300 ms and the ISI was 1700 ms. The subject was required to judge whether the item was presented to the left or to the right side of the fixation



**Figure 1.** Schematic illustration of the experimental task is shown. During an encoding task (left), pictures of concrete objects are successively presented one at a time either to the left or the right of a fixation point. In the deep-encoding condition, the subject judged whether the picture was a man-made or natural object and pressed the corresponding button. In the shallow-encoding condition, the subject judged whether the picture was presented to the left or the right of a fixation point and pressed the corresponding button. A retrieval task (a recognition test) followed the encoding task. During the retrieval task (right), 12 target items (Old), 12 distractor items (New), and 12 items that were repetitions of the distractor item (Rep) were presented one at a time at the center of the screen. Twelve null events with fixation point (Null) were also included in the test. The subject was instructed to judge whether the picture was old (i.e., shown during the encoding task) or new (i.e., not shown during the encoding task) and to press the corresponding button. The repetition item was judged as a new item. There were 8 runs, each of which comprised a study-test cycle.

point and to press the corresponding button. In the shallow-encoding condition, in order to facilitate the LOP effect, each list included 2 additional items that had not been displayed during the recognition task. Before the commencement of each run, the subject was told which encoding condition they should engage in during the subsequent run. Immediately after completing the tasks in the encoding condition, the subject was provided with a brief instruction regarding a retrieval task.

Following the instruction, the subject engaged in a retrieval task during which the subject's brain activity was measured using either fMRI or ERP. During the retrieval task, 12 target items (i.e., the items studied during encoding), 12 distractor items (i.e., the items that were not studied during encoding), 12 repetition items, and 12 null events (with fixation point) were randomly presented on the screen. The repetition items were pictures that had already been presented as distractor items earlier in the run. The repetition lag (i.e., number of items) between the presentation of a picture as a distractor item and that as a repetition item was either 0 or 2; 6 items were repeated immediately, and the remaining 6 were repeated after 2 intervening items. The item was presented at the center of the screen for a duration of 500 ms, and the ISI was 4500 ms for both the deep- and shallow-encoding conditions. The subject was instructed to judge whether the presented item was "old" or "new" and to press the corresponding button. The repetition item had to be judged as a "new" item. During the experiment, a subject participated in 8 runs; each of these runs comprised a study-test cycle. In the fMRI session, the stimuli were projected onto a transparent screen, which was hung from the bore of a magnet at a distance of 75 cm from the subject's eyes. The subjects viewed the stimuli through a tilted mirror that was attached to the head coil of the scanner. In the ERP session, the stimuli were presented on a 15-inch cathode ray tube (CRT) monitor at a distance of 60 cm from the subject's eyes. An identical task paradigm and stimulus set were used for each of the fMRI and ERP sessions. Each subject received a training session with regard to the task just before the experimental session. The mean accuracy (hit minus false alarm [FA] rate and the proportion of correct responses to repetition items) and the mean reaction time (RT) were computed for each subject and condition. The group mean values of the behavioral data are shown in Tables 1 and 2. The mean accuracy data were analyzed using a 1-way analysis of variance (ANOVA) with the encoding condition (deep and shallow) as the factor. The RT data were analyzed using a 2-way ANOVA with the encoding condition and memory condition (hit, correct rejection [CR], and repetition) as factors.

### The fMRI Data Acquisition and Analysis

Functional images of the whole brain were obtained in an axial orientation using a 3-T magnetic resonance imaging scanner (Siemens,

**Table 1**

Accuracy data

Session	Encoding condition	Hit - FA	Rep
fMRI	Deep	0.74 (0.10)	0.91 (0.05)
	Shallow	0.58 (0.17)	0.89 (0.07)
ERP	Deep	0.89 (0.08)	0.96 (0.05)
	Shallow	0.78 (0.11)	0.94 (0.07)

Note: Hit - FA, hit minus false alarm; Rep, the proportion of correct response for the repeated item. Standard deviation in parentheses.

**Table 2**

RT data

Session	Encoding condition	Memory condition		
		Hit	CR	Rep
fMRI	Deep	813 (191)	827 (186)	719 (123)
	Shallow	778 (187)	805 (134)	720 (130)
ERP	Deep	805 (124)	811 (131)	736 (105)
	Shallow	828 (173)	789 (131)	737 (108)

Note: Rep, repetition; CR, correct rejection. Standard deviation in parentheses.

Munich, Germany) that was equipped with a single-shot echo planar imaging (EPI) (TR [time repetition] = 2.3 s, TE [time echo] = 30 ms, flip angle = 80°, 64 × 64 matrix and 36 slices, voxel size = 3 × 3 × 3 mm) and was sensitive to blood oxygen level-dependent contrast (Ogawa and others 1992). After discarding the first 6 images, the next 110 successive images in each run were subjected to the analysis. A high-resolution anatomical T1-weighted image was also acquired (magnetization-prepared rapid gradient echo, TR = 2.5 s, TE = 4.38 ms, flip angle = 8°, 256 × 256 matrix and 192 slices, voxel size = 0.75 × 0.75 × 1 mm) for each subject. The fMRI experiment was controlled using the presentation software (Neurobehavioral Systems Inc., Albany, CA).

Data were analyzed using SPM2 (The Wellcome Department of Imaging Neuroscience, London, UK). First, all the volumes were realigned spatially to the last volume, and the signal in each slice was realigned temporally to that obtained in the middle slice using a sinc interpolation. The resliced volumes were then normalized to the standard Montreal Neurological Institute space (Evans and others 1993) by using a transformation matrix obtained from the normalization process of the mean EPI image of each individual subject to the EPI template image. The normalized images were spatially smoothed with an 8-mm Gaussian kernel.

Following preprocessing, the statistical analysis of each individual subject was conducted using the general linear model (Friston and others 1995). At the first level, each event was modeled as a hemodynamic response function and its temporal derivative. Low-pass and high-pass frequency filters were applied to the time series data. The images were scaled to a grand mean of 100 over all voxels and scans within a session. In the subsequent analysis, the following 6 conditions were modeled separately for the deep- and shallow-encoding conditions: 1) Hit, correct response for the target item; 2) Miss, incorrect response for the target item; 3) FA, incorrect response for the distractor item; 4) CR, correct response for the distractor item; 5) Repetition (Rep), correct response for the repetition item; and 6) other responses. Parameter estimates for each condition and for the difference between these conditions were calculated from the least mean square fit of the model to the time series data. Images of parameter estimates representing event-related activity at each voxel were created for each condition and subject.

At the second level, the results for each subject were entered into the random effects model by applying a 1-sample *t*-test to the contrast images to create a group statistical parametric map. The following spatial maps of voxels showing significant activation were created: 1) Hit versus CR (deep + shallow), 2) Hit versus CR (deep), 3) Hit versus CR (shallow), 4) Rep versus CR, 5) Hit versus Rep, and 6) interaction effect between the memory and encoding conditions, that is, (Hit vs. CR in the deep-encoding condition) versus (Hit vs. CR in the shallow-encoding condition). The statistical threshold was set at  $P = 0.001$ , uncorrected for multiple comparisons for height, and at  $k = 20$  voxels for spatial extent.

The regions with significant activation are listed in Table 3 and Supplementary Table 1 in terms of their peak coordinates, *T*-values, voxel size, and region names. These regions were rendered on the surface of a standard brain as shown in Figure 2. The clusters in the following frontoparietal areas are indicated in Figure 2; the anterior prefrontal cortex (aPFC), posterior prefrontal cortex (pPFC), ventral prefrontal cortex (vPFC), medial prefrontal cortex (mPFC, not shown), and inferior parietal lobule (IPL). The mean and standard error (SE) of the parameter estimates that were extracted from the region of interest (ROI) in these areas in each of the Hit, Rep, and CR conditions are plotted in Figure 3. The spherical ROIs with radii of 8 mm were drawn on each region using the MarsBaR software (Brett and others 2002). The coordinates of the center of each ROI are indicated in the legend of Figure 3. The results of the interaction effect between the memory (Hit vs. CR) and encoding conditions (deep vs. shallow) are listed in Table 4; these results have been superimposed on a T1-weighted image in Figure 4. The parameter estimates extracted from the left inferior frontal gyrus (IFG) and intraparietal sulcus (IPS) and the significant correlation between the responses in these 2 regions are shown in Figure 4. The significant result obtained for the hippocampal region is shown in Supplementary Figure 2.

The neural correlates of familiarity may not be appropriately examined by the Rep versus CR subtraction because the Rep items

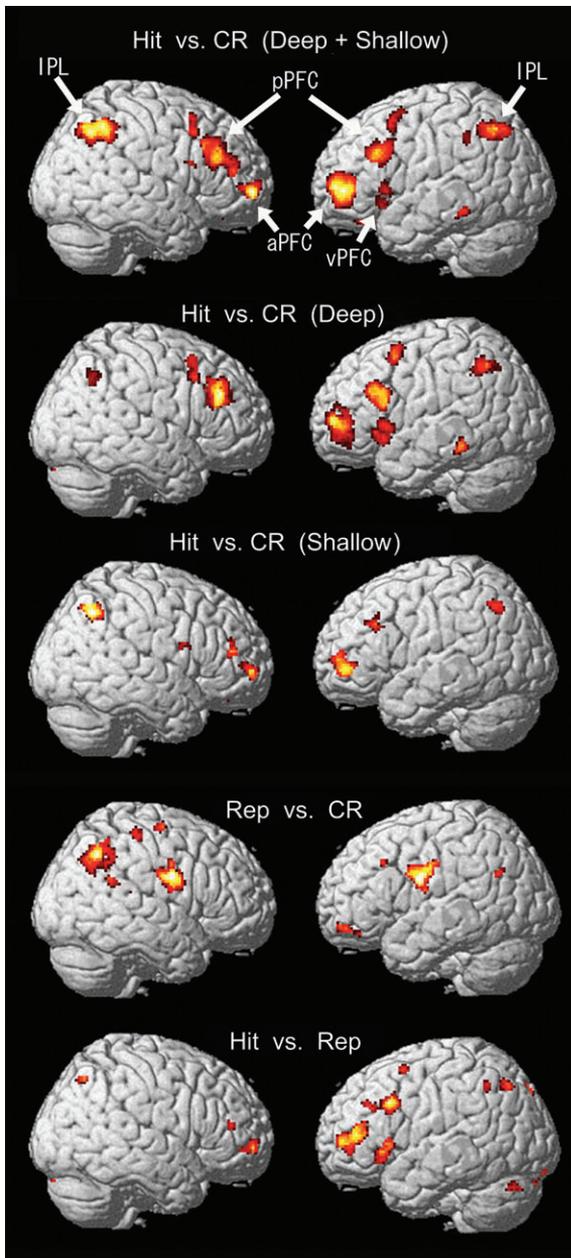
**Table 3**

Regions with significant difference in activation between the memory conditions (Hit, CR, and Rep)

Voxels	<i>T</i> -value	<i>x</i> , <i>y</i> , <i>z</i> (mm)	L/R	Region
<b>a) Hit – CR</b>				
107	5.13	-44, 14, 52	L	Middle frontal gyrus
698	8.80	50, 34, 36	R	Middle frontal gyrus
282	7.70	30, 58, 2	R	Middle frontal gyrus
102	5.73	42, 14, 54	R	Middle frontal gyrus
824	8.57	-38, 50, 0	L	Inferior frontal gyrus
404	6.73	-44 20 30	L	Inferior frontal gyrus
52	4.86	-44, 18, 2	L	Inferior frontal gyrus
25	4.66	42, 12, 20	R	Inferior frontal gyrus
35	6.61	-16, 38, -18	L	Orbital gyrus
24	4.93	18, 34, -18	R	Orbital gyrus
365	7.18	-4, 32, 40	L	Medial prefrontal cortex
584	5.23	-40, -56, 48	L	Inferior parietal lobule
865	8.11	48, -50, 48	R	Inferior parietal lobule
51	6.13	-62, -40, -14	L	Inferior temporal gyrus
27	5.63	-50, -42, 40	L	Supramarginal gyrus
216	5.17	6, -74, 46	R	Precuneus
27	4.36	2, -34, 24	R	Posterior cingulate gyrus
67	5.04	-34, 20, -6	L	Insula
190	8.20	-6, 12, 4	L	Caudate nucleus
330	5.72	14, 16, 8	R	Caudate nucleus
<b>b) Rep – CR</b>				
21	4.45	-44, 24, 36	L	Middle frontal gyrus
442	6.41	-56, 2, 32	L	Precentral gyrus
375	6.95	56, -2, 28	R	Precentral gyrus
40	4.94	36, -12, 64	R	Precentral gyrus
66	5.20	-36, 56, -12	L	Orbital gyrus
62	4.54	38, -30, 58	R	Central sulcus
417	5.65	42, -58, 42	R	Inferior parietal lobule
24	4.71	-36, -52, 28	L	Angular gyrus
36	4.56	-38, -60, 26	L	Angular gyrus
44	4.84	48, -48, 24	R	Angular gyrus
88	4.90	18, -64, -8	R	Fusiform gyrus
57	4.53	42, -18, 18	R	Insula
<b>c) Hit – Rep</b>				
137	6.57	24, 54, -2	R	Superior frontal gyrus
202	5.53	-46, 18, 32	L	Middle frontal gyrus
28	4.63	-34, 6, 58	L	Middle frontal gyrus
218	6.16	-42, 20, 4	L	Inferior frontal gyrus
358	5.97	-48, 42, 14	L	Inferior frontal gyrus
21	4.38	44, 40, 14	R	Inferior frontal gyrus
48	4.62	-10, 28, 40	L	Medial prefrontal cortex
43	4.35	-8, 36, 26	L	Anterior cingulate gyrus
67	4.62	-28, -70, 46	L	Inferior parietal lobule
53	4.55	-36, -52, 46	L	Inferior parietal lobule
34	4.46	32, -68, 50	R	Inferior parietal lobule
27	5.20	-46, -72, -28	L	Inferior temporal gyrus
35	5.12	-32, -20, -12	L	Hippocampus
41	5.23	-4, -42, 10	L	Precuneus
83	4.82	-4, -86, 44	L	Cuneus
25	4.56	-14, -96, -18	L	Occipital gyrus
82	5.10	6, -86, -28	R	Cerebellum
1939	9.00	-16, 0, 14	L	Caudate nucleus
	7.87	14, -4, 18	R	Caudate nucleus

Note: Height threshold;  $P = 0.001$  (uncorrected), extent threshold;  $k = 20$  voxels. L/R: left/right.

are judged based on both recollection and familiarity. The CR and Rep conditions also differ with regard to the fact that the repeated items require incongruent motor responses because the subjects are previously exposed to the items as “new” items. To further isolate the familiarity process, we compared the brain activity observed when the repeated items were presented immediately after the new items (Rep0) with that observed when the items were presented after 2 intervening items (Rep2). The reasoning is that recollection-based judgment is similar in these conditions, whereas because familiarity decreases more rapidly than recollection (Yonelinas 2002; Yonelinas and Levy 2002), there could be a greater reduction in familiarity in the Rep2 condition as compared with that in the Rep0 condition. The result that the mean RT is significantly shorter for Rep0 condition than that for the Rep2 condition ( $669 \pm 112$  vs.  $771 \pm 142$  ms,  $F = 5.08$ ,  $P = 0.03$ ) supports this hypothesis as familiarity is a fast and automatic process (Yonelinas 2002). Therefore, we predicted that the Rep0 versus Rep2 subtraction



**Figure 2.** Significant differences in activation between the conditions are rendered on the standard brain of SPM2. The statistical threshold is set at  $P = 0.001$  (uncorrected) for height and  $k = 20$  voxels for extent. First row: Hit versus CR (deep + shallow), second row: Hit versus CR (deep), third row: Hit versus CR (shallow), fourth row: Rep versus CR, fifth row: Hit versus Rep. See Table 3 and Supplementary Table 1 for coordinates,  $T$ -values, voxel size, and region names. In the first row, the location of each ROI from where the parameter estimates were extracted is indicated by way of an arrow.

may elucidate the neuronal representation of familiarity. The contrast images pertaining to the difference between the Rep0 and Rep2 conditions were created and entered into a 1-sample  $t$ -test (the analysis was inclusively masked by a binary image representing the Rep vs. CR at  $P = 0.05$ , uncorrected). The statistical threshold was set at  $P = 0.001$ , uncorrected, and  $k = 20$  voxels.

In a recent review by Wagner and others (2005), the authors suggested that there is a distinct role in each of the IPL and IPS in the left hemisphere, and several factors modulate the parietal responses at retrieval. We have identified the IPS region that was specifically affected by the LOP effect at encoding; that is, the region is therefore more likely to be related to recollection than familiarity. In order to further

investigate the region-specific effect of the LOP effect, we explored the parietal region that is equally activated in the 2 encoding conditions using a conjunction analysis. The analysis was performed by entering the contrast images representing the Hit versus CR condition in the deep-encoding condition and those representing the Hit versus CR condition in the shallow-encoding condition into a random effects model. The conjunction of these 2 conditions (threshold at  $P = 0.001$ , uncorrected) was exclusively masked by the binary image of the interaction effect between the memory and encoding conditions (i.e., retrieval success regions that were specifically activated in the deep-encoding condition, statistical threshold at  $P = 0.01$ , uncorrected). The cluster that was identified in this analysis and the cluster showing a significant LOP effect are superimposed on the anatomical image of a single subject in Figure 5.

### Structural Equation Modeling

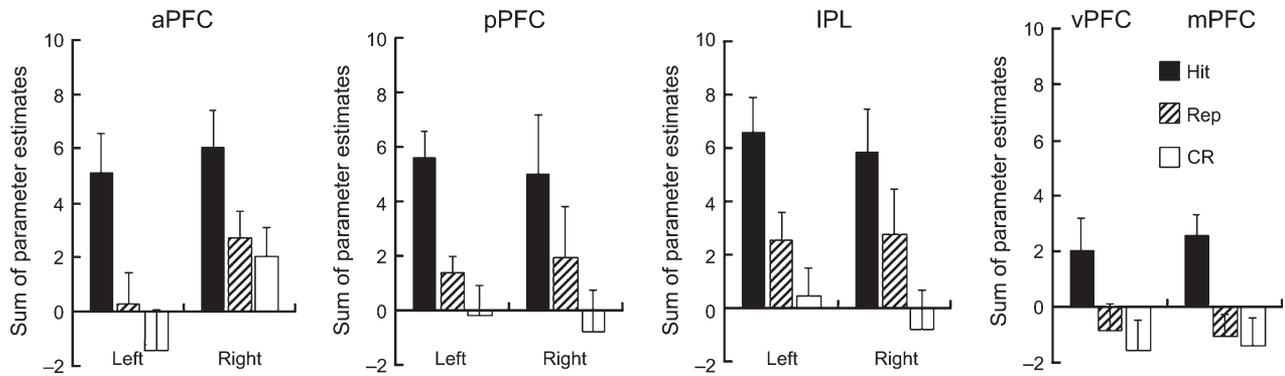
The aim of this analysis was to construct an anatomical model involved in retrieval success and to estimate the strength and significance of the connectivity between the regions, as determined by the path coefficient. The anatomical model consists of the 8 separable regions that were identified by the Hit versus CR subtraction and the connections specified between these regions and their directions. The regions comprised the aPFC, pPFC, mPFC, vPFC, and IPL in the left and right hemispheres, as indicated in Figure 2 and the legend of Figure 3. The parameter estimates of these ROIs representing the difference in activation between the Hit and CR conditions were extracted and entered as variables. In SEM, the variables were considered in terms of covariance structure with the parameters (interregional connection) being estimated by minimizing the differences between the observed covariance and those implied by a predicted model. We constructed the model in a step-by-step manner rather than by testing a single theoretical model. SEM was performed using the AMOS software (version 5, SmallWaters Co., Chicago, IL) by applying a generalized least square algorithm.

The process begins with a default model that has 18 mutual paths comprising each of the following 9 pairs of regions: left IPL and left pPFC, left pPFC and left mPFC, left pPFC and left vPFC, left pPFC and left aPFC, right IPL and right pPFC, right pPFC and right aPFC, left IPL and right IPL, right pPFC and left mPFC, and left aPFC and right aPFC. In the first step, SEM was performed on the default model with 18 paths in order to estimate the coefficient of each path. Subsequently, from the 18 paths in the model, the path having the smallest coefficient was eliminated. In the next step, SEM was computed on a new model with 17 paths; again, the path having the smallest coefficient was eliminated. This procedure was repeated 9 times until no path had a coefficient of less than 0.3. The standardized path coefficient that was eliminated from the model in each step ranged from 0.02 to 0.23. In the final step, a goodness-of-fit value, expressed as the  $\chi^2$  value, was computed, and the statistical threshold was set at  $P = 0.05$ . The final model that was constructed by this procedure is schematized as a path diagram with standardized path coefficients, as depicted in Figure 6.

The constructed model was applied to the data corresponding to the deep- and shallow-encoding conditions (Hit vs. CR) in order to test whether the path coefficients differed between encoding conditions. When the model was applied to the Rep versus CR condition, no path coefficient survived the statistical threshold of  $P = 0.05$ . Therefore, another model of the Rep versus CR condition was constructed with 4 anatomical regions including the left IPL, right IPL, left premotor (PM,  $x, y, z = -56, 2, 32$ ), right PM ( $x, y, z = 56, -2, 28$ ), and the mutual paths. SEM was performed on this model with the statistical threshold set at  $P = 0.05$  ( $\chi^2$  test).

### ERP Data Acquisition and Analysis

The electroencephalograph (EEG) was recorded from 13 international 10-20 system scalp locations (Fz, Cz, Pz, F7, F8, F3, F4, P3, P4, T5, T6, O1, and O2) referenced to the tip of nose using Ag/AgCl electrodes. In order to monitor horizontal and vertical eye movements, 2 electrodes were placed one to the left of the left eye and one above it. Interelectrode impedance was set below 8 k $\Omega$ . The data were recorded from 200 ms before the stimulus onset to 1000 ms after the onset using the BIOPAC MP100 system (Monte System Co., Tokyo, Japan), with a sampling rate



**Figure 3.** The mean and SE of the parameter estimates that were extracted from the 8 ROIs (left and right aPFC, left and right pPFC, left and right IPL, left vPFC, and left mPFC) in the 16 subjects are shown. The coordinates of the center of ROIs are as follows—aPFC: left, -44, 46, 8, and right, 28, 56, 0; pPFC: left, -44, 20, 30, and right, 50, 34, 36; IPL: left, -40, -58, 44, and right, 46, -54, 46; vPFC: left, -44, 18, 2; mPFC: left, -8, 30, 40.

**Table 4**

Regions with significant interaction between memory (Hit vs. CR) and encoding (deep vs. shallow) conditions

Voxels	T-value	x, y, z (mm)	L/R	Region
28	5.98	-32, -50, 38	L	Intra parietal sulcus
39	5.41	-56, 16, 22	L	Inferior frontal gyrus

Note: Height threshold;  $P = 0.001$  (uncorrected), extent threshold;  $k = 20$  voxels.

of 1000 Hz. The data were filtered using a bandpass of 0.1–35 Hz and corrected to a 200-ms baseline prior to the stimulus onset. Trials in which the EEG or eye movements exceeded  $\pm 100 \mu\text{V}$  were eliminated from the averaging process by visual inspection. The ERP experiment was controlled by the presentation software (Neurobehavioral Systems Inc.).

EEG data were sorted according to each response type, as noted in The fMRI Data Acquisition and Analysis, and the average ERP waveforms were calculated for each subject and condition using the EPLYZER software (Kissei Comtec Co., Ltd., Matsumoto, Japan). In each subject and in each condition, a positive deflection from 300 to 1000 ms was identified at the frontoparietal electrodes (Fz, Cz, Pz, F3, F4, P3, and P4) after the stimulus onset. This component was divided into 3 time windows, namely, 300–450, 450–600, and 800–1000 ms. The mean amplitude was calculated in each time window and entered into a 2-way ANOVA with the condition and electrode as factors. The statistical threshold was set at  $P = 0.05$  (Greenhouse-Geisser corrected). The results of the ANOVA conducted on the mean amplitudes are shown in Table 5. The grand mean waveforms of the 16 subjects were created in each of the Hit, Rep, and CR conditions and are shown in Figure 7. With regard to the fMRI analysis using the Rep0 and Rep2 conditions, the ERPs of these conditions were also compared in terms of the mean amplitude and peak latency of the frontoparietal electrodes (Fz, Cz, Pz, F3, F4, P3, and P4).

In order to segregate the large positive deflection associated with episodic memory retrieval into several subcomponents, ICA was applied to the ERP data. The difference waves between the Hit and CR conditions and that between the Rep and CR conditions were computed and averaged for each subject. Using the EEGLAB software (version 4.4.1, Delorme and Makeig 2004) implemented in MATLAB (MathWorks, MA), ICA was performed separately on the 2 grand average difference waves that were measured from the 13 electrode sites. Among the 13 temporally independent components created in this process, we were particularly interested in the components that had frontoparietal distribution and demonstrated maximal potential within the time window of 300–600 ms. A component in the later time window (600–800 ms) that was related to the prefrontal activity was also examined. The waveforms and the topographic map of 4 frontoparietal ICA components are illustrated in Figure 8. For the purpose of comparison, a topographic map of the scalp ERP at the peak latency

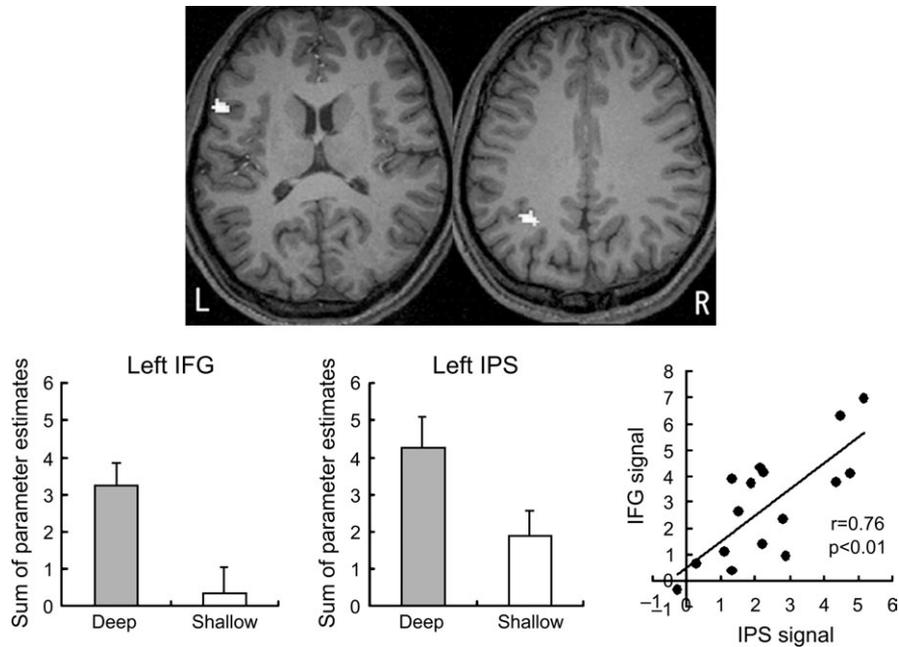
corresponding to the peak of each ICA component is also shown in this figure.

## Results

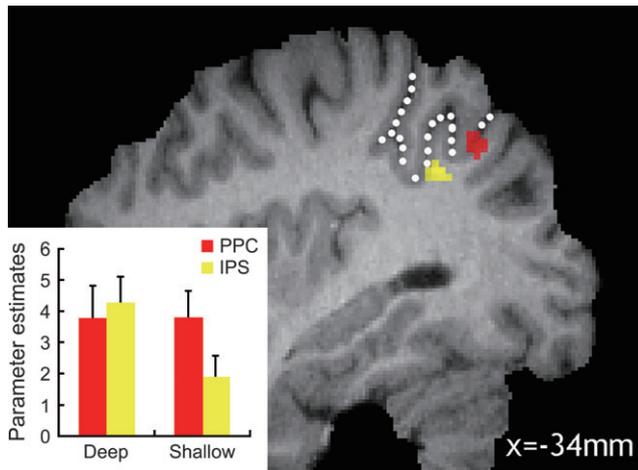
### Behavioral Data

With respect to the fMRI session, the mean Hit – FA rate was significantly higher in the deep-encoding condition than in the shallow-encoding condition ( $F = 10.1$ ,  $P = 0.003$ , Table 1); however, the mean accuracy for the Rep item did not differ between the conditions ( $F = 0.62$ ,  $P = 0.43$ ). With respect to the ERP session, the mean Hit – FA rate was significantly higher in the deep-encoding condition than in the shallow-encoding condition ( $F = 10.1$ ,  $P = 0.003$ ); however, the mean accuracy for the Rep item did not differ between the conditions ( $F = 0.61$ ,  $P = 0.44$ ). We performed a supplementary 2-way ANOVA for these data with the encoding condition and session as factors. With regard to the mean Hit – FA rate, the main effect of the encoding condition ( $F = 19.5$ ,  $P < 0.001$ ) and the session ( $F = 31.1$ ,  $P < 0.001$ ) was significant, but the interaction effect was not ( $F = 0.69$ ,  $P = 0.41$ ). With regard to accuracy for the Rep item, the main effect of the session ( $F = 8.19$ ,  $P < 0.001$ ) was significant; however, the main effect of the encoding condition ( $F = 1.23$ ,  $P = 0.27$ ) or the interaction effect was not significant ( $F < 0.001$ ,  $P = 0.98$ ). Thus, encoding manipulation succeeded in increasing memory performance in the deep condition; however, it did not affect the proportion of correct responses in the case of the repeated items.

With respect to the fMRI session, the mean RT differed between the memory conditions ( $F = 3.15$ ,  $P < 0.05$ , Table 2) but not between the encoding conditions ( $F = 0.32$ ,  $P = 0.57$ ); further, no interaction effect was observed ( $F = 0.10$ ,  $P = 0.90$ ). Fisher's least square difference (LSD) test revealed that during the fMRI session, the RT was significantly shorter for the Rep condition than for the CR condition ( $P < 0.05$ ). With respect to the ERP session, the mean RT differed between the memory conditions ( $F = 9.79$ ,  $P < 0.001$ ) but not between the encoding conditions ( $F = 0.002$ ,  $P = 0.96$ ); further, no interaction effect was observed ( $F = 0.24$ ,  $P = 0.78$ ). Fisher's least square difference (LSD) test revealed that during the ERP session, the RT was significantly shorter for the Rep condition than for either the Hit ( $P < 0.01$ ) or the CR condition ( $P < 0.001$ ). We conducted a 2-way ANOVA with both memory condition and session as factors and with the encoding conditions collapsed. A significant main effect of



**Figure 4.** The interaction effect between the encoding condition (deep vs. shallow) and the memory condition (Hit vs. CR) is superimposed on a high-resolution  $T_1$ -weighted image of a single subject. Top: the activity of the regions in the left IFG and the IPS associated with retrieval success was greater in the deep-encoding condition as compared with that in the shallow-encoding condition. Bottom: columns indicate the mean activity for retrieval success (Hit – CR) in the left IFG (left) and the IPS (middle) in the deep- and shallow-encoding conditions. Bars indicate one SE. Bottom right: the difference in activity between the deep and shallow conditions was computed for each subject and region. These values were significantly and positively correlated with one another. The correlation coefficient and significance level are indicated in the figure.



**Figure 5.** The left parietal region involved in retrieval success (Hit vs. CR) has 2 subregions. In the cluster shown in red (the PPC), the level of activation is not affected by the manipulation of LOP at encoding, whereas in the yellow cluster (the IPS; this region is also shown in Fig. 4) activity significantly differed between the deep- and shallow-encoding conditions. The IPS region is located in the anterior and medial part of the left parietal cluster, and the PPC region is located in the posterior and lateral part. An inset bar graph shows the mean and SE of the activity observed in these regions in the 2 encoding conditions. The white dots in the figure indicate the IPS. The clusters are superimposed on a  $T_1$ -weighted image of a single subject at  $x = -34$  mm.

memory condition ( $F = 5.55$ ,  $P < 0.01$ ) and no main effect of session ( $F = 0.09$ ,  $P = 0.76$ ) or interaction effect ( $F = 0.28$ ,  $P = 0.75$ ) was observed. The fact that the response speed of the CR of the nonstudied items was accelerated by the repetition indicates a behavioral priming effect.

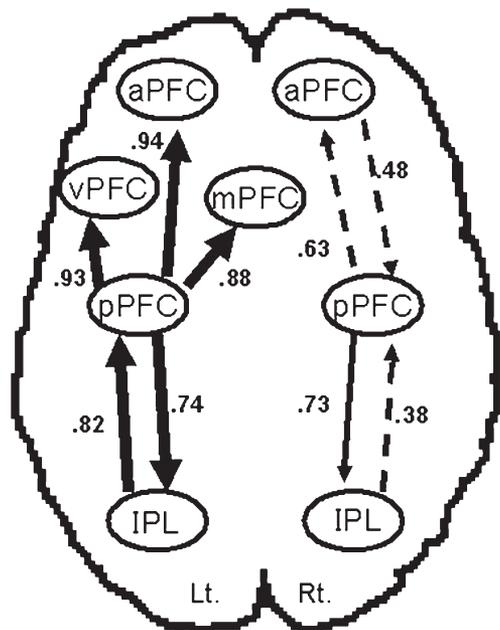
#### The fMRI Data

The neural correlates of episodic memory retrieval involved significant activation in the frontoparietal regions of the left and

right hemispheres, as shown in Figure 2 and Table 3. The prefrontal activity was predominantly observed in the Hit versus CR condition, whereas in the Rep versus CR condition, the prefrontal activity was lower; instead, the ventral part of the precentral gyrus was activated. The subtraction of the Hit versus Rep condition revealed that the left prefrontal regions are significantly active in the Hit condition as compared with those in the Rep condition. These results indicate that the majority of the left prefrontal activity was associated with the conscious and successful recognition of the old items; however, this association was not likely to be observed with the repetitive presentation of items. The bilateral IPL was activated in the Hit versus CR condition, whereas in the Rep versus CR condition, the parietal activation in the right hemisphere was greater than that in the left. Activity in the bilateral parietal areas remained significant when the Rep condition was subtracted from the Hit condition.

The parameter estimates of the frontoparietal regions were extracted from the individual contrast image in each of the Hit, CR, and Rep conditions. Eight ROIs in the aPFC, pPFC, and IPL of the bilateral hemisphere were chosen along with the vPFC and mPFC of the left hemisphere, as shown in Figure 2. In all the ROIs, the signal was larger in the Hit condition than in the Rep or CR condition (Fig. 3). The difference in signal between the Rep and CR conditions was larger in the IPL than in the other regions, particularly in the right hemisphere. Supplementary analyses with these ROI data showed that the difference between the Rep and CR conditions was significant only in the IPL region ( $P < 0.05$ , a 2-way ANOVA with hemisphere and memory condition as factors and post hoc Fisher's LSD test). These ROI data indicate that the parietal region was more responsive both to the old items and the rejected repeated items than to the new items. The analysis comparing the Rep0 and Rep2 conditions showed that a single region in the right

inferior parietal area ( $x, y, z = 56, -44, 30; T = 5.72; P = 0.001$ , uncorrected;  $k = 23$  voxels) had greater activation in the Rep0 condition than in the Rep2 condition. Therefore, based on the reasoning provided in Materials and Methods, the right inferior parietal area is more likely to be related to familiarity-based judgment than to recollection-based judgment (Supplementary Fig. 1).



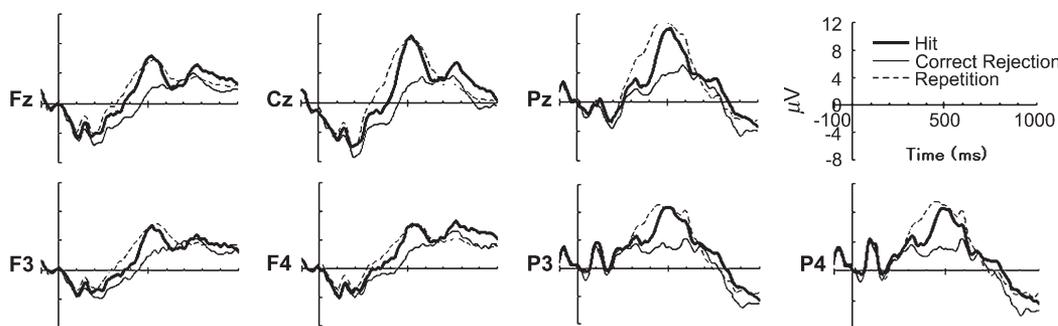
**Figure 6.** The result of the SEM is schematized as a path diagram. Thick and thin filled lines indicate the significance of the path at  $P = 0.01$  and at  $P = 0.05$ , respectively. A broken line indicates a nonsignificant ( $P > 0.05$ ) path. A numerical value by the line is a standardized path coefficient. The path coefficients in the left hemisphere are greater and more significant than those in the right hemisphere. There was a bidirectional path between the IPL and the pPFC of the left hemisphere. The left pPFC has unidirectional paths to the aPFC, vPFC, and mPFC. Each variable has an error term that has been omitted from the figure.

**Table 5**

Results for comparisons between the memory conditions on mean ERP amplitude in 2 time windows

	Hit versus CR	Hit versus Rep	CR versus Rep
300–450 ms	<0.01	<0.01	<0.001
450–600 ms	<0.01	NS	<0.01

Note: NS, not significant. The significant results survived Greenhouse–Geisser correction.



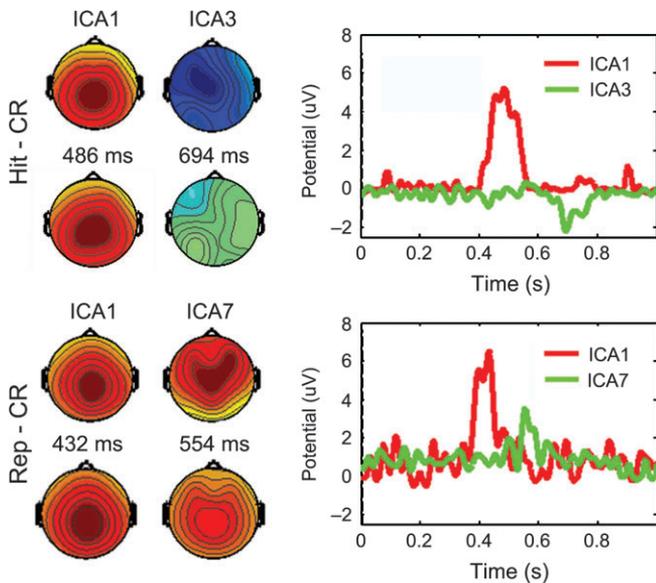
**Figure 7.** The grand mean waveforms of the 16 subjects that were measured at Fz, Cz, Pz, F3, F4, P3, and P4 electrodes are shown. For the Hit (thick line) and Rep (broken line) conditions, the waveform diverged from the CR condition (thin line) at about 300 ms after the stimulus onset. The positive deflection of the Rep condition exceeded that of the Hit condition from 300 to 450 ms after the stimulus onset. The original waveforms are smoothed by using a 30-Hz low-pass filter.

The LOP manipulation during encoding significantly affected neural activation during the successful retrieval of old items. In the deep-encoding condition, the frontoparietal regions demonstrated significant activation with regard to the Hit versus CR subtraction, whereas the activity in some of these clusters was diminished in the shallow-encoding condition (Fig. 2, Supplementary Table 1). A particularly significant interaction effect was detected between the memory condition (Hit vs. CR) and the encoding condition (deep vs. shallow) in the IFG and IPS of the left hemisphere, as shown in Figure 4 and Table 4. In Figure 4, the mean and SE of the difference in parameter estimates between the Hit and CR conditions are separately plotted for the deep- and shallow-encoding conditions. Thus, in both the IFG and the IPS, neural activity associated with retrieval success (Hit minus CR) was significantly greater in the deep-encoding condition than in the shallow-encoding condition. In addition, the difference in signal between the 2 encoding conditions in the IFG was observed to be significantly and positively correlated with that in the IPS across subjects (Fig. 4, Pearson's correlation coefficient,  $r = 0.76, P < 0.01$ ).

A large parietal cluster associated with the retrieval success was separated into 2 subregions; one of these regions was affected by the LOP manipulation at encoding and the other was not. The conjunction analysis revealed that the posterior parietal cortex (PPC) (a red cluster in Fig. 5;  $x, y, z = -40, -60, 46, T = 3.91, P = 0.001$ , uncorrected,  $k = 53$  voxels) had an equivalent level of activation in the deep- and shallow-encoding conditions (Fig. 5, inset graph). Another cluster in the IPS that demonstrated a significant effect of LOP on the Hit versus CR condition (a yellow cluster in Fig. 5, see also Fig. 4) was located to the anterior of and medially to the PPC.

The left hippocampus demonstrated greater activation in the Hit condition than in the Rep condition (Supplementary Fig. 2 and Table 3). The significance of the difference between the Hit and CR conditions with regard to the hippocampal signal survived the height threshold ( $x, y, z = -32, -20, -10, T = 4.07, P = 0.001$ ) but not the extent threshold ( $k = 3$  voxels). No significant difference was observed between the Rep and CR conditions with regard to hippocampal activation. The degree of hippocampal activation between the deep- and shallow-encoding conditions did not differ significantly ( $T = 0.28, P > 0.3$ ).

The result of SEM is schematized in Figure 6 as a path diagram. The goodness-of-fit value, as determined by the  $\chi^2$  value, was 25.8, and it survived the threshold of  $P = 0.05$  level. Overall, standardized path coefficients in the left hemisphere are larger



**Figure 8.** The topographic map (left) and time course (right) of the ICA component are shown. Under the topographic map of each ICA component, the topographic map of the ERPs at the peak latency corresponding to the peak of each ICA component is shown. With regard to the Hit – CR condition (top), 2 components (ICA1 and ICA3) are particularly relevant to the frontoparietal network. The ICA1 was distributed in the centroparietal region and peaked at 486 ms after the stimulus onset. The ICA3 was located frontocentrally and peaked at 694 ms after the stimulus onset. With respect to the Rep – CR condition (bottom), 2 components were distributed in the centroparietal region. The ICA1, which peaked at 432 ms after the stimulus onset, had centroparietal distribution; and the ICA7, which peaked at 554 ms after the stimulus onset, had a more anterior and bilateral localization.

and more significant than those in the right hemisphere. The left IPL had bidirectional paths to the left pPFC. The left pPFC had unidirectional paths to each of the mPFC, vPFC, and aPFC. All the remaining coefficients in this model are positive. This indicates that, for example, when the activity in the left pPFC increases by one SD, the activity in the left vPFC increases by 93% of the SD. These results imply that the functional connectivity among the regions in the frontoparietal network, particularly in the left hemisphere, is significant when the subject successfully recognizes an old item. When the model was applied separately to the 2 encoding conditions, the path coefficients were significant only in the deep-encoding condition. In the left hemisphere, the paths between the IPL and pPFC (0.75,  $P < 0.01$  and 0.63,  $P < 0.05$ ) and those from the pPFC to the aPFC (0.91,  $P < 0.01$ ) and to the mPFC (0.75,  $P < 0.01$ ) are significant in the deep-encoding condition (values in parentheses are the standardized coefficients and significance levels). In contrast, in the shallow-encoding condition, no path coefficient was observed to survive the statistical threshold of  $P = 0.05$ . For the Rep versus CR condition, the path coefficients between the left and right IPL were significant (from left to right, 0.72,  $P < 0.05$ ; from right to left, 0.73,  $P < 0.01$ ).

#### ERP Data

Each of the grand mean ERP waveforms corresponding to the Hit, CR, and Rep conditions are plotted in Figure 7. The results for a 2-way ANOVA and post hoc comparisons between memory conditions with regard to the mean amplitude are shown in Table 5. With regard to memory condition, the result for the time window from 800 to 1000 ms is not reported as it did not survive the Greenhouse–Geisser correction at the  $P = 0.05$  level.

In the time window of 300–450 ms, 3 possible comparisons between the memory conditions were significant at the  $P = 0.01$  level. In the Pz electrode, the amplitude of the Rep and Hit conditions diverged from the CR condition at about 300 ms after the stimulus onset. Particularly, between 300 and 450 ms, the mean amplitude of the Rep condition was higher than that of the Hit condition. In the 450- to 600-ms time window, the mean amplitude of the CR condition was significantly lower than that of the Hit or Rep condition. The amplitude of the Hit and Rep conditions peaked at about 500 ms after the stimulus onset in the frontoparietal electrodes. In the 450- to 600-ms time window, the mean amplitude of the Hit and Rep conditions did not differ significantly. For both time windows, the interaction effect of the memory condition and the electrode was significant ( $P < 0.01$ ); however, the main effect of the electrode was not observed to be significant. The interaction effect of the memory condition and the encoding condition (deep vs. shallow) did not survive the statistical threshold.

With relevance to the Rep0 versus Rep2 subtraction in the fMRI analysis, we compared the mean amplitude between the Rep0 and Rep2 items within the time window of 400–500 ms. The mean RT is significantly shorter for Rep0 condition than that for the Rep2 condition ( $632 \pm 99$  vs.  $735 \pm 114$  ms,  $F = 7.36$ ,  $P = 0.01$ ). In the frontoparietal electrodes, the mean amplitude corresponding to the Rep0 items was significantly higher than that corresponding to the Rep2 items ( $P = 0.03$ , Greenhouse–Geisser corrected). In the same group of electrodes, the peak latency for the parietal positivity was significantly shorter for the Rep0 items than for the Rep2 items ( $P = 0.001$ , Greenhouse–Geisser corrected).

In order to differentiate the frontoparietal positivity associated with the successful retrieval of old items, ICA decomposition was performed on the difference wave between the Hit and CR conditions. As shown in Figure 8, the ICA1 is the largest component within the time window of 300–600 ms (peak at 486 ms) and is distributed in the centroparietal region. During the time window of 600–800 ms, the ICA3, which is the largest component in the frontal region, peaked at 694 ms after the stimulus onset. The topographic distribution of these ICAs paralleled a spatial map of the activation that was measured by fMRI (Hit vs. CR, Fig. 2); that is, the parietal positivity of the ICA1 paralleled the bilateral IPL activation, and the frontopolar activity of the ICA3 paralleled the bilateral prefrontal activation.

The result for the difference wave between the Rep and CR conditions revealed that the ICA1 was distributed in the parietal region and peaked at 432 ms after the stimulus onset (Fig. 8). This peak occurred 54 ms earlier than the peak of the ICA1 corresponding to the Hit versus CR condition. Within the same time window of 300–600 ms, the ICA7, which is the second largest component in the frontocentral region, had a slightly anterior and bilateral localization and peaked at 554 ms after the stimulus onset. Spatial maps of the increased signal in the Rep versus CR condition (Fig. 2) mirror the topographic map of these ICAs. When the topographic maps of difference waveforms that have and have not been decomposed by the ICA are compared (Fig. 8), it is noteworthy that the activity in these frontoparietal regions has similar topographical patterns.

#### Discussion

The results of the present study revealed that the neural correlates for retrieval success that were elucidated by comparing

the Hit and CR conditions were distributed in the frontoparietal regions of the brain and that the activity in some of these regions was affected by LOP manipulation at encoding. The left parietal lobule was divided into 2 subregions based on the effectiveness of LOP manipulation; the anteromedial region located in the IPS was modulated by the LOP effect, whereas the posterolateral region located in the PPC was not. The right parietal activation differed between the items that were repeated immediately and those that were repeated after 2 intervening items. These results indicate that the left IPS is more likely to be related to recollection than to familiarity and the right parietal lobule is more likely to be related to familiarity than to recollection during a picture recognition task. The SEM analysis revealed that during successful retrieval, the functional connectivity within the frontoparietal network was more significant in the left hemisphere than in the right hemisphere. The ERP results that show the old-new effect indicate that the centroparietal positivity evoked by the repeated item preceded the positivity evoked by the old items. The ICA decomposition of the differential wave data indicated that the temporal difference between the Hit and Rep conditions with regard to parietal activity was approximately 50 ms.

### *The fMRI and SEM*

Frontoparietal involvement in retrieval success has been consistently observed in neuroimaging studies using a recognition or source memory test with words (Konishi and others 2000; McDermott and others 2000; Donaldson and others 2001), faces (Leveroni and others 2000), and pictures (Cansino and others 2002; Shannon and Buckner 2004; Achim and Lepage 2005). In most of these studies, the regions related to retrieval success have been investigated by comparing the hit items and correctly rejected items. One possible explanation for this phenomenon is that the frontoparietal network is engaged in active recollection from a past episode because greater activation was observed in these areas in the "remember" condition than in the "know" condition during the remember/know judgment task (Henson and others 1999; Wheeler and Buckner 2004; Wagner and others 2005). The results of the present study are consistent with these results and adds to the evidence indicating that the neural correlates corresponding to recollection and those corresponding to familiarity are different. That is, the simple repetition of items also activated the right IPL to a greater extent in response to the new items; furthermore, the level of parietal activity was modulated by the repetition lag. Because familiarity decreases more rapidly with time than recollection, the present results suggest that with regard to picture stimuli, it is more likely that the activation in the right IPL reflects familiarity-based judgment than it does recollection-based judgment.

Several studies of perceptual priming have demonstrated that as compared with novel items, repeated items enhanced cortical activity; this phenomenon is known as "repetition enhancement" (Henson and others 2002). As observed in the present study, these activated regions are detected in the parietal and PM areas during tasks using pictures (Koutstaal and others 2001) and faces (Henson and others 2002). In their study using a word recognition task, Jessen and others (2001) also showed that the bilateral parietal cortices demonstrated greater activation in the case of the repeated word than in the case of the novel word. However, greater activity in a particular region for the repeated items than for the new items does not

necessarily indicate that the region is specifically involved in familiarity because the correct responses to the repetition items also include the recollection of the previous exposure to that item. In addition, the subject experiences interference in responding to the repeated item as "new" because of having previously seen that item. Although it is difficult to isolate these processes, we hypothesized that comparing the Rep0 and the Rep2 conditions would facilitate the clarification of this issue. The fact that the Rep0 items elicit significantly faster RT than the Rep2 items also indicates that the difference in activation between these conditions reflects familiarity-based judgment. The result of a recent fMRI study by Yonelinas and others (2005) showing that activity in the right IPL correlates with the subject's familiarity confidence may support the results of the present study. However, problems with regard to the differentiation between implicit memory/priming and familiarity still persist, and further investigations are required to differentiate these processes.

Recent fMRI studies have investigated the effect of encoding manipulation on retrieval success by varying the number of item presentation (Velanova and others 2003; Wheeler and Buckner 2003), by dividing attention (Kensinger and others 2003), and by changing the instructions (Kahn and others 2004) during encoding; this is done in order to reveal the brain region that is associated with recollection. However, the results of these imaging studies are inconsistent with regard to the relationship between parietal activity and task manipulation. Two fMRI studies that examined the effect of encoding manipulation by varying the number of item presentation revealed that there was a significant difference in parietal activation between the conditions (Velanova and others 2003; Wheeler and Buckner 2003). A study employing the LOP procedure at encoding also showed that the items studied under the deep-encoding condition evoked greater parietal activation than those studied under the shallow-encoding condition (Shannon and Buckner 2004). On the other hand, division of attention at encoding did not affect the parietal activity (Kensinger and others 2003). When the subject was given 2 encoding instructions (i.e., "image" or "read"), the parietal activity did not differ between the instructions (Kahn and others 2004). The most relevant literature is a study by Shannon and Buckner (2004) wherein the LOP procedure was employed during a word encoding task. Similar to the results of the present experiment, their study demonstrated that the parietal activity associated with retrieval success produced by the deeply encoded item is greater than that produced by the shallowly encoded item. In contrast, the results of the study by Kensinger and others (2003) revealed that activation in the left dorsal prefrontal cortex, but not in the left parietal lobe, is greater in the "easy" condition than it is in the "hard" condition (easy and hard are analogous to deep and shallow, respectively). The present study revealed that the effect of encoding manipulation is predominantly observed in the frontal and parietal areas of the left hemisphere during a picture recognition task; this indicates a functional relationship between these regions and recollection.

The involvement of the parietal lobe in the Hit versus CR condition that has been reported by several authors (Kensinger and others 2003; Velanova and others 2003; Wheeler and Buckner 2003; Kahn and others 2004; Shannon and Buckner 2004) is indicative of a functional heterogeneity in this area with regard to recollection/familiarity-based judgment. A recent review by Wagner and others (2005) suggested that

recollection-sensitive parietal foci were identified in the left PPC, whereas familiarity-sensitive foci were found in the left IPS. In the present study, however, the left parietal cluster that was delineated by the Hit versus CR subtraction had 2 subregions; the region that is sensitive to the LOP was located in the IPS (anterior and medial part of the cluster) and the other region that was insensitive to the LOP was located in the PPC (posterior and lateral part of the cluster). We confirmed the localization of these subregions in each individual subject and found that in 15 of 16 subjects the 2 regions were distinct (threshold was reduced to  $P = 0.05$ , uncorrected). The inconsistency between the results of the present study and those of Wagner and others (2005) may be attributed to several factors such as stimulus type, the size of study depth effect, encoding task, and type of recognition test.

The results of SEM also revealed that although the pictures were used as stimuli, the functional connectivity among the activated regions in the left hemisphere is greater than that in the right hemisphere. This may be due to retrieval being cued by the name and/or meaning of the items because the significance of connectivity is found only in the deep-encoding condition. These findings are unique to SEM because the results of the fMRI experiment showed the bilateral activation pattern corresponding to the Hit versus CR condition (deep + shallow) and no indication of functional lateralization was detected. A path diagram shows that a mutual relationship exists between the IPL and pPFC; this suggests that there are forward as well as backward influence mechanisms between the regions. In addition, the pPFC had a positive effect on the aPFC, vPFC, and mPFC, and no significant path from the other prefrontal regions were observed. This may indicate that the pPFC-IPL axis plays a pivotal role in the retrieval success network. The results that only the mutual paths between the left and right IPL are significant in the Rep versus CR condition may be related to the fact that there is little involvement of the prefrontal control process in the Rep condition.

Lastly, there was a functional differentiation between the frontoparietal network and the left hippocampus; the retrieval success activity was affected by encoding manipulation in the former but not in the latter. The result of the present study is inconsistent with those reported by Rugg and others (1997) where the LOP effect at encoding resulted in the differential activation of the left hippocampus at retrieval. In their study (Rugg and others 1997), the subjects correctly recognized 96% of the deeply encoded words and 65% of the shallowly encoded words, whereas in the present study, the hit rate was 83% and 68% in the deep- and shallow-encoding conditions, respectively. Thus, the effect of the LOP at encoding that was reported by Rugg and others is double of that observed in the present study. The difference between the experiments with regard to the LOP effect is a possible explanation for the discrepancy. The second explanation is that the results for the shallow-encoding condition in the study by Rugg and others (1997) were confounded by the miss responses because they used positron emission tomography and a block design experiment.

### **ERP and ICA**

The present ERP data shows the typical “old-new” effect in the centroparietal electrodes that was found in the previous studies using words (Rugg, Mark, and others 1998; Rugg, Walla, and others 1998; Allan and others 2000; Rugg and Allan 2000), pictures (Kazmerski and Friedman 1997; Schloerscheidt and

Rugg 1997; Ranganath and Paller 1999; Curran and Cleary 2003), and faces (Pallar and others 2003) as stimuli. A unique aspect of the present study is that the Hit and Rep conditions are incorporated into a single run in order to delineate the time course of these memory processes. The results that the Rep item produced a rise in parietal positivity earlier than the CR item corresponded with the results reported by Kim and others (2001). The latter used a continuous recognition task and showed an earlier parietal positivity in response to an immediately repeated word than to a new word. These results are in accordance with the behavioral data, which suggests that the mean RT was faster for the Rep than for the other conditions, and with the psychological model indicating that familiarity-based judgment occurs earlier than recollection-based judgment (Yonelinas 2002). However, as noted in the fMRI section, there are several drawbacks in this comparison. To further dissociate these processes, we compared the mean amplitude and peak latency between the Rep0 and Rep2 conditions and found that the Rep0 condition evoked greater and earlier parietal positivity as compared with the Rep2 condition. Thus, the results of the ERP experiment parallel those of the fMRI experiment, which indicate that the right parietal lobe had a greater activation in response to the Rep0 items than to the Rep2 items.

Our study did not predict that the encoding manipulation would have no significant effect on the centroparietal positivity. An explanation for this inconsistency is required because several previous studies have demonstrated that correct recognition of deeply encoded items produces greater parietal positivity than shallowly encoded items (Rugg, Mark, and others 1998; Rugg, Walla, and others 1998; Allan and others 2000; Rugg and others 2000; Pallar and others 2003). First, most of the previous studies that found a significant LOP effect used words (Rugg, Mark, and others 1998; Rugg, Walla, and others 1998; Rugg and others 2000) or word stems (Allan and others 2000) as stimuli. Pictorial material, such as the line drawing used in the present study, is more memorable than a word; this could eliminate the effect of encoding manipulation at retrieval. Second, in the present study, the difference in memory performance (Hit - FA rate) between the deep and shallow conditions (11%) is smaller than that observed in the previous study (20-50%). Third, a significant region in the parietal lobe that was located in the depth of the sulcus had neural responses that were difficult to detect with the scalp electrodes.

The results of the ICA parallel those of the scalp potentials; the ICA1 of the Rep versus CR condition peaked earlier by approximately 50 ms than that of the Hit versus CR condition. The 2 components were distributed predominantly in the centroparietal regions, as observed in the scalp topography for each condition. Additional distribution patterns were found in the frontocentral area for the Hit versus CR condition and in the bilateral central areas for the Rep versus CR condition. In the former case, the frontocentral activity that peaked at F3-Cz position is likely to be mirroring the prefrontal activity observed in the fMRI experiment. Lastly, the latter pattern, which most likely reflects the activation in the ventral PM areas, may be related to the functional property of the region that converges multimodal information to achieve goal-directed actions (Rizzolatti and others 2002).

In conclusion, the present study differentiated the brain regions in the frontoparietal network that are involved in recollection-based judgment from those that are involved in

familiarity-based judgment. The left frontoparietal regions are more likely to be related with recollection than with familiarity, whereas the activity in the right parietal lobule is likely to be influenced by familiarity. The SEM indicates that the strength of functional connectivity in the neural network of the left hemisphere is particularly important for retrieval success. The results of the ERP and ICA that showed an earlier rise of parietal activity in response to the repetition items than to the other items parallel behavioral as well as fMRI findings.

### Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>.

### Notes

We greatly appreciate valuable help of Dr Hideki Ohira and Ms Yoko Ichikawa for the experiment. This work was supported by Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science. *Conflict of Interest:* None declared.

Address correspondence to Tetsuya Iidaka MD, Department of Psychiatry, Nagoya University, Graduate School of Medicine, Tsurumai, Showa, Nagoya, Aichi 466-8550, Japan. Email: iidaka@med.nagoya-u.ac.jp.

### References

- Achim AM, Lepage M. 2005. Dorsolateral prefrontal cortex involvement in memory post-retrieval monitoring revealed in both item and associative recognition tests. *Neuroimage* 24:1113-1121.
- Allan K, Robb WG, Rugg MD. 2000. The effect of encoding manipulations on neural correlates of episodic retrieval. *Neuropsychologia* 38:1188-1205.
- Amano S, Kondo T. 1999. NTT database series, "lexical properties of Japanese." Tokyo, Japan: Sansendo.
- Brett M, Anton J, Valabregue R, Poline JP. 2002. Region of interest analysis using an SPM toolbox. 8th International Conference on Functional Mapping of the Human Brain, Sendai, Japan: Elsevier Science. 497 p.
- Buckner RL, Wheeler ME. 2001. The cognitive neuroscience of remembering. *Nat Rev Neurosci* 2:624-634.
- Cansino S, Maquet P, Dolan RJ, Rugg MD. 2002. Brain activity underlying encoding and retrieval of source memory. *Cereb Cortex* 12:1048-1056.
- Craik FIM, Lockhart RS. 1972. Levels of processing: a framework for memory research. *J Verb Learn Verb Behav* 11:671-684.
- Curran T, Cleary AM. 2003. Using ERPs to dissociate recollection from familiarity in picture recognition. *Brain Res Cogn Brain Res* 15:191-205.
- Delorme A, Makeig S. 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* 134:9-21.
- Donaldson DI, Petersen SE, Buckner RL. 2001. Dissociating memory retrieval processes using fMRI: evidence that priming does not support recognition memory. *Neuron* 31:1047-1059.
- Evans AC, Collins DL, Mills DR, Brown ED, Kelly RL, Peters TM. 1993. 3D statistical neuroanatomical models from 305 MRI volumes. *Proc IEEE Nucl Sci Symp Med Imaging* 1-3:1813-1817.
- Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ. 1995. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp* 2:189-210.
- Henson RN, Rugg MD, Shallice T, Josephs O, Dolan RJ. 1999. Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *J Neurosci* 19:3962-3972.
- Henson RN, Shallice T, Gorno-Tempini ML, Dolan RJ. 2002. Face repetition effects in implicit and explicit memory tests as measured by fMRI. *Cereb Cortex* 12:178-186.
- Jessen F, Flacke S, Granath DO, Manka C, Scheef L, Papassotiropoulos A, Schild HH, Heun R. 2001. Encoding and retrieval related cerebral activation in continuous verbal recognition. *Brain Res Cogn Brain Res* 12:199-206.
- Kahn I, Davachi L, Wagner AD. 2004. Functional-neuroanatomic correlates of recollection: implications for models of recognition memory. *J Neurosci* 24:4172-4180.
- Kazmerski VA, Friedman D. 1997. Old/new differences in direct and indirect memory tests using pictures and words in within- and cross-form conditions: event-related potential and behavioral measures. *Brain Res Cogn Brain Res* 5:255-272.
- Kensinger EA, Clarke RJ, Corkin S. 2003. What neural correlates underlie successful encoding and retrieval? A functional magnetic resonance imaging study using a divided attention paradigm. *J Neurosci* 23:2407-2415.
- Kim M, Kim J, Kwon JS. 2001. The effect of immediate and delayed word repetition on event-related potential in a continuous recognition task. *Brain Res Cogn Brain Res* 11:387-396.
- Konishi S, Wheeler ME, Donaldson DI, Buckner RL. 2000. Neural correlates of episodic retrieval success. *Neuroimage* 12:276-286.
- Koutstaal W, Wagner AD, Rotte M, Maril A, Buckner RL, Schacter DL. 2001. Perceptual specificity in visual object priming: functional magnetic resonance imaging evidence for a laterality difference in fusiform cortex. *Neuropsychologia* 39:184-199.
- Leveroni CL, Seidenberg M, Mayer AR, Mead LA, Binder JR, Rao SM. 2000. Neural systems underlying the recognition of familiar and newly learned faces. *J Neurosci* 20:878-886.
- McDermott KB, Jones TC, Petersen SE, Lageman SK, Roediger HL III. 2000. Retrieval success is accompanied by enhanced activation in anterior prefrontal cortex during recognition memory: an event-related fMRI study. *J Cogn Neurosci* 12:965-976.
- Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K. 1992. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci USA* 89:5951-5955.
- Paller KA, Hutson CA, Miller BB, Boehm SG. 2003. Neural manifestations of memory with and without awareness. *Neuron* 38:507-516.
- Ranganath C, Paller KA. 1999. Frontal brain potentials during recognition are modulated by requirements to retrieve perceptual detail. *Neuron* 22:605-613.
- Rizzolatti G, Fogassi L, Gallese V. 2002. Motor and cognitive functions of the ventral premotor cortex. *Curr Opin Neurobiol* 12:149-154.
- Rugg MD, Allan K. 2000. Event-related potential studies of memory. In: Tulving E, Craik FIM, editors. *The Oxford handbook of memory*. New York: Oxford University Press. p 521-538.
- Rugg MD, Allan K, Birch CS. 2000. Electrophysiological evidence for the modulation of retrieval orientation by depth of study processing. *J Cogn Neurosci* 12:664-678.
- Rugg MD, Fletcher PC, Frith CD, Frackowiak RS, Dolan RJ. 1997. Brain regions supporting intentional and incidental memory: a PET study. *Neuroreport* 8:1283-1287.
- Rugg MD, Mark RE, Walla P, Schloerscheidt AM, Birch CS, Allan K. 1998. Dissociation of the neural correlates of implicit and explicit memory. *Nature* 392:595-598.
- Rugg MD, Walla P, Schloerscheidt AM, Fletcher PC, Frith CD, Dolan RJ. 1998. Neural correlates of depth of processing effects on recollection: evidence from brain potentials and positron emission tomography. *Exp Brain Res* 123:18-23.
- Schloerscheidt AM, Rugg MD. 1997. Recognition memory for words and pictures: an event-related potential study. *Neuroreport* 8:3281-3285.
- Shannon BJ, Buckner RL. 2004. Functional-anatomic correlates of memory retrieval that suggest nontraditional processing roles for multiple distinct regions within posterior parietal cortex. *J Neurosci* 24:10084-10092.
- Snodgrass JG, Vanderwart M. 1980. A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. *J Exp Psychol Hum Learn* 6:174-215.
- Velanova K, Jacoby LL, Wheeler ME, McAvoy MP, Petersen SE, Buckner RL. 2003. Functional-anatomic correlates of sustained and transient processing components engaged during controlled retrieval. *J Neurosci* 23:8460-8470.
- Wagner AD, Shannon BJ, Kahn I, Buckner RL. 2005. Parietal lobe contributions to episodic memory retrieval. *Trends Cogn Sci* 9:445-453.

- Wheeler ME, Buckner RL. 2003. Functional dissociation among components of remembering: control, perceived oldness, and content. *J Neurosci* 23:3869-3880.
- Wheeler ME, Buckner RL. 2004. Functional-anatomic correlates of remembering and knowing. *Neuroimage* 21:1337-1349.
- Yonelinas AP. 2002. The nature of recollection and familiarity: a review of 30 years of research. *J Mem Lang* 46:411-517.
- Yonelinas AP, Levy BJ. 2002. Dissociating familiarity from recollection in human recognition memory: different rates of forgetting over short retention intervals. *Psychon Bull Rev* 9: 575-582.
- Yonelinas AP, Otten LJ, Shaw KN, Rugg MD. 2005. Separating the brain regions involved in recollection and familiarity in recognition memory. *J Neurosci* 25:3002-3008.