

S. M. Daselaar, M. S. Fleck and R. Cabeza

J Neurophysiol 96:1902-1911, 2006. First published May 31, 2006; doi:10.1152/jn.01029.2005

You might find this additional information useful...

Supplemental material for this article can be found at:

<http://jn.physiology.org/cgi/content/full/01029.2005/DC2>

This article cites 64 articles, 20 of which you can access free at:

<http://jn.physiology.org/cgi/content/full/96/4/1902#BIBL>

This article has been cited by 10 other HighWire hosted articles, the first 5 are:

Role of Amygdala Connectivity in the Persistence of Emotional Memories Over Time: An Event-Related fMRI Investigation

M. Ritchey, F. Dolcos and R. Cabeza

Cereb Cortex, November 1, 2008; 18 (11): 2494-2504.

[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)

The Effects of Aging on the Neural Correlates of Subjective and Objective Recollection

A. Duarte, R. N. Henson and K. S. Graham

Cereb Cortex, September 1, 2008; 18 (9): 2169-2180.

[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)

Dissociation between Explicit Memory and Configural Memory in the Human Medial Temporal Lobe

A. R. Preston and J. D. E. Gabrieli

Cereb Cortex, September 1, 2008; 18 (9): 2192-2207.

[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)

Contributions of the medial temporal lobe to declarative memory retrieval:

Manipulating the amount of contextual retrieval

I. Tendolkar, J. Arnold, K. M. Pettersson, S. Weis, A. Brockhaus-Dumke, P. van Eijndhoven, J. Buitelaar and G. Fernandez

Learn. Mem., August 21, 2008; 15 (9): 611-617.

[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)

Scenes Unseen: The Parahippocampal Cortex Intrinsically Subserves Contextual Associations, Not Scenes or Places Per Se

M. Bar, E. Aminoff and D. L. Schacter

J. Neurosci., August 20, 2008; 28 (34): 8539-8544.

[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)

Updated information and services including high-resolution figures, can be found at:

<http://jn.physiology.org/cgi/content/full/96/4/1902>

Additional material and information about *Journal of Neurophysiology* can be found at:

<http://www.the-aps.org/publications/jn>

This information is current as of April 19, 2009 .

Triple Dissociation in the Medial Temporal Lobes: Recollection, Familiarity, and Novelty

S. M. Daselaar,^{1,2} M. S. Fleck,^{2,3} and R. Cabeza^{2,3}

¹Swammerdam Institute for Life Sciences, Faculty of Science, University of Amsterdam, Amsterdam, The Netherlands; ²Center for Cognitive Neuroscience and ³Psychological and Brain Sciences, Duke University, Durham, North Carolina

Submitted 30 September 2005; accepted in final form 23 May 2006

Daselaar, S. M., M. S. Fleck, and R. Cabeza. Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. *J Neurophysiol* 96: 1902–1911, 2006. First published May 31, 2006; doi:10.1152/jn.01029.2005. Memory for past events may be based on retrieval accompanied by specific contextual details (recollection) or on the feeling that an item is old (familiarity) or new (novelty) in the absence of contextual details. There are indications that recollection, familiarity, and novelty involve different medial temporal lobe subregions, but available evidence is scarce and inconclusive. Using functional magnetic resonance imaging (MRI), we isolated retrieval-related activity associated with recollection, familiarity, and novelty by distinguishing between linear and nonlinear oldness functions derived from recognition confidence levels. Within the medial temporal lobes (MTLs), we found a triple dissociation among the posterior half of the hippocampus, which was associated with recollection, the posterior parahippocampal gyrus, which was associated with familiarity, and anterior half of the hippocampus and rhinal regions, which were associated with novelty. Furthermore, multiple regression analyses based on individual trial activity showed that all three memory signals, i.e., recollection, familiarity, and novelty, make significant and independent contributions to recognition memory performance. Finally, functional dissociations among recollection, familiarity, and novelty were also found in posterior midline, left parietal cortex, and prefrontal cortex regions. This is the first study to reveal a triple dissociation within the MTL associated with distinct retrieval processes. This finding has direct implications for current memory models.

INTRODUCTION

A fundamental aspect of memory function is the ability to determine whether or not a present event happened in the past; that is, the ability to recognize events as old or new. It is generally agreed that old/new recognition is dependent on the integrity of the medial temporal lobes (MTLs), which include the hippocampus proper and surrounding parahippocampal gyrus (PHG). In support of this idea, functional neuroimaging studies have directly related MTL activity to successful recognition performance (Daselaar et al. 2001; Donaldson et al. 2001; Eldridge et al. 2000; Nyberg et al. 1996). However, the precise contribution of different MTL structures to recognition memory remains uncertain.

In particular, recognition memory is assumed to involve at least two qualitatively different processes: recollection and familiarity (Yonelinas 2002). *Recollection* refers to memory retrieval accompanied by the recovery of specific contextual details, whereas *familiarity* refers to the feeling that an item is old in the absence of confirmatory contextual information.

There is considerable debate about whether the hippocampus and PHG make separate contributions to recollection and familiarity. Some patient data suggest that hippocampal lesions impair recollection but not familiarity, suggesting that the latter process is mediated by adjacent PHG regions (Baddeley et al. 2001; Holdstock et al. 2002; Yonelinas et al. 2002), whereas others found that hippocampal damage leads to similar deficits in recollection and familiarity (Stark and Squire 2003; Stark et al. 2002). The results of functional neuroimaging studies also do not indicate a clear-cut dissociation. On one hand, findings from false memory (Cabeza et al. 2001) and visual adaptation paradigms (Goh et al. 2004) suggest that posterior PHG regions track item-specific perceptual features, whereas the hippocampus supports retrieval of contextual information. On the other hand, studies using both relational encoding (Davachi et al. 2003; Ranganath et al. 2004) and retrieval (Eldridge et al. 2000; Kahn et al. 2004; Prince et al. 2005; Yonelinas et al. 2001, 2005) paradigms have indicated a similar role for posterior hippocampal and parahippocampal regions in context-based memory.

A matter that adds to the discussion is that familiarity may be based not only on an oldness signal but also on a *novelty* signal. Although at the behavioral level, these two types of signals cannot be distinguished, there are indications that at the neural level, both activity increases (familiarity) and decreases (novelty) can contribute to familiarity-based recognition. Single-cell recording studies in monkeys have identified neurons in the rhinal cortex that show decreased firing rates to repeated presentations of visual stimuli. It has been proposed that these reductions contribute to familiarity-based recognition by signaling the relative novelty of stimuli (Brown and Aggleton 2001). Functional magnetic resonance imaging (fMRI) studies in humans also indicate a role for the rhinal cortex in novelty detection. Several experiments that compared old items to new items (Cansino et al. 2002; Henson et al. 2003; Herron et al. 2004; Rombouts et al. 2001) or to items incorrectly classified as new (Weis et al. 2004a,b) showed an activation decrease at or near rhinal cortex. Furthermore, a recent fMRI study indicated a direct relation between decreased activity in the rhinal cortex and the level of perceived familiarity (Gonsalves et al. 2005).

In addition to the rhinal cortex, there is also electrophysiological evidence for a role of the hippocampus in novelty detection. Intracranial recordings in surgical patients with implanted electrodes have revealed an event-related brain poten-

Address for reprint requests and other correspondence: S. Daselaar, University of Amsterdam, Amsterdam, The Netherlands (E-mail: s.m.daselaar@uva.nl).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

tial, known as the AMTL-N400, which originates from anterior MTL and shows a greater response to novel relative to previously studied words and pictures (Elger et al. 1997; Fell et al. 2004; Fernandez et al. 1999; Grunwald et al. 1998, 1999; Trautner et al. 2004). The AMTL-N400 is reduced in patients with hippocampal sclerosis (Grunwald et al. 1998), and its magnitude is directly correlated with neuronal density in the CA1 field of the hippocampus (Grunwald et al. 1999). At the same time, recordings from a more posterior site within the hippocampus has revealed another event-related potential, known as the hippocampal late negative component (LNC), that is greater for old than for new items (Grunwald et al. 1998, 2003; Klaver et al. 2005). Hence, together with aforementioned fMRI evidence linking posterior hippocampus to recollection, electrophysiological findings are suggestive of an anterior/posterior dissociation within the hippocampus regarding oldness (recollection) and novelty.

The main goal of the present event-related functional MRI (fMRI) study was to disentangle the contribution of different PHG and hippocampal regions to recollection, familiarity, and novelty using a recognition task with confidence ratings. In each recognition trial, the old/new decision was followed by a confidence rating (low to high), yielding a combined *oldness scale* from 1 = definitely new to 6 = definitely old. According to theoretical models of recognition memory, familiarity reflects the assessment of quantitative memory strength, whereas recollection reflects a threshold retrieval process whereby qualitative information about a previous event is retrieved (Yonelinas 2002). These models predict that familiarity should increase gradually as a function of perceived oldness (i.e., a continuous linear function), whereas recollection should be associated only with the highest level of confidence, reflecting the retrieval of confirmatory contextual information (i.e., a nonlinear function) (Yonelinas 2001a, 2002). This idea has been confirmed by behavioral studies in which participants classified items as recollected ("remember") or familiar ("know") (Yonelinas 2001b) or retrieved specific contextual information (Yonelinas 1999). Thus we predicted that familiarity-related activity and novelty-related activity during retrieval should increase (familiarity signal) or decrease (novelty signal) continuously as a function of oldness (from 1 to 6), whereas recollection-related activity should show a nonlinear oldness function (flat from 1 to 5, sharp increase for level 6). Hence, throughout this paper, we will use the terms familiarity, novelty, and recollection as labels for these activation patterns. Critically, we additionally tested whether the MTL regions identified by the different oldness functions actually make unique contributions to recognition performance by employing multiple regression analyses based on individual trial activity.

A second goal of the study was to investigate the contribution of brain regions outside MTL to recollection, familiarity, and novelty. A recent fMRI study in which participants were asked to classify items as recollected or familiar reported recollection/familiarity dissociations between subregions of posterior midline and left parietal regions (Yonelinas et al. 2005). In the present study, we investigated whether these dissociations can also be observed when using continuous confidence ratings and defining recollection versus familiarity according to the shape of activation functions. Furthermore, lesion and neuroimaging findings also indicate a prominent role for different prefrontal cortex (PFC) regions in recognition

memory. For instance, ventrolateral PFC has been associated with retrieval of relational information (Eldridge et al. 2000; Henson et al. 1999; Passingham et al. 2000; Prince et al. 2005), whereas right dorsolateral PFC has been implicated with monitoring of stimulus novelty (Schacter et al. 1996; Stuss et al. 1994). Thus we predicted that ventrolateral PFC regions would be associated with recollection and right dorsolateral PFC with novelty.

METHODS

Participants

Fourteen right-handed young participants (6 female) with an average age of 21.7 ± 2.4 (SD) yr were recruited from the Duke University community and paid for participation. Written informed consent was obtained for each participant, and the study met all criteria for approval from the Duke University Institutional Review Board.

Experimental protocol

Prior to scanning, participants studied an intermixed list of 120 English words and 80 pronounceable nonwords at a rate of 2 s per item within the context of a lexical decision task. Participants responded whether the target was an English word or not, and they were told that there would be a later memory test for the English words. Functional scanning occurred ~30 min after this study phase. During the scan session, participants performed two kinds of tasks, a recognition memory task and a nonmnemonic perceptual judgment task. These tasks were presented across six experimental runs (4 recognition and 2 perceptual, counterbalanced in order across participants), each lasting 442 s. During the recognition memory blocks, participants saw an equal mix of old words shown during the earlier lexical decision task and completely new words (60 total words per block). Each trial consisted of two phases. Participants first made an old/new judgment on the presented words (3.4 s) and were then prompted to report their confidence (1.7 s) for their answer from 1 (lowest confidence) to 4 (highest confidence), followed by an inter-trial interval between 0 to 5.4 s. The perceptual judgment task involved participants viewing rectangles unevenly divided into two colored sections, blue and orange, by a random jagged line. Participants determined which color had the greater surface area. Again, this judgment was followed by a confidence rating. Data from the perceptual task are reported elsewhere (Fleck et al. 2005).

Stimulus materials

The critical stimuli consisted of 240 five-letter words that were selected from the MRC psycholinguistic database (<http://www.psy.uwa.edu.au/MRCDataBase/mrc2.html>). The words were of moderate frequency (mean: 39), concreteness (mean: 504), and imageability (mean: 510).

fMRI scanning

Images were collected using a 4T GE scanner. High-resolution T1-weighted structural images (256×256 matrix, TR 12 ms, TE 5 ms, FOV 24 cm, 68 slices, 1.9 mm slice thickness, 0 mm spacing) were collected first. Coplanar functional images were subsequently acquired using an inverse spiral sequence (64×64 image matrix, TR 1700 ms, TE 31 ms, FOV 24 cm, 34 slices, 3.8 mm slice thickness). Scanner noise was reduced with ear plugs, and head motion was minimized with foam pads. Stimuli were presented with LCD goggles (Resonance Technology). Behavioral responses were recorded with a four-key fiber-optic response box (Resonance Technology).

Data analysis

Preprocessing and data analysis were performed using Statistical Parametric Mapping software implemented in Matlab (SPM2; Wellcome Department of Cognitive Neurology, London, UK). After discarding initial volumes to allow for scanner stabilization, images were slice-timing corrected and motion-corrected, then spatially normalized to the Montreal Neurological Institute (MNI) template and smoothed using a Gaussian kernel of 8 mm FWHM. For each subject, trial-related activity was modeled by convolving a vector of trial onsets with a canonical hemodynamic response function (HRF) within the context of the General Linear Model (GLM). Locations of activations that fell within MTL were checked on each individual participant.

Oldness function analyses

To identify regions associated with recollection, familiarity, and novelty, we employed a parametric approach. As a first step, we created an oldness scale by combining the old/new judgments with the four confidence levels, yielding an eight-point oldness scale (1 = definitely new, 8 = definitely old). Because the lowest confidence level (level 1) was not used at all by one participant and only sparsely used by the other participants, we dropped this level from further analyses. Based on the remaining six levels (1 = definitely new, 6 = definitely old), we created separate oldness functions to model recollection and familiarity/novelty. Recollection was modeled by a nonlinear function that is flat from 1 to 5 with a sharp increase for level 6 (i.e., 1 1 1 1 1 6), whereas familiarity (i.e., 1 2 3 4 5 6) and novelty (i.e., 6 5 4 3 2 1) were modeled as positive and negative contrasts of a continuous linear function. For the sake of completeness, we also included a nonlinear novelty function (i.e., 6 1 1 1 1 1) for comparison with the linear novelty contrast (see following text). Next, we created separate GLMs for the linear and the nonlinear functions in which trial onsets for both old and new items were collapsed across accuracy and confidence and modulated by the different oldness functions using the first-order parametric modulation option integrated in SPM2.

Subsequently, group averages were calculated for each parametric regressor using random effects analyses. Finally, to assess recollection-, familiarity-, and novelty-related activities, the parametric regressors were directly compared using paired *t*-test at $P < 0.05$, and inclusively masked at $P < 0.005$ with the relevant main effects (i.e., recollection-related activity = nonlinear oldness > linear oldness masked with nonlinear oldness; familiarity-related activity = linear oldness > nonlinear oldness masked with linear oldness; novelty-related activity = linear novelty > nonlinear novelty masked with linear novelty). Regions showing nonlinear novelty functions are reported as supplementary materials. Critically, mean centering (Euclidean normalization) the linear and nonlinear regressors did not result in significant differences in the minima ($P = 0.24$), maxima ($P = 0.58$), and range ($P = 0.90$) of the parametric scaling factors. Given that we had very specific predictions about the areas within MTL, posterior midline cortex, left parietal cortex, and PFC that would show linear and nonlinear oldness patterns, we used statistical thresholds that were uncorrected for multiple comparisons. Therefore strictly speaking, our results should be interpreted with some caution.

Individual trial analysis

To examine whether the different MTL regions that were identified by the oldness function analyses make separate contributions to recognition memory, we conducted a second analysis based on individual trial activity. As a first step, we created a GLM model in which each individual trial was modeled by a separate covariate, yielding different parameter estimates for each individual trial and for each individual subject. The validity of this design was confirmed by the fact that we obtained highly comparable results based on linear contrasts of the individual trial parameter estimates compared with

those obtained with a standard GLM model (see supplemental data¹). Moreover, a similar procedure has been successfully applied in a previously published fMRI study (Rissman et al. 2004). As a second step, mean activity was extracted for each individual trial from the different MTL regions that were identified by the oldness function analyses. For each individual subject, these values were subsequently entered into a multiple regression model with activity in the different MTL regions (i.e., regions showing recollection-related activity, familiarity-related activity, novelty-related activity) as independent variables, and the 6-point oldness scale as the dependent variable. Finally, to assess group effects, the resulting parameter estimates (beta weights) were submitted to a one-sample *t*-test, thresholded at $P < 0.05$.

RESULTS

Behavioral data

The overall proportion of correctly recognized words was 0.71 ± 0.14 (mean \pm SD) and the proportion of false alarms was 0.22 ± 0.09 leading to a d' score of 1.43 ± 0.6 . Table 1 lists mean accuracy, reaction times (RTs), and frequency data for the six oldness levels. We analyzed the effects of oldness on accuracy and RT measures with two separate one-way (oldness: 1–6) ANOVAs. The results showed a significant effect of oldness on both RTs ($P = 0.001$) and accuracy ($P < 0.0001$). Follow-up *t*-test revealed that behavioral responses associated with the highest oldness level were different from all the other levels. They were made significantly faster (level 6 vs. level 1, $P = 0.002$; level 6 vs. level 2, $P = 0.0003$; level 6 vs. level 3, $P < 0.0001$; level 6 vs. level 4, $P < 0.0001$; level 6 vs. level 5, $P < 0.0001$) as well as more accurately (level 6 vs. level 1, $P = 0.007$; level 6 vs. level 2, $P < 0.0001$; level 6 vs. level 3, $P < 0.0001$; level 6 vs. level 4, $P < 0.0001$; level 6 vs. level 5, $P < 0.0001$). Thus behavioral results are generally in line with the assumption that recollection is primarily associated with the highest oldness level.

fMRI oldness function analyses

Table 2 lists regions showing recollection-, familiarity-, and novelty-related activity. As noted in the INTRODUCTION, we predicted recollection/familiarity/novelty dissociations within MTL, and within three other brain regions, the posterior midline region, left parietal cortex, and PFC. The results confirmed our predictions.

MTL. Within MTL, there was a triple dissociation. The posterior half of the hippocampus showed recollection-related activity (see Fig. 1A), the posterior PHG showed familiarity-related activity (B), and finally, anterior hippocampal and rhinal regions showed novelty-related activity (C). As illustrated by line graphs, the posterior half of the hippocampus showed a nonlinear oldness function with a sharp increase for the highest oldness level. In contrast, posterior parahippocampal activity increased continuously as a function of oldness (familiarity). Finally, activity in anterior hippocampal and rhinal regions showed a novelty pattern with a continuous activity decrease with increasing levels of oldness. Anatomical localization of the MTL activations was confirmed at the individual-subject level.

¹ The online version of this article contains supplemental data.

TABLE 1. Behavioral and frequency data for the six oldness levels

	Oldness Level					
	1	2	3	4	5	6
Response times, s	1.47 ± 0.25	1.48 ± 0.25	1.59 ± 0.23	1.69 ± 0.30	1.47 ± 0.26	1.26 ± 0.25
Accuracy, %	89.4 ± 10.1	78.5 ± 12.0	68.7 ± 14.5	55.3 ± 16.45	74.4 ± 15.2	98.6 ± 2.9
Frequency, % of total trials	8.8 ± 5.5	15.8 ± 7.5	19.2 ± 7.5	9.0 ± 4.4	11.5 ± 5.9	19.0 ± 10.5

Values are means ± SD.

The dissociations in MTL were further confirmed by 2 (region 1, region 2) × 6 (oldness: 1–6) ANOVAs showing significant region × oldness interactions between mean activity in the posterior half of the hippocampus and posterior PHG ($P = 0.02$), posterior and anterior halves of the hippocampus ($P = 0.005$), posterior half of the hippocampus and rhinal cortex ($P < 0.0001$), posterior PHG and anterior half of the hippocampus ($P = 0.02$), and finally, a trend for an interaction between posterior PHG and rhinal cortex ($P = 0.06$). In addition, a 3 (posterior hippocampus, posterior PHG, sum of the 2 novelty MTL regions) × 6 (oldness: 1–6) ANOVA including all three MTL signals (recollection, familiarity, and novelty) also yielded a highly significant region × oldness interaction ($P < 0.0001$).

As a final confirmation of the dissociations in MTL, we compared the residual mean square (ResMS)—an established measure of goodness of fit—generated by the different GLM analyses incorporating the linear and nonlinear oldness functions. As expected, we found that the posterior hippocampus showed a smaller ResMS for the increasing nonlinear

(ResMS = 1611 ± 588) than for the linear model (ResMS = 1,616, ± 590), the posterior PHG for the linear (ResMS = 597 ± 215) than for the increasing nonlinear model (ResMS = 599 ± 217), the anterior hippocampus for the linear (ResMS = 1,046 ± 372) than for the decreasing nonlinear model (ResMS = 1,090 ± 387), and finally, the rhinal cortex also for the linear (ResMS = 2,166 ± 1,613) than for the decreasing nonlinear model (ResMS = 2,299 ± 1,590). Although the differences between the models were small across participants, they were consistently in the same direction (posterior hippocampus, 13/14 participants; posterior PHG, 13/14; anterior hippocampus, 13/14; rhinal cortex, 12/14) indicating a highly reliable difference in ResMS. The consistency in the direction of the difference was confirmed in all four MTL regions (posterior hippocampus, posterior PHG, and anterior hippocampus, $P = 0.0018$; rhinal cortex, $P = 0.0129$) by means of a signed-rank test.

OTHER BRAIN REGIONS. Within posterior midline, there was a dissociation between a retrosplenial/ventral posterior cingulate

TABLE 2. Brain regions associated with recollection, familiarity, and novelty

Region	Side	BA	x	y	z	T-values linear	T-values nonlinear
<i>Recollection</i>							
Post. Hippocampus	L	—	-26	-26	-11	3.57	5.31
	R	—	30	-23	-11	2.44	3.59
Retrosplenial cortex	L	29/30	-4	-43	20	3.01	5.12
Ventral Post. Cingulate cortex	—	23	0	-23	33	9.81	11.59
Parietotemporal cortex	L	39/40	-45	-65	31	5.07	6.82
Ventrolateral PFC	L	47	-27	14	-20	3.23	4.74
	R	47	34	17	-20	3.28	5.51
Occipital cortex	—	18	0	-81	-2	1.69	5.93
Medial PFC	L	10	-4	59	-3	4.19	5.56
<i>Familiarity</i>							
Posterior Parahipp. cortex	L	35/36	-34	-41	-8	3.23	1.98
Dorsal Post. Cingulate cortex	—	31	0	-31	44	7.33	5.35
Precuneus	L	7	-15	-68	34	4.17	3.05
Parieto-occipital cortex	L	19/39	-38	80	32	5.06	3.30
Cuneus	R	18/31	15	-58	17	4.91	1.55
Anterior Cingulate	—	24	0	30	12	4.39	1.86
<i>Novelty</i>							
Anterior Hippocampus	L	—	-19	-8	-16	3.56	0.00
Rhinal cortex	R	28/36	27	-4	-27	3.36	-0.2
Putamen	R	—	30	15	-4	4.07	1.03
Lateral Temporal cortex	L	21	-64	-11	-3	5.96	-0.86
	L	—	-45	-23	-18	4.15	-1.4
	R	—	49	-22	5	3.87	-1.6
Medial Parietal cortex	L	7	-11	-52	62	4.88	-0.78
Anterior Cingulate	R	32	4	17	41	4.91	2.24
Broca's Area	L	44	-49	2	31	6.04	0.76
Dorsolateral PFC	R	46	56	5	28	5.46	0.11
	R	—	45	38	19	4.45	1.94
	R	—	30	13	52	3.57	-2.06
Cerebellum	L	—	-11	-42	-23	5.46	-1.51

PFC, prefrontal cortex.

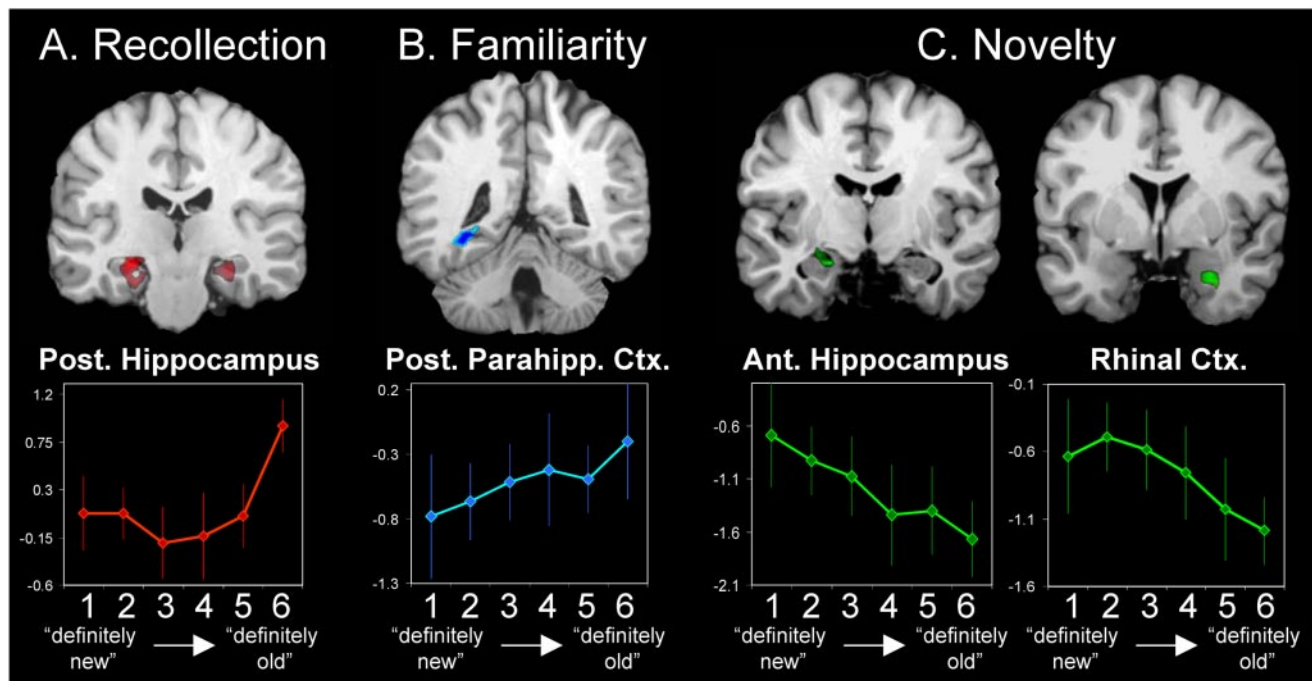


FIG. 1. A triple dissociation within the medial temporal lobe (MTL) regarding recollection, familiarity, and novelty. The line graphs display peak effect sizes as a function of the 6-point oldness scale. The vertical bars indicate SEs.

region (BA 23/30), which was associated with recollection (see Fig. 2A), and a dorsal posterior cingulate region (BA 31, see Fig. 2B) and the precuneus (BA 7, see Fig. 2C), which were associated with familiarity. As shown by the graphs, the retrosplenial/ventral posterior cingulate activity showed a non-linear oldness function, whereas the dorsal posterior cingulate and precuneus activation showed a continuous oldness function. The dissociation in posterior midline was confirmed by 2 (region: region 1, region 2) \times 6 (oldness: 1–6) ANOVAs showing significant region \times oldness interactions between mean activity in retrosplenial/ventral posterior cingulate and dorsal posterior cingulate ($P < 0.0001$) and between retrosplenial/ventral posterior cingulate and precuneus ($P < 0.0001$).

Within left parietal cortex, there was a dissociation between a parieto-temporal region (BA 39/40), which was associated with recollection (see Fig. 2D) and a parieto-occipital region (BA 39/19), which was associated with familiarity (see Fig. 2E). As depicted by the graphs, the parieto-temporal activation showed a nonlinear oldness function, whereas the parieto-occipital region showed a continuous oldness function. This dissociation was confirmed by a 2 (region: parieto-temporal cortex, parieto-occipital cortex) \times 6 (oldness: 1–6) ANOVA showing a significant region \times oldness interaction ($P < 0.0001$). Within PFC, ventrolateral PFC was associated with recollection, whereas a right dorsolateral PFC region showed novelty-related activity. The graphs show a nonlinear oldness function in ventrolateral PFC (see Fig. 2F), but a continuous activity decrease (novelty) in right dorsolateral PFC (see Fig. 2G). Again, the dissociation in PFC was confirmed by 2 (region: region 1, region 2) \times 6 (oldness: 1–6) ANOVAs showing a significant region \times oldness interaction ($P < 0.0001$) between mean activity in right dorsolateral PFC region and both left ($P < 0.0001$) and right ($P < 0.0001$) ventrolateral PFC.

fMRI individual trial analyses

To examine if the different MTL structures make separate contributions to recognition memory, we performed a multiple regression analysis with mean individual trial activity in the PHG familiarity region, the hippocampal recollection region, and the combined signal of the two novelty regions, anterior hippocampus and rhinal cortex, as independent variables and the oldness scale as dependent variable. The results revealed significant contributions of each of the three signals with a negative beta value for the novelty regions (anterior hippocampus + rhinal cortex: beta = -0.16 , $P < 0.0001$; posterior hippocampus: beta = 0.10 , $P = 0.008$; posterior PHG: beta = 0.10 , $P = 0.001$).

The fact that all three types of MTL regions showed significant beta values based on the regression analysis indicates that each of these regions was *uniquely* (i.e., after controlling for the contribution of the other 2 areas) correlated with the oldness scale. This implies that these regions make separate contributions to recognition performance, suggesting that recollection, familiarity, and novelty are relatively independent processes.

DISCUSSION

We found a triple dissociation within MTL associated with recollection, familiarity, and novelty. First, posterior half of the hippocampus showed recollection-related activity. Second, posterior PHG showed familiarity-related activity. Finally, an anterior hippocampal region and the rhinal cortex showed novelty-related activity.

In addition, functional dissociations regarding recollection, familiarity, and novelty were found outside MTL in posterior midline, left parietal cortex, and PFC regions. We discuss these

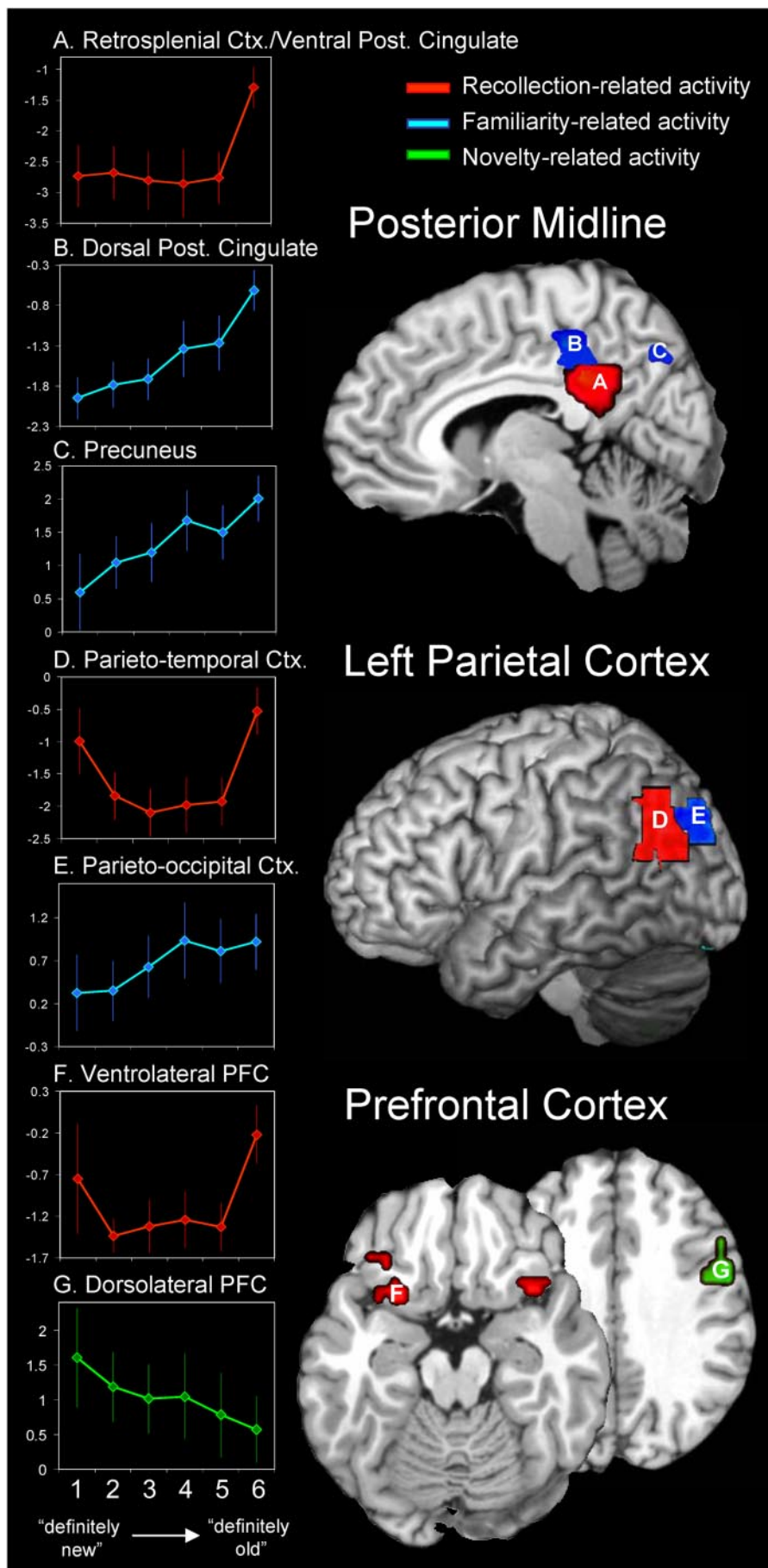


FIG. 2. Brain regions outside MTL showing recollection-, familiarity-, and novelty-related activity. The line graphs display peak effect sizes as a function of the 6-point oldness scale. The vertical bars indicate SEs.

findings in MTL and other brain regions in separate sections in the following text.

MTL

The posterior half of the hippocampus was associated with recollection (see Fig. 1A). Activity in this region showed a nonlinear oldness function increasing sharply only for the highest oldness rating. The finding of recollection-related activity in the posterior half of the hippocampus is consistent with the results of several previous fMRI studies using remember/know and relational memory paradigms (Eldridge et al. 2000; Kahn et al. 2004; Prince et al. 2005; Wheeler and Buckner 2004; Yonelinas et al. 2005). The present finding is also in line with lesion evidence in both animals (Fortin et al. 2004) and humans (Baddeley et al. 2001; Holdstock et al. 2002; Yonelinas et al. 2002), indicating selective relational memory deficits after hippocampal damage. The present study adds to these findings by showing that the posterior half of the hippocampus operates in an all-or-none fashion, selectively mediating memory processes that lead to high confidence retrieval, which are assumed to reflect the recovery of confirmatory contextual information (Yonelinas 2001a, 2002). In general, our results provide further support for the view that the hippocampus plays a fundamental role in relational memory processes (Eichenbaum et al. 1992).

Posterior PHG was associated with familiarity (see Fig. 1B). Activity in this region showed a continuous increase in activity with increasing levels of oldness. The finding that posterior PHG tracks stimulus familiarity is in line with previous fMRI studies that associated activity in this region with item-based perceptual retrieval processes (Cabeza et al. 2001; Goh et al. 2004). At the same time, this finding is not in agreement with studies that related activity in posterior PHG to recollection and relational memory processes (Davachi et al. 2003; Eldridge et al. 2000; Kahn et al. 2004; Prince et al. 2005; Ranganath et al. 2004; Yonelinas et al. 2001, 2005). Although we do not have a clear-cut explanation for this inconsistency, it may be that certain parts of posterior PHG contribute to familiarity, whereas other parts contribute to recollection. In terms of anatomical connectivity, posterior PHG receives direct input from several uni- and polymodal regions in visual, temporal, and parietal cortex and provides about a third of the sensory input to the hippocampus (Suzuki and Amaral 1994). The strong connection of posterior PHG with sensory areas fits well with evidence that familiarity depends more heavily on perceptual processing than recollection (Yonelinas 2002). For instance, there are indications that perceptual fluency, the ease with which perceptual information is extracted from a stimulus, plays a role in familiarity judgments. Because prior exposure to a stimulus facilitates subsequent perceptual processing, it has been proposed that perceptual fluency can be used as an index of oldness during recognition tasks (Jacoby 1991). Supporting this idea, fluency manipulations, such as presenting a particular word more clearly than other words in a recognition test, affects familiarity more than recollection (Jacoby 1991; Whittlesea and Leboe 2000; Yonelinas 2002). Thus given these behavioral findings and the strong anatomical connections of posterior PHG with perceptual regions, the increase in activity in this region with oldness may reflect an increased reliance on perceptual fluency during familiarity-based recognition.

Two anterior MTL regions, the anterior half of the hippocampus and the rhinal cortex showed novelty-related activity (see Fig. 1C). Specifically, activity in these regions showed a continuous decrease with increasing levels of oldness. The finding of a novelty signal in the anterior half of the hippocampus is consistent with *in vivo* recordings in humans (Grunwald et al. 1998, 1999) showing that this region is more activated for new than for old items. This finding is also consistent with the results of a fMRI study of artificial grammar learning in which anterior hippocampal activity decreased linearly with repeated presentations, whereas the opposite occurred for posterior hippocampal activity (Strange et al. 1999). In this particular study, the novelty signal in the anterior half of the hippocampus was sensitive to perceptual features of the stimuli, a finding consistent with the notion of familiarity. The finding of a novelty signal in rhinal cortex is consistent with a recent fMRI study, which also showed continuous activity decreases near this region as a function of the level of perceived familiarity (Gonsalves et al. 2005). At the same time, the finding that this region showed *decreased* activity with increasing levels of familiarity, seems to contradict previous fMRI findings indicating an opposite relationship during memory encoding, i.e., *increased* rhinal activity with increasing levels of familiarity as assessed by a subsequent recognition test (Ranganath et al. 2004). However, these findings can easily be reconciled by the view that novelty detection contributes to successful encoding (Habib and Lepage 1999; Ranganath and Rainer 2003; Tulving et al. 1996). According to the novelty-encoding view, greater novelty activity for a study item will lead to better encoding and thus to increased familiarity for that same item on a subsequent recognition test.

Following the novelty-encoding account, it could be argued that the activation we found in anterior MTL reflected encoding processes rather than novelty *per se*. To test this idea, we conducted a follow-up behavioral experiment using the same method as in the fMRI study but with the addition of second recognition test, which included correctly rejected new items from the first recognition test mixed with another set of novel items. We reasoned that if greater anterior MTL activity for items classified as “definitely new” reflected encoding processes, then these items should be better remembered in the second test than those classified as “probably new.” However, this was not the case: performance in the second recognition test was not affected by perceived novelty in the first test (see Fig. S2, Supplemental data). This finding indicates that novelty detection during retrieval is not identical to episodic encoding.

A possible mechanism by which hippocampus and rhinal cortex can modulate novelty processes is through efferent projections to the nucleus basalis of Meynert (NBM). This region provides cholinergic input to almost the entire neocortex (Mesulam 2004). There is abundant evidence that acetylcholine (ACh) plays a critical role in attention and memory-related processes (Rasmusson 2000; Sarter and Bruno 1997; Woolf 1998). Furthermore, ACh increases baseline firing rates of cortical neurons and enhances activity evoked by novel stimuli (Gu 2002). Thus it has been suggested that hippocampal and rhinal regions mediate novelty- and attention-related processes through the regulation of cortical input of ACh (Ranganath and Rainer 2003). Clarifying the specific contributions of anterior half of the hippocampus and rhinal cortex to novelty processes requires further research.

The finding of both familiarity and novelty patterns in MTL raises the question whether these two signals are mechanistically distinct. As noted, from a behavioral point of view, positive familiarity and negative familiarity (novelty) can be seen as two sides of the same effect. Yet, our fMRI data clearly indicate that, on the brain level, these two effects are distinguishable. Regression analyses based on individual trial activity indicated that recollection-, familiarity-, and novelty-related MTL regions make separate contributions to recognition performance. Thus together with the recollection pattern in posterior half of the hippocampus, our findings provide preliminary support for a triple-process model of recognition memory incorporating recollection, familiarity, and novelty. However, more research is required to determine whether familiarity and novelty are truly different processes rather than two different aspects of the same process.

Finally, it should be noted that despite our specific predictions, some caution in interpreting our results is appropriate because we identified the different MTL regions using a slightly lower threshold ($P < 0.005$) than conventionally used in event-related fMRI studies ($P < 0.001$). In fact, the anterior MTL regions did not survive a $P < 0.001$ threshold in the standard regression analysis. However, the individual trial analysis confirmed the contribution of the anterior MTL regions to recognition performance, and showed a highly significant effect ($P < 0.0001$). Hence, collectively, the two analyses clearly support our conclusions.

Other brain regions

Within the posterior midline region, the retrosplenial/ventral posterior cingulate cortex was associated with recollection (see Fig. 1A), whereas both the dorsal posterior cingulate cortex (B) and precuneus (C) were associated with familiarity. These results are generally in agreement with a recent fMRI study by Yonelinas and colleagues (2005). Using a remember/know paradigm with graded levels of know, they also reported a functional dissociation within the posterior midline region regarding familiarity and recollection. Similar to the present findings, they found familiarity-related activity in the precuneus. Although, contrary to our results, they found recollection-related activity both in dorsal posterior cingulate cortex and retrosplenial/ventral posterior cingulate cortex. The reason for this discrepancy in findings is unclear but may relate to methodological differences, such as the employment of parametric oldness functions in the present study. The current finding that the retrosplenial/ventral posterior cingulate cortex showed a recollection pattern, whereas the dorsal posterior cingulate cortex showed a familiarity pattern fits well with neuroanatomical studies in monkeys. These studies have found that the retrosplenial/ventral posterior cingulate cortex has strong connections with posterior MTL regions, including posterior half of the hippocampus, whereas the dorsal posterior cingulate region has dense connections with visuo-spatial areas (Kobayashi and Amaral 2003). Such an interpretation fits well with aforementioned evidence that familiarity depends more heavily on perceptual processing than recollection (Yonelinas 2002).

Within left posterior parietal cortex, a parieto-temporal region was associated with recollection (see Fig. 1D), whereas a parieto-occipital region was associated with familiarity (E).

Again, these findings are in agreement with the study by Yonelinas and colleagues (2005). In that study, a parieto-temporal region also showed recollection-related activity, whereas a more posterior parietal region showed familiarity-related activity. The functional heterogeneity of these parietal subregions is consistent with evidence regarding the connectivity of these regions and with the perceptual properties attributed to familiarity. Regarding connectivity, the location of the recollection-related parieto-temporal area approximates that of region 7a in macaque monkeys. This region receives strong reciprocal connections from the CA1 area of the hippocampus (Clower et al. 2001; Suzuki and Amaral 1994) and has therefore been proposed to be directly involved in memory functions (Shannon and Buckner 2004). Regarding the properties of familiarity processes, the proximity of the familiarity-related parieto-occipital region to secondary visual cortex suggests that this region may have a greater role in visuo-perceptual processes.

Within PFC, a ventrolateral PFC region was associated with recollection (Fig. 1F), whereas a right dorsolateral PFC region showed novelty-related activity (G). The finding of recollection-related activity in ventrolateral PFC is consistent with previous functional neuroimaging studies of relational memory retrieval (Eldridge et al. 2000; Henson et al. 1999; Passingham et al. 2000; Prince et al. 2005). This finding also fits well with lesion evidence in animals. Monkeys with ventrolateral PFC lesions are severely impaired on a visual association task (Rushworth et al. 1997), and disconnection of the temporal and frontal cortex also results in severe deficits in visual association learning (Eacott and Gaffan 1992).

The finding of novelty-related activity in right dorsolateral PFC is in line with the notion that this region has a role in rejecting lures. Clinical studies indicate that patients with damage to right dorsolateral PFC show deficits in detecting stimulus novelty. They make excessive repetitions during free recall tasks (Stuss et al. 1994) and show unusually high false alarm rates during recognition (Schacter et al. 1996). Thus the current finding of novelty-related activity in right dorsolateral PFC fits well with these previous lesion findings.

Finally, it should be noted that the interpretation of the oldness functions in parieto-temporal cortex and ventrolateral PFC deserves some caution. As shown in Fig. 1, D and F, these regions did not show a clear-cut recollection pattern but rather a U-shaped function. Activity in these regions was not only high for the most confident old responses (level 6) but also for the most confident new responses (level 1). In the fMRI study by Yonelinas and colleagues, they observed similar U-shaped patterns in several brain regions including the parieto-temporal cortex. One possible explanation they suggested is that some form of recollection may also play a role in confidently rejecting novel items (see also, Rotello and Heit 2000). Alternatively though, this pattern could reflect nonmemory processes associated with high confidence decisions or desirability aspects.

Conclusions

The study yielded a triple dissociation associated with recollection, familiarity, and novelty within MTL. A posterior hippocampal region was associated with recollection, whereas a posterior PHG region was associated with familiarity. Fi-

nally, both anterior half of the hippocampus and rhinal cortex showed novelty-related activity. This is the first study to show a triple MTL dissociation within the same task and within the same participants.

In addition, functional dissociations were found outside MTL. Within the posterior midline region, the retrosplenial/ventral posterior cingulate cortex was associated with recollection, and the precuneus and dorsal posterior cingulate cortex, with familiarity. Within the left posterior parietal cortex, a parieto-temporal region was associated with recollection, whereas a parieto-occipital region was associated with familiarity. Finally, within PFC, a ventrolateral PFC region was associated with recollection, whereas right dorsolateral PFC showed novelty-related activity.

Taken together, our findings demonstrate the existence of different brain regions that are differentially involved in recollection, familiarity, and novelty processes. This finding supports the recollection/familiarity distinction and suggests that these processes are independent. The issue about whether or not recollection and familiarity/novelty processes are independent has been controversial in the behavioral memory literature following reports of correlations between behavioral measures of recollection and familiarity (Curran and Hintzman 1995, 1997). The present fMRI evidence contributes to this debate by showing anatomical dissociations between these processes that fit better with the assumption of independence.

REFERENCES

- Baddeley A, Vargha-Khadem F, and Mishkin M.** Preserved recognition in a case of developmental amnesia: implications for the acquisition of semantic memory? *J Cogn Neurosci* 13: 357–369, 2001.
- Brown MW and Aggleton JP.** Recognition memory: What are the roles of the perirhinal cortex and hippocampus? *Nat Rev Neurosci* 2: 51–61, 2001.
- Cabeza R, Rao SM, Wagner AD, Mayer AR, and Schacter DL.** Can medial temporal lobe regions distinguish true from false? An event-related functional MRI study of veridical and illusory recognition memory. *Proc Natl Acad Sci USA* 98: 4805–4810, 2001.
- Cansino S, Maquet P, Dolan RJ, and Rugg MD.** Brain activity underlying encoding and retrieval of source memory. *Cereb Cortex* 12: 1048–1056, 2002.
- Clower DM, West RA, Lynch JC, and Strick PL.** The inferior parietal lobule is the target of output from the superior colliculus, hippocampus, and cerebellum. *J Neurosci* 21: 6283–6291, 2001.
- Curran T and Hintzman DL.** Violations of the independence assumption in process dissociation. *J Exp Psychol Learn Mem Cogn* 21: 531–547, 1995.
- Curran T and Hintzman DL.** Consequences and causes of correlations in process dissociation. *J Exp Psychol Learn Mem Cogn* 23: 496–504, 1997.
- Daselaar SM, Rombouts SARB, Veltman DJ, Raaijmakers JGW, Lazeron RHC, and Jonker C.** Parahippocampal activation during successful recognition of words: a self-paced event-related fMRI study. *Neuroimage* 13: 1113–1120, 2001.
- Davachi L, Mitchell JP, and Wagner AD.** Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. *Proc Natl Acad Sci USA* 100: 2157–2162, 2003.
- Donaldson DI, Petersen SE, and Buckner RL.** Dissociating memory retrieval processes using fMRI: evidence that priming does not support recognition memory. *Neuron* 31: 1047–1059, 2001.
- Eacott MJ and Gaffan D.** Inferotemporal-frontal disconnection: the uncinate fascicle and visual associative learning in monkeys. *Eur J Neurosci* 4: 1320–1332, 1992.
- Eichenbaum H, Otto T, and Cohen NJ.** The hippocampus—what does it do? *Behav Neural Biol* 57: 2–36, 1992.
- Eldridge LL, Knowlton BJ, Furmanski CS, Bookheimer SY, and Engel SA.** Remembering episodes: a selective role for the hippocampus during retrieval. *Nat Neurosci* 3: 1149–1152, 2000.
- Elger CE, Grunwald T, Lehnertz K, Kutas M, Helmstaedter C, Brockhaus A, Van Roost D, and Heinze HJ.** Human temporal lobe potentials in verbal learning and memory processes. *Neuropsychologia* 35: 657–667, 1997.
- Fell J, Dietl T, Grunwald T, Kurthen M, Klaver P, Trautner P, Schaller C, Elger CE, and Fernandez G.** Neural bases of cognitive ERPs: more than phase reset. *J Cogn Neurosci* 16: 1595–1604, 2004.
- Fernandez G, Effern A, Grunwald T, Pezer N, Lehnertz K, Dumpelmann M, Van Roost D, and Elger CE.** Real-time tracking of memory formation in the human rhinal cortex and hippocampus. *Science* 285: 1582–1585, 1999.
- Fleck MS, Daselaar SM, Dobbins IG, and Cabeza R.** Role of prefrontal and anterior cingulate regions in decision-making processes shared by memory and non-memory tasks. *Cereb Cortex* In Press.
- Fortin NJ, Wright SP, and Eichenbaum H.** Recollection-like memory retrieval in rats is dependent on the hippocampus. *Nature* 431: 188–191, 2004.
- Goh JO, Siong SC, Park D, Gutchess A, Hebrank A, and Chee MW.** Cortical areas involved in object, background, and object-background processing revealed with functional magnetic resonance adaptation. *J Neurosci* 24: 10223–10228, 2004.
- Gonsalves BD, Kahn I, Curran T, Norman KA, and Wagner AD.** Memory strength and repetition suppression: multimodal imaging of medial temporal cortical contributions to recognition. *Neuron* 47: 751–761, 2005.
- Grunwald T, Beck H, Lehnertz K, Blumcke I, Pezer N, Kurthen M, Fernandez G, Van Roost D, Heinze HJ, Kutas M, and Elger CE.** Evidence relating human verbal memory to hippocampal N-methyl-D-aspartate receptors. *Proc Natl Acad Sci USA* 96: 12085–12089, 1999.
- Grunwald T, Lehnertz K, Heinze HJ, Helmstaedter C, and Elger CE.** Verbal novelty detection within the human hippocampus proper. *Proc Natl Acad Sci USA* 95: 3193–3197, 1998.
- Grunwald T, Pezer N, Munte TF, Kurthen M, Lehnertz K, Van Roost D, Fernandez G, Kutas M, and Elger CE.** Dissecting out conscious and unconscious memory (sub)processes within the human medial temporal lobe. *Neuroimage* 20, Suppl 1: S139–145, 2003.
- Gu Q.** Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. *Neuroscience* 111: 815–835, 2002.
- Habib R and Lepage M.** Novelty assessment in the brain. In: *Memory, Consciousness, and the Brain*, edited by Tulving E. Philadelphia: Psychology Press, 1999, p. 256–277.
- Henson RA, Rugg MD, Shallice T, Josephs O, and Dolan RJ.** Recollection and familiarity in recognition memory: An event-related functional magnetic resonance imaging study. *J Neurosci* 19: 3962–3972, 1999.
- Henson RN, Cansino S, Herron JE, Robb WG, and Rugg MD.** A familiarity signal in human anterior medial temporal cortex? *Hippocampus* 13: 301–304, 2003.
- Herron JE, Henson RN, and Rugg MD.** Probability effects on the neural correlates of retrieval success: an fMRI study. *Neuroimage* 21: 302–310, 2004.
- Holdstock JS, Mayes AR, Roberts N, Cezayirli E, Isaac CL, O'Reilly RC, and Norman KA.** Under what conditions is recognition spared relative to recall after selective hippocampal damage in humans? *Hippocampus* 12: 341–351, 2002.
- Jacoby L.** A process dissociation framework—separating automatic from intentional uses of memory. *J Mem Language* 30: 513–541, 1991.
- Kahn I, Davachi L, and Wagner AD.** Functional-neuroanatomic correlates of recollection: implications for models of recognition memory. *J Neurosci* 24: 4172–4180, 2004.
- Klaver P, Fell J, Dietl T, Schur S, Schaller C, Elger CE, and Fernandez G.** Word imageability affects the hippocampus in recognition memory. *Hippocampus* 15: 704–712, 2005.
- Kobayashi Y and Amaral DG.** Macaque monkey retrosplenial cortex. II. Cortical afferents. *J Comp Neurol* 466: 48–79, 2003.
- Mela CF and Kopalle PK.** The impact of collinearity on regression analysis: the asymmetric effect of negative and positive correlations. *Appl Econ* 34: 667–677, 2002.
- Mesulam MM.** The cholinergic innervation of the human cerebral cortex. *Prog Brain Res* 145: 67–78, 2004.
- Nyberg L, McIntosh AR, Houle S, Nilsson LG, and Tulving E.** Activation of medial temporal structures during episodic memory retrieval. *Nature* 380: 715–717, 1996.
- Passingham RE, Toni I, and Rushworth MF.** Specialisation within the prefrontal cortex: the ventral prefrontal cortex and associative learning. *Exp Brain Res* 133: 103–113, 2000.
- Prince SE, Daselaar SM, and Cabeza R.** Neural correlates of relational memory: successful encoding and retrieval of semantic and perceptual associations. *J Neurosci* 25: 1203–1210, 2005.

- Ranganath C and Rainer G.** Neural mechanisms for detecting and remembering novel events. *Nat Rev Neurosci* 4: 193–202, 2003.
- Ranganath C, Yonelinas AP, Cohen MX, Dy CJ, Tom SM, and D'Esposito M.** Dissociable correlates of recollection and familiarity within the medial temporal lobes. *Neuropsychologia* 42: 2–13, 2004.
- Rasmusson DD.** The role of acetylcholine in cortical synaptic plasticity. *Behav Brain Res* 115: 205–218, 2000.
- Rissman J, Gazzaley A, and D'Esposito M.** Measuring functional connectivity during distinct stages of a cognitive task. *Neuroimage* 23: 752–763, 2004.
- Rombouts SA, Barkhof F, Witter MP, Machielsen WC, and Scheltens P.** Anterior medial temporal lobe activation during attempted retrieval of encoded visuospatial scenes: an event-related fMRI study. *Neuroimage* 14: 67–76, 2001.
- Rotello CM and Heit E.** Associative recognition: a case of recall-to-reject processing. *Mem Cognit* 28: 907–922, 2000.
- Rushworth MF, Nixon PD, Eacott MJ, and Passingham RE.** Ventral prefrontal cortex is not essential for working memory. *J Neurosci* 17: 4829–4838, 1997.
- Sarter M and Bruno JP.** Cognitive functions of cortical acetylcholine: toward a unifying hypothesis. *Brain Res Brain Res Rev* 23: 28–46, 1997.
- Schacter DL, Curran T, Galluccio L, Milberg WP, and Bates JF.** False recognition and the right frontal lobe: a case study. *Neuropsychologia* 34: 793–808, 1996.
- Shannon BJ and Buckner RL.** Functional-anatomic correlates of memory retrieval that suggest nontraditional processing roles for multiple distinct regions within posterior parietal cortex. *J Neurosci* 24: 10084–10092, 2004.
- Stark CE, Bayley PJ, and Squire LR.** Recognition memory for single items and for associations is similarly impaired following damage to the hippocampal region. *Learn Mem* 9: 238–242, 2002.
- Stark CE and Squire LR.** Hippocampal damage equally impairs memory for single items and memory for conjunctions. *Hippocampus* 13: 281–292, 2003.
- Strange BA, Fletcher PC, Henson RN, Friston KJ, and Dolan RJ.** Segregating the functions of human hippocampus. *Proc Natl Acad Sci USA* 96: 4034–4039, 1999.
- Stuss DT, Alexander MP, Palumbo CL, Buckle L, Sayer L, and Pogue J.** Organizational strategies of patients with unilateral or bilateral frontal lobe injury in word list learning tasks. *Neuropsychology* 8: 355–373, 1994.
- Suzuki WA and Amaral DG.** Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. *J Comp Neurol* 350: 497–533, 1994.
- Trautner P, Dietl T, Staedtgen M, Mecklinger A, Grunwald T, Elger CE, and Kurthen M.** Recognition of famous faces in the medial temporal lobe: an invasive ERP study. *Neurology* 63: 1203–1208, 2004.
- Tulving E, Markowitsch HJ, Craik FM, Habib R, and Houle S.** Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cereb Cortex* 6: 71–79, 1996.
- Weis S, Klaver P, Reul J, Elger CE, and Fernandez G.** Temporal and cerebellar brain regions that support both declarative memory formation and retrieval. *Cereb Cortex* 14: 256–267, 2004a.
- Weis S, Specht K, Klaver P, Tendolkar I, Willmes K, Ruhlmann J, Elger CE, and Fernandez G.** Process dissociation between contextual retrieval and item recognition. *Neuroreport* 15: 2729–2733, 2004b.
- Wheeler ME and Buckner RL.** Functional-anatomic correlates of remembering and knowing. *Neuroimage* 21: 1337–1349, 2004.
- Whittlesea BW and Leboe JP.** The heuristic basis of remembering and classification: fluency, generation, and resemblance. *J Exp Psychol Gen* 129: 84–106, 2000.
- Woolf NJ.** A structural basis for memory storage in mammals. *Prog Neurobiol* 55: 59–77, 1998.
- Yonelinas AP.** The contribution of recollection and familiarity to recognition and source-memory judgments: a formal dual-process model and an analysis of receiver operating characteristics. *J Exp Psychol Learn Mem Cogn* 25: 1415–1434, 1999.
- Yonelinas AP.** Components of episodic memory: the contribution of recollection and familiarity. *Philos Trans R Soc Lond B Biol Sci* 356: 1363–1374, 2001a.
- Yonelinas AP.** Consciousness, control, and confidence: the 3 Cs of recognition memory. *J Exp Psychol Gen* 130: 361–379, 2001b.
- Yonelinas AP.** The nature of recollection and familiarity: A review of 30 years of research. *J Mem Language* 46: 441–517, 2002.
- Yonelinas AP, Hopfinger JB, Buonocore MH, Kroll NE, and Baynes K.** Hippocampal, parahippocampal and occipital-temporal contributions to associative and item recognition memory: an fMRI study. *Neuroreport* 12: 359–363, 2001.
- Yonelinas AP, Kroll NE, Quamme JR, Lazzara MM, Sauve MJ, Widaman KF, and Knight RT.** Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. *Nat Neurosci* 5: 1236–1241, 2002.
- Yonelinas AP, Otten LJ, Shaw KN, and Rugg MD.** Separating the brain regions involved in recollection and familiarity in recognition memory. *J Neurosci* 25: 3002–3008, 2005.