Medial Temporal Lobe Involvement in an Implicit Memory Task: Evidence of Collaborating Implicit and Explicit Memory Systems from fMRI and Alzheimer’s Disease

We used a prototype extraction task to assess implicit learning of a meaningful novel visual category. Cortical activation was monitored in young adults with functional magnetic resonance imaging. We observed occipital deactivation at test consistent with perceptually based implicit learning, and lateral temporal cortex deactivation reflecting implicit acquisition of the category’s semantic nature. Medial temporal lobe (MTL) activation during exposure and test suggested involvement of explicit memory as well. Behavioral performance of Alzheimer’s disease (AD) patients and healthy seniors was also assessed, and AD performance was correlated with gray matter volume using voxel-based morphometry. AD patients showed learning, consistent with preserved implicit memory, and confirming that AD patients’ implicit memory is not limited to abstract patterns. However, patients were somewhat impaired relative to healthy seniors. Occipital and lateral temporal cortical volume correlated with successful AD patient performance, and thus overlapped with young adults’ areas of deactivation. Patients’ severe MTL atrophy precluded involvement of this region. AD patients thus appear to engage a cortically based implicit memory mechanism, whereas their relative deficit on this task may reflect their MTL disease. These findings suggest that implicit and explicit memory systems collaborate in neurologically intact individuals performing an ostensibly implicit memory task.

Keywords: Alzheimer’s, explicit memory, fMRI, implicit memory, medial temporal

Introduction

Implicit memory facilitates behavior without conscious awareness of either the prior learning process or the resulting knowledge. Numerous studies demonstrating good performance on implicit memory tasks by amnesics, despite their inability to recall or recognize specific training items (e.g., Graf and Schacter 1985; Squire 1986; Nissen and Bullimer 1987; Squire and Knowlton 1995; Reed et al. 1999; Reber, Martínez, et al. 2003; Golby et al. 2005), have provided compelling evidence for the independence of implicit and explicit memory systems. Although investigators have thus posited that implicit learning does not involve medial temporal lobe (MTL) structures such as the hippocampus, the mutual exclusivity of implicit and explicit memory processes has recently been questioned. Evidence suggests that 2 distinct memory processes can be employed within a single experimental task: Investigators have attributed improved performance on ostensibly implicit tasks to explicit memory for training stimuli (Willingham et al. 1989; Poldrack and Packard 2003; Schott et al. 2005). In a task in which amnesics initially exhibit unimpaired performance, further training enhances performance only for neurologically healthy subjects (Knowlton et al. 1994), and MTL involvement has been implicated in healthy subjects’ performance advantage (Poldrack et al. 2001). Some investigators have further proposed that the MTL, a brain area generally associated with explicit learning and retrieval of episodic knowledge, is part of the system supporting implicit memory performance (Beauregard et al. 1998).

Research in implicit learning and memory has tended to employ stimuli devoid of semantic content (e.g., Nissen and Bullmer 1987; Willingham et al. 1989; Ashby et al. 1998; Reber et al. 1998; Reber, Gitelman, et al. 2003; Reber, Martínez, et al. 2003), such as dot patterns (e.g., Posner and Keele 1968; Squire and Knowlton 1995; Reber et al. 1998; Aizenstein et al. 2000; Reber, Gitelman, et al. 2003), letter strings (e.g., Reber 1967; Fletcher et al. 1999; Skosnik et al. 2002; Reber, Martínez, et al. 2003), and arbitrary geometric shapes (Schacter et al. 1990, 1997). Implicit memory has thus often been associated with perceptual tasks. Moreover, it has been claimed that patients with Alzheimer’s disease (AD), a condition associated with reasonable implicit learning on perceptually based tasks despite severely impaired episodic memory (Butters et al. 1988), selectively demonstrate impaired implicit memory on semantic tasks (Fleischman et al. 1997, 2005; Fleischman and Gabrieli 1998). Thus, our goals were twofold: 1) to assess the contribution of episodic memory to performance of an ostensibly implicit learning task, and 2) to examine implicit memory for semantically meaningful material.

Functional neuroimaging has provided new insights into the neuroanatomic substrates of implicit memory. Two common observations emerge from among many studies (e.g., Squire et al. 1992; Schacter et al. 1996, 1997; Cabeza et al. 1997; Reber et al. 1998; Petersson et al. 1999; Poldrack et al. 2001; Skosnik et al. 2002; Nyberg et al. 2003; Reber, Gitelman, et al. 2003; Vuilleumier et al. 2005): First, implicit learning tends to involve occipital and striatal regions, presumably reflecting visual-perceptual processing and habit learning, respectively. Second, implicit learning is associated with relative deactivation of relevant brain regions, particularly in visual association cortex. Such deactivation on implicit memory tasks is thought to reflect perceptual fluency, that is, diminished processing demands that result from repeated exposure and accrued familiarity with similar-appearing material (Schacter and Buckner 1998; Fletcher et al. 1999; Aizenstein et al. 2000; Reber, Gitelman, et al. 2003; Kelly, Garavan, et al. 2005). In the present study, we used functional magnetic resonance imaging (fMRI) to observe cortical recruitment in healthy young subjects while they implicitly acquired, and were subsequently tested on, a novel category. We also examined performance of AD patients participating in the same task as a behavioral protocol. MTL
structures are profoundly compromised in AD (Arnold et al. 1991; Braak and Braak 1991), and thus we used analyses of AD patients' performance to help interpret the contribution of these regions to the young subjects' performance.

Previous work used fMRI to demonstrate competition between explicit memory (supported by the MTL) and implicit memory (supported by the caudate) in a habit learning task (Poldrack et al. 2001; Foerde et al. 2006). In the present study, by contrast, we address the collaborative involvement of explicit and implicit memory, using a different implicit memory procedure—prototype extraction. Thus, this study is in keeping with other work that posits concurrent use of the 2 independent memory systems. The prototype extraction protocol was designed to examine implicit learning of non-semantic visual categories such as dot patterns (Posner and Keele 1968; Squire and Knowlton 1995; Reber et al. 1998, 1999; Aizenstein et al. 2000; Reber, Gitelman, et al. 2003), and has been adapted for categories of pictorial objects constructed of discrete features (Reed et al. 1999). Subjects are initially exposed to category exemplars that are derived from a prototype, without being informed of the items' categorical nature until the start of a subsequent test session. During the test session, subjects judge category membership for stimuli that include category members and items that vary from the prototype to greater and lesser extents. AD patients have been shown to achieve above chance performance on prototype extraction tasks (Keri et al. 1999; Reed et al. 1999; Eldridge et al. 2002; Bozoki et al. 2006).

We expected the fMRI imaging study in young adults to show relative deactivation in occipital areas for category members compared with nonmembers, consistent with other imaging studies of implicit learning of visually based categories. We also monitored MTL activation because of this brain region's potential role in supporting an additional explicit memory contribution to an ostensibly implicit memory task. If both MTL and cortical regions play roles in prototype extraction, moreover, we would expect AD patients to acquire the category at a level that exceeds chance, commensurate with their levels of preserved cortical functioning; but their limited MTL functioning should impair their performance relative to controls.

A second goal of the present study was to extend findings on implicit learning of material with meaningful content, and hence we used the prototype extraction procedure with semantically meaningful stimuli. fMRI studies have assessed implicit acquisition of artificial grammars, considered to be conceptual rather than perceptual in nature (Reber et al. 1998; Reber, Martinez, et al. 2003), and patients with AD are able to acquire an artificial grammar (Reber, Martinez, et al. 2003). However, the conceptual nature of this kind of material has been questioned, as apparent learning can be at least partially attributed to superficial perceptual similarities among stimuli (Knowlton and Squire 1996; Lieberman et al. 2004). Studies of semantic priming, which draw on implicit semantic memory, have yielded equivocal results in AD (Nebes 1989; Glosser et al. 1998). Although apparently intact semantic priming has been demonstrated in non-AD amnesics (Levy et al. 2004), implicit memory studies of semantic material failed to demonstrate above chance performance in AD patients (Heischman et al. 1997; Heischman and Gabrieli 1998). However, these latter studies seem confounded by executive resource demands selectively required by the semantic tasks, such as mental search procedures involved in word generation. Thus, executive impairment in AD (LaFleche and Albert 1995; Libon et al. 2007) may have influenced patients' performance in the semantic, but not in the perceptual, tasks. The present report assesses implicit learning from a unique perspective by employing an established protocol for perceptual category learning in order to assess acquisition of a meaningful novel category. If a semantic category can be acquired with the prototype extraction technique, the imaging study might show deactivation in posterolateral temporal cortex that is implicated in semantic memory (Martin et al. 1996; Josephs 2001; Kensinger et al. 2003; Grossman et al. 2007). Moreover, to the extent that implicitly acquiring a meaningful concept does not depend on the MTL, AD patients might be able to learn this meaningful category with the prototype extraction technique.

Methods: fMRI Study

Subjects

Nine healthy young volunteers (5 female) participated in this study. The mean age was 20.3 (±2.0); mean education was 14.4 (±1.8) years. All were right-handed, native English speakers. Informed consent was obtained under a protocol approved by the Institutional Review Board at the University of Pennsylvania.

Stimuli

We created a set of 64 unique images of realistic novel animals comprising all possible combinations of 6 features, each with 2 variants: snout (pointed or blunt), legs (short or long), neck (raised or lowered), color (yellow or red), tail (straight or curled), and tooth (fang-like or tusk-like). Ranking of the 6 features' contribution to inter-item resemblance judgments was obtained as follows: All possible animal pairs were formed, and 10 young volunteers rated each pair for interitem similarity. With successive multidimensional scaling analyses for 1 through 6 dimensions performed on the ratings, head, leg, color, and neck emerged as the features contributing the most to similarity assessments. We refer to these as "contributing" features, and to the remaining 2 (tail and tooth) as "noise" features. We created a category by randomly choosing one variant of each of the 4 contributing features, that is, pointed snout, short legs, yellow color, and upright neck. Category membership was determined as follows: MEMBERS contained at least 3 of these 4 contributing feature variants; AMBIGUOUS items contained exactly 2 of the contributing variants; NONMEMBERS contained 1 or 0. Four of the MEMBERS contained all four contributing feature variants (with different combinations of noise feature variants), and thus embodied the central tendency of the category. We refer to these 4 MEMBERS as prototypical. The variants of the noise features were evenly represented among each type of stimulus. Examples are shown in Supplementary Material (1). As detailed elsewhere (Koenig et al. 2006, 2007; Koenig and Grossman 2007), subjects appear to treat these stimuli as a conceptual category rather than an exclusively perceptual category. For example, individual features' diagnosticity appears to reflect relevance specific to classifying animals, rather than purely perceptual characteristics, and accuracy of category membership judgments declines when the category set is reconfigured so that membership involves noise features. We have previously demonstrated that this novel category can be learned by young subjects (Koenig et al. 2005) and by AD patients (Koenig et al. 2007) by explicit categorization processes. Stimuli consisted of 50 items, reduced from the complete set because of time constraints, and comprised 20 MEMBERS, 14 AMBIGUOUS items, and 16 NONMEMBERS.

Procedure

Exposure Session

The exposure session took place while subjects were being scanned. The series of training items was back-projected on a screen visible via a system of mirrors; presentation was controlled via computer. Consistent with most prototype extraction studies (e.g., Reber et al.
1998, 1999; Reber, Gitelman, et al. 2003), instructions were minimal: Subjects were told that they would see a series of animals, and were instructed to look at them. The intention was to ensure that subjects attended to each trial without unduly promoting deliberate semantic or perceptual processing of the stimuli. During the session, subjects saw a sequence of forty 12-s trials, each displaying a single animal that remained on the screen for 9 s. The sequence consisted of 8 randomly ordered nonprototype MEMBERS (i.e., items containing exactly 3 contributing category feature variants), shown in 5 successive sets. Thus, subjects saw each training MEMBER 5 times, and were exposed to each categorical feature variant and combination of feature variants an equal number of times, presented in no discernible pattern.

Test Session
Following the exposure session, subjects were told that the pictures they had just seen were all the same kind of animal, called crutters. They were then told that they would see another sequence of animals, some of which would be crutters and some of which would not be, and that they were to indicate for each item whether it was a crutter or not. Test items consisted of the 50-item stimulus set, presented in a fixed pseudorandom order in which no more than 5 items of any type (e.g., NONMEMBERS) appeared sequentially. The MEMBERS included the 4 prototypical items and 16 items that contained exactly 3 contributing feature variants: the 8 items that had previously been seen during the exposure session (“old” MEMBERS), and 8 comparable items seen for the first time at test (“new” MEMBERS). Subjects responded by a right-hand press for “yes” and a left-hand press for “no” on a hand-held button-box. Test items appeared 12 seconds apart, and remained on the screen until a button-press response. Responses were recorded via the computer controlling the image presentation.

Imaging Data Acquisition and Statistical Analysis
We used an event-related approach to data acquisition, carried out in a 1.5T GE prototype Echospeed scanner capable of ultrafast imaging. Event-related data acquisition allowed us to group and compare images corresponding to specific stimuli. Each imaging session began with a 10–15 min acquisition of 5 mm thick adjacent slices for determining regional anatomy. This included sagittal localizer images (time repetition [TR] = 500 ms, time echo [TE] = 10 ms, 192 × 256 matrix), T2-weighted axial images (FSE, TR = 2000 ms, T2eff = 85 ms), and T1-weighted axial images used for FMRI anatomic localization (TR = 600 ms, TE = 14 ms, 192 × 256 matrix). Gradient echoplanar images were acquired for detection of alterations of blood oxygenation accompanying mental activity. All images were acquired with fat saturation, a rectangular field of view of 20 × 15 cm, flip angle of 90°, an effective TE of 50 ms, a TR of 2000 ms, a 64 × 40 matrix, and 5 mm slice thickness, resulting in a voxel size of 3.75 × 3.75 × 5 mm. The echoplanar acquisitions consisted of 18 contiguous slices every 2 s. To minimize susceptibility artifact, a separate acquisition lasting 1–2 min was needed for phase maps to correct for distortion in echoplanar images (Alsop et al. 1995). We also inspected raw data of individual subjects. Raw data were stored by the MRI computer on DAT tape and then processed off-line.

Initial data processing was carried out with Interactive Data Language (Research Systems) on a Sun (Santa Clara, CA) SunBlade workstation. Raw image data were reconstructed using a 2D FFT with a procedure that minimized artifact due to magnetic field inhomogeneities. Individual subject data were then prepared for statistical parametric mapping (SPM 99) developed by the Wellcome Department of Imaging Neuroscience (http://www.filion.ucl.ac.uk/spm/software/spm99). The images in each subject’s time series were registered to the initial image in the series. The images were then aligned to a standard coordinate system and spatially smoothed with an 8 mm Gaussian kernel to account for small variations in the location of activation and sulcal anatomy across subjects. Low-pass temporal filtering was implemented to control autocorrelation with a first-order autoregressive method. To ensure that patterns of activation reflected successful categorization, we analyzed activation at test only for accurate responses to MEMBER and NONMEMBER stimuli, which included 78% of these trials.

A random-effects approach to statistical analysis was adopted. For the test session, 3 independent models were computed on the subject level, using the following variables as separate conditions: MEMBERS versus NONMEMBERS, Old Members versus New Members, and First Half versus Second Half. This latter model was used for the exposure session as well. Images corresponding to these conditions were convolved with the canonical HRF and entered into a first-level analysis. Contrast images were created for each condition and fed into a second-level f-test. Statistical contrasts were converted to Z-scores for each compared voxel. We used a statistical height threshold of $P < 0.001$ uncorrected for multiple comparisons. The extent criterion of a cluster was set to a 20 voxel threshold, so the effective statistical threshold of activated regions exceeded a $P$ value of 0.05 corrected for multiple comparisons (Forman et al. 1995). Peak voxel values were converted from Montreal Neurological Institute coordinates to Talairach coordinates (Talairach and Tournoux 1988) using the program MNISTAL (ftp://ftp.mrc-cbu.cam.ac.uk/pub/imaging/MNISTAL/mni2tal.m).

fMRI Study: Results and Discussion

Behavioral Observations
Subjects demonstrated an endorsement pattern at test indicative of category learning based on prototype extraction; that is, they endorsed MEMBERS most frequently and NONMEMBERS least frequently. Scores are shown in Figure 1A. A repeated-measures analysis of variance (ANOVA) confirmed the effect of stimulus type, $\text{F}_{2,16} = 30.36, \text{P} < 0.001$. Post hoc LSD t-tests showed that endorsements for MEMBERS exceeded that for AMBIGUOUS items, $\text{P} = 0.006$, which in turn exceeded that for NONMEMBERS, $\text{P} = 0.003$. This graded pattern indicates that subjects did not derive the unspecified 3-out-of-4-features “rule” underlying the category structure, as applying this rule would have resulted in rejections of AMBIGUOUS items as well.

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Figure 1. Behavioral performance at test in young controls during imaging. (A) Endorsement of MEMBERS, AMBIGUOUS items, and NONMEMBERS. (B) Variability of endorsements of old and new MEMBERS.
as of NONMEMBERS. To confirm that subjects did not rely on other deliberate strategies such as simpler 1- or 2-feature rules, we compared the results with a hypothetical "perfect prototype-extraction" pattern, that is, one in which endorsement rates for items with 4, 3, 2, 1, or 0 prototypical features would be, respectively, 100%, 75%, 50%, 25%, and 0%. Assuming no biases for particular features, this would yield endorsement rates of 63% for each prototypical feature variant, 38% for each nonprototypical feature variant, and 50% for each noise feature variant. Individual subjects approximated this pattern: Mean endorsements of prototypical variants ranged from 67% to 69%; mean endorsements of nonprototypical variants ranged from 39% to 43%; and mean endorsements of noise patterns ranged from 47% to 64%. Thus, categorization judgments were consistent with endorsements based on degree of prototypicality, and no subjects based endorsements on an individual feature or pair of features.

Implicit prototype extraction should result in potentially higher endorsements of prototypes, even though prototypes were not seen during the exposure period, as these items best embody the extracted central tendency of the acquired category. In contrast, explicit memory could result in a performance advantage for old MEMBERS relative to new MEMBERS, because only the former class of items was seen during the exposure period. There was a high endorsement rate for prototypical MEMBERS of 92%, compared with 83% endorsement of old MEMBERS and 74% endorsement of new MEMBERS. These scores were highly correlated: Pearson’s r for comparisons between prototypical MEMBERS and old MEMBERS, between prototypical MEMBERS and new MEMBERS, and between old and new MEMBERS were, respectively, 0.91 (P = 0.001), 0.87 (P < 0.005), and 0.72 (P < 0.05). An ANOVA confirmed a difference among the endorsement scores, F2,16 = 5.59, P = 0.01, and a within-subjects linear contrast confirmed the pattern of increasing accuracy from new MEMBERS to old MEMBERS to prototypes, F1,8 = 9.69, P = 0.01. Consistent with implicit learning, endorsements for prototypical MEMBERS reliably exceeded endorsements both for old MEMBERS, t(8) = 3.11, P = 0.01, and for new MEMBERS, t(8) = 2.51, P = 0.05, whereas the difference between endorsements for old MEMBERS relative to new MEMBERS was not reliable, P = 0.17. We also examined distinctions between old and new MEMBERS with an item analysis, and found that endorsement patterns between old and new MEMBERS differed in variability, t(7) = 3.13, P < 0.05, as shown in Figure 1B. This suggests that the high endorsement of old MEMBERS was more stable across items than was the endorsement of new MEMBERS, consistent with explicit memory for studied items. Hence, we observed behavior suggestive of both implicit and explicit memory. This contrasts with the results of our previous fMRI study in which young subjects were explicitly taught the same novel animal category by either a similarity-based process, whereby comparisons were made to a specified prototype, or a rule-based process, in which defining features were specified (Koenig et al. 2005). In that study, subjects who categorized by similarity endorsed prototypical members most frequently while endorsing old and new MEMBERS equivalently (and with equal variability), suggesting that episodic memory for studied items provides no detectable advantage when categorization judgments rely on explicit comparisons with a specified prototype. Subjects who categorized by an explicit rule-based process endorsed all 3 MEMBER types equivalently, suggesting that prototypicality has no detectable advantage when categorization judgments rely on explicit rules. Thus, categorization judgments in the present implicit learning study appear to reflect processes that differ from those employed in these explicit learning tasks.

### Imaging Observations

#### Exposure Session

The observed areas of activation are summarized in Table 1; coordinates represent activation peaks, and Brodmann areas reflect processes that differ from those employed in these explicit learning tasks.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Activations and deactivations during implicit acquisition of a meaningful category</th>
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<tbody>
<tr>
<td>Anatomic area</td>
<td>Brodmann area</td>
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<tr>
<td>Exposure phase</td>
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<tr>
<td>L middle frontal</td>
<td>9</td>
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<tr>
<td>L dorsal anterior cingulate</td>
<td>32</td>
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<tr>
<td>L parietal-occipital</td>
<td>19</td>
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<tr>
<td>R inferior frontal</td>
<td>47</td>
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<tr>
<td>R temporal</td>
<td>37</td>
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<td>R medial temporal</td>
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<td>R parietal-occipital</td>
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<td>R caudate</td>
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<tr>
<td>Deactivation over time (second half &lt; first half)</td>
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<tr>
<td>L temporal-parietal</td>
<td>40/22</td>
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<tr>
<td>L striatum</td>
<td>–28</td>
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<tr>
<td>Increased activation over time (second half &gt; first half)</td>
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<tr>
<td>B occipital</td>
<td>18/19</td>
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<tr>
<td>Test phase</td>
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<tr>
<td>L inferior frontal</td>
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<td>L inferior parietal</td>
<td>39</td>
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<tr>
<td>L lateral temporal</td>
<td>37/22/21</td>
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<tr>
<td>L medial temporal</td>
<td>–24</td>
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<td>L thalamus</td>
<td>–20</td>
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<td>B parietal</td>
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<td>B anterior cingulate</td>
<td>32</td>
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<td>R middle frontal</td>
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<td>Deactivation over time (second half &lt; first half)</td>
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<tr>
<td>B occipital</td>
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<td>L lateral temporal</td>
<td>22/21/20</td>
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<tr>
<td>Increased activation over time (second half &gt; first half)</td>
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<tr>
<td>R posterior cingulate</td>
<td>23/31</td>
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<tr>
<td>L caudate</td>
<td>–24</td>
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<tr>
<td>L medial temporal</td>
<td>–32</td>
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<td>Deactivation for members (MEMBERS &lt; NONMEMBERS)</td>
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<td>L medial frontal</td>
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<td>L occipital</td>
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<tr>
<td>R parietal/occipital</td>
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<td>Activation for members (MEMBERS &gt; NONMEMBERS)</td>
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<td>L inferior frontal</td>
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<tr>
<td>L medial temporal</td>
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<tr>
<td>Right occipital</td>
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<td>Activation for old members (old &gt; new)</td>
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<td>L lateral temporal</td>
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with general attention, working memory, and visual perception; they are considered further in Supplementary Material (2).

We assessed areas that exhibited relative deactivation or increased activation over the course of the session; that is, reduction in activation during the second half of the session relative to the first half. In the second half of the exposure phase relative to the first, Figure 2B shows relative deactivation in left inferior parietal-posterior temporal and left striatal regions, presumably indicating increasingly efficient use of these regions as the exposure session progressed. The striatum is thought to contribute to habit learning (Knowlton et al. 1996; Ashby et al. 1998; Doeller et al. 2005), and this area has shown deactivation in previous neuroimaging studies of implicit memory (Reber et al. 1998; Aizenstein et al. 2000). Decreased activation in temporal-parietal regions has been observed during both implicit and explicit learning (Aizenstein et al. 2000); these regions have been suggested as mediating a variety of functions, including attention and monitoring (Kelly and Garavan 2005), multimodal integration (Beauchamp et al. 2004), and semantic processing (Grossman, Koenig, et al. 2002; Grossman et al. 2003; Kensinger et al. 2003; Grossman et al. 2007). Only the occipital region showed increased activation in the second half of exposure relative to the first, suggesting ongoing perceptual processing during acquisition.

Test Session
Like the exposure session, the observed areas of activation at test, which are summarized in Table 1, support processes involved in both implicit and explicit category learning. Significant MTI activation was evident throughout the test session (Fig. 2C), suggesting explicit encoding of the newly seen test items and/or explicit retrieval of MEMBERS seen during the exposure phase. Other areas of activation included frontal, parietal, cingulated, and occipital regions, reflecting general attention, monitoring, retrieval, and visual processing; these are considered further in Supplementary Material (3).

We examined patterns of relatively decreased and increased activation in 2 different ways. The first analysis, analogous to that used in the exposure session, involved change over the course of the test session, and thus reflected continued learning that occurred subsequent to the exposure session. Relative deactivation in the second half of the test session compared with the first half occurred in 2 areas (Fig. 2D). One area was ventral temporal-occipital cortex: deactivation in occipital regions is a hallmark of implicit memory, both in categorization (Reber et al. 1998) and priming (Schott et al. 2005). The other area was the left posterolateral temporal cortex, and may reflect implicit learning of the semantic aspect of the novel category. Consistent with this, we observed activation in this same region throughout test for new MEMBERS relative to old MEMBERS (Fig. 2E), suggesting that the items seen during the exposure session were treated as a semantic category at test. This left temporal area has been implicated in semantic processing (Grossman, Koenig, et al. 2002, 2003; Grossman et al. 2007), including semantic priming (Kensinger et al. 2003), and hence activation changes in this region may reflect increasing efficiency in semantic processing.

Increased activation in the second half of the test session was observed in left posterior cingulate, left striatal, and left MTL regions. Posterior cingulate activation has been associated with successful retrieval and explicit recollection of stimuli (Achim and Lepage 2004; Schott et al. 2005), and MTI activation may also reflect recall of items initially seen during the earlier phase of test. Striatal activation suggests ongoing habit learning (Knowlton et al. 1996; Ashby et al. 1998; Doeller et al. 2005), perhaps reflecting ongoing implicit learning as items unlike those seen during the exposure session are introduced. To explore the relation of the MTI activation and...
the learning of items seen earlier in the test phase, we used a small volume correction (SVC) to create a 20 mm radius region of interest (ROI) around the peak MTL voxel \( (x = -24, y = 3, z = -14) \); this was applied to individual subjects’ contrast files, and the total number of significantly activated voxels was extracted. This method was employed in order to capture the full anatomic distribution of associated changes in this region, based on control data. We avoided using a larger ROI which would provide less interpretable results from other anatomic regions, and we did not use a smaller ROI so that we could capture the extent of MTL activation under this condition. Activation in this ROI for NONMEMBERS during the first half of the test session (when items of this type were still novel), but not in the second half, was highly correlated with judgment accuracy of all items, Spearman’s \( r = 0.74, P < 0.05 \) (1-tailed), suggesting a link between encoding novel test items and successful categorization.

Our second analysis of activation differences compared activation for judging MEMBERS versus NONMEMBERS throughout the test session; that is, the “categorical fluency effect” (Reber, Gitelman, et al. 2003) characteristic of implicit categorization studies. Relative deactivation occurred in left occipital, right parietal, and left medial frontal areas, whereas activation occurred in left MTL, left prefrontal, left inferior frontal, and right occipital regions (Fig. 2F). Again, the observed occipital deactivation is indicative of implicit learning, and is consistent with patterns observed in other perceptually based prototype extraction tasks. Activation of the MTL region suggests engagement of an explicit memory mechanism for retrieving members, consistent with multiple roles for this region, that is, retrieval well as encoding (described above). Other areas of activation are considered in Supplementary Material (4).

To further examine the role of left temporal engagement, which we posit reflects the semantic nature of our stimuli, we compared temporal deactivation for members with analogous occipital deactivation. Using the same SVC technique described previously, a 20 mm ROI was applied around the peak voxel in the left posterior temporal region \( (x = -44, y = -55, z = -14) \) that had shown relative deactivation over time. Another ROI was similarly created around the peak voxel in the occipital region \( (x = -20, y = -76, z = 30) \) that had shown relative deactivation for MEMBERS. Deactivation for MEMBERS relative to nonmembers strongly correlated in these 2 regions, Pearson’s \( r = 0.74, P < 0.05 \), suggesting category fluency effects for both the perceptual and the semantic aspects of the stimuli.

**Summary**

Subjects’ endorsement patterns were consistent with implicit acquisition of the category from the repeated presentations of MEMBERS during the exposure period, along with some contribution from explicit memory. Implicit category learning is indicated by the relative occipital deactivation over time during test, as well as by occipital deactivation for MEMBERS relative to NONMEMBERS during test. These results parallel the findings of previous implicit categorization studies involving visual-perceptual stimuli. Moreover, the semantic nature of the implicitly learned material is suggested by relative posterolateral temporal deactivation seen during both exposure and test, as well as correlated deactivations in occipital and lateral temporal regions for MEMBERS relative to NONMEMBERS. Subjects thus seem to have acquired a representation of the novel animals as a semantic category as well as a visual-perceptual category.

MTL activation seems to contribute in multiple ways: encoding during the exposure session, and, at test, recalling old MEMBERS from previous exposure as well as encoding new items. This is consistent with theories of hippocampal function that propose activation during both the formation and subsequent access of memory stores (Prince et al. 2005). Greater MTL activation during the second versus the first half of the test session, along with a correlation between successful behavioral performance and MTL activation for NONMEMBERS early in the test session, suggest that this region contributes to additional learning subsequent to the exposure session.

**Methods: AD Study**

We further examined the collaborative role of episodic memory during performance of an ostensibly implicit memory task by evaluating AD patients. Although degeneration can occur in frontal and temporal cortical areas, the hallmark of these patients’ illness is profound MTL disease resulting in significant episodic memory deficits. We previously demonstrated that AD patients can learn to categorize a novel animal category by an explicit similarity-based process with performance indistinguishable from that of healthy control subjects, and that their performance does not correlate with measures of episodic memory (Koenig et al. 2007). If implicit memory is relatively preserved, patients’ performance on the present prototype extraction task should exceed chance. Moreover, if episodic memory contributes to performance, then patients’ performance should not equal that of healthy controls. High resolution structural MRI scans should show uniformly severe MTL atrophy, emphasizing the minimal contribution of this region to performance in AD. However, the contribution of occipital and lateral temporal cortex in this task should be reflected in a correlation of AD patients’ judgments with cortical volume in these regions.

**Subjects**

Participants included 24 AD patients (14 female), mean age 74.0 (±8.4) with 14.7 (±3.1) years of education. The diagnosis of AD, rendered by an experienced behavioral neurologist (MG), was based on NINCDS-ADRDA criteria (McKhann et al. 1984). These include a progressive episodic memory deficit early in the disease process, associated with naming and language difficulty, visual impairment, and/or executive limitations. We excluded patients with other causes of dementia such as vascular disease or hydrocephalus, psychiatric disorders such as primary depression or psychosis, medical illnesses or metabolic conditions that may have resulted in progressive intellectual decline, and/or other medical conditions that may have an impact on cognitive performance. None of the patients was taking sedating medications at the time of testing. These patients had mild to moderate dementia [mean MMSE 21.6 (±3.3)]. Performance on a verbal list-learning task [a mean of 0.36 (±0.67) words recalled out of 10 at a 2-min delay following 3 learning trials] was significantly impaired relative to a cohort of 25 healthy age- and education-matched seniors, \( Z \) score = –3.16, \( P < 0.001 \). These patients were also significantly impaired on both the pictorial version [mean accuracy 46.83 (±4.50) out of 52; \( Z \) score = –2.56] and the verbal version [mean accuracy 43.85 (±6.81) out of 52; \( Z \) score = –6.25] of the Pyramids and Palm Trees task, a standard measure of semantic memory. Their performance on a reverse digit-span task [mean digits produced 3.91 (±0.67)] was 15.5 (±2.6) years, and their mean MMSE was 22.8 (±3.1). Their scores on verbal list-learning [0.56 (±0.81)], pictorial [4.71 (±0.61)] and verbal [4.44 (±4.26)] versions of Pyramid and Palm Trees task, and reverse digit-span [4.00 (±1.22)] were comparable to the larger group.
of AD patients. Eleven healthy seniors (9 female), mean age 71.9 (±7.4) with 15.8 (±2.6) years of education were included as controls to clarify the effect of the AD patients’ disease on their performance apart from effects of normal aging. Ages and education levels were statistically equivalent across healthy seniors and AD patients, P > 0.30. Informed consent for patients and for controls was obtained under a protocol approved by the Institutional Review Board at the University of Pennsylvania.

**Procedure**
Stimuli were presented on a laptop computer. Exposure stimuli and instructions were unchanged from the fMRI study, except that stimulus items appeared every 8 seconds, and remained on the screen for 6 seconds. During the test session, subjects were shown a sequence comprising the entire set of 64 items, which included 20 MEMBERS—consisting of the 8 old members, 8 new members, and 4 prototypes (as in the fMRI protocol), 24 AMBIGUOUS items, and 20 NONMEMBERS. Instructions were unchanged from the fMRI study. Subjects responded at test by pressing keys labeled “yes” and “no” on the right and left sides of the laptop keyboard, respectively, and items remained on the screen until a button-press response, for a maximum of twelve seconds.

**Imaging Procedure**
High resolution structural MRI scans were available in the 6-patient subset to establish cortical and MTL volume using a modulated version of voxel-based morphometry (VBM). Images were acquired by a GE Horizon Echospeed 1.5 T MRI scanner in 4 patients and by a Siemens 3 T MRI scanner in 2 patients. Each study began with a rapid sagittal T1-weighted image to determine patient position. Next, high resolution T1-weighted 3D spoiled gradient echo images were acquired with TR = 35 ms, TE = 6 ms, slice thickness of 1.3 mm, flip angle of 30°, matrix = 128 x 256, and in-plane resolution of 0.9 x 0.9 mm (1.5 T) or TR = 1620 ms, TE = 3 ms, slice thickness 1.0 mm, flip angle 15°, matrix = 192 x 256, and in-plane resolution 0.9 x 0.9 mm (3 T). The brain volumes were normalized using a novel symmetric normalization (SyN) algorithm to derive the optimal average shape and appearance to a local T1 template consisting of 12 healthy seniors and 50 patients (1.5 T dataset) or 15 healthy seniors and 75 patients (3 T dataset), as appropriate to the 2 patient subgroups. Each symmetric normalization transformation thus is composed of an affine and diffeomorphic component that is optimized in a 4 level multisolution pyramid. The Jacobians of the diffeomorphic maps generated by SyN are combined with a probabilistic segmentation method (FMRIB’s Automated Segmentation Tool (FAST) (Zhang et al. 2000)) that labels the brain volumes into gray matter, white matter, cerebrospinal fluid, and other with inhomogeneity correction) to generate normalized, spatially varying estimates of gray matter volume for each individual (Avants and Gee 2004). The analysis included all voxels containing any gray matter. Implicit masking (i.e., use of a dummy value to exclude voxels with a value of 0) was used to ignore zeros, and global calculation was omitted. Using SPM2, the gray matter volume was smoothed with a 4-mm FWHM Gaussian filter to minimize individual gyral variations. In SPM2, the cortical volumes of the 6 patients were contrasted with a cohort of 30 age-matched healthy seniors using a 2-sample t-test to identify the anatomic distribution of significant atrophy (voxel height corrected for multiple comparisons by FDR at P < 0.05, and cluster volume corrected for multiple comparisons at P < 0.05). SPM2 also was used to perform a regression analysis relating performance accuracy at test to cortical and MTL volume in the AD patients. Measures of performance accuracy consisted of d’ prime scores (Wickens 2002) obtained from the percentage of correct endorsements of MEMBERS (“hits”) and incorrect endorsements of NONMEMBERS (“false alarms”), hence, these scores reflected accurate judgments of MEMBERS while accounting for any “yes bias.” These scores were correlated with 2 areas of occipital and one area of lateral temporal cortical deactivation observed in the young fMRI subjects, as well as with MTL activation, by placing a 20 mm spherical ROI over the regression map centered at each of the occipital and lateral temporal coordinates derived from the fMRI study, along with a standard MTL area provided by the SPM2 program. Because of the very small size of the voxels in the VBM analysis, we accepted a voxel height threshold of P < 0.001 uncorrected and a cluster threshold of P < 0.001 corrected for multiple comparisons.

**AD Study: Results and Discussion**

**Behavioral Observations**
Healthy seniors and AD patients both demonstrated learning (see Fig. 3A). For the healthy seniors, an ANOVA showed a main effect of stimulus type, F20.2 = 34.74, P < 0.001, and endorsements for each type of stimulus differed from the others, P < 0.003 for each comparison. Likewise, for the AD patients, an ANOVA showed a main effect of stimulus type, F2.41 = 22.51, P < 0.001, and endorsements for each type of stimulus differed from the others, P < 0.01 for each comparison. Like the young subjects, the endorsement patterns of the healthy seniors and the patients were consistent with prototype extraction, although compared with the young subjects, these 2 older subject groups tended to overendorse nonprototypical stimuli: Individual healthy seniors’ mean endorsements of prototypical feature variants ranged from 66% to 70%; mean endorsements of nonprototypical variants ranged from 48% to 52%; and mean endorsements of noise patterns ranged from 56% to 62%. Individual AD patients’ mean endorsements of prototypical variants ranged from 63% to 68%; mean endorsements of nonprototypical variants ranged from 54% to 59%; and mean endorsements of noise patterns ranged from 55% to 67%. Although 2 AD patients focused on 1 particular feature, these

![Figure 3. Endorsements at test by AD patients and healthy seniors. (A) Endorsements of MEMBERS, AMBIGUOUS items, and NONMEMBERS. (B) Endorsements of NONMEMBERS for each half of the test session.](https://academic.oup.com/cercor/article-abstract/18/12/2831/363393)
individuals’ judgments did not affect the performance means of the group of 24 patients.

Healthy seniors’ scores for MEMBERS and AMBIGUOUS items were above chance (P < 0.001 and P < 0.02, respectively), whereas their scores for NONMEMBERS did not differ from chance, P = 0.20 (consistent with their overendorsement of nonprototypical feature variants). Healthy seniors endorsed prototypical MEMBERS, new MEMBERS, and old MEMBERS equivalently, F_{2,20} = 0.02, ns. The healthy seniors showed a learning advantage that the AD patients did not (see below): Unlike the young fMRI subjects, whose initially high accuracy rates for all item types precluded evidence of continued category learning over the course of testing, healthy seniors demonstrated additional learning during the test phase. An ANOVA assessing changes in endorsement patterns over time showed a linear contrast interaction for stimulus type × time (i.e., first vs. second half of the test session) that was marginally significant, F_{1,18} = 3.14, P = 0.09. This reflects the increasing level of accurate judgments of NONMEMBERS over the course of testing, in contrast with the stable level of accurate judgments of MEMBERS. Figure 3B shows the change over time in judgments of NONMEMBERS, confirmed in lower endorsements (i.e., more accurate judgments) in the second half of the test session relative to the first, t(9) = 2.40, P < 0.04.

Although AD patients demonstrated category acquisition, they were not as accurate as their healthy counterparts; they endorsed MEMBERS and rejected NONMEMBERS less frequently than did the healthy seniors. The flatter slope in AD patients’ endorsement profile relative to that of healthy seniors, evident in Figure 3A, was confirmed in an ANOVA with a group × stimulus interaction, F_{2,64} = 3.70, P = 0.03.

Like the healthy seniors, AD patients’ scores for MEMBERS and AMBIGUOUS items were both above chance (P < 0.001), and their scores for NONMEMBERS did not differ from chance, P = 0.92 (Fig. 1A). They likewise endorsed prototype MEMBERS, old MEMBERS, and new MEMBERS equivalently, F_{2,42} = 0.47, ns. In contrast to the improved performance in judging NONMEMBERS over the course of testing demonstrated by the healthy seniors, AD patients maintained the same relative endorsement patterns for all types of stimuli over both halves of the test session, and their judgments of NONMEMBERS hovered around chance. The consistency of endorsement patterns was confirmed in an ANOVA assessing changes in endorsement patterns over time that showed no linear contrast interaction for stimulus type × time, F_{1,44} = 0.71, ns. The AD patients’ relatively stable endorsements of NONMEMBERS are compared with those by healthy seniors in Figure 3B.

AD patients’ performance did not correlate with any of the psychometric measures assessing episodic memory, working memory, and semantic memory listed previously. This parallels findings for similarity-based categorization in our previous study of explicit category acquisition involving the same stimulus set (Koenig et al. 2007). In that study, AD patients’ success at similarity-based categorization (involving comparisons to a specified prototype), which was equivalent to that of control subjects, likewise showed no correlations with measures of episodic memory, working memory, and semantic memory. These results suggest that the novel animal category is learnable without recourse to episodic memory, and is consistent with episodic memory playing an added role, resulting in the superior performance of neurologically healthy subjects in the present implicit learning study. In contrast, although AD patients’ performance at rule-based categorization in the explicit category acquisition study (requiring assessment of specified features), which was impaired relative to that of control subjects, likewise did not correlate with episodic memory, it did correlate with measures of working memory and semantic memory. The distinction between these correlations and the lack of correlations between psychometric measures and categorization performance in the current study suggests that the AD patients’ impaired performance in the current study does not reflect difficulty with executive resource demands such as working memory.

**Imaging Observations**

Table 2 summarizes the anatomic distribution of significant atrophy in the 6 AD patients for whom imaging was available. The categorization test performance of these 6 patients was representative of the entire AD patient group: The full group’s endorsements of MEMBERS, AMBIGUOUS items, and NONMEMBERS were 73%, 60%, and 50%, whereas the subgroup’s scores were 71%, 61%, and 52%. Severe atrophy is apparent in the MTL, as illustrated in Figure 4A, consistent with much previous work demonstrating atrophy of this region in AD, and precluding involvement of this region in AD patients’ performance. Cortical atrophy is also present in ventral temporal, lateral temporal, and frontal cortical regions. The ROI analysis demonstrated a significant relationship between successful performance and the occipital and temporal cortical volumes implicated in young subjects’ implicit memory performance (Fig. 4B). Thus, these observations are consistent with the contribution of occipital and lateral temporal cortex to successful implicit memory performance in AD.

**Summary**

The data suggest that AD patients, like healthy seniors, acquired a meaningful novel category by viewing examples of category exemplars during the exposure session. Given their profound episodic memory deficit, AD patients’ ability to exceed chance in their selective endorsements of MEMBERS presumably was based on their implicit memory capacity. However, AD patients were less accurate than were healthy control subjects in their categorization judgments of both MEMBERS and NONMEMBERS. Moreover, the healthy seniors showed evidence of additional learning during the test phase,

**Table 2**

<table>
<thead>
<tr>
<th>Anatomic area</th>
<th>Talairach coordinates (x, y, z)</th>
<th>Z-score</th>
<th>Cluster-level, P-value</th>
<th>Voxel-level, P-value</th>
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</thead>
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<tr>
<td>L occipital</td>
<td>52/25 29/35 12/48 12/32 12/26</td>
<td>4.2</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>R occipital</td>
<td>60/32 26/42 10/50 10/48 10/56</td>
<td>4.2</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>L medial temporal</td>
<td>3/23 3/24 3/25 3/26 3/27</td>
<td>4.2</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>R medial temporal</td>
<td>4/34 4/35 4/36 4/37 4/38</td>
<td>4.2</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>L middle temporal</td>
<td>5/24 5/25 5/26 5/27 5/28</td>
<td>4.2</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>R middle temporal</td>
<td>6/25 6/26 6/27 6/28 6/29</td>
<td>4.2</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>L cingulate</td>
<td>7/24 7/25 7/26 7/27 7/28</td>
<td>4.2</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>R cingulate</td>
<td>8/25 8/26 8/27 8/28 8/29</td>
<td>4.2</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>L inferior parietal</td>
<td>9/26 9/27 9/28 9/29 9/30</td>
<td>4.2</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>R inferior parietal</td>
<td>10/27 10/28 10/29 10/30 10/31</td>
<td>4.2</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>L caudate</td>
<td>11/27 11/28 11/29 11/30 11/31</td>
<td>4.2</td>
<td>0.000</td>
<td>0.000</td>
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<tr>
<td>R caudate</td>
<td>12/28 12/29 12/30 12/31 12/32</td>
<td>4.2</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>RDI analysis (correlation with performance)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ROI</td>
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<tr>
<td>Left temporal ROI</td>
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<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Occipital ROI</td>
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<td>3.1</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Occipital ROI</td>
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<td>3.1</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>No significant clusters</td>
<td></td>
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</tr>
</tbody>
</table>

**ROI**: Regional brain activity.
whereas the AD patients did not. As we have shown elsewhere that AD patients can learn to categorize this novel animal category in a manner indistinguishable from healthy seniors under explicit similarity-based learning conditions (Koenig and Grossman 2007; Koenig et al. 2007), their performance decrement in the present study is unlikely to reflect some aspect of the stimuli such as visual or semantic complexity. Rather, we suggest that, as with the young fMRI subjects, there is an explicit memory component that facilitates the healthy seniors’ performance on this otherwise implicit memory task, which the AD patients cannot exploit because of their MTL disease. Evidence consistent with this interpretation comes from the AD imaging study. A representative subset of these patients showed significant MTL atrophy relative to healthy seniors; this atrophy was severe enough to preclude involvement of this region with patients’ performance. Moreover, a regression analysis relating performance at test to gray matter volume showed that MEMBER judgment accuracy was significantly associated with the same occipital and lateral temporal volume that area and occipital deactivation for MEMBERS. The pattern of engagement of lateral temporal regions is consistent with increasingly efficient processing of semantic information; that is, a “semantic fluency” effect analogous to the perceptual fluency described above and similar to findings in semantic priming studies (Kensinger et al. 2003). The observations of lateral temporal involvement differentiate this study from previous studies of implicit memory that employed purely perceptual stimuli such a dot patterns, as well as letter-string artificial grammars which may constitute conceptual stimuli, but are not semantically meaningful.

Evidence for the contribution of an explicit memory mechanism was seen in the activation of the MTL region in young adults. This was observed throughout both the exposure period and the test session. We observed greater activation of this area in the second half of the test session relative to the first half, and greater activation for MEMBERS than NONMEMBERS throughout the test session. The MTL may have played a role in several aspects of learning. During exposure, medial temporal activation may have supported encoding of study items, and/or recognition of items as they were repeatedly shown. At test, medial temporal activation may have supported recall of previously studied MEMBERS and/or additional learning that may have occurred during test itself. Indeed, a correlation between successful categorization judgments and medial temporal activation during NONMEMBER trials early in the test session suggests that this area supported encoding of novel test stimuli during the test session.

The hallmark of AD is impaired explicit memory, caused by the disease severely affecting the medial temporal region. Although the AD imaging study must be interpreted cautiously because of the small number of studied patients for whom structural MRI scans were available, significant MTL atrophy

**General Discussion**

Our findings from an fMRI study of young adults and behavioral and imaging studies of patients with AD suggest that implicit and explicit memory systems collaborate in the performance of an ostensibly implicit memory task for neurologically healthy individuals, whereas AD patients can implement only an explicit memory system. Specific evidence came from monitoring the neural basis for young subjects’ performance during a prototype extraction task. These subjects learned the novel category reliably, endorsing most MEMBERS and rejecting most NONMEMBERS at test. There were behavioral indications of contributions from both implicit and explicit memory: Subjects reliably endorsed unstudied prototypes more than studied MEMBERS, consistent with explicit memory. They also were more stable in their high endorsements for studied MEMBERS than for comparable items seen for the first time at test. Such endorsement patterns alone cannot distinguish between the contributions of implicit and explicit memory, because the superiority of prototype MEMBERS over old MEMBERS, and that of old MEMBERS over new MEMBERS, are also predicted by models of category learning that assume only a single, explicit memory system (e.g., Medin and Schaffer 1978; Nosofsky and Zaki 1998; Smith 2007).

The observed neural activity underlying these behavioral observations provides stronger support for the collaborative involvement of implicit and explicit memory systems in task performance. Patterns of brain activity consistent with previous imaging studies of implicit learning included relative deactivation in occipital areas during test. This characteristic indication of implicit memory for visual-perceptual stimuli is thought to reflect perceptual fluency. We observed occipital deactivation for MEMBERS relative to NONMEMBERS throughout the test session, and relative deactivation for MEMBERS over time as well. In addition, we observed reduced activation of left posterolateral temporal cortex for MEMBERS relative to NONMEMBERS throughout the test session, along with a correlation between deactivation for MEMBERS in that area and occipital deactivation for MEMBERS. The pattern of engagement of lateral temporal regions is consistent with increasingly efficient processing of semantic information; that is, a “semantic fluency” effect analogous to the perceptual fluency described above and similar to findings in semantic priming studies (Kensinger et al. 2003). The observations of lateral temporal involvement differentiate this study from previous studies of implicit memory that employed purely perceptual stimuli such a dot patterns, as well as letter-string artificial grammars which may constitute conceptual stimuli, but are not semantically meaningful.

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**Figure 4.** Medial temporal and cortical atrophy in AD. (A) Axial and coronal slices through the medial temporal region showing significant bilateral atrophy, blue arrowheads indicate MTL atrophy, blue arrowheads indicate MTL atrophy. (B) Regression analysis showing the distribution of significant correlation between MEMBER judgment accuracy (d’ prime) at test and gray matter volume in AD in ROI’s determined by areas of deactivation in young fMRI subjects. No correlations were found for a standardized (as provided by SPM2) hippocampal ROI.
was evident in the VBM analysis of atrophy in these patients. Despite their profound MTL disease, AD patients demonstrated reliable implicit acquisition of a meaningful novel animal category, exceeding chance in their endorsement of MEMBERS, and endorsing MEMBERS more than NONMEMBERS. This is consistent with previous studies showing successful implicit learning in AD (Kert et al. 1999; Eldridge et al. 2002; Reber, Martinez, et al. 2003; Golby et al. 2005; Bozoki et al. 2006). We also found a correlation between successful performance in AD and cortical volume in the occipital area in which we observed involvement in the young fMRI subjects. Previous fMRI work with implicit memory in AD has shown involvement of a similar area (Sperling et al. 2003; Golby et al. 2005).

Our observations extend findings of successful implicit memory in AD to a more naturalistic and semantically meaningful category. Paralleling our unique observation of lateral temporal activation in association with this category in young adults, we also found a significant correlation between performance accuracy and lateral temporal cortical volume in AD. Previous findings of selective decrements in implicit learning of conceptual material compared with perceptual material in AD (Fleischman et al. 1997; Fleischman and Gabrieli 1998) may have reflected task-related confounds, such as requiring executive resources (e.g., for word generation) only in conceptual tasks. Indeed, we have previously observed performance decrements in AD patients’ acquisition of our novel category by a resource-demanding rule-based process (Koenig et al. 2007) that recruits frontal cortical areas in healthy subjects (Koenig et al. 2005). In contrast, the present study, which only required yes/no responses to presented stimulus displays, imposed minimal executive resource demands. Still, the AD patients’ performance on the current task was somewhat impaired relative to that of neurologically healthy control subjects, including both fewer endorsements of MEMBERS and fewer rejections of NONMEMBERS. Moreover, AD patients showed no evidence of further learning after the categorical nature of the stimuli was made clear at the beginning of the test session, consistent with their profound episodic memory deficit and in contrast with healthy seniors’ increasingly accurate performance in judging NONMEMBERS. The differences in performance between the AD patients and their healthy counterparts are in keeping with the imaging results, which suggest that neurologically intact individuals use the MTL region to enhance their performance beyond that resulting exclusively from a cortically based implicit memory system.

An alternative explanation for the performance deficit in AD could be their impaired semantic memory (Cox et al. 1996; Grossman et al. 1996, 1998; Garrard et al. 1998, 2005), although the lack of a correlation between the patients’ performance on the novel categorization task and measures of semantic memory for familiar items suggests that semantic memory impairment is unlikely to entirely account for the AD patients’ performance deficits. Semantic memory impairment could conceivably affect AD patients’ ability to acquire our novel semantic category even if their faculty for implicit learning of perceptual material is intact, because, unlike healthy individuals, they would then have to rely entirely on the perceptual properties of the stimuli. Although there has been controversy surrounding the presence and nature of semantic memory difficulty in AD (Koenig and Grossman 2007), one contributing factor may be the distribution of cortical disease. Activation studies of semantic memory using explicit probes frequently activate posterolateral temporal cortex (Martin et al. 1996; Josephs 2001; Grossman, Smith, et al. 2002; Kensinger et al. 2003; Koenig et al. 2005; Grossman, White-Devine, et al. 2007), a multimodal association region with reciprocal projections involving modality-specific association cortices (Mesulam 2000). Limited functioning of posterolateral temporal neocortex appears to be associated with semantic memory difficulty in AD (Grossman et al. 1997; Desgranges et al. 1998; Grossman, Koenig, et al. 2003). This area partially overlaps the region of posterolateral temporal deactivation seen during the fMRI study. Although this factor cannot be ruled out, AD patients may have performed as well as they did because this posterolateral temporal area may be only partially compromised in the mild AD participants in this study. Moreover, AD patients have shown compensatory activation in adjacent cortical regions during a semantic challenge (Grossman, Koenig, et al. 2003).

Our observations of MTL involvement in a task incorporating semantically meaningful material in an implicit learning protocol raise the further question of similar MTL involvement with perceptual material. Previous findings of equivalent performance in perceptual implicit tasks by AD patients and their healthy counterparts (e.g., Squire and Knowlton 1995; Fleischman et al. 1997; Fleischman and Gabrieli 1998; Reed et al. 1999; Reber et al. 2003; Golby et al. 2005) suggest that healthy subjects either do not engage the MTL in such tasks, or that episodic memory, if present, provides no further performance advantage. In particular, the unimpaired performance of AD patients on prototype extraction tasks involving dot patterns, in contrast their performance decrements in our prototype extraction task of novel animals, would seem to suggest that even if episodic memory for individual studied items might be helpful in category learning, healthy individuals only engage such memory for meaningful material. However, it is also possible that individual dot patterns are not readily memorable, in contrast with our individual animals, which each have a discernable structure and are clearly distinguishable from one another. That is, the difficulty of remembering dot patterns might not reflect their lack of meaning per se, but their apparent uniformity. The left temporal deactivation that we observed in our young subjects, in parallel with occipital deactivation typically observed in implicit studies of perceptual stimuli, suggests that it is particular patterns of cortical engagement, rather than MTL involvement, that differentiate learning of semantic versus perceptual material in an ostensibly implicit task. Consistent with this, Prince et al. (2005) found different patterns of cortical engagement in the formation of relational word-pair memories based on either semantic or perceptual associations, but found that an area of the hippocampus was the only brain region recruited under both conditions. Hence, although we speculate that it was not the semantic nature per se of our novel animal stimuli that elicited MTL involvement, future investigations are needed to determine whether the MTL contributes selectively to the acquisition of semantic material, or whether it is involved in perceptual learning as well.

In sum, the picture emerging from this study suggests that multiple memory mechanisms can work in tandem to support performance on an implicit memory task (Curran and Keele 1993; Poldrack and Packard 2003; Lieberman et al. 2004; Foerde et al. 2006). This was demonstrated in the fMRI study by the observed occipital deactivation indicative of implicit learning of
visually presented material, and temporal deactivation reflecting implicit acquisition of the semantically meaningful nature of the novel category, along with MTL activation supporting episodic memory. Further support was evident in the behavioral and imaging results from the AD study. The AD patients' implicit memory performance, although indicative of successful learning, was limited in comparison to their healthy counterparts. The episodic memory component associated with the MTL region was unavailable to AD patients, who appeared to rely exclusively on implicit memory to acquire the novel category. We found temporal and occipital cortices correlated with AD patients' test performance. The data suggest that AD patients' deficit is primarily due to their profound MTL disease, which precludes the additional contribution of explicit memory, as observed in neurologically healthy individuals, to performance on an otherwise implicit learning task.

**Supplementary Material**

Supplementary material can be found at: [http://www.cercor.oxfordjournals.org/](http://www.cercor.oxfordjournals.org/)

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**Notes**

Conflict of Interest: None declared.

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