Fragments of a Larger Whole: Retrieval Cues Constrain Observed Neural Correlates of Memory Encoding

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Laying down a new memory involves activity in a number of brain regions. Here, it is shown that the particular regions associated with successful encoding depend on the way in which memory is probed. Event-related functional magnetic resonance imaging signals were acquired while subjects performed an incidental encoding task on a series of visually presented words denoting objects. A recognition memory test using the Remember/Know procedure to separate responses based on recollection and familiarity followed 1 day later. Critically, half of the studied objects were cued with a corresponding spoken word, and half with a corresponding picture. Regardless of cue, activity in prefrontal and hippocampal regions predicted subsequent recollection of a word. Type of retrieval cue modulated activity in prefrontal, temporal, and parietal cortices. Words subsequently recognized on the basis of a sense of familiarity were at study also associated with differential activity in a number of brain regions, some of which were probe dependent. Thus, observed neural correlates of successful encoding are constrained by type of retrieval cue, and are only fragments of all encoding-related neural activity. Regions exhibiting cue-specific effects may be sites that support memory through the degree of overlap between the processes engaged during encoding and those engaged during retrieval.

Keywords: encoding, episodic memory, fMRI, recognition, retrieval, transfer-appropriate processing

Introduction

Human neuroimaging studies have investigated the brain mechanisms that underlie memory formation with an experimental procedure in which neural activity is used to predict whether an event is successfully encoded. This is accomplished by segregating event-related neural activity according to subsequent memory performance (Brewer et al. 1998; Wagner et al. 1998; for review see Wagner et al. 1999; Paller and Wagner 2002). One insight that has been gained from this approach is that no single set of brain regions is associated with encoding information into long-term memory under all circumstances. Rather, the particular cortical regions that predict encoding success differ depending on the nature of the study task, even when material is held constant (Baker et al. 2001; Davachi et al. 2001; Otten and Rugg 2001a; Otten et al. 2002; Fletcher et al. 2003; Mitchell et al. 2004). During study tasks that encourage the processing of semantic attributes, encoding-related activity has primarily been observed in prefrontal cortex. During non-semantic study tasks, by contrast, activity occurs in posterior regions, including lateral parietal and occipital cortex (Davachi et al. 2001; Otten and Rugg 2001a; Otten et al. 2002).

The sensitivity of encoding-related activity to the processing demands of the study task indicates that the particular brain regions associated with long-term memory encoding depend on the nature of the processing engaged while items are initially encountered. Many of the regions that show encoding effects in a specific study task are a subset of those selectively engaged by the online demands of the task (Wagner et al. 1998; Otten and Rugg 2001a; Otten et al. 2002; Fletcher et al. 2003). These findings support a model of memory encoding that postulates that encoding is a natural consequence of the online processing of an event (Kolers 1973; Tulving and Thomson 1973; Craik and Tulving 1975). The nature of this processing determines the qualitative nature of the information stored in a memory representation.

However, long-term memory performance not only relies on the processes engaged while events are initially encountered but also those engaged at retrieval. Thus, successful memory retrieval depends on an interaction between study and test processing. Morris et al. (1977), for example, demonstrated that memory performance is not always better when information is semantically processed at study. When the memory test encouraged the use of phonological rather than semantic information to probe memory, performance was found to be better for study items that had been encoded in a phonologically rather than a semantically oriented study task. These and subsequent findings led to the idea that memory depends on compatibility between processing engaged during encoding and retrieval (the notion of "transfer-appropriate processing," Roediger et al. 1989, or "encoding specificity," Tulving and Thomson 1973). The greater the overlap between encoding and retrieval operations, the greater the likelihood that retrieval will be successful.

An important implication of the transfer-appropriate processing principle is that what constitutes optimal encoding of a stimulus event depends to a large extent on how memory for the event is probed. This raises the intriguing possibility that the neural correlates of encoding depend on how memory is tested, even when study task is held constant. Here, this possibility is considered by assessing whether the brain regions associated with successful encoding differ according to type of retrieval cue. Event-related functional magnetic resonance imaging (fMRI) signals were obtained while healthy young adults viewed a series of words describing objects. For each word, a mental image had to be created of the object to enable a size judgment (is the object's height greater than its width?). One day later, a recognition memory test followed. Critically, half of the studied objects were cued with a corresponding spoken word, and half with a corresponding picture.

The imagery-encoding task was chosen to encourage the processing of multiple attributes of the words, including visual,

semantic, and phonological features. On the assumption that there is variation across trials in the kind of stimulus attributes that are given most emphasis during the encoding task, the information stored in memory will differ across individual words. Thus, the different classes of retrieval cues will overlap to a greater or lesser extent with the representations for the different study items. With spoken-word cues, overlap may be greatest when phonological features of the study items were emphasized during encoding. With picture retrieval cues, study emphasis on visual and object-level structural features should result in the best overlap. The question of interest was whether the brain regions that predict encoding success reflect these varying degrees of overlap and accordingly differ depending on type of retrieval cue.

Materials and Methods

Participants

Twenty-two native English-speaking volunteers were paid to take part in the experiment, the procedures of which were approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology joint Medical Ethics Committee. All subjects gave informed consent prior to participating. All reported themselves to be healthy with normal vision and hearing and without neurological and psychiatric histories. The analyses presented here are based on 18 subjects (mean age 25 years, 6 women, all but one right handed); the remaining 4 subjects did not forget at least 12 words when cued with either a picture or a spoken word.

Tasks and Protocol

The experiment consisted of an incidental study task performed in the MRI scanner, followed by a surprise recognition memory test using the Remember/Know procedure to separate responses based on recollection and familiarity (Tulving 1985). During the study task, subjects saw a series of words describing objects, presented one at a time. For each word, they were asked to form a mental image of the object, and decide whether the height of the object as depicted in that image was greater than its width. As objects can be imagined in a number of ways, subjects were encouraged to envision the object in a manner that they considered a typical view of that object. One of 2 buttons had to be pressed on a hand-held response box according to each decision. Responses were given with the left and right index fingers (responding hand counterbalanced across subjects). Both speed and accuracy were stressed. Before entering the scanner, subjects were familiarized with the study task and given a short practice list. The study task proper was presented in a single block of about 18 min.

Approximately 1 day after completing the MRI scan (mean delay 23 h), subjects came back to the laboratory to perform a recognition memory test. No mention was made of a memory test until this point in the experiment. Subjects were seated in front of a computer monitor and were asked to wear a pair of headphones. They received an intermixed sequence of spoken words and pictures, both denoting objects. An informative cue was presented before each item to indicate the upcoming stimulus modality. All objects seen the previous day were presented again, along with objects not encountered before in the experiment. Half of the studied objects were cued with a corresponding spoken word, and half with a corresponding picture. Similarly, half of all new objects were presented in the form of a spoken word and half in the form of a picture.

For each trial, subjects had to make a yes/no recognition judgment as to whether or not they had seen that object during the study task. One of 2 buttons on a custom-made response box was pressed with the left and right index fingers according to each decision (responding hand balanced across subjects). If subjects indicated that they recognized the object as having been presented before, a further "remember" or "know" judgment had to be made. If subjects remembered something specific about when the object was presented at study, they were asked to give a "remember" judgment. If no specific information could be retrieved, but the item simply felt familiar, they were asked to give a "know"

judgment. Responses were given with the same buttons and fingers as the initial yes/no judgment (responding hand balanced across subjects). The task was self-paced (i.e., the system waited for both an old/new and remember/know response to be made), though both speed and accuracy were stressed. The memory test was presented in 2 parts, preceded by a short practice list.

At the end of the experiment, volunteers performed a naming task to determine if any of the pictures were not recognizable. All pictures encountered during the experiment were presented again. Volunteers named the object in each picture out loud, or said "don't know" in case they did not recognize the object. The experimenter wrote down the answers. At the completion of the naming task, volunteers were debriefed about the nature of the experiment and paid for their time.

Visual stimuli were shown one at a time in central vision on a black background. Inside the MRI scanner, words were projected in white uppercase letters for 500 ms onto a mirror in direct view of the reclining volunteer. A neutral warning stimulus (an exclamation mark) was presented 800 ms before each word. During the memory test outside the scanner, pictures were presented for 1000 ms on a computer monitor. Auditory words (mean duration of 619 ms) were spoken in a male voice and presented bilaterally at a comfortable sound level. At 1200 ms before each test item, the word "look" or "listen" was presented. This cue indicated whether the modality of the upcoming stimulus would be visual or auditory. At study, the time between successive word onsets ranged between 3.8 and 18.9 s (mean of 5.6 s). At test, the time between successive stimulus onsets varied according to response times. The next trial began 500 ms after a "new" or "remember/know" response was given. The naming task was also self-paced. At both study and test, a fixation point (a plus sign) was continuously present on the screen other than when visual stimuli were presented. For pictures, the largest dimension (height or width) of each image subtended a visual angle of 3°. Words subtended approximate visual angles of 1° vertically and 2.5–6° horizontally.

Stimulus Lists

A total of 288 objects were turned into visual words, spoken words, and pictures. The objects were taken from a wide range of categories, including animals, food, tools, furniture, clothing, and vehicles. Pictures were digitized color photographs of objects, selected from the Hemera Photo Objects collection (Volumes 1 and 2). Each picture was easy to identify and had a unique name (that is, its name unambiguously referred to only that object). Three sets of 90 objects were chosen pseudorandomly from the pool. Across volunteers, these sets were rotated across the *picture cue*, *spoken-word cue*, and *new* conditions. The set used for the *new* condition was split; half of the items were presented as pictures and half as spoken words. The remaining objects in the pool were used to create practice lists.

The study list consisted of a pseudorandom sequence of 180 critical words, interspersed with 90 fixation-only trials ("null events") to allow the estimation of the fMRI response in each experimental condition. Two filler words were added to the beginning of the list. The test list consisted of a pseudorandom sequence of 135 spoken words and 135 pictures. Ninety of the spoken words were studied objects, and 45 were new. Ninety of the pictures were studied objects, and 45 new. All sequences were generated with the restriction that at most 5 consecutive trials were of the same stimulus type.

Image Acquisition

Scanning took place during the study phase only. A 1.5-T Siemens Sonata scanner was used to acquire T_2*-weighted echoplanar images (EPI) (64 × 64, 3 × 3 mm, TE = 40 ms) with blood oxygenation level–dependent (BOLD) contrast. Each EPI volume consisted of 30 3-mm-thick axial slices separated by 1.5 mm, positioned to cover all but the most superior region of the brain and the cerebellum. Functional images were acquired during one session, comprising 390 volumes acquired continuously with an effective repetition time of 2.7 s/volume. T_1-weighted anatomical volume images were obtained at the end of the study phase.

Data Analysis

The data were analyzed using Statistical Parametric Mapping (Friston et al. 1995), version SPM2 (www.fil.ion.ucl.ac.uk/spm/software/spm2/).

The first 5 volumes in each session were discarded to allow for T_1 equilibration effects. The remaining volumes were realigned to the first volume in the series and corrected for residual motion artefacts resulting from field inhomogeneities (Andersson et al. 2001). Volumes were then corrected for different slice acquisition times, normalized to a standard EPI template based on the Montreal Neurological Institute (MNI) reference brain in Talairach space, resliced to a voxel size of 3 × 3 mm, and smoothed with an isotropic 8-mm full-width half-maximum Gaussian kernel.

The volumes comprising the study phase were treated as a time series. The variance in BOLD signal was decomposed with a set of regressors in a General Linear Model. Neural activity related to the presentation of each study item was modeled with a delta function representing stimulus onset, convolved with 3 orthogonal response functions: a canonical hemodynamic response function and its temporal and dispersion derivatives (Friston et al. 1998). The temporal and dispersion derivatives did not add substantial information and are not reported. Activity was modeled separately for study items receiving "remember," "know," and "new" judgments in the subsequent recognition test, and items not responded to or not identified in the naming task. These regressors, together with a regressor representing the mean over scans, comprised the full model. The data and model were high-pass filtered to a cut-off of 1/128 Hz.

Parameter estimates were computed for events of interest. Non-sphericity of the error covariance was accommodated by an AR(1) model, in which the temporal autocorrelation was estimated by pooling over suprathreshold voxels (Friston et al. 2002). The parameters for each covariate and the hyperparameters governing the error covariance were estimated using Restricted Maximum Likelihood. Contrasts of parameter estimates comprised the data for the second-stage analyses, which treated participants as a random effect. Images were transformed into statistical parametric maps (SPMs) of the Z statistic. Effects of interest were estimated with across-subject one-sample t-tests of linear contrasts of parameter estimates. The principal interest was in differences between study activity associated with items that were remembered versus forgotten in the subsequent memory test ("subsequent memory effects"). Regions showing subsequent memory effects were identified by computing the difference between the parameter estimates for the regressors for "remember" versus "new" responses, and "know" versus "new" responses (see text for further details). Unless specified otherwise, effects were thresholded at $P < 0.001$, uncorrected for multiple comparisons. Only activations involving contiguous clusters of at least 5 voxels are reported. Stereotactic coordinates correspond to the standard MNI normalized canonical brain.

Results

Task Performance

Study
The imagery task was performed with a mean reaction time (RT) of 1609 ms (standard deviation [SD] 392 ms). Not surprisingly, RTs did not differ depending on how an item would be cued in the subsequent recognition test (Student's $t_{17} < 1$). Importantly, however, RTs also did not differ depending on subsequent memory performance. Items given a "remember" versus a "new" judgment in the recognition test (see below) were responded to at study with mean RTs of 1634 versus 1617 ms, respectively, when cued with a spoken word, and 1627 versus 1591 ms, respectively, when cued with a picture; both $t_{17} < 1$. Study RTs also did not differ between items subsequently given a "know" versus a "new" judgment. Accuracy of study performance was not considered as the taller/wider judgment does not have an objective correct answer.

Test
Memory performance is shown in Table 1. Recognition accuracy was indexed by the discrimination measure p(Hit) – p(False

Table 1
Recognition memory performance

Word type	Recognition judgment		
	Remember	Know	New
Proportion of responses			
Old			
Spoken word	0.46 (0.16)	0.24 (0.14)	0.31 (0.13)
Picture	0.39 (0.14)	0.23 (0.12)	0.38 (0.14)
New			
Spoken word	0.05 (0.07)	0.11 (0.09)	0.85 (0.09)
Picture	0.05 (0.07)	0.13 (0.09)	0.82 (0.10)

Note: Values are across-subject means (SD). Values for "know" judgments are unadjusted for being mathematically constrained by "remember" responses.

Alarm) (Snodgrass and Corwin 1988), separately for "remember" and "know" responses. To provide an index of familiarity, "know" responses were adjusted for being mathematically constrained by "remember" responses (Yonelinas and Jacoby 1995). For responses based on recollection, recognition accuracy was higher with spoken word than with picture cues (0.41 vs. 0.34; $t_{17} = 3.15$, $P = 0.006$). Similarly, responses based on familiarity were also more accurate with spoken word than with picture cues (0.31 vs. 0.25; $t_{17} = 2.22$, $P = 0.040$).

For 2 reasons, the fMRI analyses below focus on study words that were given a "remember" versus a "new" judgment in the recognition test. In keeping with earlier event-related studies of memory encoding (Rugg et al. 2002), the primary interest here is in the neural correlates of encoding processes supporting episodic memory (recollection). In addition, the signal-to-noise ratio for study words subsequently given a "know" response was relatively low. The number of events in this category was approximately half that of items subsequently given a "remember" response, "know" responses were accompanied by considerably more false alarms than "remember" responses, and only 15 of the 18 subjects contributed enough "know" trials to assess subsequent memory effects. For completeness, however, subsequent memory effects for "know" responses will be briefly considered as recognition accuracy was above zero for this response category.

fMRI Data

Subsequent Memory Effects for ''Remember'' Responses
Regions associated with successful episodic encoding were identified by contrasting fMRI activity between words that were subsequently recollected (i.e., given a "remember" judgment in the subsequent recognition memory test) and words that were subsequently forgotten (i.e., given a "new" judgment). Following earlier practices (e.g., Uncapher and Rugg 2005), regions associated with encoding irrespective of how memory was probed were isolated by identifying voxels that demonstrate reliable subsequent memory effects that do not differ significantly ($P > 0.05$) in size according to type of retrieval cue. To this end, the main effect of subsequent memory was exclusively masked by the bidirectional subsequent memory by retrieval cue interaction. As encoding has been shown to be associated with signal increases as well as decreases (Otten and Rugg 2001b), the main effect was computed separately for each directional contrast (Recollected > Forgotten and Forgotten > Recollected, each thresholded at $P < 0.001$ uncorrected). The interaction SPM constituting the exclusive mask was thresholded at a liberal $P < 0.05$ uncorrected (the more liberal the

masking threshold, the more conservative the masking procedure for bringing out regions common to both types of retrieval cue).

As listed in Table 2 and illustrated in Figure 1, relative to forgotten words, subsequently recollected words were associated with increased activity in bilateral frontal cortex and right posterior hippocampus, and decreased activity in medial parietal, medial prefrontal, and lateral parietal cortex. Analyses of variance on the parameter estimates from the regions' peak voxels supported the idea that encoding-related activity in all but 2 of these regions was invariant across type of retrieval cue ($F_{1,17}$ values for the interaction between subsequent memory and cue type ranged between 0.01 and 1.87, $P > 0.189$). Activity in right frontal and lateral parietal cortex displayed a tendency towards being cue dependent (interaction $F_{1,17}$ values of 3.85 and 3.67, respectively, $P < 0.072$). All regions demonstrated reliable subsequent memory main effects ($F_{1,17}$ values between 15.79 and 53.33, $P < 0.001$).

The question of whether the neural correlates of successful encoding differ depending on how memory is probed was addressed with SPM contrasts that identify regions uniquely associated with each type of retrieval cue. This was accomplished with a 3-step masking procedure (cf. Uncapher and Rugg 2005). First, subsequent memory effects were computed separately for spoken-word and picture cues (thresholded at $P < 0.001$ uncorrected). Second, these subsequent memory effects were exclusively masked to eliminate voxels common to the 2 contrasts. Finally, the masked contrasts were inclusively masked with the relevant SPM interaction contrast (thresholded at $P < 0.01$ uncorrected). The final step was performed separately for spoken-word and picture cues, and signal increases and signal decreases. Together, this procedure identifies voxels where subsequent memory effects are reliable ($P < 0.001$) for one retrieval cue, and where in addition activity is significantly larger ($P > 0.01$) than for the other retrieval cue.

Table 3 lists the regions demonstrating probe-dependent subsequent memory effects. As illustrated in Figure 2, activity in right frontal cortex, right occipital cortex, and left fusiform gyrus predicted success of encoding, but only when memory was cued with a spoken word. These effects took the form of increased fMRI signals for words that were later recollected as opposed to forgotten. In contrast, when memory was cued with a picture, activity in right lateral parietal cortex, posterior cingulate, left prefrontal cortex, and 2 regions of left superior temporal cortex predicted success of encoding (see Figure 3). With the exception of lateral parietal cortex, these differences took the form of signal decreases for recollected relative to forgotten words. Supplementary analyses of variance on the parameter estimates of the regions' peak voxels supported the reliability of subsequent memory by retrieval cue interactions ($F_{1,17}$ values between 7.41 and 23.06, $P < 0.014$), and the specificity of subsequent memory effects to either spoken-word or picture cues.

Subsequent Memory Effects for ''Know'' Responses

Neural correlates of encoding-related processes that support later recognition on the basis of a sense of familiarity were
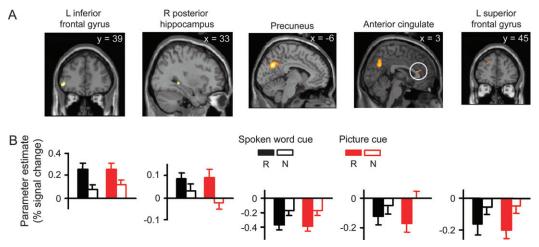
Table 2

Regions showing subsequent memory effects for "remember" responses irrespective of how memory is probed

Location (x, y, z)	Peak Z (nr of voxels)	Region	Brodmann area	Direction of effect
−48, 39, −3	3.74 (16)	Left inferior frontal gyrus	47	R > F
33, −39, −3	3.64 (5)	Right posterior hippocampus		R > F
60, 9, 36	3.63 (5)	Right precentral/inferior frontal gyrus	6/44	R > F
−6, −66, 30	4.88 (166)	Precuneus	7/31	F > R
3, 27, 15	3.56 (8)	Anterior cingulate	24	F > R
48, −54, 27	3.53 (7)	Right inferior parietal lobe	39/40	F > R
−21, 45, 33	3.29 (5)	Left superior frontal gyrus	9	F > R

Note: Z values refer to the peak of the activated cluster, the size of which is indicated in brackets. Coordinates refer to the MNI reference brain. R = recollected (given "remember" judgment in later recognition test), F = forgotten (given "new" judgment).

Figure 1. Cue-independent subsequent memory effects for "remember" responses. (*A*) Brain regions where activity predicted success of episodic encoding of visually presented words irrespective of how memory was probed in a subsequent recognition memory test. Significant clusters of activated voxels (*P* < 0.001) are rendered onto the MNI normalized canonical brain. See Table 2 for coordinates. Activity in left inferior frontal gyrus and right posterior hippocampus was larger for all study words that were later recollected versus forgotten. Activity in precuneus, anterior cingulate, and left superior frontal gyrus was smaller for study words that were later recollected as opposed to forgotten. (*B*) Quantification of cue-independent subsequent memory effects (i.e., differences between subsequently recollected and subsequently forgotten words). Parameter estimates (in percent signal change, relative to grand mean over all voxels, vs. fixation baseline) from an SPM2 analysis for the voxels of maximum activation in the subsequent memory clusters displayed in (*A*). Values are shown separately for spoken-word and picture cues, and separately for study words subsequently given a "remember" (R) and "new" (N) response. Error bars represent the standard error of the mean.

Table 3

Regions showing probe-dependent subsequent memory effects for "remember" responses

Location (x, y, z)	Peak Z (nr of voxels)	Region	Brodmann area	Direction of effect
Spoken-word cues				
57, 3, 27	3.98 (5)	Right precentral/inferior frontal gyrus	6/44	R > F
39, −84, 3	3.88 (5)	Right middle occipital gyrus	19	R > F
−51, −60, −18	3.69 (26)	Left fusiform gyrus	37	R > F
Picture cues				
36, −48, 54	3.43 (6)	Right inferior parietal lobe	40	R > F
−3, −45, 24	3.83 (15)	Posterior cingulate	23	F > R
−15, 60, 30	3.75 (10)	Left superior frontal gyrus	9/10	F > R
39, −24, 30	3.62 (5)	Right inferior parietal lobe	40	F > R
−51, −60, 18	3.61 (14)	Left superior temporal gyrus	22/39	F > R
−39, −57, 24	3.59 (12)	Left superior temporal gyrus	39	F > R

Note: Z values refer to the peak of the activated cluster, the size of which is indicated in brackets. Coordinates refer to the MNI reference brain. R = recollected (given "remember" judgment in later recognition test), F = forgotten (given "new" judgment).
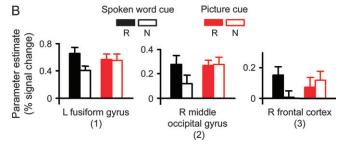

Figure 2. Subsequent memory effects for "remember" responses specific to spoken-word cues. Brain regions where activity predicted success of episodic encoding of visually presented words but only when memory was cued with a spoken word. Significant clusters of activated voxels ($P < 0.001$) are rendered onto the cortical surface of the MNI normalized canonical brain. Coordinates are listed in Table 3. (A) Regions displaying encoding-related fMRI signal increases. Words that were subsequently recollected with a spoken-word cue were associated at study with greater activity in left fusiform gyrus, right middle occipital gyrus, and right frontal cortex relative to word that were subsequently forgotten. Numbers refer to the quantification of the activity shown in (B). (B) Quantification of spoken-word–specific subsequent memory effects. Parameter estimates (in percent signal change, relative to grand mean over all voxels, vs. fixation baseline) for the voxels of maximum activation in the clusters displayed in (A) for study words subsequently given a "remember" (R) and "new" (N) response. Values are shown separately for spoken-word and picture cues. Error bars represent the standard error of the mean.

assessed by contrasting fMRI activity between words that were subsequently given a "know" judgment and words that were subsequently given a "new" judgment. These analyses were based on those 15 of the 18 subjects who gave at least 12 "know" recognition judgments. The dependency or independency of encoding-related regions to the way in which memory was probed was established with the same masking procedure as described above for "remember" responses.

Regions demonstrating reliable subsequent memory effects for "know" responses are listed in Table 4. Irrespective of the

way in which memory was probed, words later judged as familiar rather than new were at study associated with increased activity in bilateral inferior parietal cortex, just posterior to the postcentral gyrus and just below superior parietal cortex. Decreased activity was observed in a more inferior part of left lateral parietal cortex, near the angular gyrus. The cue independency of these regions was substantiated by analyses of variance on the parameter estimates from the regions' peak voxels. These analyses showed reliable main effects of subsequent memory ($F_{1,14}$ values between 17.20 and 29.96, $P < 0.001$) but no subsequent memory by retrieval cue interactions ($F_{1,14}$ values between 0.17 and 2.10, $P > 0.170$).

As observed for "remember" responses, several regions demonstrated cue-dependent subsequent memory effects for "know" responses. Activity in left superior parietal cortex, right temporal and fusiform cortex, left occipital cortex, and right prefrontal cortex predicted success of encoding but only when memory was probed with a spoken word. Activity in these regions was larger for words later given a familiarity judgment rather than a new judgment. The parameter estimates of the regions' peak voxels exhibited reliable subsequent memory by retrieval cue interactions ($F_{1,14}$ values between 9.29 and 26.79, $P < 0.009$), and follow-up analyses confirmed the specificity of the subsequent memory effects to spoken-word cues. No region showed a picture-specific subsequent memory effect.

Discussion

The findings demonstrate that neural activity associated with successful encoding depends on the way in which memory is probed. Activity in different brain regions predicted whether a visually presented word would be remembered 1 day later depending on whether memory was cued with a spoken word or a picture. Thus, the successful encoding of information into long-term memory is not supported by a single set of brain regions under all circumstances. Previous work has shown that the particular regions that are engaged depend on the type of processes employed while information is initially encountered (Davachi et al. 2001; Otten and Rugg 2001a; Otten et al. 2002). The present findings show that, in addition, the engagement of regions varies according to how memory is probed, even when study task and study material are held constant.

Why does encoding-related activity vary according to type of retrieval cue? As noted in the Introduction, memory is thought to depend on the degree to which processes engaged at study overlap with those engaged at test (Tulving and Thomson 1973; Roediger et al. 1989). The processes used to encode a new experience determine, at least in part, the strength and contents of the resulting memory representation (Kolers 1973; Tulving and Thomson 1973; Craik and Tulving 1975). Retrieval cues may tap into a particular memory representation with varying degrees of success depending on the similarity between the information provided by the cue and that stored in the memory. Indeed, memory performance was slightly better with spoken-word than picture cues, presumably because spoken words and visual words overlap to a greater extent than pictures and visual words (Price 2000; Hornberger et al. 2004). Brain regions that exhibit cue-dependent subsequent memory effects may therefore be sites that reflect the processing of those aspects of the study episode that are utilized during the retrieval process.

A practical implication of the present findings is that the brain regions predictive of memory formation in any experiment are
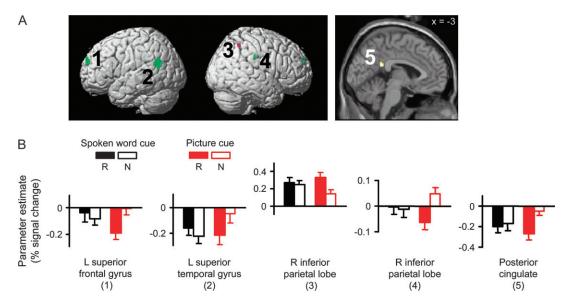
Figure 3. Subsequent memory effects for "remember" responses specific to picture cues. Brain regions where activity predicted success of episodic encoding of visually presented words but only when memory was cued with a picture. Significant clusters of activated voxels ($P < 0.001$) are rendered onto the MNI normalized canonical brain. See Table 3 for coordinates. (A) Regions displaying differential encoding-related fMRI activity. Regions shown in red demonstrated signal increases, those shown in green signal decreases. Words that were recollected with a picture cue were associated at study with greater activity in a superior region of right inferior parietal cortex and smaller activity in a more inferior region of right inferior parietal cortex, left superior frontal gyrus, left superior temporal gyrus, and posterior cingulate. Numbers refer to the quantification of the activity shown in (B). (B) Quantification of the effects shown in (A). Parameter estimates (in percent signal change, relative to grand mean over all voxels, vs. fixation baseline) for the voxels of maximum activation in the subsequent memory clusters for study words subsequently given a "remember" (R) and "new" (N) response. Estimates are shown separately for spoken-word and picture cues. Error bars represent the standard error of the mean.

Table 4

Regions showing subsequent memory effects for "know" responses

Location (x, y, z)	Peak Z (nr of voxels)	Region	Brodmann area	Direction of effect
Probe independent				
−57, −30, 51	3.94 (11)	Left inferior parietal lobe	40	K > F
30, −51, 54	3.93 (13)	Right inferior parietal lobe	40	K > F
−39, −48, 63	3.84 (10)	Left superior/inferior parietal lobe	7/40	K > F
42, −42, 48	3.76 (8)	Right inferior parietal lobe	40	K > F
−39, −60, 33	3.25 (5)	Left inferior parietal lobe	39/40	F > K
Probe dependent (specific to spoken-word cues)				
−21, −54, 51	4.04 (19)	Left superior parietal lobe	7	K > F
63, −57, −3	3.79 (5)	Right middle temporal gyrus	21	K > F
−15, −57, 0	3.78 (9)	Left lingual gyrus	18/19	K > F
39, −9, −27	3.64 (6)	Right fusiform gyrus	20	K > F
27, 21, 27	3.59 (11)	Right middle frontal gyrus	9	K > F
−30, −72, 24	3.57 (12)	Left superior occipital/angular gyrus	19/39	K > F

Note: Analyses are based on those 15 of the 18 subjects who had at least 12 "know" responses. Z values refer to the peak of the activated cluster, the size of which is indicated in brackets. Coordinates refer to the MNI reference brain. K = familiar (given "know" judgment in later recognition test), F = forgotten (given "new" judgment).

only a fragment of all encoding-related activity. On any occasion, the subsequent memory approach will only reveal regions that are associated with features of the encoding episode that are essential for its later retrieval. Regions important for encoding, but not associated with features used during the particular circumstances of retrieval, are not revealed. Thus, encoding-related regions are constrained by the way in which memory is probed. Constraints can be imposed because the memory test taps into different types of memory. For example, qualitatively different subsequent memory effects have been observed depending on whether the memory test draws upon recollection versus familiarity (Davachi et al. 2003; Ranganath et al. 2004), or explicit versus implicit memory (Schott et al. 2006). The present findings suggest that constraints can also be imposed within the same memory system by varying the type of retrieval cue.

There have been several reports that successful encoding is associated with different patterns of neural activity across populations. For example, activity in prefrontal and temporal cortex has been found to vary between older and younger individuals (Morcom et al. 2003), and patients with left medial temporal damage appear to receive an increased contribution from the right hemisphere during verbal encoding (Richardson et al. 2003). Such differences are typically interpreted in terms of the type of processes or strategies employed during encoding. The present data open up the possibility that such effects arise because different populations approach the memory test in different ways, perhaps focusing on different features to probe memory. A similar explanation may be proposed for differences that emerge as a result of experimental manipulations within a group. In general, any interpretation of differences in encoding-related neural activity should take the particular circumstances of encoding as well as retrieval into account.

Although the primary interest of the present experiment concerned episodic encoding, it is interesting to note that cue-dependent subsequent memory effects were observed for "remember" as well as "know" responses. This suggests that the degree to which study and test processes overlap not only affects neural correlates of encoding operations that support later recollection but also those supporting later recognition on the basis of a sense of familiarity. This adds to the idea that familiarity can be influenced by conceptual processing (e.g., Wagner and Gabrieli 1998). Few MRI studies have thus far been able to assess subsequent memory effects for familiarity-based responses (for exceptions see Brewer et al. 1998; Davachi and Wagner 2002; Davachi et al. 2003; Ranganath et al. 2004), with most focusing on differentiations within the medial temporal

lobe (Davachi and Wagner 2002; Davachi et al. 2003; Ranganath et al. 2004). Here, distinct regions showed subsequent memory effects for words later judged as familiar. Some of these regions were independent of the way in which memory was probed, whereas others were only involved when the retrieval cue consisted of a spoken word. The lack of cue-specific effects for picture cues may have a cognitive basis. However, it may also highlight a limitation of the present study in detecting familiarity-based effects. Memory was poorer with picture than spoken-word cues, and on the whole only a subset of subjects made enough "know" judgments to compute subsequent memory effects for this stimulus class. Thus, relatively little statistical power was available to detect subsequent familiarity effects.

As noted above, the present findings provide strong evidence that overlap between encoding and retrieval operations plays a role in the neural correlates of encoding. However, the precise functional role of each region demonstrating cue-dependent subsequent memory effects is less straightforward. In light of the focus on episodic encoding and the limited power associated with "know" trials, the explanations offered below address the regions associated with words subsequently given "remember" judgments. With spoken-word retrieval cues, activity in left fusiform gyrus and small regions of right frontal and occipital cortex predicted success of encoding. The region in the posterior part of left fusiform cortex virtually overlaps with the "visual word form area" identified by Cohen et al. (2000, 2002). It has been suggested that this area is particularly important for the processing of orthographic aspects of visual word stimuli. On this account, subsequent memory effects in this region may reflect the benefit to memory of a more extensive analysis of a word's orthography. This may result in a memory representation that is especially likely to be retrieved with spoken-word cues, either because enhanced orthographic analysis benefits subsequent processing of phonological and semantic attributes that are shared across visual and spoken words, or because the processing of a word's visual form primes the processing of its auditory form. In this respect, it is worth noting that the unimodal nature of the "visual word form area" has been challenged (see Price and Devlin 2003).

With picture retrieval cues, activity in left superior temporal gyrus (near the angular gyrus), left superior frontal gyrus, posterior cingulate, and right lateral parietal cortex predicted encoding success. Most of these regions, especially those in frontal and temporal cortex, have been implicated in the processing of phonological and semantic aspects of a word (e.g., Price 2000). It may therefore seem surprising that these regions show subsequent memory effects uniquely associated with picture cues. A remarkable characteristic of the effects in these regions, however, is that with one exception, there was an inverse relationship between fMRI activity and encoding success. That is, the likelihood that an item would subsequently be recollected was larger when fMRI activity in these regions was smaller.

It has previously been recognized that memory encoding can be influenced by signal decreases as well as signal increases (Otten and Rugg 2001b; see also Wagner and Davachi 2001; Daselaar et al. 2004). Although the role of decreased fMRI activity in memory encoding is not yet understood, one possibility is that it occurs in regions that support cognitive processes that are detrimental to laying down certain kinds of memories. In the present case, allocating fewer resources to phonological and semantic processes may enable a fuller analysis of imagery-based features. The more study processing could focus on mental imagery, the more pictorial information may have been stored in the resulting memory representation. As a consequence, the representation may have been more readily accessible with a picture retrieval cue. In support of this idea, the only region to show increased fMRI activity for words subsequently recollected with picture cues was lateral posterior parietal cortex (Brodmann Area 40). This region has generally been implicated in spatial attention and mental imagery (Cabeza and Nyberg 2000), especially when imagery involves the manipulation of an internally generated image (e.g., Alivisatos and Petrides 1997).

Although most brain regions showed cue-specific subsequent memory effects, several showed encoding-related activity irrespective of how memory was probed. Cue-independent subsequent memory effects for "remember" responses were observed in left inferior and left superior frontal gyrus, right posterior hippocampus, and in regions of the medial surface of parietal and frontal cortex. The superior frontal region was close to that showing a picture-specific subsequent memory effect. This suggests that it is not only the recruitment of functionally diverse brain regions that determines success of encoding with different retrieval cues but also the extent to which a functionally homogeneous region is recruited (cf. Uncapher and Rugg 2005).

Subsequent memory effects in prefrontal and parietal regions are a common finding in semantic study tasks with verbal material (see Wagner et al. 1999; Paller and Wagner 2002, for review). These regions may therefore be core regions that support memory encoding when access to meaning is involved. Given that the identity of each object needed to be discerned at both encoding and retrieval regardless of type of retrieval cue, it is likely that semantic attributes played an important role in the present circumstances (cf. Price 2000). Activity in left prefrontal cortex may reflect the degree to which information is manipulated in semantic working memory (Buckner and Koutstaal 1998; Gabrieli et al. 1998), the outcome of which is relayed to the medial temporal lobe where disparate elements of an episode are bound into a cohesive representation (e.g., Cohen et al. 1999). The fact that encoding-related activity was found in the hippocampus irrespective of type of retrieval cue suggests that such binding operations do not differ depending on the nature of the information that is bound. The right dominance of hippocampal effects may reflect the processing of nonverbal attributes of the words (Kelley et al. 1998; Wagner et al. 1998; McDermott et al. 1999).

Without further evidence, one can only speculate about the functional significance of cue-specific encoding regions. Regardless of the precise functional role of the regions showing subsequent memory effects, however, the present findings clearly demonstrate that neural activity associated with successful encoding differs depending on the type of cue given to retrieve a memory (cf. Lewis et al. 2005). Thus, what constitutes optimal encoding of a stimulus event depends on how memory for the event is probed. This supports a model of memory encoding that states that encoding is a by-product of online processing of an event (Kolers 1973; Craik 2002; see also Otten and Rugg 2001a), the effectiveness of which is determined by the nature of the processes engaged at encoding, those engaged during subsequent retrieval, and the degree of overlap between the two. Interesting questions for future research include how a retrieval cue makes contact with a stored representation, and whether

enriching the retrieval environment with multiple retrieval cues enables access to previously unavailable stored memories.

Notes

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