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AN INVESTIGATION OF IMPLICIT MEMORY THROUGH LEFT TEMPORAL LOBECTOMY FOR EPILEPSY

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Abstract

Temporal lobe epilepsy patients have demonstrated a relative preservation in the integrity of implicit memory procedures. We examined performance in a verbal implicit and explicit memory task in left anterior temporal lobectomy patients (LATL) and healthy normal controls (NC) while undergoing fMRI. We hypothesized that despite the relative integrity of implicit memory in both the LATL patients and normal controls, the two groups would show distinct functional neuroanatomic profiles during implicit memory. LATLs and NCs performed Jacoby's Process Dissociation Process (PDP) procedure during fMRI, requiring completion of word stems based on the previously studied words or new/unseen words. Measures of automaticity and recollection provided uncontaminated indices of implicit and explicit memory, respectively. The behavioral data showed that in the face of temporal lobe pathology implicit memory can be carried out, suggesting implicit verbal memory retrieval is non-mesial temporal in nature. Compared to NCs, the LATL patients showed reliable activation, not deactivation, during implicit (automatic) responding. The regions mediating this response were cortical (left medial frontal and precuneus) and striatal. The active regions in LATL patients have the capacity to implement associative, conditioned responses that might otherwise be carried out by a healthy temporal lobe, suggesting this represented a compensatory activity. Because the precuneus has also been implicated in explicit memory, the data suggests this structure may have a highly flexible functionality, capable of supporting implementation of either explicit memory, or automatic processes such as implicit memory retrieval. Our data suggest that a healthy mesial/anterior temporal lobe may be needed for generating the posterior deactivation perceptual priming response seen in normals.

Keywords

implicit memory; epilepsy; temporal lobe; automaticity

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1. Introduction

Dominant, typically left, temporal lobe epilepsy (LTLE) provides a unique model for investigations of implicit and explicit memory. LTLE patients who have undergone left anterior temporal lobectomy (LATL) demonstrate deficits in explicit verbal memory procedures, while implicit memory remains relatively intact (Zaidel, Oxbury, & Oxbury, 1994) (Zaidel, Esiri, & Beardsworth, 1998) (Del Vecchio, Liporace, Nei, Sperling, & Tracy, 2004). Explicit memory is characterized as a conceptually-driven, conscious recollection of previously stored information, regulated by an intentional “top-down” network (Ciaramelli, Grady, & Moscovitch, 2008; Soto, Humphreys, & Rotshtein, 2007). Implicit memory is considered to reflect either data-driven or conceptually-driven processing systems, unintentional and automatic in their implementation, best measured by indirect tests of memory such as word-stem completion, word-fragment completion, word-association generation, category-exemplar generation tasks, or repetition priming (Graf, Squire, & Mandler, 1984). The anatomic structures subserving explicit memory are well-established, involving a hippocampal dependent system (Degonda et al., 2005; Eichenbaum & Lipton, 2008; L.R. Squire & Zola-Morgan, 1991), with other structures such as posterior parietal cortex (Wagner, Shannon, Kahn, & Buckner, 2005) and anterior prefrontal cortex (Rugg & Curran, 2007) crucially involved. While much work has been done to help define the functional neuroanatomy of implicit memory, there continues to be debate about whether it is truly a hippocampal-independent system.

Patients with hippocampal damage and anterograde amnesia seem able to show the benefits of repetition or perceptual priming, suggesting that these cognitive systems utilize a perceptual or “bottom up” network that is hippocampal independent (Cabeza & Nyberg, 2000; Schacter & Buckner, 1998). Amnesic patients also demonstrate intact conceptual priming, suggesting this priming system is hippocampal independent (Billingsley, McAndrews, & Smith, 2002). However, there is counter evidence implicating temporal lobe structures in implicit memory. For instance Zaidel et al. correlated neuronal density in hippocampal subfields and found associations between CA1 integrity and implicit memory performance (word-stem completion) in left, but not right, temporal lobectomy patients (Zaidel, et al., 1998) (Billingsley, et al., 2002; Schendan, Searl, Melrose, & Stern, 2003; Weber, Kügler, & Elger, 2007). Also, some studies in motor skill learning have suggested the hippocampus is involved in implicit memory when evaluated through tasks such as motor sequence learning (Schendan, et al., 2003). Other studies have found implicit memory paradigms can activate the medial temporal lobe structures in healthy controls in a fashion that suggests lateralized material specific effects are present (Weber, et al., 2007). One way of reconciling these examples of hippocampal involvement in implicit memory is to emphasize the relational nature of the task, with the implementation of implicit encoding and retrieval occurring through neural-response learning rather than a neural tuning mechanism (Schacter, Dobbins, & Schnyer, 2004). From this perspective, implicit memory can be seen as stemming from the mesial temporal lobe’s expertise in associative memory (see (Cohen et al., 1999)).

Neuroimaging studies to date suggest that implicit memory is distinct from explicit memory (Donaldson, Petersen, & Buckner, 2001), with implicit memory characterized by reduced neural activity of key cortical regions (Buckner, Koutstaal, Schacter, & Rosen, 2000; Schacter & Buckner, 1998; Schott et al., 2005), such as left frontal gyrus, left inferior prefrontal cortex, inferior temporal regions (Buckner, et al., 2000; Wagner, Koutstaal, Maril, Schacter, & Buckner, 2000), occipital, and occipitotemporal cortex (Badgaiyan, Schacter, & Alpert, 1999; Buckner et al., 1995; Reber, Gitelman, Parrish, & Mesulam, 2003; L.R. Squire et al., 1992). These decreases emerge from experimental paradigms that gauge a subject’s response to recently observed stimuli, an effect called “repetition suppression” (Henson,

2003; Schacter, Wig, & Stevens, 2007). Subsequent work by Dobbins and colleagues provide a response learning explanation of these repetition-related neural reductions (Dobbins, Schnyer, Verfaellie, & Schacter, 2004). With regard to perceptual priming, the involved areas will depend on the nature of the stimulus with occipital cortex mediating visual stimuli and superior temporal regions mediating auditory stimuli (Blaxton, 1999; Gabrieli, 1998; Schacter & Badgaiyan, 2001; Schacter & Buckner, 1998; Schacter, et al., 2007; L.R. Squire, 1995).

In contrast, in conceptual priming, a performance benefit arises strictly from the semantic aspects of a stimulus, and is associated with neural activity reductions in the inferior/superior temporal, and left prefrontal regions (Demb et al., 1995; Raichle et al., 1994; Verfaellie & Keane, 1997). Based on a study by Blaxton and colleagues, the distinction between data-driven perceptual memory and conceptually-driven memory may be particularly important in the context of epilepsy as they found that left temporal lobe epilepsy patients failed to show a breakdown in data-driven memory, but produced abnormal performance on conceptually-driven memory tasks (Blaxton, 1992).

To date, the major neuroanatomical studies of implicit memory in epilepsy have been hampered by problems such as the influence of implicit on explicit memory and vice versa (Billingsley, et al., 2002; Blaxton, 1992; Zaidel, et al., 1994). For instance, the Blaxton study (Blaxton, 1992) counterbalanced the order of the implicit and explicit tasks, making it possible for implicit memory processes to be contaminated by explicit memory under certain experimental conditions.

In our previous behavioral study we utilized a Process Dissociation Procedure (PDP), based on the work of Jacoby (1991) to separate and quantify implicit (also referred to as automatic) and explicit (also referred to as intentional) forms of memory (Jacoby, 1991). We demonstrated that LATL patients performed worse than normal controls (NC) on a measure of explicit memory, but performed similarly on an implicit memory measure. The data demonstrated the integrity of implicit memory in LATL patients and implied a potential dissociation in the functional neuroanatomy of these two forms of verbal memory in LATL patients (Del Vecchio, et al., 2004).

The goal of the present study was to determine the functional neuroanatomy associated with implicit memory processing in LATL, as a means of clarifying the role of medial temporal memory structures. The PDP was utilized in a single task, containing both direct and indirect tests of memory in order to quantify both explicit and implicit word retrieval (Cermak, Verfaellie, Sweeney, & Jacoby, 1992; Jacoby, 1991; Verfaellie & Treadwell, 1993). Regardless of whether one counterbalances, or conducts implicit or explicit memory tasks first, none have the advantage of the Jacoby approach, which combines the measures in one task, overcoming the problem of task equivalence (e.g., differing task demands, differing task difficulty,) and task order. Such task differences pose rival hypotheses for the study data and results, rival factors that are not at work in the Jacoby method. Lastly, the approach also putting them in opposition to each other to verify which is stronger in a given provides a way of quantifying automatic and intentional forms of memory by individual during a given task.

We predicted that LTL patients would show impaired explicit verbal memory retrieval scores, while leaving implicit memory retrieval relatively intact because of the latter's potential implementation by extra-temporal lobe structures. We hypothesized that despite the relative integrity of implicit memory in both the LATL patients and normal controls, the two groups would show distinct functional neuroanatomic profiles during implicit memory. We expected our LATL patients would show a set of brain deactivations consistent with an

impairment in the temporal-lobe based conceptual priming system, and a relative preservation of a posterior perceptual priming system, which would operate on the visual dimensions and word form recognition properties of the task. In contrast, we expected our NCs to engage both conceptual and perceptual processing systems given the integrity of the frontal/temporal circuits and occipital regions that implement these systems.

2. Material and Methods

2.1. Participants

Table 1 displays the sample demographic characteristics and memory performance scores. A total of 16 NCs and 12 LATL patients were recruited for the study. All four left-handed LATL patients demonstrated left hemisphere dominance through the intracarotid-amobarbital exam conducted at the Thomas Jefferson University Comprehensive Epilepsy Center (Tracy et al., 2009). The LATL patients completed the pre-surgical algorithm of the TJU Comprehensive Epilepsy Center, received a left anterior temporal lobectomy, and were at least six months post-surgery but less than three years post-surgery when completing the current study. Details of the Thomas Jefferson Comprehensive Epilepsy Center algorithm are described in Sperling et al. (M. R. Sperling et al., 1992). The anterior temporal lobectomy (ATL) procedure involves an “en bloc” resection. Details of the Thomas Jefferson Comprehensive Epilepsy Center algorithm are described in Sperling et al. (M. Sperling et al., 1992). The anterior temporal lobectomy (ATL) procedure involves an “en bloc” resection. The typical anterior temporal lobectomy procedure involves resection of 4-5 cm of tissue back from the temporal pole. It is important to note that all the patients displayed strong evidence that their pathology was unilateral and limited to the temporal lobe, otherwise surgery would not have been undertaken. In no case was there evidence of an ictal focus outside the one mesial temporal lobe. We understand that seizure spread and evidence from other measures such as PET, spectroscopy, gray matter volume or white matter studies, etc., often implicate abnormalities outside the temporal lobe in temporal lobe epilepsy. This is a carefully chosen sample of patients with localization-related epilepsy with no evidence of pathology outside the epileptic temporal lobe, and sufficient confidence about the focus of the pathology and ictus (surface or depth electrode EEG findings) to undertake a unilateral temporal lobectomy. We should note that all LATL subjects underwent surgery at least six months prior to being scanned at the Thomas Jefferson Comprehensive Epilepsy Center.

Table 2 displays clinical information on the patients. All patient participants met the following inclusion criteria: unilateral left hippocampal sclerosis or gliosis as identified through MRI, unilateral left-sided temporal lobe seizure onset through surface video/EEG recordings, Verbal, Performance and Full-Scale IQ's of at least 80. LATL and NC participants were excluded from the study on any of the following grounds: medical illness with central nervous system impact other than epilepsy; head trauma; prior or current alcohol or illicit drug abuse; and psychiatric diagnosis or hospitalization for a Diagnostic and Statistical Manual of Mental Disorders, IV psychiatric disorder. Note, Beck Depression Inventory scores were collected, and epilepsy patients with depression were permitted in light of the high co-morbidity of depression and epilepsy (Tracy, Johnson, Sperling, Cho, & Glosser, 2007). The patients were scanned approximately two years after surgery, well beyond the acute effects of surgery, allowing for a period of potential cognitive reorganization of memory function. The healthy, normal controls were recruited from the Thomas Jefferson University community. Participants provided written informed consent and were paid for participation. The study was approved by the University Institutional Review Board for Research with Human Subjects.

2.2. fMRI Procedure

Whole-brain BOLD contrast functional images were collected on a GE LX 1.5 tesla scanner with a quadrature RF coil at the following parameters: 26 parallel axial slices, single-shot echoplanar imaging sequence, TE= 54 ms, TR= 4.0 seconds (interleaved collection, contiguous), FOV= 24 cm, 128mm² data matrix, flip angle=90⁰, bandwidth = 62kHz. The in-plane resolution was 1.875 mm² with 4 mm thickness. Two scanning runs were carried out to complete the task with the initial 2 volumes dropped from each fMRI run to allow for T1 equilibration effects. T1-weighted images (26 slices) were collected using a standard spin-echo pulse sequence in positions identical to the functional scans to provide an anatomical reference to determine slice location of the echoplanar images (TE=9ms, RG=450ms, 256×256 mm).

2.3. Experimental Task Procedure

The task was constructed with the same parameters as described in our prior work (Del Vecchio, et al., 2004), which was based on the experimental procedure and design of Jacoby (1991), experiment 3, though adapted for the fMRI environment. A graphical depiction of the PDP procedure, and the contribution that explicit (recollection) or implicit (automatic) memory processes make to various task responses is provided in Figure 1.

The words used in this experiment comprised a pool of 141 five-letter nouns of low, medium, and high frequency (Thorndike, 1944), originally used by Jacoby (1998). The 40 selected words were divided into a set of 30 study list or target words and 10 words that would not appear in the later test phase. The words had equal response pool size in the English language (the number of possible five-letter word completions for the stems) (Thorndike, 1944). To avoid primacy and recency effects, the ten additional words served as buffer items with five placed at the beginning and end of the list, and these were not included in the analyses. The resulting study list was composed of 30 study list items and 10 buffer items. During the learning phase, words were presented one word at a time on a Macintosh computer by using customizable experimental laboratory software (Superlab Pro; Version 2.0.4, Cedrus Corporation, San Pedro, CA, U.S.A.). The character size of the stimuli was 3 × 5 cm, and all were presented in lower case. Words were presented in white letters on a black background in the center of the screen and appeared for 1.5 seconds, followed by 0.5 seconds of blank screen. Participants were instructed to read the words aloud and to remember them for a later memory test. Study list words were presented during the test phase under one of two conditions: inclusion or exclusion. After the learning phase, subjects would promptly enter the MRI scanner for the test phase of the experiment. Subjects were able to see the experimental stimuli in the center of their visual fields through a mirror mounted on the headcoil that allowed view of a rear projection screen. Word stems consisting of the initial three letters of a five-letter word followed by two dashes were presented one stem at a time on the screen (i.e., sha--). The test list consisted of 30 three letter word stems corresponding to the 30 study list words. Each of the tested three-letter word stems had at least one other English word with the same first three letters on the study list, but only one of the completions would appear in the study list (i.e., mer--; mercy, merge, merit, merry). Fifteen novel/new stems with words not on the study list were included in the experiment, as they are needed to estimate our recollection and automaticity measures. Word stems were presented in lower-case letters in the center of the computer screen. For each study word, half of the stems were chosen randomly to be in the inclusion test condition, and the other half were randomly assigned to the exclusion condition with the number of low, medium, and high frequency words counterbalanced across the two conditions. Lastly, the order of presentation for the inclusion (15 trials), exclusion (15 trials) and control variables (15 trials) were randomized, allowing for a good intermixture of the trials in one large list (45 trials) of word stems. During the test phase, each word stem was

shown with an experimental prompt placed above it indicating either “NEW” or “OLD”, centered two lines above the word stems in capital letters. The prompt remained on the screen with the stem until the stem disappeared. The instructions utilized were those of (Jacoby, 1991). Participants were told that with each stem they were to try to remember the studied item and use the stem as a cue for recall of the word presented in the previous study list. However, they were also told that recall of a previously identified, studied word would not always be possible because some of the stems could only be completed with a novel word. The OLD prompt cued the participant to use a recalled word from the study list (inclusion condition), while the NEW prompt cued the participant to use a novel word to complete the stem (exclusion condition). In the exclusion condition participants were explicitly told to not use a word from the study list and to avoid accidentally using these words because their goal was to use a novel word. Participants were also told that if they could not come up with a novel word for the NEW prompt, they should complete the stem with the first 5-letter word that came to mind. A buffer period followed the word stem which consisted of an asterisk displayed for 3 seconds and then a response cue consisting of a bulls-eye like symbol that would be displayed for 2 seconds. During the response cue, subjects were instructed to speak into an air duct microphone made of plastic used with our MR compatible audio communication systems (Avotec, Inc.). The microphone was placed directly in front of the subject’s mouth, about a half to three-quarters inch away. This proximity greatly improved the signal-to-noise ratio of the subject’s voice to the background scanner noise, and allowed the experimenter to record the subject’s verbal responses. This response period was followed by an inter-trial interval period to allow for hemodynamic decay of the signal associated with speech. Here, the subject was shown an asterisk for 14 seconds before the next trial began. If they were unable to provide a response, participants were told to attempt a suitable completion for the word stem given the allotted time to do so (4 seconds), and then wait until the next trial was initiated. Participants could not change their response if they realized they responded with a word from the study list in the exclusion condition. Each of the successful word stem completions had to be five letters long, and no plurals or proper names were scored as correct. The control word stems only used the NEW prompt to avoid confusing the participant by searching for a word that did not exist on the study list. Mixed into the experiment, subjects also received a passive reading condition (10 trials) where they would read a full word (five letters long) and repeat it during the response period. The test (retrieval) phase utilized two different word orders with the subjects randomly assigned to either order in a counterbalanced fashion. Both word orders used the same study/target list. The task was completed in two scanning runs lasting 10 minutes 48 seconds and 10 minutes 27 seconds, respectively (odd number of trials necessitated the first run having one extra trial). Each run featured a 30 second baseline rest condition where subjects viewed a fixation point (asterisk) on the screen. In total, subjects completed 15 word stems in the inclusion condition, 15 word stems in the exclusion condition, 15 control stems and 10 passive reading trials.

2.4. Variable construction and statistical analyses

To obtain purer, uncontaminated measures of these memory processes Recollection (explicit memory) and Automaticity (implicit memory) scores were calculated utilizing responses during the inclusion and exclusion conditions (see (Del Vecchio, et al., 2004; Jacoby, Stephen Lindsay, & Toth, 1992). Trials with no response were excluded from the analyses and computations of the Automaticity and Recollection measures.

The probability of responding with an OLD word in the *inclusion condition* is the probability of recollection plus the probability of a word coming automatically to mind. A probability score was calculated after taking the total number of study words correctly given by the participant, and then dividing that number by the total possible study word

completions (i.e., 15). In contrast, an OLD word is produced during the *exclusion condition* when it automatically comes to mind and one is unable to recollect that it was presented earlier. The probability measure for the exclusion condition was calculated in an identical manner. A high inclusion score and low exclusion score is associated with a higher probability of recollection. The probability of an OLD word originating from an automatic basis of responding is the probability of responding with a study-list word during the exclusion condition divided by the failure of recollection (n.b., performance uncontaminated by explicit memory). Last, the probability of correctly solving the 15 novel/control stems with the NEW prompt during the exclusion condition provided a measure of base-rate word-stem completion skill. The Automaticity and Recollection scores served as covariates of interest and were the primary variables in our statistical analyses described below (see Figure 2).

We should note that both implicit and explicit processes may be at work in each and every trial. However, over the course of multiple trials, a bias toward automatic and explicit responding can be calculated, and it is this summary bias measure that we capture for each individual in our Automaticity and Recollection measures. These continuous variables do not make an all or nothing assumption about implicit or explicit recollection, i.e., they do not assume that explicit recollection is or is not present, or that automaticity either failed or not.

2.5. Image Post-processing and Statistical Analysis

Volumes within an fMRI run were co-registered or computationally aligned to correct for interscan movement with the mean volume of the time series used as the reference. All volumes were transformed into standard anatomical space using the Statistical Parametric Mapping normalization procedure (Friston et al., 1995; Friston et al., 1994; Talairach & Tournoux, 1988). Volumes then underwent spatial smoothing (8mm³ FWHM) to increase signal-to-noise and account for residual inter-subject differences in anatomy. A high-pass filter removed low frequency fluctuations. Whole brain analyses using the general linear model (GLM) procedure of the Statistical Parametric Mapping software (SPM '08, <http://www.fil.ion.ucl.ac.uk/spm>) was used to create an event-related design containing sinusoid waveforms, each representing the six experimental and control events (correct inclusion, incorrect inclusion, correct exclusion, incorrect exclusion, control and reading). Movement parameters were included in the model as regressors of no interest.

Statistical contrasts used the appropriate linear compound of parameter estimates with a T-statistic computed at every voxel. We first isolated the BOLD signal activation during the 4 second display of the Stem Completion when memory retrieval processes, either implicit or explicit, would be operative and maximal. This period included 4 events: correct inclusion, incorrect inclusion, correct exclusion, and incorrect exclusion. The Reading and Control conditions were subtracted from this to produce a subject-specific first-level statistical contrast that controlled for both passive reading and word generation related cognitive processes (Stem Completion contrast). To isolate the activation associated with implicit retrieval, a contrast solely with the New Incorrect trials was utilized as these trials should show strong implicit retrieval relative to explicit retrieval. To isolate the activation associated with explicit retrieval, the New Correct trials were utilized, as explicit retrieval was likely to be strong relative to implicit retrieval during these trials. The Reading and Control conditions served as the comparison condition for the New Incorrect and New Correct contrasts, utilized above. Lastly, to test for neural suppression during implicit retrieval, the New Incorrect and Stem Completion trials were subtracted from the baseline rest condition to form Deactivation contrasts.

The resulting subject-specific contrasts were then entered into separate random effects models focusing on the activation associated with the Automaticity and Recollection

measures as a covariate of interest in Analysis-of-Covariance (ANCOVA) analyses with Experimental Group as the between-subjects factor (run separately for each covariate). To examine activation associated with LATL status and higher Automaticity scores, we coded the design matrix columns involving Automaticity to capture this combination of effects (LATL Automaticity main effect), and ran this contrast in the context of the New Incorrect and Stem Completion contrasts (separate analyses). Similar analyses were run involving the NC group (NC Automaticity main effect). Comparable main effect analyses were utilized to examine the effects of group status and Recollection scores in the context of the New Correct and Stem Completion contrasts (LATL Recollection main effect). The New Correct trials capture activity for trials that reflect successful explicit recollection. However, because such success does not preclude the concurrent presence of implicit memory processes, honing in on the activation that varies as a function of explicit Recollection, reflecting the participant's bias on the task, brings us closer to capturing regions most sensitive to explicit retrieval processes. The same logic holds for the New Incorrect trials, the Automaticity covariate, and capturing the brain regions most sensitive to implicit retrieval processes.

To directly compare the groups for differences in Automaticity, we utilized an interaction term that compared the groups on Automaticity performance, highlighting activation in the NC's Automaticity scores relative to the LATL group's scores. The reverse interaction term highlighted activation in the LATL's Automaticity scores relative to the NC group's scores. These interactions involving Automaticity were run in the context of the New Incorrect and Stem Completion contrasts (separate analyses). Comparable interaction effect analyses were utilized to examine the effects of Recollection, run in the context of the New Correct and Stem Completion contrasts. To examine neural suppression, the above interaction terms involving Automaticity were run in the context of the Deactivation contrasts (Baseline rest minus New Incorrect or Baseline rest minus Stem Completion).

Following the above statistical analyses, only clusters of activation surviving a corrected height threshold of at least $p < 0.05$ and a corrected extent threshold consistent with image smoothness are reported (Friston et al., 2004). As memory performance can vary by age (Borson, 2010), any obtained statistically significant finding was re-analyzed with age as a covariate in the model to determine if the findings associated with Automaticity or Recollection changed as a function of this factor.

3. Results

3.1. Behavioral Results

The behavioral data showed a statistically significant difference in explicit memory task performance between LATL patients and NCs, but not in implicit memory performance (See Table 1). LATL patients had a significantly lower mean inclusion score than NC's, suggesting that this group had a lower probability of correctly answering with a word from the study list during the OLD condition. In contrast, LATL patients and the NCs had similar and statistically equivalent mean exclusion scores, reflecting the probability of answering with a word from the study list during the NEW condition. Consistent with this, NCs had a significantly greater mean Recollection score than the LATL patient group. Likewise, LATL patients and NCs demonstrated only slight and non-significant differences in their mean Automaticity scores.

3.2. Explicit Retrieval (Recollection Covariate) Results

The ANCOVA interaction analyses testing for group differences in Recollection (NC minus LATL or LATL minus NC) are shown in Table 3. The statistically significant results are as follows. In the context of the Stem Completion contrast there was a group difference in the

activation associated with higher Recollection, with NC's relative to the LATL group showing stronger activation in the right midbrain (mamillary body), left inferior frontal cortex, and left lentiform (putamen). The ANCOVA main effect analyses (see Table 3) examining activation associated with NC status and higher Recollection scores in that group revealed right hemisphere involvement including the right inferior parietal lobe and precuneus in the context of the New Correct contrast.

3.3. Implicit Retrieval (Automaticity Covariate) Results

The ANCOVA interaction analyses (see Table 3) testing for group differences in Automaticity are shown in Table 3. The statistically significant results are as follows. For the LATL patients the main effect analyses (LATL status and Automaticity scores) in the context of the Stem Completion contrast produced a rich set of activations (see Figure 3) in the left hemisphere involving the striatum (left lateral globus pallidus, also the right putamen), claustrum, precuneus, medial frontal gyrus, and paracentral lobule. Note, NC's did not produce significant results activating the medial temporal lobe.

3.4. Deactivation and Age Related Results During Implicit Retrieval

Potential deactivation during implicit retrieval was assessed by the contrast utilizing the Baseline rest condition minus the New Incorrect trials or the Stem Completion trials (see Table 3). The statistically significant results are as follows. The ANCOVA interaction analyses testing for group differences in Automaticity (NC minus LATL) revealed right lingual gyrus, parahippocampal, and left pulvinar deactivation in the context of the New Incorrect contrast (see Table 3 and Figure 4). In the context of the Stem Completion contrast, the NC compared to the LATL group showed quite similar deactivation involving the right lingual gyrus, medial occipital gyrus, and right parahippocampus.

The ANCOVA main effect analyses examining deactivation associated with NC status and higher Automaticity scores in the context of the Stem Completion Deactivation contrast revealed greater deactivation in the lingual gyrus bilaterally and the right middle temporal gyrus. The main effect analyses reflecting LATL status and higher Automaticity scores produced a trend, but showed deactivation in the cingulate and left temporal gyrus.

As our experimental groups did differ in age, an Age covariate (mean centered age scores were used) was examined in the context of the key contrasts (run separately): Stem Completion trials, New Correct, and New Incorrect, with the Reading and Control conditions used as the comparison condition. In all instances, for both the NC and the LATL groups, the Age covariate yielded a null result and nearly identical activation results were obtained for the key contrasts of interest.

4. Discussion

Given the behavioral differences in Recollection, we suspected that the functional neuroanatomy associated with our Recollection measure would differ in the NC and LATL groups. An analysis comparing the groups on the Recollection covariate showed that the NC's produced greater activation in the left inferior frontal gyrus, a region that is part of Broca's area in most individuals, and subcortical areas (e.g., left putamen). In association with NC status and high Recollection scores, there was evidence of right precuneus and right inferior parietal activation extending superiorly. The left inferior frontal region has been implicated in explicit memory (Rugg & Curran, 2007) and word retrieval (Thompson-Schill et al., 1998). The left parietal lobe including the precuneus has been associated with explicit memory retrieval (Wagner, et al., 2005), thus the nature of the parametric response to the

Recollection measure in specific regions of the right hemisphere, including the precuneus is not clear.

The LATL group showed Automaticity-related activation in the left precuneus, left medial frontal gyrus, striatum (lateral globus pallidus, right putamen), left paracentral lobule, and left claustrum in the context of the Stem Completion trials, but this was not evident in the trials isolating the New Incorrect trials, the trials most closely linked to automatic responding. Analyses focusing on the New Incorrect condition, however, did involve fewer trials and, therefore, were lower in terms of statistical power than those involving all the trials (i.e., Stem Completion condition). This may explain why the Stem Completion condition tended to produce more statistically reliable activations and deactivations throughout the results of our study.

There is work consistent with the notion of precuneus involvement in automatic memory retrieval. For instance, Wagner et al. (2005) reports activity in the precuneus during both the correct recognition of old items, reflective of episodic memory, and the incorrect rejection of old items, seeming to indicate dominance of implicit memory processes. We should note that the precuneus has high interconnectivity with the other regions that appeared with it in the New Incorrect contrast (paracentral lobule, putamen, and medial frontal gyrus, see (Cavanna & Trimble, 2006). Since the precuneus has no connections with sensory cortices but high interconnectivity with these other regions, some authors have argued that it may play a role in integrating and associating information and is closely tied to self-referenced mental imagery and episodic memory retrieval (Cavanna & Trimble, 2006). The anterior region appears more associated with reinstatement of self-referenced images, including words. In contrast, the posterior section appears to be associated with successful episodic memory retrieval, particularly if autobiographic in nature (Lundstrom, Ingvar, & Petersson, 2005; Lundstrom et al., 2003). In the setting of our task, where the precuneus activation in the LATL group is certainly anterior, but extends posteriorly, the above suggests the precuneus potentially reflects visual imagery of the primed material toward the goal of successful retrieval of the full word.

Regarding the striatum and medial prefrontal cortex findings in the LATL group during automatic responding, this activation may reflect associative learning or conditioning as these areas have been implicated in the acquisition of conditioned responses. The medial prefrontal cortex appears to mediate “trace” and contextual fear conditioning (Gilmartin & Helmstetter, 2010). This conditioning requires the association of a conditioned stimulus with an aversive unconditioned response across a temporal gap. This is certainly quite different from the paired learning and conditioned response present in our task. In our task, a familiar word is read and memorized, and the strength of association between the subsequently viewed word stem (stimulus) and its remaining letters creates a bias in the stem completion process. Interestingly, fear conditioning, much like implicit learning, occurs automatically, without intention, and is often accomplished outside of awareness. The striatum (e.g., lentiform and putamen) are involved in associative learning, particularly in the context of reward preferences (O’Doherty, Buchanan, Seymour, & Dolan, 2006), instrumental conditioning (O’Doherty et al., 2004), and the mapping of visual-to-motor responses (Buch, Brasted, & Wise, 2006), although the associative learning need not involve a motor response (Romero, Bermudez, Vicente, Perez, & Gonzalez, 2008). There is also evidence from monkey studies that the learning-related neural responses of medial frontal/premotor cortex and striatum may function as a coordinated module (Brasted & Wise, 2004). In light of the above, we suspect our LATL patients, lacking temporal lobe structures well-versed in encoding associative connections (Cohen, et al., 1999), compensated for this by taking advantage of the ability of medial frontal cortex and the striatum to engage in associative activity and encode a conditioned response.

Note, there is evidence in humans of precuneus involvement in explicit memory (Vincent et al., 2006; Wagner, et al., 2005). Therefore, activation of this structure during implicit retrieval in the LATL patients suggests that in the absence of an intact mesial temporal lobe memory system, this area can also be active in search and retrieval mechanisms even if these processes are occurring implicitly, outside of awareness. Based on our results, we propose that in the setting of an anterior temporal lobectomy, the precuneus may perform mnemonic processing on material that can support implicit memory.

Regarding deactivation responses and possible neural suppression, we found that compared to the patients the NC's with higher Automaticity scores produced greater deactivation in a posterior brain region involving the lingual gyrus and parahippocampal region. This is generally consistent with the structures (perceptual cortices) connected with perceptual priming as described by Schacter and Dobbins who posit a set of posterior (e.g., occipital) regions for perceptual priming, and a set of inferior temporal and prefrontal regions for conceptual priming (Schacter, et al., 2007). If, indeed, perceptual priming was at work in the NC's, the processing involved to recover a word to complete the stem would have to bias the underlying brain representation quickly as our subjects only saw the primed words once during the learning phase of our memory task. This stands in contrast to other studies such as Dobbins and colleagues (2004), where the perceptual priming effect was gained after three stimulus exposures. Given the lack of reliable deactivation responses in the LATL group, we conclude that normative perceptual or conceptual priming responses were not present, and that their Automaticity response during stem completion was mediated by neural activation in the areas described above, not deactivation and neural suppression.

Does our data represent reorganization of implicit memory in our LATL patients? If by reorganization one means simply that functionality (e.g., for implicit memory) is maintained or restored in the face of a lost brain area, then, yes, reorganization has occurred. If by reorganization one means recruitment of a new brain area to carry out a function, or compensate for a function, of the impaired area through a process such as functional substitution, our data would also still imply reorganization. For instance, implementation of implicit memory, absent the mesial temporal lobe, may take a different form, involving increased reliance on the medial frontal cortex and striatum for compensatory, substitutive associative activity, contributing to the encoding and expression of a well-associated word stem completion response that without pathology, seizures, and surgery might otherwise have been carried out by the anterior temporal lobe. As noted earlier, the precuneus may have also played a role in mental-imagery mediated retrieval of the primed material. We must acknowledge that our study is not definitive with regard to reorganization, nor does our study distinguish the relative integrity of conceptual versus perceptual implicit memory processes in our patients.

As a caveat, we did not examine the order of trial presentation and such effects may be important as the behavioral effects in the task may initially be driven by top-down mechanisms, and later reflect the movement toward automatic processing after repeated stimulus presentations and response to the stems. We should also note that word-stem completion tasks are affected by the orthographic, linguistic, semantic, perceptual and emotional responses potentially invoked by the word stimuli. These variables likely played some unspecified role in the observed responses. Our temporal lobe epilepsy group and healthy controls did differ in age. The literature regarding the effect of aging on explicit episodic memory are strong and clear (Brickman & Stern, 2009), and our groups did not differ in explicit memory performance. However, the literature on implicit memory and priming is mixed and less certain, with some evidence suggesting that conceptual priming but not perceptual priming varies by age (Brickman & Stern, 2009). As noted, we found no effects of age in our imaging data, with no change in our results after a re-examination of

our key findings with age as a covariate. It should also be noted that some of our null findings should be tempered by the fact that estimates produced by the process dissociation procedure have been criticized as low in reliability, and, as such, have a reduced chance of reaching statistical significance (Jacoby, 1998). The estimates produced by the process dissociation procedure are known to depend on many factors such as the instructions provided to participants, the mixture of previously studied and non-studied items in a test list, and the amount of time per item available for retrieval. We acknowledge that we cannot in our study estimate the effects of all the factors and have not run controlled studies of these factors. Lastly, as noted earlier, both implicit and explicit processes may well have been at work in each and every trial. We did not isolate these processes at the level of the individual trial. However, over the course of multiple trials, a bias toward automatic and explicit responding can be detected, and it is this summary bias measure that we captured for each individual in our Automaticity and Recollection measures.

In summary, our data make clear that in the face of temporal lobe pathology implicit memory can be carried out, confirming our prior results indicating that implicit verbal memory retrieval is non-hippocampal/non-mesial temporal in nature (Delvecchio et al., 2004). Our LATL did not show the normative neural suppression response involving either perceptual and conceptual priming. This may suggest that this normal response is predicated on an intact mesial temporal lobe system, an idea that is certainly worth exploring further. Instead, our LATL patients showed only a reliable activation response during implicit memory retrieval, with the regions involved extra-temporal in nature involving the left medial frontal cortex, precuneus, and the striatum. The medial frontal cortex and striatum findings may represent a compensatory activity, contributing to the encoding and expression of a well-associated word stem completion response that without pathology, seizures, and surgery might otherwise have been carried out by the temporal lobe. The precuneus may have played a role in mental-imagery mediated retrieval of the primed material. However, because the precuneus has also been implicated in explicit memory, our data suggests that this structure has a highly flexible functionality in terms of retrieving stored information, particularly when structures such as the hippocampus and anterior temporal lobe are missing. Importantly, our data may indicate that the precuneus can be involved in controlled processing functions such as explicit retrieval or automatic non-executive processes such as implicit retrieval (Tracy et al., 2003). Future research which may want to examine right anterior temporal lobectomy patients to further disambiguate different implicit memory processes and their relevant neuroanatomy. It remains to be understood whether regional differences within the precuneus truly exist for these two types of retrieval processes. Just as multiple sites brain are involved in episodic memory retrieval (Rugg, Otten, & Henson, 2002), it appears that multiple brain sites work in tandem as part of a circuit to carry out implicit memory retrieval.

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Experimental Condition and Prompt (4 secs)	Delay (3 secs)	Subject Response Period (2 secs)	Intertrial Interval (14 sec)	Joint Contribution Of Memory Processes
<u>INCLUSION CONDITION</u>				
OLD sha - -		Shark ¹	*	<u>OLD CORRECT:</u> Recollection Automaticity
		Shake	*	<u>OLD INCORRECT:</u> Failed Recollection Failed Automaticity
<u>EXCLUSION CONDITION</u>				
NEW cle - -		Clean ¹	*	<u>NEW INCORRECT:</u> Failed Recollection Automaticity
		Clerk	*	<u>NEW CORRECT:</u> Recollection Failed Automaticity
<u>READING CONDITION</u>				
Train		Train	*	None (Visual Processing, Reading Control)
<u>CONTROL CONDITION</u>				
pla - -		Plane	*	None (Word Generation Control)

¹ Study-List Word

Figure 1.
Graphical depiction of the experimental events and PDP procedures with the joint contribution of explicit (recollection) or implicit (automatic) memory processes.

Equation 1 (Probability of OLD Words, Inclusion Condition)

Inclusion test score = # OLD words from previous list.

The probability of responding with a previously seen word in the inclusion condition is the probability of recollection plus the probability of a word coming automatically to mind. The probability was calculated after taking the total number of study words given by the participant and then dividing that number by the total possible study-word completions, all during the Inclusion Condition.

Equation 2 (Probability of OLD Words, Exclusion Condition)

Exclusion test score = # OLD words from previous list.

An old word will be produced during the exclusion condition when it automatically comes to mind and one is unable to recollect that it was presented earlier. The probability was calculated after taking the total number of study words given by the participant and then dividing that number by the total possible study-word completions, all during the Exclusion Condition.

Equation 3

Recollection = inclusion test score – exclusion test score.

The probability of recollection is the probability of completing a stem with a study-list word during the inclusion condition minus the probability of completing a stem with a study-list word in the exclusion condition.

Equation 4

Automaticity = exclusion test score / (1 – R).

The probability of an old word originating from an automatic basis of responding is the probability of responding with an old, study-list word during the exclusion condition divided by the failure of recollection (n.b., memory performance uncontaminated by explicit memory).

From Jacoby and colleagues Jacoby et al. (1991)

Figure 2.
Process Dissociation Procedure (PDP) Formulas.

Figure 3. ANCOVA main effect activation results associated with the Automaticity covariate in the context of the Stem Completion contrast for the LTLE group.

Figure 4. ANCOVA interaction results showing group differences in Automaticity (NC minus LTLE) in the context of the Deactivation New Incorrect contrast.

Table 1

Characteristics of the Study Participants

Variable	Left Temporal Lobe Epilepsy Patients (n=12)	Normal Controls (n=16)
# of males/females	5 / 7	10 / 6
	Mean	Mean
Age **	43.9 ± 11.6	27.2 ± 7.4
Years of Education	14.5 ± 2.5	16.3 ± 2.0
Edinburgh Handedness score	36.38 ± 86.3	86.3 ± 14.2
Exclusion Score	0.39 ± 0.13	0.36 ± 0.18
Automaticity score	0.48 ± 0.13	0.52 ± 0.15
Inclusion Score *	0.56 ± 0.18	0.68 ± 0.11
Recollection Score *	0.17 ± 0.20	0.32 ± 0.19
Surgery to Scan Interval	24.3 months ± (6.7)	NA
VIQ	95.7 ± 12.0	NA
PIQ	105.5 ± 14.1	NA
FSIQ	100.6 ± 11.7	NA

* P<.05. Inclusion, t[26]= 2.24. Recollection, t[26]=2.2.

** P<.001. Age, t[26]=-4.6.

Table 2

Patient Clinical Information

Patient No.	Age (years)/gender	Handedness	Neuro-pathology	Type of seizures	Sz freq (month)	duration of epilepsy (years)	Medications at date of scan (dose)
1	41/Female	Left	MTS	CPS	CPS 2.5	13	Lamictal (300 mg., hs)
2	21/ Female	Right	MTS	CPS + CPS w ²	CPS 2	10	Trileptal (500mg., BID)
3	46/ Female	Right	Gliositis	CPS + CPS w ²	CPS 5 CPSw ² 0.5	38	Keppra (100 mg.,TID), Lamictal (200 mg.,BID)
4	35/ Male	Right	MTS	SPS + CPS	SPS 6 CPS 1.5	6	Dilantin (300 mg.,BID)
5	38/ Female	Right	Gliositis	CPS	CPS 5	23	Lamictal (100 mg.,BID), Meclizine (25 mg., PRN), Norethindrone (5 mg.)
6	47/ Female	Left	Gliositis	CPS	CPS 6	17	None
7	70/ Male	Right	Gliositis	CPS + GTC	CPS 4 GTC 1/yr	6	None
8	47/ Male	Left	MTS	CPS	CPS 3	34	None
9	43/ Female	Right	MTS	CPS	8	21	Depakote (250 mg.,TID), Synthroid (100microg), Oscal (500 mg.,TID), Klonopin (.5 to 1 mg)
10	48/ Male	Left	MTS	CPS	2	Unknown	Lamictal (200 mg., TID), Keppra (500 mg.,BID)
11	38/ Male	Right	MTS	SPS + CPS + GTC	SPS 300, CPS 15, GTC 1/yr	9	Trileptal (500 mg.,BID), Oxcarbazepine (PRN)
12	53/ Female	Right	MTS	CPS + CPS w ²	CPS 10, GTC 1/yr	49	Lamictal (225-300 mg. daily), Metoprolol (25 mg., BID), Celebrex (200 mg.)

MTS= Mesial temporal sclerosis CPS= Complex Partial Seizures SPS= Simple Partial Seizures GTC= General Tonic-Clonic Seizures

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ANCOVA analyses (main effects and interactions) assessing Recollection and Automaticity in and between the NC and LTLE groups.

Table 3

Covariate	Cluster Level			Maxima	Tailrach			Brain Region area
Analysis	Subject Group	P _{corrected}	K _E	Z	x	y	z	
Contrast								
Recollection activation								
Interaction								
New Correct	NC-LTLE	Null						
	LTLE-NC	Null						
Stem Completion	NC-LTLE	0.036	229	3.11	4	-12	-9	R Midbrain (Mam body)
				3.07	-44	20	17	L IFG (BA 45)
				3.03	-28	-4	4	L Lent Nuc (Putamen)
Main Effect								
New Correct	NC	0.009	277	3.82	28	-44	57	R Parietal Lobe (BA 40)
				3.51	44	-36	53	R IPL (BA 40)
				3.24	4	-55	58	R Precuneus (BA 7)
Stem Completion	LTLE	Null						
	NC	Null						
	LTLE	Null						
Automaticity activation								
Interaction								
New Incorrect	NC-LTLE	Null						
	LTLE	Null						
Stem Completion	NC	Null						
	LTLE	Null						
Automaticity activation								
Interaction								
New Incorrect	NC-LTLE	Null						
	LTLE-NC	Null						
Stem Completion	NC-LTLE	Null						
	LTLE-NC	Null						

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Covariate	Cluster Level		Maxima	Tailrach			Brain Region area
Analysis	Subject Group	P _{corrected}	K _E	Coordinates			
Contrast				Z	x	y	z
Main Effect							
New Incorrect	NC	Null					
	LTLE	Null					
Stem Completion	NC	Null					
	LTLE	0.000	520	3.62	-24	-8	-3
				3.59	-36	-4	4
				3.36	32	-16	-3
		0.005	315	3.54	-12	-59	55
				3.43	-4	-16	60
				3.32	-4	-44	61
Automaticity deactivation							
Interaction							
New Incorrect deactivation	NC-LTLE	0.05	228	3.73	8	-54	3
				3.38	12	-43	-11
				3.02	-4	-35	5
Stem Completion deactivation	LTLE-NC						
	NC-LTLE	0.007	322	3.75	8	-54	3
				3.22	36	-66	7
				3.14	12	-43	-11
Main Effect							
New Incorrect deactivation	NC	Null					
	LTLE-NC	Null					
	LTLE	Null					
Stem Completion deactivation	NC	0.001	448	4.13	8	-54	3
				3.81	-12	-63	-17
				3.37	36	-58	10

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R= Right, L= Left, BA= Brodmann Area, Lent Nuc = Lentiform Nucleus, IFG = Inferior Frontal Gyrus, IPL=Inferior Parietal Lobule, Mam body=Mamillary body, LGP=Lateral Globus Pallidus, MFG= Medial Frontal Gyrus, Paracent Lob = Paracentral Lobule, Med Occ=Medial Occipital, Mid Temp=Middle Temporal, G = gyrus.