Published in final edited form as:

J Cogn Neurosci. 2012 June ; 24(6): 1398–1410. doi:10.1162/jocn_a_00220.

The path to memory is guided by strategy: distinct networks are engaged in associative encoding under visual and verbal strategy and influence memory performance in healthy and impaired individuals

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Abstract

Given the diversity of stimuli encountered in daily life, a variety of strategies must be used for learning new information. Relating and encoding visual and verbal stimuli into memory has been probed using various tasks and stimulus-types. Engagement of specific subsequent memory and cortical processing regions depends on the stimulus modality of studied material; however, it remains unclear whether different encoding strategies similarly influence regional activity when stimulus-type is held constant. In this study, subjects encoded object pairs using a visual or verbal associative strategy during functional magnetic resonance imaging (fMRI), and subsequent memory was assessed for pairs encoded under each strategy. Each strategy elicited distinct regional processing and subsequent memory effects: middle / superior frontal, lateral parietal, and lateral occipital for visually-associated pairs and inferior frontal, medial frontal, and medial occipital for verbally-associated pairs. This regional selectivity mimics the effects of stimulus modality, suggesting that cortical involvement in associative encoding is driven by strategy, and not simply by stimulus-type. The clinical relevance of these findings, probed in two patients with recent aphasic strokes, suggest that training with strategies utilizing unaffected cortical regions might improve memory ability in patients with brain damage.

Keywords

fMRI; human; associative; stroke; encoding

INTRODUCTION

While certain brain regions are commonly reported to show general subsequent memory effects, some regions only show effects for specific stimulus-types being encoded or tasks being used. During visual or picture-based encoding, subsequent memory effects have often been reported in regions including right prefrontal, superior parietal, lateral occipital, and fusiform cortex, whereas during verbal or word-based encoding, effects are often reported in

regions including left inferior frontal, parietal, superior temporal, lingual, and medial frontal cortex (Kim, 2011).

An unanswered question remains, however, regarding whether these differences in regional memory responses for visual and verbal stimuli are due to the bottom-up processing of the stimuli or to the top-down strategy being used to form the memory. The influence that the implemented associative strategy has on regional activity is of considerable importance to the design and interpretation of memory studies. Whether instructed or uninstructed, subjects will use a strategy for encoding, retrieving, and relating items. If regional activity is dependent on the strategy employed, instructing subjects to perform a relational processing step during encoding could itself influence the subsequent memory effects. Given the large number of studies in which subjects are instructed to perform a relational processing step during encoding, a better understanding of what is driving these subsequent memory effects is needed.

Additionally, determining whether the strategy or the stimulus-type dictates which brain regions are more engaged in encoding could have clinical relevance. It is well established that regional neocortical atrophy occurs in neurodegenerative disorders (Dickerson et al., 2009; Listerud, Powers, Moore, Libon, & Grossman, 2009; Mummery et al., 2000). If the brain regions engaged during encoding are dependent on the stimulus-type, there is little flexibility in the system and patients will struggle when encountering stimuli that require the function of damaged regions for processing and encoding. However, if the brain regions engaged during encoding are driven by the strategy being employed, such findings could hold clinical significance in their implications for rehabilitation strategies for patients with regional brain damage or neurodegenerative disease.

Currently, it remains unclear whether regional encoding activity is fixed to the stimulus-type or driven by the employed strategy. Therefore, the present studies examine whether visual and verbal strategies influence regional subsequent memory effects if the stimulus-type is held constant. In Experiment 1, regional brain responses were examined using rapid-event-related functional magnetic resonance imaging (fMRI) while subjects associated pairs of visually-presented nameable objects using either a visual imagery or verbal rehearsal strategy. Despite the robust differences in regional subsequent memory effects seen when visual versus verbal stimuli are encoded, the prediction was that similar regional distinctions would be seen when the stimulus-type is held constant and subjects are instructed to use a visual versus a verbal strategy. Experiment 2, a modified behavioral version of Experiment 1, was conducted in two patients recovering from recent aphasic strokes. By examining the impact of using an instructed visual or verbal associative encoding strategy relative to the patients' own natural strategy, the theoretical implications of Experiment 1 were applied to demonstrate potential clinical relevance.

MATERIALS AND METHODS

Experiment 1

Subjects—Seventeen healthy volunteers (mean age = 24.8 ± 3.2 years, four males) were recruited from the University of California, San Diego (UCSD) community and the

surrounding area. All subjects gave informed consent approved by the UCSD Institutional Review Board and had normal or corrected vision. Subjects received monetary compensation for their time. Two subjects were excluded from analyses due to poor behavioral performance.

Stimuli—Two-hundred and sixty-eight color images of everyday objects were used as stimuli in this experiment. Twelve images were used for practice trials prior to scanning to ensure that subjects understood the instructions. While in the scanner, subjects were shown 256 images presented in concurrent pairs for encoding; each item was shown once resulting in 128 image pairs. One object from each pair was presented to the subject during the post-scan recognition test. Images were acquired from Rossion and Pourtois color Snodgrass images (Rossion & Pourtois, 2004) and Hemera object library (Hemera Technologies Inc).

Experimental Procedure—During the associative encoding task in the scanner, subjects were shown pairs of concurrently presented images, with each pair presented for 2 seconds followed by blank screen for 3 seconds (Figure 1A). All items were paired pseudorandomly to remove obvious semantic, verbal, or visual relationships within pairs. The order of the runs and the pairs assigned to each task type were counterbalanced to prevent systematic confounding effects due to the nameability of each object. A fixation cross was presented during jittered interstimulus intervals ranging between 1.5 and 10.5 seconds. The interstimulus intervals were calculated to optimize the study design for modeling the hemodynamic response to trials (Dale, 1999; Dale & Buckner, 1997). Subjects were instructed to encode and associate 64 pairs, split evenly among two functional runs, using the visual strategy of imagining the two items visually merged during the 3-second blank screen following the presentation of the pair without verbalizing the object names (e.g. Figure 1, “Visual”). Subjects were instructed to encode and associate the other 64 pairs, split evenly among two additional functional runs, using the verbal strategy of creating a compound word made up of the names of the two objects and rehearsing it during the 3-second blank screen following the presentation of the pair without visualizing the objects (e.g. Figure 1, “Verbal”). Subjects were given a button box and were asked to press a button whenever a pair of objects appeared on the screen to make sure that subjects were attending to each image pair. One hundred and twenty-eight image pairs were presented to subjects in the scanner across four 331-second runs. Each image was presented once.

Following the encoding task in the scanner, subjects completed a self-paced post-scan recognition test examining subsequent memory for the associative pair and strategy used (Figure 1B). Subjects were shown one item from each pair previously viewed during the encoding task, i.e. the “cue” item. For each of the 128 stimuli, subjects were asked to verbally report to the examiner their answers to three questions. First, subjects were asked if they visually or verbally associated the cue item with its pair. Second, the examiner read aloud the names of three items, and subjects were asked to indicate which of those three choices was the pair of the cue item. Third, subjects were asked to report their confidence in identifying the correct pair: ‘Not Very,’ ‘Somewhat,’ or ‘Very’ confident. This recognition test lasted approximately 30 minutes.

Functional MRI Parameters—Subjects were scanned using a 3T GE scanner at the Keck Center for Functional MRI at the University of California, San Diego. Functional images were acquired using gradient-echo, echo-planar, T2*-weighted pulse sequence (repetition time = 2.5 s; one shot per repetition; echo time = 30; flip angle = 90°; bandwidth = 31.25 MHz). Forty slices covering the brain were obtained perpendicular to the long axis of the hippocampus with $3.4 \times 3.4 \times 4$ mm voxels. Field maps were acquired to measure and correct for static field inhomogeneities (Smith et al., 2004). A T1-weighted structural scan was acquired in the same plane and with the same voxel size as the functional scans. A high resolution structural scan was also acquired sagittally using a T1-weighted ($1 \times 1 \times 1$ mm) inversion recovery prepared fast spoiled gradient recalled sequence.

Data Analysis—Structural data were transformed into Talairach space (Talairach & Tournoux, 1998) by AFNI using nearest-neighbor interpolation (Cox, 1996) after standard landmarks, including the anterior and posterior commissures, were manually defined on the anatomical scans. Medial temporal lobe (MTL) alignment between subjects was then optimized using the region of interest large deformation diffeomorphic metric mapping (ROI-LDDMM) alignment technique (for more details on these methods see Hales & Brewer, 2011; Miller, Beg, Ceritoglu, & Stark, 2005).

After functional data from each run were field-map corrected (Smith et al., 2004), slices were temporally aligned and co-registered using a three-dimensional image alignment algorithm, voxels outside the brain were eliminated using a threshold mask of the functional data, and functional runs were corrected for motion and concatenated, all using the AFNI suite of programs (Cox, 1996). A 4.0 mm FWHM Gaussian filter was also applied to smooth the functional data from each run. A general linear model was constructed using multiple regression analysis; six motion regressors obtained from the registration process were included along with eight behavioral regressors based on subsequent memory performance. Subjects' behavioral trials were sorted based on accuracy and subject ratings of associative memory confidence. Trials were first divided into those in which subjects were instructed to associate the items visually versus verbally. Each of those two groups of trials were then divided into one of four outcomes based on memory performance and confidence: 'high-confidence' if the correct pair item was identified by the subject with a response of "Very" confident; 'medium-confidence' if the correct pair was identified by the subject with a response of "Somewhat" confident; 'low-confidence' if the correct pair was identified by the subject with a response of "Not Very" confident; or 'incorrect' if the correct pair item was not identified. Therefore, there were eight trial outcomes: 'Visual-high-confidence,' 'Visual-medium-confidence,' 'Visual-low-confidence,' 'Visual-incorrect,' 'Verbal-high-confidence,' 'Verbal-medium-confidence,' 'Verbal-low-confidence,' and 'Verbal-incorrect.' For each outcome, a hemodynamic response function was derived from the fMRI data using signal deconvolution with tent basis functions and a defined time window of 17.5 seconds following the onset of each pair of items (Cox, 1996). Multiple linear regression analysis was used to examine activity for 'high-confidence' correct items encoded using a visual versus a verbal associative strategy (i.e. 'Visual-high-confidence' versus 'Verbal-high-confidence'). To examine subsequent memory effects within each associative encoding strategy, a weighted approach was used to identify brain regions that responded linearly to

the four memory conditions (i.e. incorrect < low-confidence < medium-confidence < high-confidence) across the whole brain.

Functional data underwent the same Talairach and ROI-LDDMM transformations as were applied to the anatomical data. Whole brain voxel-wise t -tests ($p < 0.05$, two-tailed) carried out across all 15 subjects were conducted to examine which brain regions showed more activity for successful associative encoding using a visual versus verbal strategy and which regions showed a significant linearly weighted subsequent memory effect within each strategy separately. In order to correct for multiple comparisons and yield a whole brain significance value of $p < 0.05$ corrected for all comparisons (based on Monte Carlo simulations), functional clusters of least 12 contiguous voxels were identified in these conditions. When a whole brain significance value of $p < 0.001$ was used for illustrative purposes, functional clusters of least 4 contiguous voxels were required in order to correct for multiple comparisons. Average hemodynamic response functions were extracted for each condition and cluster of interest, and timecourses were displayed for illustrative purposes (Kriegeskorte et al., 2009). An ANOVA was conducted to examine visual and verbal incorrect and high-confidence correct responses in the functional regions identified in the ‘Visual-high-confidence’ versus ‘Verbal-high-confidence’ contrasts. This analysis was performed to examine strategy $\times$ memory interactions within strategy-specific regions.

Experiment 2

Subjects—Participants included two female patients with focal lesions localized to the left inferior frontal lobe due to a very recent stroke (Figure 6A) and four healthy controls (mean age = 54.3 ± 2.1 years). Patient 1, age 79, was tested 37 days post-stroke, and Patient 2, age 46, was tested 13 days post-stroke. Both subjects gave informed consent approved by the UCSD Institutional Review Board and had normal or corrected vision. Subjects received monetary compensation for their time.

Additional Patient Information—Patient 1 was a 79-year-old female with hypertension, hyperlipidemia, left subclavian steel syndrome, and tobacco use. She had been in her normal state of health until the day of admission, when she noted, upon making a phone call, that she was unable to speak. Evaluation in the UCSD emergency department revealed a National Institute of Health Stroke Scale of 4 for severe Broca’s nonfluent aphasia and a subtle facial droop, and given that less than three hours had passed since the onset of symptoms, the patient received tissue plasminogen activator. Computed tomography suggested severe atherosclerotic disease interpreted to be the result of long-term tobacco use. MRI showed an acute ischemic stroke in the anterior middle cerebral artery distribution, and magnetic resonance angiography showed high grade stenosis versus blockade of the anterior insular division of the left middle cerebral artery. She was kept in the ICU for 24 h for close monitoring and antiplatelet therapy was initiated. The patient was ambulatory and had no detectable motor deficits. Physical therapy, occupational therapy, and speech therapy were consulted and followed the patient during her stay. She was discharged with near complete resolution of her speech symptoms.

Patient 2 was a 46-year-old female with no significant past medical history who awoke on the day of admission with an inability to speak, except to answer 'yes' or 'no.' Upon presentation to the hospital, her National Institute of Health Stroke Scale was 2 for severe Broca's nonfluent aphasia. There were no other neurologic abnormalities. She was started on aspirin 325 mg daily immediately following her admission. An MRI was obtained confirming an acute stroke in the left frontal lobe as well as a punctuate infarct (less than 2 mm in diameter) slightly lateral to the right occipital pole. There was also an old subclinical right frontal lobe stroke noted on MRI. Magnetic resonance angiography was normal. Hypercoagulability screening was negative. Physical therapy, occupational therapy, and speech therapy were consulted and followed the patient during her stay. She was discharged with ability to create full sentences, but remained with inappropriate pauses in speech, some difficulties in spelling, and occasional dropped prepositions, pronouns and articles. She was ambulatory and had no motor deficits. She was sent home on 325 mg of aspirin daily and was asked to discontinue her oral contraceptive.

Stimuli—Two-hundred and fifty-six of the stimuli used in Experiment 1 were used in Experiment 2.

Experimental Procedure—The task used for behavioral testing was presented to the subjects on a laptop. Subjects were shown eight sets of encoding and retrieval runs. All items were paired pseudorandomly to remove obvious semantic, verbal, or visual relationships within pairs, and stimulus pairs were randomly assigned to each run. During each encoding run, subjects were shown 16 pairs of concurrently presented images. Each pair was presented for 2 seconds followed by a 3-second blank screen and 5-second fixation cross before the next pair was presented. Following the 16th pair, subjects were given approximately 10 seconds of a distracter task, in which they were asked to count backwards by a certain interval from a particular starting number (e.g. "Count backwards aloud from 47 by 4s..."). Once they counted four numbers aloud, the experimenter advanced to the retrieval run. Subjects were given a retrieval run following each encoding run. During retrieval, subjects were shown one item from each of the 16 pairs at the top of the screen and three choice images at the bottom of the screen. The position of the correct pair, which was one of the three choice images, varied pseudorandomly between left, center, and right locations. The lure images were two unpaired items from the prior encoding run, so that all three choice images were from the same encoding session. Subjects responded by verbally identifying or pointing to their choice image, and the experimenter pressed the key that corresponded with the selected image, which advanced the run to the next question. The retrieval runs were self-paced. List presentation order allowed assessment for practice effects. For the first three encoding runs, subjects were instructed to associate and remember the pairs and they were not told to use any particular strategy. For the fourth and eighth encoding runs, subjects were given the verbal strategy instructions used in Experiment 1. For the fifth, sixth, and seventh runs, subjects were given the visual strategy instructions used in Experiment 1.

Data Analysis—The number of pairs correctly identified for each run was calculated, and averages were calculated for each strategy (own, verbal, and visual).

RESULTS

Experiment 1

Behavioral Analysis—Subjects' memory for the strategy was accurate relative to chance performance (visual: $t_{(14)} = 7.854$, $p < 0.001$; verbal: $t_{(14)} = 4.586$, $p < 0.001$) and performance did not differ between strategies ($p > 0.05$). Subjects successfully identified the correct associative pair on visual trials ($65 \pm 4\%$ SEM; $t_{(14)} = 8.034$, $p < 0.001$) and on verbal trials ($58 \pm 3\%$ SEM; $t_{(14)} = 8.527$, $p < 0.001$) relative to chance performance of 33%. Of these trials, subjects reported that they were "Very" confident on 39% ($\pm 5\%$ SEM) of the visual-correct trials and on 20% ($\pm 3\%$ SEM) of the verbal-correct trials.

fMRI Analysis—Controlling the type of stimulus and focusing on successfully encoded associative pairs, the effects of using a visual versus a verbal strategy could be isolated. Brain regions were identified where the size of the BOLD response was greater when subjects successfully encoded pairs of items with high confidence using the visual associative strategy relative to the verbal associative strategy and vice-versa. Regions identified by this contrast ($p < 0.05$, corrected for multiple comparisons) are listed in Table 1. Greater response for visually- relative to verbally-encoded pairs was seen in bilateral middle frontal gyrus (BA 6), inferior and superior parietal cortices (BA 40 and 7), and lateral occipital cortex (BA 19 / 39; Figure 2). There were a large number of voxels showing a greater response for verbally- relative to visually-encoded pairs at this threshold causing single clusters to encompass multiple peaks of activation; for illustration, a threshold of $p < 0.001$, corrected for multiple comparisons, was used in order to highlight distinct foci of activity for this contrast. Regions identified at this threshold are also listed in Table 1. Greater response for verbally- relative to visually-encoded pairs was seen in left inferior frontal (BA 45) and precentral (BA 4) gyri or adjacent sulci and bilateral frontal operculum (BA 45 / 47 / 13), medial frontal cortex (BA 6), and medial occipital cortex (BA 19, 18, 30/18; Figure 3). Given that the type of stimulus was the same for both conditions and the only difference was the use of a visual or verbal associative strategy, these differences in regional activity for associative encoding are, therefore, driven by the utilized strategy.

Within-strategy subsequent memory effects were examined using a linear weighted model to isolate regions consistent with the following listing from least to greatest: incorrect, correct with low confidence, correct with medium confidence, and correct with high confidence ($p < 0.05$, corrected). Regions isolated using this model for visually and verbally encoded pairs are listed in Table 2. Under a visual associative strategy, positive subsequent memory effects were seen in left inferior frontal (BA 9, 47) and middle / superior frontal (BA 6) gyri (Figure 4). Under a verbal associative strategy, positive subsequent memory effects were seen in left medial frontal gyrus (BA 6), prefrontal cortex, and medial occipital cortex (BA 18; Figure 5). Left prefrontal regions showed subsequent memory effects for both the visual and verbal encoding strategies. While these regions had distinct foci of peak intensity, a conjunction analysis of the two conditions revealed three small regions of overlap (centered at coordinates $-38, 8, 24$; $-46, 32, 6$; and $-50, 21, 0$). Additionally, an ANOVA of the responses within the strategy-specific regions (functionally defined by the effect of strategy analysis, listed in Table 1) showed a memory $\times$ strategy interaction or trend within bilateral

lateral occipital (left: $F_{(1,14)} = 15.162$, $p < 0.01$; right: $F_{(1,14)} = 6.434$, $p < 0.05$), bilateral medial occipital (left: $F_{(1,14)} = 3.918$, $p = 0.068$; right: $F_{(1,14)} = 3.996$, $p = 0.065$), bilateral inferior frontal (left: $F_{(1,14)} = 3.686$, $p = 0.075$; right: $F_{(1,14)} = 7.108$, $p < 0.05$), and bilateral medial frontal ($F_{(1,14)} = 4.042$, $p = 0.064$) regions.

Experiment 2

Behavioral Analysis—Patient 1 had difficulty with the task, performing poorly in all three strategy conditions. She correctly identified the pair in 42% of trials using her own strategy, 38% of trials using a verbal strategy, and 42% of trials using a visual strategy. All three values did not differ from chance (i.e. 33%, $p > 0.1$). Patient 2, however, showed differences in behavioral performance due to strategy; she identified the correct pair in 77% of trials using her own strategy, 59% of trials using a verbal strategy, and 100% of trials using a visual strategy. The behavioral results are represented in Figure 6B. Practice effects were not evident for either patients or controls across the eight retrieval runs; percent correct scores for each run are listed in Table 3. The healthy control subjects correctly identified the pair in 99% of trials using their own strategy, 84% of trials using a verbal strategy, and 99% of trials using a visual strategy. Thus, in contrast to the patients, the controls were not impaired when using their own, natural strategy.

DISCUSSION

The current study examined the effects of using a visual-strategy compared to a verbal-strategy for associative encoding. Subjects were shown the same type of stimulus under both associative encoding strategies, which allowed isolation of regional brain responses due to the utilized strategy (Experiment 1). This design also allowed within-strategy subsequent memory effects to be compared for the two associative encoding strategies. Based on finding greater left inferior frontal involvement under a verbal relative to a visual strategy, patients with focal lesions localized to this region were tested on a modified behavioral version of this study (Experiment 2). Although one patient had impaired memory performance for all strategies, one patient showed impaired performance when using both the verbal strategy and her own strategy relative to the visual strategy.

Strategy effects

Prior studies examining the encoding of visual or verbal stimuli have reported different patterns of cortical activity for each stimulus-type (Achim, Bertrand, Montoya, Malla, & Lepage, 2007; Baker, Sanders, Maccotta, & Buckner, 2001; Bernstein, Beig, Siegenthaler, & Grady, 2002; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Cansino, Maquet, Dolan, & Rugg, 2002; Demb et al., 1995; Deshpande, Hu, Lacey, Stilla, & Sathian, 2010; Ferber, Humphrey, & Vilis, 2005; Fletcher et al., 2002; Fletcher, Stephenson, Carpenter, Donovan, & Bullmore, 2003; Gottlieb, Uncapher, & Rugg, 2010; Grady, McIntosh, Rajah, & Craik, 1998; Grill-Spector, Kourtzi, & Kanwisher, 2001; Harrison & Tong, 2009; Heun et al., 1999; Hocking & Price, 2009; Iidaka, Sadato, Yamada, & Yonekura, 2000; Kapur et al., 1994; Kapur et al., 1996; Kirwan, Wixted, & Squire, 2008; Kohler, Moscovitch, Winocur, & McIntosh, 2000; Lacey, Flueckiger, Stilla, Lava, & Sathian, 2010; Lee, Robbins, Pickard, & Owen, 2000; Park & Rugg, 2008; Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000; Rama,

Sala, Gillen, Pekar, & Courtney, 2001; Rugg, Otten, & Henson, 2002; Uncapher & Wagner, 2009; Wagner et al., 1998). Kim (2011) recently published a meta-analysis of 74 fMRI studies looking at subsequent memory effects for item or associative encoding of verbal or pictorial material. This meta-analysis indicated that left inferior frontal gyrus was more active for encoding verbal material, while bilateral fusiform, occipital, hippocampal, and posterior parietal regions were more active for encoding pictorial material.

In accordance with such findings, the present study found distinct regions recruited for encoding visual- versus verbal-associations, even though the same type of stimulus was presented under both conditions. Furthermore, these distinct regions were the same as those often reported when visual versus verbal stimuli are encoded. The present findings, therefore, suggest that differences in reported activity during studies using various stimulus-types may be driven by the strategies used and not by the types of stimuli encountered. It should be noted, however, that subjects likely used some degree of verbal processing during the visual strategy task and vice versa given that the stimuli were inherently conducive to both visual *and* verbal processing. Therefore, despite primary engagement in the instructed strategy, some use of the uninstructed strategy would also be expected.

Although, across all subjects, more pairs were correctly identified with high confidence for visual trials than for verbal trials, this effect was not global as there was also substantial individual variability across subjects as to which strategy had more high-confidence correct trials. Additionally, the between-strategy analysis used only trials matched across the two strategies for highest confidence, and accuracy for these judgments was high for both strategies. Thus, the differences in regional activity for associative encoding were likely driven by strategy and not by other factors related to confidence.

Within-strategy subsequent memory effects

Within-strategy subsequent memory effects were also seen in regions more responsive to a particular strategy. Given that both encoding conditions involved associating the same type of stimulus, distinct subsequent memory effects can be attributed to the subjects' use of different instructed strategies. While most effects were in regions more responsive for that strategy, some were in regions selective for the other strategy. For example, left inferior frontal regions were more active during successful verbal, than visual, encoding (Figure 3), but showed subsequent memory effects within both strategies (Figures 4 and 5).

The current findings support the claim that some cortical regions engaged during processing of an event are also important for its successful encoding (Rugg et al., 2002). Otten and Rugg (2001) helped to elucidate the influence task has on brain regions recruited during episodic memory encoding. Their study found that incidental encoding of single words engaged distinct regions when subjects made animacy versus syllable judgments about the words, possibly reflecting the effects of level of processing within the verbal domain. The present findings identify additional influences on the neural correlates of episodic encoding and extend what is known about subsequent memory activity by showing how use of different domain-based processing strategies to associatively encode visual stimuli can engage diverse subsequent memory networks.

Implications for encoding studies

Evidence that using different encoding strategies influences regional responses, even when the stimuli remain constant, has important implications for designing and interpreting studies of successful memory formation. Without instruction, subjects likely use a strategy related to the type of stimuli they are encoding; this explanation fits with the patterns of cortical activity reported when studies use visual versus verbal stimuli. Subjects' individual predilection for one strategy over another may also have an effect, and is a topic for further examination, but such individual differences are expected to have minimal impact on group data as more robust group effects dominate the resulting activations. In the absence of explicit strategy instruction, strategy remains influenced by the stimulus-type or modality.

Examining brain activity in response to the use of different encoding strategies is an important area of research; however, the current findings have cautionary implications. Many studies have examined different levels of processing, i.e. deep versus shallow encoding or relational versus item encoding. If the instructions for the two types of processing differ in their demand on using visual or verbal encoding strategies, there could be confounding effects between strategy use and level of processing. Given the current findings that explicit strategy use dominates over implicit effects of the presented stimulus-type, such potential confounds are an important consideration for designing future studies.

Potential clinical applications

Impairments that result from neurological disease or damage can extend beyond primary cognitive findings to impact memory. Once the affected brain regions are identified, an important component of rehabilitation is targeting and retraining intact brain regions and pathways to reorganize and compensate for the impairment. The processes and treatments involved in functional reorganization of motor pathways have been extensively studied in patients after suffering a stroke (Ward, 2004). Theoretically, the same principles could be applied to rehabilitating patients with damage in non-motor brain regions that cause different functional deficits. For example, following focal damage or a stroke to the left inferior frontal lobe, a patient is likely aphasic, and although other brain regions remain unaffected, this patient can have disproportionate difficulty remembering grocery lists or verbal directions. However, results from Experiment 1 suggest that brain regions engaged during an encoding task are not locked to the stimulus-type, but are flexible and can be controlled by top-down influences of the employed strategy. Therefore, individuals might improve memory performance by using a strategy that avoids the damaged tissue.

This hypothesis was tested in two patients with recent strokes localized to the left inferior frontal lobe. Although the two patients suffered damage to very similar brain regions, their behavioral performances on the task differed. Patient 1 performance was not above chance levels using any of the three strategies, suggesting poor general memory ability. Patient 2, however, was younger and, aside from the isolated infarction, in otherwise good health. She exhibited memory impairment when using her own associative encoding strategy, and this deficit became more pronounced when she used a verbal strategy. Greater impairment with using a verbal strategy was not surprising given the finding of enhanced left inferior frontal engagement during verbal associative encoding in Experiment 1. However, when she was

instructed to abandon the verbal strategy and only use a visual strategy, her performance improved to 100% for all three runs. This improvement occurred despite her reluctance to use a strategy she considered suboptimal for a ‘verbal person’ like herself. Her impaired memory performance when using her own strategy was possibly due to continued use of a strategy that was no longer ideal given her brain damage. By abandoning the verbal strategy, she no longer relied on the integrity of this brain region and showed marked improvement in her memory encoding ability, bringing her performance to the level of controls. Regardless of the specific elements of the patient’s natural associative encoding strategy, the directed visual strategy afforded improvement in her memory performance, reflecting compensation perhaps through engagement of unaffected parietal regions.

The results of the first experiment elucidate how engagement in a particular associative strategy dictates which brain regions are recruited for encoding. Such findings are relevant to both past and future investigation into regional brain involvement in encoding. In addition, the outcome of the second experiment suggests additional implications of these findings for extending beyond basic research and toward developing possible targets within clinical treatment. It, therefore, may be valuable to provide patients with adaptive memory strategies that avoid damaged brain regions and engage spared regions.

Acknowledgments

This work was supported by the National Institute of Neurological Disorders and Stroke K23 NS050305 and the University of California, San Diego Departments of Neurosciences and Radiology. JBH is supported by the National Science Foundation through the Graduate Research Fellowship Program.

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Figure 1.

Experimental design. *A*, Example of the encoding task used in the scanner illustrated with a sample pair of objects. Each stimulus pair was presented for 2 seconds, followed by 3 seconds of blank screen during which subjects associated the objects using the instructed strategy. Under the visual associative encoding condition, subjects were instructed to visualize the two objects as merged, without verbalizing their names. Under the verbal associative encoding condition, subjects were instructed to combine and rehearse the names of the two objects, without visualizing the objects. Following the 3-second blank screen and before the next pair was presented, a fixation cross appeared on the screen for a jittered 1.5-10.5-second interstimulus interval. *B*, Example of the post-scan recognition test. Subjects were shown one object from each pair previously viewed during the encoding task, and they were asked to verbally report to the experimenter their answers to three questions (a, b, and c). After the subjects reported if each item was part of a visual or verbal association (a), the experimenter read the subjects three choice pair items, one of which was the correct pair. Subjects then reported which of those three choices they recognized as the pair (b) and their confidence in selecting the correct pair (c).

Figure 2.

Visual associative encoding engages bilateral middle frontal, lateral parietal, and lateral occipital regions. Statistical activation maps for regions showing increased activity during highly-confident associative encoding using the visual strategy relative to the verbal strategy ($p < 0.05$, corrected for multiple comparisons) are overlaid on the pial surface of the Talairach and Tournoux N27 average brain and on a coronal slice of a mean anatomical scan image across all 15 subjects. Functional clusters located in bilateral middle frontal (BA 6), inferior and superior parietal (BA 40 and 7), and lateral occipital (BA 19, 39) regions were used for time-course analyses. Graphs depict the time course of percent signal change in these regions for the visual and verbal associative encoding of object pairs subsequently recognized with high-confidence. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus pair onset.

Figure 3.

Verbal associative encoding engages bilateral inferior frontal, medial frontal, and medial occipital regions. Statistical activation maps for regions showing increased activity during highly-confident associative encoding using the verbal strategy relative to the visual strategy ($p < 0.001$, corrected for multiple comparisons) are overlaid on the pial surface of the Talairach and Tournoux N27 average brain and on a coronal slice of a mean anatomical scan image across all 15 subjects. Functional clusters located in left inferior frontal (BA 45), bilateral frontal operculum (BA 47/13, 45/13), left precentral (BA 4), bilateral medial frontal (BA 6), and bilateral medial occipital (BA 19, 18, 18/30) regions were used for time-course analyses. Graphs depict the time course of percent signal change in these regions for the visual and verbal associative encoding of object pairs subsequently recognized with high-confidence. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus pair onset.

Figure 4.

Visual strategy influences regional subsequent memory effects. Statistical activation maps for regions identified using a linear weighted model of increasing subsequent memory confidence, from subsequently forgotten to subsequently recognized with high-confidence pairs, under the visual associative encoding strategy ($p < 0.05$, corrected for multiple comparisons) are overlaid on the pial surface of the Talairach and Tournoux N27 average brain. Functional clusters located in left inferior frontal (BA 47, 9) and left middle / superior frontal (BA 6) regions were used for time-course analyses. Graphs depict the time course of percent signal change in these regions for trials in which visually-encoded object pairs were identified correctly with high-confidence, correctly with medium-confidence, correctly with low-confidence, or incorrectly; the average response for all verbal trials is also depicted. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus pair onset.

Figure 5.

Verbal strategy influences regional subsequent memory effects. Statistical activation maps for regions identified using a linear weighted model of increasing subsequent memory confidence, from subsequently forgotten to subsequently recognized with high-confidence pairs, under the verbal associative encoding strategy ($p < 0.05$, corrected for multiple comparisons) are overlaid on the pial surface of the Talairach and Tournoux N27 average brain. Functional clusters located in left prefrontal, left medial frontal (BA 6), and left medial occipital (BA 18) regions were used for time-course analyses. Graphs depict the time course of percent signal change in these regions for trials in which verbally-encoded object pairs were identified correctly with high-confidence, correctly with medium-confidence, correctly with low-confidence, or incorrectly; the average response for all visual trials is also depicted. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus pair onset.

Figure 6.

Encoding strategy influences memory performance in patient with focal brain damage. *A*, Axial diffusion-weighted brain images for Patient 1 and 2 following strokes localized to the left inferior frontal lobe. *B*, Graphs depict each patient's recognition memory performance for pairs encoded using their own strategy (light grey), the verbal strategy (white), and the visual strategy (dark grey). Patient 1 performed close to chance (33%) under all three encoding strategy conditions. For Patient 2, relative to her memory performance when using her own strategy, she showed further impairment under the verbal strategy, but improvement under the visual strategy. The error bars illustrate the standard deviation, the y-axis represents the percent of trials in which they selected the correct pair, and the horizontal dashed line marks the chance level of 33% correct.

Table 1

Regional effects of associative strategy on high-confidence encoding.

Region	BA	Volume*	x	y	z	t-values
<i>Visual > Verbal[†]</i>						
L / R middle frontal gyrus	6	1088	-26	-9	56	3.46
	6	1088	22	-9	56	3.52
L / R inferior parietal lobule	40	1856	58	-29	40	4.56
	40	3136	-54	-29	36	4.26
	40	1472	34	-41	40	3.32
L / R superior parietal lobule	7	1920	-18	-73	52	3.79
	7	1216	14	-65	52	3.29
L / R lateral occipital cortex	39	6144	46	-69	24	5.80
	19	5824	-30	-81	36	4.52
<i>Verbal > Visual[†]</i>						
R cingulate	30	326592	22	-57	8	7.01
<i>sub-clusters at higher threshold[‡]</i>						
L inferior frontal gyrus	45	1344	-42	19	4	6.69
L / R frontal operculum	47/13	576	-30	23	0	5.80
	45/13	320	30	27	8	5.39
B medial frontal gyrus	6	896	-2	-5	64	6.56
L precentral gyrus	4	832	-50	-9	48	5.45
L postcentral gyrus	5	256	-26	-37	60	4.61
L / R medial occipital cortex	30/18	8320	22	-57	8	7.01
	19	448	-26	-61	0	5.66
	19	320	-18	-65	4	5.47
	18	256	-22	-73	16	5.16
L / R cingulate	31	320	-2	-17	44	5.26
	30	256	22	-49	12	5.11
L white matter	-	576	-30	-49	4	6.00
	-	256	-30	-41	20	5.18

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Region	BA	Volume [*]	x	y	z	t-values
R cerebellum	–	256	–30	–37	24	5.35
	–	3328	30	–65	–48	4.88
	–	896	26	–33	–24	3.29
Brain stem	–	1664	–2	–29	–32	3.31

^{*} cluster volumes (mm³); coordinates correspond to the voxel of maximum intensity for each cluster

[†] $p < 0.05$ corrected for multiple comparisons

[‡] $p < 0.001$ corrected for multiple comparisons

Table 2

Regional subsequent memory effects within a visual or verbal associative strategy.

Region	BA	Volume*	x	y	z	t-values
<i>Visual subsequent memory regions[†]</i>						
L inferior frontal gyrus	47	2176	-42	35	0	3.40
	9	832	-34	11	24	2.91
L middle / superior frontal gyrus	6	2688	-26	11	52	4.88
<i>Verbal subsequent memory regions[†]</i>						
L prefrontal cortex	45	15232	-26	35	16	7.32
L medial frontal gyrus	6	1216	-6	15	44	4.41
L medial occipital cortex	18	2240	-10	-69	-4	3.35
L superior temporal gyrus	13	17600	-42	-45	20	5.50
R insula	13	1536	26	27	12	3.77
	-	1728	38	-65	-28	3.37
R white matter	-	20032	30	-45	4	5.65
	-	2048	22	11	24	3.50
	-	1152	26	-5	24	3.33

* cluster volumes (mm³); coordinates correspond to the voxel of maximum intensity for each cluster; only positive activations listed

[†] $p < 0.05$ corrected for multiple comparisons

Table 3

Percent correct performance for patient and controls.

Run	1	2	3	4	5	6	7	8
Strategy	Own	Own	Own	Verbal	Visual	Visual	Visual	Verbal
Patient 1	38	38	50	44	38	31	56	31
Patient 2	81	75	75	56	100	100	100	63
Controls *	98; (94-100)	100; (100)	98; (94-100)	77; (56-100)	98; (94-100)	100; (100)	98; (94-100)	91; (69-100)

* average and range of percent correct across the 4 control subjects