fMRI Differences in Encoding and Retrieval of Pictures Due to Encoding Strategy in the Elderly

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Abstract: Functional MRI (fMRI) was used to examine the neural correlates of depth of processing during encoding and retrieval of photographs in older normal volunteers ($n = 12$). Separate scans were run during deep (natural vs. man-made decision) and shallow (color vs. black-and-white decision) encoding and during old/new recognition of pictures initially presented in one of the two encoding conditions. A baseline condition consisting of a scrambled, color photograph was used as a contrast in each scan. Recognition accuracy was greater for the pictures on which semantic decisions were made at encoding, consistent with the expected levels of processing effect. A mixed-effects model was used to compare fMRI differences between conditions (deep-baseline vs. shallow-baseline) in both encoding and retrieval. For encoding, this contrast revealed greater activation associated with deep encoding in several areas, including the left parahippocampal gyrus (PHG), left middle temporal gyrus, and left anterior thalamus. Increased left hippocampal, right dorsolateral, and inferior frontal activations were found for recognition of items that had been presented in the deep relative to the shallow encoding condition. We speculate that the modulation of activity in these regions by the depth of processing manipulation shows that these regions support *effective* encoding and *successful* retrieval. A direct comparison between encoding and retrieval revealed greater activation during retrieval in the medial temporal (right hippocampus and bilateral PHG), anterior cingulate, and bilateral prefrontal (inferior and dorsolateral). Most notably,

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greater right posterior PHG was found during encoding compared to recognition. Focusing on the medial temporal lobe (MTL) region, our results suggest a greater involvement of both anterior MTL and prefrontal regions in retrieval compared to encoding. *Hum. Brain Mapp.* 21:1–14, 2004.

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INTRODUCTION

Memories influence present and future actions, and without their richness “the human compass” in life is lost. Memory processes have traditionally been separated into two distinct forms, episodic and semantic, based on the type of information to be processed. Episodic memory entails encoding and retrieval of context-specific information, whereas semantic memory comprises encoding and retrieval of context-independent, general knowledge [Tulving, 1972].

Findings from both functional mapping and lesion analysis have highlighted the importance of the medial temporal lobe (MTL) region at the time of learning and its role in binding together neural activities from distributed regions of the cortex [Squire et al., 1990]. Structures within the MTL region, such as the hippocampal formation (HF) [Constable et al., 2000; Fernandez et al., 1998; Otten et al., 2001; Tulving et al., 1994] and its surrounding cortical areas, the entorhinal (ERC) [Fernandez et al., 1999a], perirhinal [Fernandez et al., 1999b; Strange et al., 2002], and parahippocampal (PHG) [Brewer et al., 1998; Stern et al., 1996; Wagner et al., 1998] cortices are believed to be essential in establishing new memories [Suzuki and Amaral, 1994].

Having to elaborate on the meaning of the stimulus to be encoded helps to ensure that its memory is better established, even when memory formation is incidental to the nominal task. This “levels of processing effect” predicts that stimuli that are more elaborately (deeply) processed will be better retrieved than stimuli that are processed on a more superficial level (shallow encoding) [Craik and Lockhart, 1972]. Functional neuroimaging studies have explored this phenomenon mostly with verbal stimuli in which semantic encoding (e.g., animacy decisions) is contrasted with superficial judgments (e.g., case) about words [Grady et al., 1998; Kapur et al., 1994; Otten et al., 2001; Wagner et al., 1998]. The most consistent finding from these studies is greater left inferior prefrontal activation associated with elaborative processing [Wagner et al., 1998]. The most prominent MTL activations associated with deep encoding are found in the left parahippocampal and fusiform gyri, with little differential activation in the hippocampus [Grady et al., 1998; Kapur et al., 1994; Otten et al., 2001; Wagner et al., 1998]. Although fewer studies have been conducted with non-verbal materials, a similar pattern of activation has been found for deeper processing of pictures, whereby left ventral prefrontal, left anterior medial temporal regions, and bilateral posterior extrastriate cortex were activated to a greater extent compared to a perceptual condition [Bernstein et al., 2002; Grady

et al., 1998, 1999]. Of interest the posterior MTL and the inferior frontal cortex have also been found to be important for successful encoding [Brewer et al., 1998; Kirchoff et al., 2000; Otten et al., 2001; Wagner et al., 1998].

If the depth of processing during encoding influences the effort or success of retrieving an item, one might expect a difference in regional activation to be associated with recognition of items that had been deeply versus superficially encoded. Although some studies have reported no difference in activation patterns associated with encoding conditions, related to level of processing during encoding tasks [Bernstein et al., 2002; Grady et al., 2001], others have reported regions associated with retrieval attempt and/or retrieval success [Buckner and Wheeler, 2001; Henson et al., 1999; Konishi et al., 2000; McDermott et al., 2000; Rugg et al., 1998]. Different frontal regions are believed to play unique roles in retrieval. For example, right BA 10 has been suggested to be involved in initiating or maintaining retrieval mode (i.e., the “readiness” to undertake retrieval whereas BA 44/6 and 45/46 have been implicated in post-retrieval monitoring (i.e., ascertaining the validity of the products of retrieval) [Buckner and Wheeler, 2001]. Areas specifically associated with successful retrieval include left dorsal middle frontal and left anterior prefrontal cortical regions [Donaldson et al., 2001]. However, the function of these various sub-regions is still a subject of considerable debate.

It is not entirely clear what role MTL structures like the hippocampus play in the reestablishment of episodic memories after consolidation has occurred. Recent evidence supports a role for the hippocampus in episodic retrieval [Eldridge et al., 2000; Nyberg et al., 1996; Schacter et al., 1999; Small et al., 2001; Stark and Squire, 2000]. The engagement of hippocampus may be important to reactivate the spatio-temporal context of encoded memories in order to successfully retrieve the memory [Eldridge et al., 2000; Stark and Squire, 2000]. Some models suggest that the hippocampus contains an “index” of stored memory representations and thus it is crucially involved in accessing long-term memory traces that are stored in the neocortex [Alvarez and Squire, 1994; Teyler and DiScenna, 1986]. Recent functional imaging studies also highlight the possible involvement of this structure in retrieval success [Eldridge et al., 2000; Nyberg et al., 1996; Stark and Squire, 2000], but whether the success of the memory trial is a criterion for hippocampal recruitment during retrieval has not been fully established. Therefore, an interaction between MTL, frontal, and other cortical regions may be required in order to carry out successful retrieval.

The primary goal of this study was to examine the functional activation patterns associated with both incidental encoding and intentional retrieval of picture photographs during fMRI scanning, by manipulating the level of processing at time of encoding (deep and shallow) in a group of older participants. We also investigated the similarities and differences in the activated neural networks in encoding and retrieval, although this was not the main focus of the current report. We chose to use a blocked vs. event-related design to study the levels of processing effect, as our eventual goal is to compare patterns of brain activation between individuals with mild cognitive impairment (MCI) [Petersen et al., 1999] and elderly controls. A blocked design increases our power to examine these differences, as we can maximize the number of tasks while minimizing time in the scanner in order to prevent excessive head movement in our subjects. An event-related design would allow us to make firmer conclusions about the involvement of brain regions in *effective* encoding and *successful* retrieval. However, we reasoned that the depth of processing manipulation stands as a weaker surrogate marker of these processes based on decades of behavioral data demonstrating these effects. We predicted differences in the extent and location of fMRI activation and behavioral performance depending on the level of processing as follows: (1) deep encoding would activate regions involved in semantic processing to a greater extent such as the left inferior frontal region and posterior MTL regions; (2) pictures that required greater semantic elaboration (deep encoding) would be better remembered; and (3) retrieval of pictures that had been deeply encoded (deep retrieval), relative to those that were superficially encoded (shallow retrieval), would be associated with greater activation in the MTL, medial parietal, and frontal lobes, regions implicated in retrieval success. For the sake of brevity, the retrieval of pictures that were deeply encoded will be referred to as deep retrieval and shallow retrieval will denote the retrieval condition for shallowly encoded items in some of the remaining text. Differential activation during the retrieval tasks may be due to differences in processing at time of encoding related to retrieval attempt, success, and/or effort. Activation patterns related to retrieval success and effort are operationally defined as overall significant task-related effects between the retrieval conditions, as we cannot examine the neuronal correlates of item-specific success because of our blocked design.

SUBJECTS AND METHODS

Participants

All participants were normal community volunteers (NC) from a larger study (The Sunnybrook Dementia Study) examining brain imaging and neuropsychological correlates in Mild Cognitive Impairment and Alzheimer's Disease. Participants underwent comprehensive neuropsychological testing as well as structural MRI to ensure they were normal for their age. They had no concomitant neurological or psychiatric disorders. Twelve individuals (6 women; 6 men)

participated in the fMRI study (mean age = 73.7 ± 5.7 years, range 64–81; mean years of education (YOE) = 15.1 ± 2.9 , range 11–19; mean Mini-Mental Status Exam (MMSE) = 28.5 ± 1.17 , range 26–30). Men and women did not differ significantly ($P \leq 0.05$) from each other on mean age, YOE, and MMSE. Subjects were excluded if they were colorblind or their vision could not be corrected during presentation of visual stimuli.

Task Design

To examine differences in memory activations, we used a blocked design with incidental encoding and yes/no recognition tasks. Stimuli consisted of color and black and white photographs of objects and animals, which were taken from a CD-Rom catalogue of photos and a set of digital photos obtained by J.M. All tasks contained a mixture of both color and black and white photographs. Stimuli were presented using MRI-compatible goggles (Silent Vision, Avotec, Inc., Jensen Beach, FL) that included adjustments for visual acuity, except the first five subjects who viewed stimuli projected onto a screen at the foot of the MRI patient table. Individual runs consisted of six 31-sec blocks of the “memory task” interleaved with five 26-sec blocks of the fixation condition. There were 5 stimuli (photographs or repeated scrambled patterns) per block with a 6-sec set of text instructions at the beginning of each block to remind subjects of the task. Each photograph was presented for 4 sec with an interstimulus interval (ISI) of 1 sec (5 stimuli per block). The incidental encoding task consisted of two imaging runs differing in the level of processing. During the deep encoding condition run, participants decided whether each photograph they saw was “natural” or “man-made.” During the shallow encoding run, participants decided whether the photograph was “in color” or “black and white.” The baseline condition consisted of a colored scrambled pattern, presented for 3 sec with an ISI of 1 sec (5 stimuli per block). Following the two encoding runs, three-dimensional T1-weighted anatomical scanning (see below) was performed during the 12-min delay between encoding and recognition. The two recognition runs followed. During these tasks, participants decided whether the photograph they saw was “old” (previously seen in the encoding runs) vs. “new” (not seen today). The recognition run for deeply encoded pictures (deep retrieval) consisted of 15 photographs from the deep encoding run and 15 new photographs. The recognition run for pictures seen under shallow encoding instructions (shallow retrieval) consisted of 15 photographs from the shallow encoding run and 15 new photographs. Both recognition conditions were also contrasted to the same baseline condition used in the encoding runs.

Accuracy and reaction time were recorded using an MRI-compatible keypad (Lumitouch; Lightwave Technologies, Surrey, BC). Participants indicated their choice by pressing the right button (for natural, color, and old photographs) or the left button (for man-made, black and white, and new photographs) with the middle or index finger of their right hand, respectively. During the baseline condition, they pressed both but-

tons when the colored scrambled pattern appeared. Stimuli were counterbalanced for color and type of photograph (natural vs. man-made) in all four-memory conditions. Deep and shallow imaging runs were counterbalanced across subjects to control for task order related effects.

fMRI Scanning

Experiments were conducted on a hospital-grade whole-body scanner operating at 1.5 Tesla magnetic field strength (Signa, GE Medical Systems, Waukesha, WI; CV/I hardware, LX8.4 software). Single-shot spiral imaging was performed with imaging parameters to optimize BOLD contrast [Ogawa et al., 1990] and included offline gridding, reconstruction, and correction for magnetic field inhomogeneity and Maxwell gradient terms (TR= 3 sec, TE=40 msec, 64×64 matrix, 30–34 slices, $3.1 \times 3.1 \times 5$ mm) [Glover and Lai, 1998]. Coronal scans were performed to maximize signal intensity in the MTL. Three-dimensional anatomical MRI scanning was performed with higher spatial resolution (fast spoiled gradient echo imaging, field of view =22 by 18 cm, flip angle/TE/TR/ = $35^\circ/5$ msec/35 msec, 256×192 , 128 slices 1.5 mm thick).

fMRI Analysis

fMRI data were analyzed using the Analysis of Functional NeuroImages (AFNI v. 2.50) statistical package [Cox, 1996]. Following motion correction and time series shifting by 6 sec to account for hemodynamic delay, a voxel by voxel box-car correlation analysis was performed to estimate brain activation as a percentage signal change. As part of the analysis, the time series data were detrended to correct for baseline drift and activation was estimated orthogonal to each subject's individual motion parameters to reduce the potential for artifacts related to head motion. A mask was created for each fMRI slice location to remove noise outside the brain and regions of low signal intensity due to susceptibility artifact. Each individual data set was transformed to Talairach space and smoothed using a 6-mm FWHM kernel to account for individual anatomical and functional variability.

Group analyses were conducted using a 4×12 mixed-effects design ANOVA with memory tasks (fixed) and subjects (random) as factors. Activation thresholds were determined using an AFNI algorithm that uses the results of Monte-Carlo simulations to address the issue of multiple comparisons, by determining the ideal cluster size and corrected P value where the user inputs the desired voxel P level, original voxel size, slice thickness, matrix size, and smoothing kernel [Forman et al., 1995]. The alpha sim output was used to cluster activations in the functional maps in Talairach space. In AFNI, the original $3.125 \times 3.125 \times 5$ mm voxel, is interpolated to $45 \times 45 \times 1$ cubic voxels when transformed into Talairach space. However, the actual spatial resolution does not change. Since the cluster size is specified as a volume (i.e., 488 μ l), it is independent of the size of an individual voxel in Talairach space. A cluster connectivity radius of 1.7 mm was chosen so that *contiguous* voxels were connected in Talairach space. Activations were deemed significant if the threshold based on the correlation coefficient

TABLE I. Recognition measures

Task	Deep retrieval	Shallow retrieval
Hit rate*	0.85 ± 0.16	0.60 ± 0.2
False alarm rate	0.095 ± 0.09	0.058 ± 0.07
d'^*	4.23 ± 1.3	3.15 ± 1.6

*Significant differences between conditions.

exceeded 0.001 for an individual voxel resulting in a corrected alpha level of $P \leq 0.05$ and a minimum cluster volume of 488 μ l (10 voxels). This threshold was used for all contrasts. Within encoding and retrieval, the manipulation (deep-baseline vs. shallow-baseline) was compared. Finally, a contrast was performed where both deep and shallow tasks were collapsed to compare (encoding-baseline) to (retrieval-baseline) activation patterns. All functional data were overlaid on a representative T1-weighted brain in Talairach space.

RESULTS

Behavioral Performance

Paired t -test analyses were used to compare differences between the deep and shallow conditions separately for encoding and retrieval on (1) accuracy (% correct) on the encoding tasks; (2) hit, false alarm rates, and d' on the recognition tasks; and (3) reaction time (RT). Due to technical difficulties with our response device, we could not record RT data for two subjects. Accuracy was significantly higher for deep (99.7 ± 0.96) vs. shallow (95.8 ± 3.80) encoding ($t_{(11)} = 3.380$, $P = 0.006$). During recognition, subjects had a significantly higher hit rate for words that had been encoded in deep vs. shallow conditions ($t_{(11)} = 4.2$, $P = 0.002$), but there were no differences in false alarm rates ($t_{(11)} = 1.2$, $P = 0.26$). (Table I). We also calculated d' , a bias-free measure of recognition sensitivity. There was a significant difference in d' between the two retrieval conditions ($t_{(11)} = 2.3$, $P = 0.045$).

For RT, there were no significant differences for the deep and shallow comparisons for encoding (1,011 vs. 1,056 msec) or retrieval (1,204 vs. 1,231 msec).

fMRI Results

Deep encoding vs. shallow encoding

To examine differences in level of processing during encoding, we contrasted deep to shallow encoding ($P \leq 0.05$, min. cluster volume = 488 μ l). A number of regions showed increased activation for this contrast (Table I and Fig. 1). Temporal lobe components included left middle temporal (BA 21 and 39) and medially the left fusiform gyrus (BA 37) and left parahippocampal gyrus (PHG, BA 35). Frontal regions included the left medial frontal (BA 10) and left superior frontal (BA 10) cortices. Deep encoding was also associated with increased activity in the right anterior cingulate gyrus (BA 24), the right medial dorsal thalamus, the left anterior thalamus, and bilateral cerebellum. The only area to

Figure 1.

Deep vs. shallow encoding, ANOVA results: Significant differences in regional activation for deep vs. shallow encoding at (corrected $P \leq 0.05$, minimum volume = 488 μ l). Data are overlaid on a representative brain in Talairach space. Talairach coordinates for activations are indicated in brackets with Broadman Areas (BA). Significant activations were found in L PHG (left parahippocampal

gyrus: BA 35, -16-35 2); L ATHAL (left anterior thalamus: -9-11 14); R D_MED THAL (right thalamus, dorsal medial nucleus: 4-11 12); L MTG (left middle temporal gyrus: BA 21, -58-11 -14); L FG (left fusiform gyrus: BA 37, -42-44 -11). In addition, the R SMG (right supramarginal gyrus: BA 40, 41-44 30) was activated to a greater extent for shallow > deep encoding.

show greater activation during shallow relative to deep encoding was the right supramarginal gyrus (BA 40).

Retrieval following deep vs. shallow encoding

To examine potential effects of the depth of encoding on subsequent retrieval, we compared the two retrieval runs, each of which was exclusive to items that had been encoded in one of the two (deep or shallow) conditions. A number of regions were significantly activated ($P < 0.05$ min. cluster volume-488 μ l) to a greater extent during retrieval of deeply encoded pictures including the left superior temporal (BA 39), the left middle/superior frontal (BA10), left hippocampus, and left cuneus. A network of right-lateralized regions was also activated and included the right inferior frontal (BA 45,46, 47), right posterior cingulate (BA 31), and right middle temporal (Fig. 2B). Bilaterally, there was greater activation of the cerebellum, caudate, and lingual gyrus for recognition of deep vs. shallow pictures. A few regions showed greater activation during recognition of items that had been encoded superficially compared to under semantic encoding. These included the left medial frontal (BA 11) and left middle frontal (BA 10) regions (Fig. 2, Table III).

Retrieval vs. encoding

We collapsed conditions (deep and shallow) to compare activations between encoding and retrieval (Fig. 3). Retrieval

produced greater overall differences in regional activation compared to encoding ($P \leq 0.05$, minimum cluster vol = 488 μ l) (Fig. 3, Table IV). Left lateralized regional activations for retrieval relative to encoding were located in the middle temporal gyrus (BA 21) and cerebellum, bilaterally in the middle frontal (BA 10/ 9), inferior frontal (BA 47) and insula (BA 13), parahippocampal gyrus (BA 28), and anterior cingulate gyrus (BA 32) (Fig. 3, Table IV). There were also greater right-lateralized, hippocampal, inferior frontal (BA 45) lentiform nucleus/putamen activations. There was greater right precuneus (BA 7), right superior temporal gyrus, right inferior temporal (BA 37), right PHG (BA 30), and left inferior parietal lobule activation for encoding relative to retrieval.

DISCUSSION

The present study extends prior findings in three important ways. First, our study successfully manipulated the depth of encoding for photographs through task instructions demonstrating a level of processing effect as has been found in numerous verbal encoding studies, but has been less frequently studied with pictorial stimuli [Grady et al., 1998]. Our finding of increased left PHG activation for deep compared to shallow encoding further highlights the importance of this region in effective encoding and supports findings from previous imaging studies. Second, the finding of in-

■ Deep > Shallow
■ Shallow > Deep

Figure 2.

Deep vs. shallow retrieval, ANOVA results: Significant differences in regional activation for deep vs. shallow retrieval at (corrected $P \leq 0.05$, minimum volume = 488 μ l). Data are overlaid on a representative brain in Talairach space. Talairach coordinates for activations are indicated in brackets with Broadman Areas (BA). Significant activations were found in L HC (left hippocampus:

–30 –22 –6); L MFG (left middle frontal, BA 10: –27 54 21); R IFG (right inferior frontal gyrus: BA 47, 49 33 –6); and R IFG (right inferior frontal gyrus: BA 46, 49 28 15). In addition, the L MFG (left middle frontal: BA 10, –35 54 –3) was activated to a greater extent for shallow > deep retrieval.

■ Retrieval > Encoding
■ Encoding > Retrieval

Figure 3.

Retrieval vs. encoding differences, ANOVA Results: Significant differences in regional activation for retrieval vs. encoding (corrected $P \leq 0.05$, minimum volume = 488 μ l). Data are overlaid on a representative brain in Talairach space. Talairach coordinates for activations are indicated in brackets with Broadman Areas (BA). Significant activations were found in: R HC (right hippocampus, 29

–21 –8); R/L IFG (right/left inferior frontal gyrus, right BA 45: 34 25 5 and left BA 47: –35 25 0); R MFG (right middle frontal gyrus: BA 9, 42 25 30); R ACING (right anterior cingulate gyrus: BA32, 5 25 37). In addition, the R PHG (right parahippocampal gyrus: BA 30, 12–44 5) was activated to a greater extent for encoding > retrieval.

TABLE II. Talairach coordinates for significant activation for encoding comparisons*

Brain region		Talairach coordinates		
		x	y	z
Deep > shallow				
Temporal	Left middle temporal (BA 21)	-58	-11	-14
	Left middle temporal (BA 39)	-47	-68	14
	Left fusiform gyrus (BA 37)	-42	-44	-11
	Left parahippocampal gyrus (BA 35)	-16	-35	2
Occipital	Left cuneus (BA 17)	-20	-92	-1
	Left/right lingual gyrus	1	86	3
Frontal	Left medial frontal (BA 10)	-3	50	8
	Right cingulate gyrus (BA 32)	7	44	10
	Left superior frontal (BA 10)	-16	62	0
Other	Left thalamus (anterior nucleus)	-9	-11	14
	Right thalamus (medial dorsal nucleus)	4	-11	12
	Right cerebellum (inferior semi-lunar lobule)	23	-68	-38
	Left cerebellum (declive)	-32	-68	-14
Shallow > deep	Right supramarginal gyrus (BA 40)	41	-44	30

*Talairach coordinates for significant activations during the deep > shallow and shallow > deep encoding comparisons (corrected $P \leq 0.05$, minimum cluster vol = 488 μ l).

creased left hippocampal activation for retrieval of material studied under deep vs. shallow conditions further supports an involvement of this structure at time of retrieval and provides additional evidence for its possible involvement in successful retrieval. Third, our study design allowed us to

examine both encoding and retrieval in the same scanning session to elucidate differences in the networks associated with these memory processes. This comparison demonstrated greater bilateral prefrontal and bilateral MTL activity during retrieval relative to encoding suggesting greater neu-

TABLE III. Significant regions of activation for retrieval tasks comparisons*

Brain region		Talairach coordinates		
		x	y	z
Deep > shallow				
Temporal	Left superior temporal (BA 39)	-55	-61	26
	Left middle temporal	-51	-73	7
	Left hippocampus	-30	-22	-6
	Right middle temporal	37	-1	-33
Parietal	Right posterior cingulate (BA 31)	15	-25	42
Occipital	Left cuneus	-12	-71	20
	Bilateral lingual gyrus	-7	-83	-4
Frontal	Left middle frontal	-27	54	21
	Left superior frontal (BA 10)	-29	55	17
	Left superior frontal (BA 9)	-39	35	31
	Right inferior frontal (BA 46)	49	28	15
	Right inferior frontal (BA 45)	50	24	12
	Right inferior frontal (BA 45)	32	23	13
	Right inferior frontal (BA 47)	49	33	-6
	Left caudate	-17	-13	21
	Left cerebellum	-14	-75	-15
	Right caudate/caudate body	17	-16	22
Other	Right cerebellum	31	-63	-33
Shallow > deep				
	Left middle frontal (BA 10)	-35	54	-3
	Left medial frontal (BA 11)	0	42	10

*Talairach coordinates for significant activations during the deep > shallow and shallow > deep retrieval comparisons (corrected $P \leq 0.05$, minimum cluster vol = 488 μ l).

TABLE IV. Significant regions of activation for memory processing (retrieval and encoding) comparisons*

		Talairach coordinates		
		<i>x</i>	<i>y</i>	<i>z</i>
Retrieval > encoding				
Temporal	Left middle temporal (BA 21)	-64	-30	1
	Left middle temporal (BA 21)	-56	-21	-4
	Left/right parahippocampal Gyrus (BA 28)	-16/16	-10	-13
	Right hippocampus	29	-21	-8
	Right fusiform gyrus	42	-27	-16
Parietal	Left cingulate gyrus/precuneus (BA 31)	-14	-41	33
	Right posterior cingulate/precuneus (BA 31)	10	-66	19
Frontal	Left middle frontal (BA 9)	-47	15	33
	Left precentral gyrus (BA 6)	-41	-5	54
	Left insula	-32	15	13
	Left inferior frontal gyrus (BA 47)	-35	25	0
	Right anterior cingulate (BA 32)	5	25	37
	Right medial frontal (BA 6)	7	27	35
	Right BA 13	30	23	-2
	Right inferior frontal (BA 45)	34	25	5
	Right middle frontal (BA 10)	33	33	17
	Right middle frontal (BA 9)	42	25	30
	Left cerebellum (declive)	-47	-67	-21
	Left thalamus/mammillary body	-13	-18	1
	Right lentiform/putamen	26	-13	8
Encoding > retrieval				
	Left inferior parietal lobule	-61	-36	29
	Right precuneus (BA 7)	19	-69	41
	Right superior temporal (BA 13)	45	-46	24
	Right inferior temporal (BA 37)	53	-55	-8
	Right parahippocampal gyrus (BA 30)	12	-44	5

*Talairach coordinates for significant activations during the retrieval > encoding and encoding > retrieval comparisons (corrected $P \leq 0.05$, minimum cluster vol = 488 μ l).

ral recruitment of these regions during retrieval. This may be related to enhanced attention or semantic processing demands.

Behavioral Differences

Recognition was greater for deeply encoded pictures relative to those seen in the shallow encoding run despite the fact that photographs were very salient. Although items from the two encoding conditions were tested in separate runs, which could lead participants to adopt different response criteria, the signal detection analysis revealed the performance advantage following deep encoding to reflect better discrimination between old and new photographs. The advantage seen here is consistent with previous studies, which have manipulated the encoding of verbal materials with animacy and phonological decisions [Brewer et al., 1998; Grady et al., 1998; Otten et al., 2001; Wagner et al., 1998]. Surprisingly, subjects performed significantly worse in the shallow vs. deep encoding conditions. That is, accuracy was slightly lower for the “black and white vs. colored” than the “natural vs. man-made” decisions. However, when we examined the mean raw scores, this corresponded to a

difference of only one point, and, therefore, may not be psychometrically significant. In retrospect, the color vs. black and white decision seems to have been more difficult in our older population than expected.

Deep vs. Shallow Encoding: fMRI Activation Patterns

We predicted that deep encoding would result in greater inferior frontal and medial temporal activation, and did indeed find this effect in the MTL. Our finding of increased parahippocampal gyrus activation is in keeping with a similar pattern found in previous studies that compared semantic processing differences for words [Brewer et al., 1998; Otten et al., 2001; Wagner et al., 1998]. The left lateralization of the activation contradicts previous suggestions of material specificity for MTL activations, where activation has been bilateral or right lateralized for pictures [Brewer et al., 1998; Kelley et al., 1998; Wagner et al., 1998]. However, our stimuli may have been easier to verbalize than pictures used in previous studies (i.e., objects here and faces or scenes in other studies), hence producing a greater left focus of activation. Similarly, Grady et al. [1998] found a common pat-

tern of cerebral blood flow activity for words and pictures of objects (also readily verbalized) that distinguished semantic from non-semantic and intentional encoding, which included the left MTL region. Their MTL region included the left insula and the PHG whereas in our study a more posterior PHG (BA 35) region was activated for deep vs. shallow encoding. Thus, our study provides additional evidence that there may be a common left lateralized semantic network for deep encoding that includes the PHG. Increased activation of the PHG may have also been important for subsequent retrieval, whereby activation of the PHG, a gateway to the hippocampus, may have resulted in a more stable memory trace being laid down. This supports previous studies showing that PHG activation during verbal and non-verbal encoding predicts successful retrieval [Brewer et al., 1998; Kirchhoff et al., 2000; Otten et al., 2001; Wagner et al., 1998].

Recent studies have highlighted the importance of the inferior frontal lobes in semantic elaboration and/or working memory and subsequent retrieval performance [Brewer et al., 1998; Wagner et al., 1998]. Our failure to find increased inferior frontal activation (BA 47) in deep encoding may be due to the fact that these regions were active in both shallow and deep encoding. Similar inferior frontal activation in both tasks may be related to similar semantic elaboration and working memory maintenance demands, posed by both deep and shallow encoding. Subjects may have used a semantic strategy in both tasks, as pictures are very salient and lend themselves to meaning based-encoding. Others [Grady et al., 1998] have found enhanced left inferior PFC activity as part of a pattern of brain activation that distinguished deep from shallow encoding of pictorial stimuli, with this effect still present in older adults [Grady et al., 1999]. Our pictures were richer and more complex than the line drawings used in those studies, however, which may account for the lack of difference in inferior prefrontal activation between our two conditions. Other regions that demonstrated greater activation during deep encoding included the left middle temporal gyrus (BA 21). This region along with the left inferior frontal gyrus, have been previously implicated as part of a network involved in higher level semantic processing, especially verbal comprehension [Vandenberghe et al., 1996]. This would be compatible with a greater semantic processing demand during deep encoding since a natural vs. man-made judgment had to be made.

The majority of levels of processing studies have concentrated on the neuroimaging correlates in the MTL and prefrontal regions. However, the contributions other regions make when deep is contrasted to shallow encoding are equally as interesting. Subcortical structures such as the thalamus and the cerebellum are frequently activated in cognitive studies, though their importance is often overshadowed by a preoccupation with cortical activations. The cerebellum traditionally has been implicated in cognition from a purely motor viewpoint, but more recently a cognitive and affective role for this structure has begun to be accepted [Leiner et al., 1991; Middleton and Strick, 2000;

Schmahmann and Pandya, 1997]. A meta-analysis of functional neuroimaging studies suggested that the cerebellum is part of the network engaged in semantic memory retrieval (episodic encoding), as well as episodic retrieval [Cabeza and Nyberg, 2000]. There are bi-directional feedback circuits between the cerebellum and the cortex that relay in the thalamus and carry distinct cerebellar outputs [Middleton and Strick, 2000]. Therefore, bilateral cerebellum activity for deep vs. shallow encoding supports the hypothesis of a bi-directional circuit for encoding that may show greater activity depending on the depth of processing.

In our study, we found greater thalamic activation in the left anterior nucleus and right medial dorsal nucleus during deep vs. shallow encoding. The thalamus, especially the anterior and medial portions, is an important relay station in the episodic memory circuit [Suzuki and Amaral, 1994]. Infarcts of the medial and anterior nuclei of the thalamus result in memory impairments [Herrero et al., 2002]. Functional MRI and ERP studies have shown the left thalamus to be involved in the activation of an integrated object representation in semantic memory from multimodal feature stimuli (e.g., picture-word) [Kraut et al., 2002a,b; Slotnick et al., 2002]. The thalamus is believed to play a role in synchronizing neural activity via oscillating rhythms with cortical areas [Herrero et al., 2002], but fMRI does not have the temporal resolution to directly measure this. Greater activation of these thalamic regions during deep relative to shallow encoding supports a role for this structure both in semantic processing and encoding.

More lateral parietal regions such as the right supramarginal gyrus (BA 40) demonstrated greater activation during shallow encoding. Other functional neuroimaging studies have implicated this parietal region (left > right) during the controlled use of phonological information and when short-term maintenance of phonological material is required [Gold and Buckner, 2002; Jonides et al., 1998]. Right-lateralized parietal activity has been attributed to attentional processes required as part of the rehearsal process, during the temporary storage of information [Jonides et al., 1998]. This area is close to our reported area of activation ($x, 42; y, -51; z, 40$ vs. Table 3: $x, 40; y, -42; z, 31$). The significance of increased activation of this region during shallow encoding is unclear, but we can speculate that this activation may reflect increased attentional demands when making a color vs. black and white compared to a natural vs. man-made decision, as suggested by the slightly worse performance during the shallow encoding task.

Retrieval Differences

We predicted that there would be differences in regional activation in the frontal and medial temporal regions related to the level of retrieval success and effort, operationalized here as depth of encoding. As expected, subjects recognized more of the deeply encoded pictures, though this was not reflected in reaction time. Some notable regions that were activated to a greater extent during retrieval of deeply en-

coded items included the left hippocampus, bilateral inferior frontal, left middle frontal (BA 10), and bilateral cerebellum.

Much effort has been devoted to elucidating the role of the hippocampus at the time of encoding, but more recent studies have suggested a role for this structure during retrieval. It has been a challenge at times to demonstrate “activation” in the hippocampus (i.e., the “recalcitrant hippocampus” [Aguirre et al., 1996] in both episodic encoding and retrieval. Differences in activation patterns or null findings may be more a reflection of the neuroimaging techniques used, Positron Emission Tomography (PET) vs. fMRI, which differ in their spatial and temporal resolution, and in the study designs, for example the type of baseline used [Stark and Squire, 2001b]. Susceptibility effects (i.e., loss of signal due to differences in magnetic field susceptibility from *dissimilar* tissues adjacent to one another, or air tissue interfaces) are also a greater issue for the anterior vs. posterior MTL in fMRI compared to PET [Schacter and Wagner, 1999]. Given the relative poverty of relevant data from functional neuroimaging studies, the precise computations of the hippocampus during memory processing remains uncertain. However, recent studies have successfully activated the hippocampus during retrieval and there is evidence for greater hippocampal activation during successful retrieval [Eldridge et al., 2000; Nyberg et al., 1996; Stark and Squire, 2000; Stark and Squire, 2001a]. Our finding of greater hippocampal activation during deep retrieval is compatible with a role in retrieval success. Successful retrieval may be associated with greater reactivation of the memory trace in the hippocampal formation along with other structures in the network engaged in episodic retrieval. However, an event-related paradigm would help best to delineate the role of the hippocampus in retrieval success more clearly by comparing fMRI signal for hits vs. correct rejections.

There is evidence that specific prefrontal regions may play different roles in memory retrieval. The anterior region of BA 10 ($x, 34; y, 54; z, 4$ mm) has often been activated during retrieval attempts [Grady et al., 2001]. It appears to be sensitive to “remembering” *per se*; it does not seem to be affected by amount of retrieval effort required by the task; it is active in verbal and non-verbal tasks and is often right-lateralized irrespective of the type of stimuli [Buckner and Wheeler, 2001]. However, there remains considerable debate about the function of this region, as other studies have found it to be involved in retrieval success [Henson et al., 2000; Konishi et al., 2000; McDermott et al., 2000]. Therefore, in our study, the retrieval mode hypothesis led to the prediction that deep and shallow retrieval would activate this region to a similar extent, as has been found in previous studies [Allan et al., 2000; Grady et al., 2001]. When we examined the group activation maps compared to baseline fixation, we found similar activations bilaterally in a region of BA 10 in both deep and shallow retrieval. However, we did find greater activation in the shallow condition in a left-lateralized region in BA 10 close to the one found in previous studies ($x, -35; y, 54; z, -3$). There was also a region that was activated to a greater extent in deep retrieval

located superior to this region in the left middle frontal gyrus, BA 10 ($x, -27; y, 54; z, 22$). The left focus of activation may be related to the verbalizable nature of the stimuli, as other studies have found a similar lateralization [Konishi et al., 2000]. Our current spatial resolution does not permit us to delineate whether these two regions in BA 10 represent activation of a similar functional region or of unique subregions within heterogeneous functional locations within the prefrontal lobe.

Another prefrontal region, BA 44/6 and more ventrally near 45/46, seems to be modulated by effort, such that greater effort results in greater local activation of this region (e.g., if retrieval is made more difficult by manipulating encoding strategies) [Buckner and Wheeler, 2001]. These dorsolateral regions have been implicated in working memory operations, such as the maintenance of information and retrieval monitoring where the products of retrieval are verified to ensure they are sufficient for the current task [Henson et al., 1999, 2000]. In our experiments, we expected greater activation of this region in the “shallow” retrieval task, as it arguably requires more effort and greater monitoring, as performance is generally worse. Surprisingly, we found the opposite. Retrieval of deeply encoded items retrieval was associated with greater activation in a right lateralized inferior frontal region of BA 46 (Table III: $x, 54; y, 27; z, 12$). As there was no manipulation or ascertainment of working memory load in this study, the explanation for the enhanced activity remains obscure. In addition, there was also additional activation for the deep retrieval condition in the right inferior frontal regions (BA 45 and 47). Right inferior prefrontal activation (BA 45) has been implicated in retrieval matching where recognition items are compared to previously encoded items [Nyberg et al., 1998; Ragland et al., 2000]. This hypothesis seems plausible, as greater activation of this region could reflect a greater ability to match stimuli successfully that would lead to more accurate memory retrieval.

Retrieval vs. Encoding

A number of studies have compared the neural correlates of episodic encoding and retrieval mostly with verbal materials [McDermott et al., 1999; Ragland et al., 2000; Schacter et al., 1999; Schmidt et al., 2002]. In our study, retrieval in general showed greater overall activation compared to encoding than did the reverse comparison. We will concentrate on the retrieval effects as they pertain to the MTL and prefrontal regions.

Most notably during retrieval, there was greater right hippocampal and bilateral PHG (BA 28) activation. Our comparisons may have not been sensitive enough to reveal encoding differences in the hippocampus for instance, but are consistent with other studies that found no significant activation in this region when this comparison was made [Ragland et al., 2000; Schmidt et al., 2002]. One verbal memory study found greater left PHG activation for encoding relative to retrieval [McDermott et al., 2000]. Similarly in our study, a right PHG region was activated to a greater extent

when encoding was compared to retrieval. If one believes the hypothesis that the hippocampus is “constantly active” while we roam the world, greater hippocampal engagement during retrieval may be due to the hippocampus being taxed to a greater extent during this memory operation than encoding, as the latter would represent a stage of typical, continual activation.

Our study provides some support for an anterior/posterior MTL distinction during encoding and retrieval [Gabrieli et al., 1997], as the anterior hippocampus and PHG were activated to a greater extent for retrieval compared to encoding, whereas the reverse comparison yielded greater posterior PHG activation. Schacter et al. [1999] examined the rostrocaudal distribution of PET MTL activations for the encoding and retrieval of novel 3-D figures. Direct within-subjects comparisons revealed that there was greater posterior MTL activation extending into the fusiform gyrus for encoding relative to retrieval, but the location of activation within the MTL was similar for both tasks when they were compared to fixation [Schacter et al., 1999]. Rostrocaudal MTL differences have been attributed to the degree of relational processing required by the task, where the anterior MTL is believed to be more involved in this process [Cohen et al., 1999; Mayes and Roberts, 2001]. It is possible that during retrieval more relational processing was required to evaluate the relationship between the target and previously encoded items stored in memory. At this time, there is not sufficient evidence from functional neuroimaging and lesion studies to map encoding and retrieval to distinct topographical regions within the MTL, but exciting new analysis techniques are promising [Zeineh et al., 2003]. However, our study does lend some support to the view of an anterior vs. posterior MTL distinction.

There is conflicting evidence as to whether encoding and retrieval require similar cognitive resources [Craik et al., 2000]. Some studies have demonstrated that under conditions of divided attention, encoding, but not retrieval accuracy performance, deteriorates [Craik et al., 2000; Naveh-Benjamin et al., 2000]. Our study demonstrates that retrieval may require greater cognitive resources, reflected in increased frontal control to execute the task. There was increased activation in several frontal regions including the inferior (BA 47) and middle frontal (BA 9/10) bilaterally. Our findings are consistent with a PET study using words in which similar areas of increased activation for retrieval such as the right middle frontal (BA 9/10) and anterior cingulate were found [Ragland et al., 2000].

The HERA (Hemispheric Encoding Retrieval Asymmetry) model based on a review of early neuroimaging studies, postulates that the right prefrontal regions are preferentially recruited during episodic retrieval, whereas the left prefrontal regions are more involved in episodic encoding and semantic retrieval [Kapur et al., 1994]. In contrast, our study provides evidence for bilateral PFC activity and supports previous studies that have shown a bilateral pattern of activation [Cabeza et al., 2002; Mottaghy et al., 1999; Ragland et al., 2000; Schmidt et al., 2002] emphasizing that the emerg-

ing picture is more complicated than originally believed. An alternative explanation for the bilateral nature of our frontal activations could be the older age of our subjects, where bilateral activity has been frequently reported [Cabeza, 2002].

Caveats and Comparisons to the Literature on Aging

Differences in activation patterns between our results and other studies may reflect age differences, as the majority of studies of brain activity during memory tasks have been carried out on young adults. The conclusions we can make relative to other studies whose prime interest was to compare memory activations between older vs. younger individuals are limited, as we did not include a young adult comparison group.

A general framework for examining differences between old and young adults is a model recently proposed by Cabeza [2002], the HAROLD (hemispheric asymmetry reduction in older adults) model based on findings from neuroimaging studies that have demonstrated a reduction in prefrontal cortex (PFC) activation asymmetry during cognitive tasks. During episodic retrieval, older adults typically show an increase in bilateral prefrontal activity compared to younger individuals who show a more right-lateralized pattern. During encoding, older individuals show a decrease in left prefrontal activity or an increase in right PFC activity. These asymmetry differences may reflect neural compensation by older adults in order to carry out the tasks more effectively or dedifferentiation, where they are unable to recruit specialized regions selectively as efficiently, resulting in bilateral activity [Cabeza, 2002]. Nevertheless, older individuals can still benefit from semantic elaboration at time of encoding, but in contrast to younger adults it is not a strategy they adopt automatically if left to their own devices [Craik and Byrd, 1982]. Findings from neuroimaging studies reveal that older adults recruit more bilateral PFC during deep vs. shallow encoding [Logan et al., 2002; Stebbins et al., 2002] and may also demonstrate a reduction in left PFC activity compared to younger adults who clearly show a left lateralized asymmetry of PFC activation [Stebbins et al., 2002]. When we examine our mean group activation patterns, we see significant task-related activity in the bilateral inferior frontal cortex in both deep and shallow encoding compared to baseline, respectively, but we cannot make any claims about relative PFC asymmetry, as we do not have a young adult comparison group. Therefore, bilateral activity could be due to the nature of the stimuli or may be related to the aging process.

Grady et al. [1999] took a network approach to study the levels of processing in words and pictures in older and younger adults, rather than simply concentrating on PFC differences as other studies have done. Both old and young benefited from deep encoding at recognition and showed a similar pattern of activity for the deep encoding of pictures but not words, where older adults showed a reduction of activity in the left PFC, suggesting a sparing of the deep

encoding network for pictures [Grady et al., 1998]. Our findings partially support these results. We found a significant increase in left PHG activation between deep and shallow encoding accompanied by a significant benefit in recognition performance from deeper processing at time of encoding. However, we found a lack of difference in PFC activation between the two encoding conditions, which may be related to the stimuli and the similar degree of semantic elaboration used by subjects in both tasks, rather than the aging process.

CONCLUSION

We demonstrated a significant level of processing effect with pictures resulting in differences in patterns of fMRI activation, a finding that has been frequently reported with words, but not with pictures. Deeper encoding resulted in greater activation of a network of regions involved in semantic processing, in the retrieval of semantic knowledge and of episodic memory encoding, such as the parahippocampal gyrus, substantiating findings from previous verbal studies which used similar manipulations. These findings suggest a common network involved in semantic encoding for pictures and words, but differential modulation of the inferior PFC depending on the salience of the picture stimuli and the degree of elaboration required by the shallow comparison task. Retrieval of deeply encoded pictures resulted most notably in greater hippocampal activation, which has been previously implicated in retrieval success. Our study also provides further evidence for the involvement of the hippocampus in episodic retrieval, substantiating the claim that this structure has a role that extends beyond initial encoding. Lastly, when comparing retrieval to encoding, there was greater activity in the anterior MTL (including hippocampus) and the inferior and dorso-lateral frontal regions during retrieval, and greater posterior PHG during encoding. This may signify greater recruitment of frontal regions, which is required in order to carry out a task that necessitates greater semantic elaboration and working memory processing, and greater hippocampal involvement for reestablishing the memory trace, relative to encoding. These findings will provide a starting point to compare the encoding and retrieval patterns in amnesic disorders such as MCI, a putative pre-cursor to Alzheimer's disease.

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