Running head: PAPEZ CIRCUIT ACTIVATION OBSERVED

Papez Circuit Activation Observed with Functional Imaging During Semantic List Learning in Healthy Adults

by

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Abstract

Word list learning tasks often indicate that hippocampal activation correlates positively with subsequent memory for list words. Therefore, we hypothesized that greater activation would be observed in the hippocampus in response to subsequently recalled and recognized words, than to words that were forgotten, during word list learning (encoding). 14 female and 12 male healthy adult participants completed a Semantic List Learning Task during fMRI. Subjects were between 17 and 70 years old (M = 37) and had between 12 and 20 years of education (M = 16). 15 different lists of 14 semantically related words were presented during the scan. To minimize working memory rehearsal and recency effects on later recall, a Brown-Peterson distractor paradigm was used. Silent free recall blocks were also used. Recall and recognition were conducted later with semantic cues, outside the scanner. Subjects performed with 39% accuracy in recall and 60% accuracy in recognition, with a significant primacy effect observed, $F(2,48) = 14.690$, $p < .001$. Primacy words averaged 5 and 8% better subsequent memory than the middle and recency words, respectively. fMRI data analysis revealed significant activation during encoding in left hippocampus and parahippocampus, as well as bilateral cingulate cortex and insula for words that were correctly remembered after scanning. Post-hoc ROI analysis of the hippocampus was also conducted for words that were later recalled compared to words that were not. Papez circuit activation, predominated by hippocampal, parahippocampal and insular activity, occurred in list learning in response to words that were later recalled or recognized. This confirms well-known associations between this circuit and successful memory encoding and later retrieval, providing a strong paradigm to investigate conditions where these circuits are damaged or disrupted.

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Papez (1937) identified a neural circuit of limbic structures that he believed to be essential for the cortical control of emotions. This circuit includes structures such as the hippocampus, parahippocampal gyrus, mammillary bodies, insula and cingulate gyrus, and is now known to also play a vital role in human memory (see Figure 1). The current study sought to understand the functional correlates of Papez circuit activity during encoding of semantic information. Because this circuit is sensitive to damage from lesions and disease which can produce dysphoria (Papez, 1937), it is critically important to design tasks that are sensitive to Papez circuit activity in order to better understand the relationship between human emotion and memory. Additionally, the evolutionary significance of a circuit that subserves both emotion and memory functions has intriguing implications for the importance of this circuit to everyday life in humans.

A Brief History of List Learning Tasks and Memory Theories

One common task employed by researchers studying memory involves asking subjects to learn a list or lists of semantically related words for later recall and/or recognition (Kellogg, 1995). List learning paradigms have high face validity, that is, they are seen as easily applicable to daily life (e.g. memorizing a grocery list before going shopping). Recall and recognition tasks are both used frequently, with better performance in recognition tasks (Kintsch, 1970). These tasks are often employed both with healthy subjects and in clinical populations in order to understand human memory and its neuroanatomical correlates.

When discussing human memory, the distinction is often made between short-term and long-term memory (STM and LTM) which are separated by the timescale in which they operate (Kellogg, 1995). Short-term memory is so named because of the rapid rate of forgetting that is observed unless items are preserved through rehearsal processes. LTM is assumed to have some fixed capacity for the number of items that can be remembered without a rigid temporal boundary, whereas STM is primarily seen as limited by the amount of time as well as the number of pieces of information that can be held. STM capacity has been shown to average about seven (plus or minus two) "chunks" or units of meaningful information (Gazzaniga, Ivry, & Mangun, 2009). The concept of STM is often expanded to include both maintenance and manipulation of stimuli, and this is referred to as working memory (WM). List learning paradigms are often used to investigate the function of these different kinds of memory in human subjects.

Central to the topic of human memory is the serial position effect which is observed under free recall conditions in list learning (Kellogg, 1995; Reed, 1996). Items presented at the beginning or end of word learning list are typically better recalled than items in the middle, known as the primacy and recency effects respectively. Words remembered from the beginning of a list are believed to represent LTM functioning whereas words remembered from the end of a list reflect retrieval from or maintenance within STM (Kellogg, 1995). Therefore, it has been argued that the serial position curve is actually the summation of two memory function curves. The first peaking in the primacy condition and sloping down thereafter primarily represents LTM function. The second, sloping up to peak in the recency condition, reflects the function of STM. This is known as the dual-process model of memory, in contrast to the single process model

which posits that both short and long-term memory are subserved by the same mechanism.

In order to separately examine the effects of these two proposed memory functions, Glanzer and Cunitz (1966) in their first experiment manipulated list item presentation rate and repetition frequency in order to understand the effects on the primacy portion of the serial position curve. They theorized that increasing time between item presentation and increasing the frequency of item presentation would facilitate the primacy but not the recency effect, as both of these manipulations are known to facilitate rote learning. The authors found that increased delay between item presentation, but not repeated presentation of items, significantly increased memory for words at the beginning but not the end of the list.

Glanzer and Cunitz (1966) next investigated the effect of interference and delayed recall on recency memory. In their second experiment, they began by asking subject to recall list items either immediately or after a 30 second delay that contained no additional task. Under this paradigm they found a significant reduction in memory for items at the end of the list in the delay condition. As a follow-up to this experiment the authors asked subjects in one group to recall words from a list immediately while others counted backwards by sevens for either 10 or 30 seconds before recall. They found that the distracting task of counting backward, which required the subjects' attention during the delay, eliminated the facilitation of memory by the recency effect, but left the primacy effect intact. Taken together, the results of this series of experiments support the theory that two distinct mechanisms underlie the effect of serial position on memory.

To explain these two separate memory mechanisms, Atkinson and Shiffrin (1968) proposed the multistore model of human memory in which information passes through multiple buffers: first into a sensory register, then to a short-term store, and finally into a long-term store. They posited that information could persist in the sensory register without rehearsal for a period of time on the order of milliseconds or seconds, for around 30 seconds in STM, and for many years in LTM. They also stated that STM is responsible for control processes, such as rehearsal, as well as for an aspect of executive functioning known as working memory. Information cannot be eliminated from short-term or sensory buffers until they are filled to their respective maximum capacity.

In a serial position test of memory for colored cards, subjects were presented with the stimuli one at a time and then tested for their knowledge of cards at different positions in the sequence (Atkinson & Shiffrin, 1968). The authors observed strong primacy and somewhat milder recency effects which they explained in terms of their multistore model. They claimed that the primacy effect could be expected as more information is transferred to long-term storage at the beginning of a list. This is because STM capacity has not yet been reached, meaning that there are fewer items competing for rehearsal, and each receives more rehearsal time before leaving the buffer. They further stated that the recency effect can also be explained by the fact that the last items on a list may still remain active in short-term storage. The authors found that they could closely fit a subject's serial position curve by accounting for such factors as individual memory capacity and rate of learning.

Rundus (1971) was interested in establishing a direct link between rehearsal and the primacy effect. To this end he asked people to say words from the list they were

learning out loud during a five second wait between presentations of each list item. He found that words at the beginning of the list received many more rehearsals than later items. He concluded that words presented early in the list filled a person's short-term storage towards maximum capacity, leaving more words competing for rehearsal by the end of the list than could be handled.

These early theories and experiments implicated two separate memory mechanisms, short and long-term memory. Investigators have used list learning tasks in healthy subjects to understand how memory normally functions. In addition, investigations with unique patient samples have highlighted the role of the Papez Circuit in learning and memory.

Clinical Patient Studies that Highlight Papez Circuit Structures Important for Memory

Individuals with significant impairments to memory functioning are often said to suffer from amnesia. The distinction is made within the literature between two sub-groups of amnestics, referred to as retrograde and anterograde amnesia. Retrograde amnesia refers to an inability to remember information from the past, in contrast to anterograde amnesia, in which a person is unable to remember and learn new information. While retrograde amnesia is thought to be chiefly related to disruptions to LTM store, anterograde amnesia is believed to be an inability to pass information from STM to LTM (Kellogg, 1995).

In order to better understand how memory operates, Scoville and Milner (1957) administered a battery of neuropsychological measures to 10 amnestic patients who had sections of their medial temporal lobes (MTL) removed. They found that the extent of a patient's memory impairment depended upon how much of their MTL had been

removed, and the more posterior the resection, the more severe the amnesia it produced. Importantly, only bilateral resections of the hippocampus resulted in severe amnesia. One patient whose entire right MTL was removed showed no residual memory deficits. These results suggested that the both hemispheres of the MTL together play a critical role in human memory.

One of these subjects is of particular interest because of a permanent inability to acquire new information as a result of surgical removal of portions of bilateral MTL. This subject, known by his initials H.M., showed normal performance on tasks that measure short-term or working memory abilities such as digit span (Scoville & Milner, 1957). However, he performed poorly on tasks that require the acquisition of new long-term memories. It seemed that his ability to pass information from STM to LTM had been disrupted. Scoville initially reported that H.M. had undergone removal of eight centimeters of his MTL, including complete bilateral resection of the hippocampus. Contrary to this claim, Corkin, Amaral, Gonzalez, Johnson, and Hyman (1997), who made use of modern magnetic resonance imaging (MRI) techniques, reported that approximately half of H.M.'s posterior hippocampus remained intact with only five centimeters of MTL having been removed. However, the remaining portions of hippocampi were atrophied, likely as a result of the loss of connections to surrounding cortex during surgery. It is important to note that while H.M. clearly had significant damage to his hippocampi, the surrounding cortex was also disrupted. This case provided support for the conclusion that MTL structures play a specific role in the formation of new long-term memories.

Another illustrative case is that of R.B., a patient who lost memory functioning in 1978 after an ischemic episode in which blood flow to his brain was reduced during heart bypass surgery (Zola-Morgan, Squire, & Amaral, 1986). R.B., who also developed anterograde amnesia, was studied by Zola-Morgan, Squire, and Amaral at the University of California, San Diego. This case is remarkable because R.B.'s lesions were found to be restricted to his hippocampi. Specifically, within each hippocampus he had suffered a lesion exclusively to CA1 pyramidal cells. This case provides strong and specific evidence for the role of the hippocampus in the encoding of new memories and its distinction from other medial temporal areas responsible for LTM storage.

In contrast to amnestics like H.M. and R.B., Warrington and Shallice (1969) report the interesting case of K.F., an epileptic who had experienced a left parietal subdural hematoma as a result of a motorcycle accident. This patient was observed to be markedly impaired on tasks such as digit span which are thought to rely on STM, but not significantly impaired on LTM tasks such as paired-associate learning. This example is reinforced by that of E.E., a patient who was studied by Markowitsch, Kalbe, Kessler, Stockhausen, Ghaemi, and Heiss, (1999). E.E. experienced a left angular gyrus lesion as a result of removal of a tumor that was the focus of multiple epileptic seizures. Neuropsychological evaluation revealed a pronounced deficit in STM, particularly for operations involving numbers or abstract verbal material, as evidenced by performance on digit span and number transcoding tasks. Furthermore, E.E. displayed a strong primacy effect, but no effect of recency, when recalling longer series of words, numbers, or sentences. Positron emission tomography (PET) data collected from E.E. while he conducted a verb generation task showed significant reduction of activation in left

Wernicke's area, which was clearly related to the lesion in that section of his cortex. The subject also showed significant activation of right temporo-polar cortex, and to a lesser extent, infero-lateral prefrontal cortex, which have been previously implicated in LTM. Taken together, these cases serve as excellent examples of a double-dissociation between short- and long-term memory function in human amnestics that provides further support for the dual-process model of memory.

To further investigate distinctions between STM and LTM, Baddeley and Warrington (1970) assessed six patients experiencing anterograde amnesia with regard to their ability to free recall a list of 10 words, either immediately after presentation or after 30 seconds of distraction. These patients showed a strong recency effect in the immediate recall condition, which indicated that their STM was relatively preserved. However, these subjects showed much poorer performance than controls for items at the beginning and middle of the list, which Baddeley and Warrington concluded was evidence of a failure to transfer information from short-term to long-term storage. Consistent with this conclusion was their finding that recall of items after a 30 second delay with no interference was almost nonexistent for the anterograde amnestics. This was in sharp contrast to controls who exhibited much better memory. However, after 60 seconds of distraction in a Brown-Peterson paradigm, the researchers found that amnestics and controls showed similar memory performance.

This finding was surprising as the authors had hypothesized that impaired LTM function in amnestics would prevent normal memory performance after such a long period of distraction (Baddeley & Warrington, 1970). They suggested that a possible explanation of these findings was that the organization of items within the long term store

was impaired, as opposed to LTM itself. The implication of these findings is that MTL structures such as the hippocampus are important to LTM and may play a role in the transfer of items from short- to long-term stores, and/or in the organization of items within LTM.

Functional MRI as a Tool to Investigate the Papez Circuit Relationship to Memory Performance

Recent advances in neuroscientific methodologies have given researchers powerful tools for non-invasive investigations of the structure and function of the human brain. Techniques such as functional magnetic resonance imaging (fMRI) have revolutionized the way in which neuroscientists study the brain. It has been long established that fMRI is an important and effective neuroscientific tool that allows researchers to localize brain activity in human subjects (Bandettini, Wong, Hinks, Tikofsky & Hyde, 1992). In particular, it is now possible to biologically validate psychological models of cognitive functioning by identifying consistent patterns of brain activity in response to given stimuli (Dupont, Samson, Le Bihan, & Baulac, 2002).

Inferences made about brain activity are based on changes in cerebral blood oxygenation, which is an indirect measure of cellular metabolism and, thus, also neural activity (Bandettini et al., 1992). It is well established that oxygenation of hemoglobin affects the T-2 weighted MRI signal of whole blood and it is these changes in oxygenation that are measured in fMRI. The change in blood oxygenation, secondary to compensatory flow following increases in neural firing, is the basis for the Blood Oxygenation Level Dependent (BOLD) signal. It is these relative shifts in the ratio of oxygenated and deoxygenated blood that are observed using fMRI (Logothetis &

Wandell, 2004). This technique allows researches to indirectly and non-invasively study the function of specific brain regions and circuits during performance of certain tasks.

Imaging Studies to Address the Role of Papez Circuit Structures in Memory

Interest in the debate between dual- and single-process models that attempt to explain the serial position curve has continued into the new millennium. Recent investigations of this question have made use of modern neuroimaging techniques such as fMRI in order to more fully answer the questions raised on both sides of the debate. Talmi, Grady, Goshen-Gottstein, and Moscovitch (2005) hypothesized that if a single process was responsible for both long and short-term memory function, then brain activation for items being held in both stores should look rather similar. On the other hand, a dual-process model would predict significant differences in the patterns of activation for items being held in short and long-term memory. To test this hypothesis, the authors presented 10 subjects with seven runs, each with two blocks of nine trials containing different twelve-word lists during fMRI. Each trial was followed by presentation of a probe word to which subjects responded by indicating if the word was from the list just seen or not. Early words (from positions 1 or 2), late words (from positions 11 and 12) and novel words were each used as probes twice per run, and mid-list words (from positions 3 through 10) were used as probes once. The remaining two trials were controls in which the words “old” and “new” were presented as stimuli and probes randomly, instead of words taken from the list. A comparison of early minus control and late minus control contrasts showed significantly greater activation in the left MTL extending from the hippocampus for early words. This finding therefore lends

credence to the dual-process explanation of serial position effects. Additional current investigations of list learning memory and serial position effects are described below.

Development of Brown-Peterson Paradigm to Focus Specifically on LTM

It has been suggested that the amount of information that will persevere in STM decreases predictably with time. By having subjects perform a distracting activity that prevented rehearsal of items held in memory for a variable amount of time, researchers have been able to show that information in STM is predictably lost as time progresses. This is known as the decay theory of memory. The most famous investigations of this theory produced what is now known as the Brown-Peterson procedure after a series of experiments by Brown (1958) and Peterson and Peterson (1959).

The experiment conducted by Brown (1958) tested the decay theory of memory. Subjects were asked to remember one to four random pairs of consonants that were presented, followed by a delay period during which subjects either copied five pairs of random numbers (the distraction condition), or simply waited four to seven seconds (the control condition), before being asked to recall the consonant pairs. Subjects remembered significantly fewer consonant pairs after distraction than in the control condition. Brown attributed this effect to the ability of subjects in the control condition to rehearse consonant pairs held in memory, thus facilitating memory at recall.

Peterson and Peterson (1959) asked undergraduates to remember three consonants over a short retention period. To prevent rehearsal of the items, the researchers required subjects to count backwards by threes starting with a number given to them after the consonants. They found that probability of correctly recalling an item declined rapidly

over an 18 second retention interval. They concluded that verbal information must be rehearsed in order to remain available in STM.

In a later study, Peterson, Peterson and Miller (1961) examined the influence of meaningfulness of list items on memory. 16 nonsense words, 16 low association words, and 16 common words with known meaningfulness values (defined in terms of usage frequency) were selected as memory items. Subjects were presented with 48 words that they spelled aloud, each followed by a three digit number from which they were asked to count backward by either threes or fours as distraction. After each distraction period, subjects were asked to recall the word they had just seen. The experimenters found that as meaningfulness of words increased, so too did memory performance. One explanation of this finding the authors provided is that greater associations between meaningful words and other items in memory facilitated recall. Therefore, in order to maximize encoding and facilitate subsequent memory we chose to use lists of semantically related words of varying frequency instead of meaningless stimuli in our experiment.

Luria (1971) examined memory functioning in multiple groups of lesion patients using the Brown-Peterson paradigm in order to determine how forgetting occurs. The two theories that he examined explain forgetting either in terms of spontaneous decay of memory traces (i.e. a storage deficit), or as a result of interference by later items (i.e. retrieval failure). Luria asked patients to recall a list of three words after a delay period that was either free from interference or that included presentation of a second list of words as a distractor. He found that a majority of lesion patients were able to recall the list under the free interval condition but not the interference condition. He concluded that the observed memory disturbances were caused by inhibition of memory traces by

interference activity and not spontaneous trace decay. This means that forgetting in this case most likely occurred at the retrieval stage.

As debates took place over whether decay or interference was to blame for the process of forgetting in human memory, Murdock (1974) published a mathematical model that not only supported Atkinson and Shiffrin's multistore model of human memory, but that also considered the relative impact of both decay and interference in forgetting. Murdock stated that interference is an active process by which memory items inhibit one another both proactively and retroactively. In contrast, decay is a passive process in which the passage of time alone is enough to cause forgetting. In an attempt to reconcile these two opposing theories, Murdock suggested that both likely take place, albeit disproportionately, with interference accounting for 85-98% of the variance and decay making up the remainder. He further stated that interference is critically important to list learning experiments and the study of LTM.

Interest in the debate between interference and decay continues as new experiments attempt to address this familiar question. Lewandowsky, Geiger, and Oberauer (2008) conducted a series of experiments using a modified Brown-Peterson task in which subjects studied a list of five consonants in order, followed by a recall period mixed with an interference task. Subjects either received no interference, or were presented with one or three distracting words to be read aloud after each recall prompt. These distractors were changed after each recall prompt or held the same throughout. The experimenters found that when repeating the same word, extending the duration of interference did not cause increased forgetting. However, when subjects repeated different words after each recall prompt, increasing the period of interference led to

greater forgetting. They concluded that the passage of time alone was not sufficient to cause forgetting under these conditions. This recent work lent additional support to the interference theory of forgetting and cast further doubt on the theory of decay.

In another recent investigation into the role of decay in forgetting, Berman, Jonides and Lewis (2009) presented subjects with four target words for several seconds followed by a probe word. Subjects were asked to decide whether or not this word was part of the set of four just seen. Probes that were not one of the current trial's target words were either novel words that had not appeared recently, or were words that were presented recently as targets during the previous trial. In this paradigm, participants are typically 50-100 ms slower to respond to a recent "no" (RN) probe than to a non-recent "no" (NRN) probe, which is known as the recent-probes effect. The authors hypothesized that increasing the time between trials would reduce the recent-probes effect if decay is occurring. By varying the inter-trial interval (ITI) between 1 and 13 seconds, the experimenters were able to show that longer ITIs did not affect the recent-probes effect as RN and NRN response times were unaffected, even after accounting for covert rehearsal and refreshing processes. From these findings, Berman, Jonides and Lewis concluded that time-based decay had little effect on short-term memory. The results of this experiment further supported the interference model of forgetting.

Clinical Studies Using Brown-Peterson Paradigms to Investigate Memory Functions and Supporting Neural Structures

Modern research has also found clinical applications for the Brown-Peterson paradigm in many patient populations, perhaps most commonly among those with epilepsy. Giovagnoli, Casazza, Ciceri, Avanzini, & Broggi (2007) used a Memory

Distractor Test (MDT) based on the Brown-Peterson paradigm to evaluate control of interference effects in recall. Recall of 30 two-syllable words was assessed immediately after presentation, or after a distraction period of 5-60 seconds during which subjects were asked to count backwards by threes. They found that patients with left temporal lobe epilepsies showed significantly impaired preoperative MDT performance compared to controls. Studies such as these demonstrate the modern applications and clinical relevance of the Brown-Peterson paradigm.

Stopford, Snowden, Thompson and Neary (2007) have also used a Brown-Peterson paradigm in a clinical setting as part of an experiment focused on memory impairment in Alzheimer's disease (AD). As part of this study, AD patients and controls completed a simplified Brown-Peterson task in which they studied a list of three semantically unrelated words followed by a distraction period and finally a recall period. Distraction conditions consisted of either a short or long delay (5 vs. 10 seconds) that was either filled by reading a series of digits as distraction, or unfilled. Additionally, a control condition was tested in which there was no distraction or delay before recall. The experimenters found that AD patients performed significantly poorer than controls after distraction and/or a delay period. The authors went on to conclude that impaired Brown-Peterson task performance was just one component of the heterogeneous cognitive profile of AD.

Brown-Peterson paradigms have been used both in healthy controls and patient populations in order to investigate human learning and memory. These cognitive tasks have given researchers a better understanding of how forgetting occurs as well as how memory can be impaired among patient groups. Further investigations which have

employed Brown-Peterson paradigms have also made use of neuroimaging techniques to better understand the neural correlates of human memory.

Factors Involved in Designing Imaging Paradigms to Assess Memory Functioning

When considering experiments that employ fMRI, there is an important distinction to be made between experimental designs, specifically block designs and event-related (ER) designs. In a block design, experimenters analyze the neuroimaging data in separate temporal blocks, which are compared for differences in regional activation. Each block contains multiple similar events that are presented in rapid succession. In an event-related design, stimuli are analyzed as discrete events, often separated by many seconds, and then different groups of events are compared. Wagner and colleagues (1998) compared block and event-related designs to better understand the differences between them in a semantic categorization task. The authors asked subjects to categorize words as being either abstract or concrete (semantic categorization condition) or by what case the word was printed in (non-semantic categorization/control condition). After categorization, subjects were asked to recognize words that were previously presented as stimuli. Behavioral results indicated that subjects showed greater subsequent memory for words presented in the semantic categorization condition than for those seen in the control condition.

In the block design, experimenters compared activation obtained during the semantic categorization condition with that from the non-semantic categorization condition. They found that activation during encoding in left prefrontal cortex, hippocampus, and fusiform gyrus was significantly greater for words in the semantic categorization block than for those in the control block (Wagner et al., 1998). In

conjunction with the behavioral results obtained, the authors claimed that the structures reported above influenced verbal encoding. However, no specific conclusions could yet be drawn about encoding differences that would predict subsequent memory.

In order to compare trials that lead to subsequent memory with those that were not remembered, Wagner and colleagues (1998) turned to an event-related design. This was accomplished by comparing activation during encoding in response to words that were later remembered with activation for those that were not. The authors found that activation in left prefrontal, parahippocampal, and fusiform areas was significantly greater in response to subsequently remembered words, regardless of whether they were seen in the semantic or the non-semantic condition. ER analysis allowed the experimenters to conclude that the aforementioned activation during encoding was predictive of subsequent memory. As the focus of this experiment was also to identify activation during encoding that would predict subsequent memory, we employed a similar paradigm as described in the method section. The major point of difference between our experiment and that of Wagner and colleagues is our choice to employ a semantic list learning task rather than one requiring semantic categorization. Further, ER design can be optimized using a jittered presentation style which can increase the signal to noise ratio in the fMRI data obtained (Dale, 1999).

Previous neuroimaging experiments that have focused on list learning have implicated the medial temporal lobe in the encoding process (Fernandez et al., 1998; Starkman, Giordani, Gebarski, & Schteingart, 2003; Strange, Otten, Josephs, Rugg, & Dolan, 2002), consistent with lesion work in animals and humans (Broadbent, Clark, Zola, & Squire, 2002). Others have observed activation during encoding in frontal

regions and Wernicke's area but not hippocampus or parahippocampus (Dupont et al., 2002). Starkman and colleagues (2003) found that among Cushing's disease patients, increases in verbal list learning task performance (following pituitary microadenoma resection) correlated positively with increases in hippocampal formation volume.

Previous studies which examined event-related potentials (ERP) in electroencephalography (EEG) have shown greater activation in response to words which were subsequently recalled than to those that were not (Rugg, 1995). However, it is difficult to identify the source of such activity with ERP data alone. Fernandez and colleagues (1998) had 13 subjects read 20 lists of 15 semantically related words while inside the scanner. In between list presentations, subjects were required to make a same/different judgment on an unrelated stimulus, and then were given 45 seconds during which to freely recall the list they had just viewed. Fernandez and colleagues were interested in identifying the structures involved in the encoding process using fMRI. Eleven of the 13 participants showed a significant correlation between the number of recalled words and activation in posterior hippocampus during the encoding block. Therefore, it was concluded that this activation represented the encoding process on which semantic list learning depends.

In a more recent experiment, Strange and colleagues (2002) asked 14 healthy normal subjects to rote memorize 30 lists of 12 words that were presented individually inside the scanner. After each list was presented, subjects completed a 30 second distraction task during which they counted aloud backwards by threes from a given random number between 81 and 99. Subjects were then given 90 seconds during which to freely recall words from the list they had just seen. Using an event-related analysis, the

researchers found that activation during encoding in MTL structures including right anterior hippocampus and bilateral parahippocampus predicted subsequent memory for early list items. They also found that left perirhinal cortex and left hippocampus activation during encoding predicted subsequent memory for all other list items. The authors concluded that these structures were critical for verbal encoding processes in human memory.

Current Design and Hypotheses

In the current experiment, we chose to employ a Brown-Peterson paradigm during fMRI in order to study the pattern of neural activation associated with encoding during a semantic list learning task. Based on what is known about list learning task performance, we hypothesized that subjects would show a significant effect of serial position on memory performance in recall and recognition. As a result of our Brown-Peterson manipulation, we expected a significant primacy effect for recall and recognition in the absence of an effect of recency (Brown, 1958; Peterson & Peterson, 1959). Furthermore, we used semantically organized lists, with semantic cues for recall to diminish the influence of STM and WM on memory performance. Because of what is known about the function of Papez circuit structures, we predicted that we would observe significant activation of medial temporal structures, including the hippocampus during encoding in response to words that were later recalled and recognized (Fernandez et al., 1998; Strange et al., 2002). We employed an event-related analysis of the neuroimaging data in order to specifically investigate activation during encoding in response to subsequently remembered words.

Method

Participants

Twenty-nine healthy adult subjects (14 males, 15 females) completed a semantic list learning task during fMRI. Three subjects (two males, one female) were excluded from analyses as outliers because of excessive false positives during recall (FP > 40). The remaining 26 subjects had a mean age of 37.46 years (*SD* = 3.54) and a mean education of 15.54 years (*SD* = 0.48, see Table 1). Subjects were recruited through use of the University of Michigan Engage website and through advertisements in the community. Participants gave their informed consent prior to participation in the study and were paid $15-30/hour of participation.

Procedure

Participants were first verbally introduced to the task by the experimenter prior to entering the scanner. Participants were told they would observe lists of categorically related words presented one at a time, and that they should silently read and remember these words to the best of their ability. They were informed that a different task would then appear for which they had to make a button-press response each time they saw the letters “x,” “y,” or “z” presented in a visual stream. This task was the “Go” portion of the “Go/No-go” paradigm previously reported (Langenecker, Bieliauskas, Rapport, Zubieta, Wilde, & Berent, 2005). Lastly, they were told that a silent recall phase would occur during which they would be asked to rehearse the words that appeared just prior to the distraction phase without vocalization or movement of the lips. Subjects were trained prior to scanning on the interference Go task by completing the Go/No-go task on a PC in order to familiarize them with the paradigm.

After scanning, subjects were asked to first complete a cued recall task in which they wrote down all the words which they could remember for each of the semantic categories presented. Subjects then completed a recognition task in which they had to identify words seen inside the scanner from a list of correct words amongst category-related and unrelated distractors. Correctly recalled words and those that were not recalled were used as regressors in an event-related analysis of the fMRI data. Correctly recognized words and those that were not recognized were used in the same manner.

Semantic List Learning Task (SLLT)

This task, designed to test learning and memory, was composed of three parts that were presented during fMRI scanning (see Figure 2). Subjects were presented with 14 words from one of 15 semantic categories during each encoding block. First a prompt with the name of the semantic category being studied was displayed for 3.5 seconds. Words were then presented for an average of 3.5 seconds each with a one to four second jitter range in which a fixation cross was presented. The total time for this encoding block was 58.25 seconds. Subjects then completed an interference task that consisted of the "Go" portion of the Go/No-go Task (Langenecker et al., 2005). For this task subjects were asked to respond to the letters "x," "y," and "z" when presented during a random letter stream (500ms each, 14 seconds total). This was intended to reduce the effect of recency during recall/recognition by preventing rehearsal (Brown, 1958; Peterson & Peterson, 1959). The final portion of the task consisted of a silent recall period that lasted for 14 seconds. Here, the participants saw the category prompt and were asked to remember words that were just presented during the previous encoding phase.

MRI protocol

The task was presented inside the scanner using E-Prime software through goggles attached to the head coil and corrective lenses when necessary. Subjects laid supine, and their responses were recorded using a five button key-press apparatus attached to the right hand. Earplugs were worn by participants inside the scanner to reduce the noise experienced from 95 dB to below 75 dB. Head motion inside the scanner was limited by foam padding and a Velcro fixation strap. A GE Sigma 3 T scanner (release VH3) was used to conduct whole brain scanning. 30 contiguous oblique-axial sections, each four millimeters thick, made up the fMRI series and were acquired using a forward spiral sequence. The image matrix was 64 x 64 over a 24 cm field of view for a 3.75 x 3.75 x 4 mm voxel. The 30-slice volume was acquired serially at 1750 ms temporal resolution for a total of 770 time points in five blocks. High- and low-resolution T-1 weighted anatomical images were obtained prior to task administration (Langenecker et al., 2009).

Statistical Analyses

Behavioral data including total hits, false positives and percent primacy, middle, and recency for both recall and recognition were entered into SPSS v. 16 for statistical analysis. There is a large age range of participants which could affect the activation results. Investigation of the effects of ageing on memory was outside the purview of this thesis. Functional imaging data were processed and analyzed using MATLAB and SPM2 software (Friston, Ashburner, Frith, Poline, Heather, & Frackowiak, 1995). Contrast images were derived from behavioral data. Functional images were normalized to fit a MNI canonical template and were smoothed at a threshold of 5 mm. False discovery rate

(FDR) correction was conducted during analysis of images at the group level, at a corrected significance level of .05, and cluster minimum of 80 mm^3. The Marsbar program was used to extract mean signal change in regions of interest for correlation with recall accuracy, false positives, and percent recall in primacy, middle and recency positions (Langenecker et al., 2009). Age was entered as a covariate in secondary analyses as it was found to have a significant positive correlation with false positives, r = .44, p = .02.

Results

Behavioral results

Participants correctly recalled an average of 81.96 words (39% accuracy, *SD* = 21.11) with 6.85 false positives (*SD* = 6.34) and correctly recognized an average of 126.23 words (60% accuracy, *SD* = 23.67) with 15.54 false positives (*SD* = 11.18). A 2*2 repeated measures ANOVA was conducted with percent recall and recognition (memory modality) as levels of within subject memory retention variable and hits and false positives (memory type) in each level of memory retention. There was a significant effect of memory modality, such that accuracy in recognition was greater than in recall, $F(1,24) = 324.3$, $p < .001$. A significant effect of memory type was also observed, with more correct hits than false positives, $F(1,24) = 190.7$, $p < .001$. Finally, there was also a significant interaction of memory modality by memory type such that the ratio of hits to false positives in recall was higher than the ratio of hits to false positives in recognition, $F(1,24) = 191.8$, $p < .001$.

Serial Position Curve for Recall and Recognition

During recall, participants averaged 43% accuracy for words in the primacy position and 38% accuracy for words in the middle and recency positions. Accuracy during recognition averaged 65% in primacy, 61% in middle, and 57% in recency. The serial position effect was also assessed with a rmANOVA. This was a 2 (recall vs. recognition modality) *3 (primacy, middle, recency positions) rmANOVA and false positives were entered as a covariate. A significant primacy effect was observed such that recall and recognition were significantly higher for words presented during the first 1/3 of each category list (see Figure 3), $F(2,48) = 14.690$, $p < .001$. Post-hoc paired samples *t*-tests showed that in recall, memory performance during the primacy period was significantly greater than during the middle, $t(25) = 5.91$, $p < .01$, and recency periods, $t(25) = 5.38$, $p < .01$. Recall during middle and recency periods was not significantly different, $t(25) = -.53$, $p = .75$. The effect of memory modality was also significant such that accuracy in recognition was greater than in recall, $F(1,24) = 114.334$, $p < .001$. However, no significant interaction between serial position and memory modality was observed, $F(2,48) = 2.277$, $p = .124$.

The serial position effect within the modified Brown-Peterson paradigm (removal of recency effect) is illustrated in Figure 3. Thus, memory recall and recognition were likely driven by LTM encoding strategies, which are known to be more dependent upon medial temporal structures (Fernandez et al., 1998; Strange et al., 2002). As our Brown-Peterson manipulation was successful in interfering with the recency effect, we suspected that the influence of STM on SLLT performance was minimized. Therefore, we included data obtained in response to words that came from all portions of each list in our analysis.

Specific analysis of recency vs. primacy effects was beyond the scope of the current investigation.

Imaging results

Recalled

During encoding of successfully recalled words, significant activation was observed bilaterally in cingulate cortex and insula, in right superior temporal cortex, globus pallidus, amygdala, paracentral lobule, and cerebellum, as well as in left hippocampus, parahippocampal gyrus, and lingual gyrus (see Table 2 and Figure 4).

Post-hoc Extraction

During secondary analysis, relationships between behavioral and neuroimaging data were explored. Correlations of mean signal change in the regions of interest (ROIs) identified above were computed for recall accuracy, number of false positives, and percent recall from primacy, middle and recency positions. As age was found to significantly correlate with false positives, it was entered as a covariate. Significant positive partial correlations were obtained between number of false positives and activation in bilateral cingulate, left lingual gyrus, and right globus pallidus (see Table 2). None of the correlations of recall accuracy or percent recall in primacy, middle or recency reached statistical significance, all rs < |.56|, ps > .09. The event-related design may not have been optimized for this process.

Not Recalled

Significant activation was observed during the encoding phase in response to words that were not successfully recalled in bilateral parahippocampal gyrus and insula,

as well as right inferior frontal gyrus, superior temporal gyrus, caudate, amygdala, left lingual gyrus and hippocampus (see Table 3).

Recalled – Not Recalled

No suprathreshold voxels were obtained in whole brain analyses. ROI analysis of the hippocampus revealed significant activation in left hippocampus and parahippocampal gyrus in recalled minus not recalled contrast (see Table 4 and Figure 5). These clusters survived small volume correction using a 5 mm radius. Once again, relationships between behavioral and neuroimaging data were explored during secondary analysis. Correlations of mean signal change in the hippocampal ROIs identified above were computed for recall accuracy, number of recall false positives, and percent recall from primacy, middle and recency positions, with age as a covariate (see Table 4). No significant correlations were obtained, all rs < | .40 |, ps > .24.

Recognized

Encoding of successfully recognized words yielded significant activations in bilateral parahippocampal cortex, insula and amygdala, as well as right superior temporal gyrus, caudate, and inferior frontal cortex similar to the pattern observed in the Recall analysis (see Table 5 and Figure 4).

Not Recognized

Significant activation was observed during encoding in right amygdala and left parahippocampal cortex in response to words which were not later recognized (see Table 6).

Recognized – Not Recognized

No suprathreshold voxels were obtained in whole brain analyses. There were also no significant activations in bilateral hippocampus ROIs using this subtraction.

Discussion

The aim of the current experiment was to study activation patterns during encoding that relate to subsequent memory through the use of a Semantic List Learning Task. Neuroimaging data was collected using fMRI in an event-related design with healthy participants. We hypothesized that our Brown-Peterson manipulation would lead to a significant primacy effect, but not an effect of recency, on the serial position curve for memory performance in recall and recognition. Furthermore, we predicted that we would observe significant activation of Papez circuit structures, including the hippocampus, during encoding in response to words that were later recalled and recognized. To diminish the role of executive functioning and STM, a Brown-Peterson paradigm was used with semantically related words, explicit recall instructions, and semantic recall cues. Investigating the function of these structures in healthy subjects is essential for understanding how they are compromised in mental disorders.

Behavioral results indicated that healthy subjects performed with greater accuracy in the recognition task than in the recall task. This result was not surprising, as recognition tasks frequently yield better performance than recall tests for the same stimuli (Kintsch, 1970). In addition we observed a higher ratio of hits to false positives in recall than in recognition which may have been a result of greater responding during recognition in general.

The significant primacy effect that was observed is in line with a wealth of research on serial position effects (Atkinson & Shiffrin, 1968; Glanzer & Cunitz, 1966; Rundus, 1971; Talmi et al., 2005). This facilitation of memory for early list items was caused by greater encoding of early items into LTM, an effect observable in fMRI (Fernandez et al., 1998; Strange et al., 2002; Talmi et al., 2005). This may have been a result of less competition for rehearsal early in the task (Atkinson & Shiffrin, 1968). The absence of a significant effect of recency was expected as a result of our Brown-Peterson manipulation (Brown, 1958; Peterson & Peterson, 1959). Taken together, these results indicated that we were successful in preventing facilitation of recent memory items by STM. This effect may have been caused by decay via prevention of rehearsal (Brown, 1958; Peterson & Peterson, 1959), and/or by interference from items in the distracting task (Berman, Jonides & Lewis, 2009; Luria, 1971; Lewandowsky, Geiger, & Oberauer, 2008).

Significant activation of the Papez circuit, including MTL structures, was observed during encoding of subsequently recalled and recognized words. This included left hippocampus and left parahippocampal gyrus during recall, which have been previously implicated in verbal encoding processes (Fernandez et al., 1998; Strange et al., 2002; Talmi et al., 2005). Therefore, we concluded that the activation observed in MTL during semantic list learning reflected encoding of verbal material into LTM. Significant activation was also observed in bilateral posterior cingulate cortex during recall, which has also been implicated in encoding (McDermott et al., 1999). Taken together, these results indicated that Papez circuit structures were important for encoding of subsequently remembered words, thus playing a vital role in human memory function.

In contrast to our findings, another fMRI experiment which focused on list learning observed activation bilaterally in ventrolateral frontal cortex during encoding, but failed to find encoding activation in hippocampus or parahippocampus (Dupont et al., 2002). However, these researchers did not make use of an interference task in their paradigm. Thus, the frontal activation observed may have reflected the influence of STM, which we attempted to minimize using a Brown-Peterson manipulation. In addition, Staresina and Davachi (2006), who had participants encoding words during an association-imagery test, found that left dorsolateral prefrontal cortex (DLPFC) activation predicted subsequent memory during free recall. This was also in contrast with the results we obtained. While the researchers did make use of an interference task in their paradigm, the association-imagery test used during encoding relied heavily on working memory and the DLPFC activation observed may have reflected this fact.

Comparison of activation data for words that were subsequently remembered with data for words that were not remembered suggested that there was relatively more activation during encoding in response to words that would be remembered later. However, direct comparison of subsequent memory via subtraction of activation for not recalled words from activation for recalled words did not yield any significant areas of activation, as was the case for recognition. Therefore, post-hoc ROI analysis of the hippocampus was conducted for both contrasts. This yielded significant areas of activation in left hippocampus and left parahippocampal gyrus in the comparison of activation for recalled and not recalled words, but not in the comparison based upon recognition success. We concluded that greater activation during encoding of left hippocampus and left parahippocampal gyrus predicted better subsequent memory.

Secondary analyses explored the relationship between functional neuroimaging data and behavioral data of interest. No significant correlations between measures of recall accuracy and activation in ROIs were obtained. This was likely an effect of the event-related design that was employed, as we had already accounted for recall and recognition accuracy in our analysis model of the neuroimaging data. Significant correlations were observed between the number of false positives in recall and activation during encoding in bilateral posterior cingulate cortex as well as right lateral globus pallidus and left lingual gyrus. Activation of the lingual gyrus has been reported during tasks that involve reading and categorizing verbal stimuli (Vitacco, Brandeis, Pascual-Marqui, & Martin, 2002), thus it is likely that this area played a role in the verbal encoding process. Posterior cingulate activity is related to semantic stores of information and also to encoding (McDermott et al., 1999). The globus pallidus has been previously implicated in the filtering of irrelevant information (McNab & Klingberg, 2002). Together, these two regions may have played a role in filtering and organizing information during encoding, which we observed as counterproductive recruitment of these areas, leading to later false positives during retrieval. On the other hand, this activity may in fact have been non-task related and actually detracted from subjects' focus on memory.

Study of the neural circuitry engaged by healthy participants during this task is essential to better identify anatomical and functional circuits that are compromised in mental illness and other brain diseases. In addition to investigating task performance in patient populations, future studies could manipulate the presence or absence of the Brown-Peterson paradigm, which we would expect to exert an effect on the serial

position curve. This may yield a greater understanding of the structures involved in both short and long-term memory and how they are important to semantic list learning tasks.

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Table 1

Participant Demographic Information

Group				Age		Education	
	N	Females	Males	*M*	*SD*	*M*	*SD*
Healthy Adult	26	14	12	37.46	3.54	15.54	0.48

Table 2

Neuroimaging Foci for Later Correctly Recalled Words (ER)

x	y	z	Lobe	Foci	BA	Z Value	Cluster Size (mm^3)	False Positives Rho
-15	-21	43	Frontal	Cingulate	31	4.89	3352	.71*
15	-21	43			31	4.08	232	.63*
20	-36	44			31	4.02	136	.72*
8	-27	53		Paracentral Lobule	6	4.97	208	.27
10	-40	58			5	4.4	280	-.10
-17	-48	-1	Occipital	Lingual	19	4.42	464	.66*
40	-58	-19	Cerebellum			4.76	88	.60
6	1	12	Sub-Cortical	Caudate		4.08	112	.21
20	-15	2		Globus Pallidus		4.08	144	.83**
-31	8	-12	Temporal	Insula	13	4.32	1536	.52
-25	-11	-20		Hippocampus		4.03	112	.30
26	-5	-15		Insula / Amygdala		5.55	2416	.38
41	3	-18		Sup. Temporal	38	4.11	208	.29

Note. * Correlation is significant at the .05 level (2-tailed).

** Correlation is significant at the .01 level (2-tailed).

Table 3

Neuroimaging Foci for Later Not Recalled Words (ER)

x	y	z	Lobe	Foci	BA	Z Value	Cluster Size (mm^3)
36	32	-9	Frontal	Inf. Frontal	47	4.34	96
-17	-48	-1	Occipital	Lingual	19	4.67	248
6	-1	12	Sub-Cortical	Caudate		4.53	168
-27	-34	-13	Temporal	Parahippocampal	36	4.38	200
26	-34	-14			36	3.88	96
26	-5	-16		Insula / Amygdala		5.21	1360
-32	-9	-13		Insula / Hippocampus		4.83	1120
45	-5	-8		Sup. Temporal	21	4.92	344
41	3	-16			38	4.28	144

Table 4

Neuroimaging Foci for Later Recalled Words – Later Not Recalled Words (ER), Hippocampus ROI

x	y	z	Lobe	Foci	BA	Z Value	Cluster Size (mm^3)	False Positives Rho
-24	-11	-20	Temporal	Hippocampus		2.98	432	-.14
-22	-42	-6		Parahippocampal	36	2.83	320	.32
-22	-25	-14			35	2.15	344	.4

Note. * Correlation is significant at the .05 level (2-tailed).

** Correlation is significant at the .01 level (2-tailed).

Table 5

Neuroimaging Foci for Later Correctly Recognized Words (ER)

x	y	z	Lobe	Foci	BA	Z Value	Cluster Size (mm^3)
36	34	-9	Frontal	Inf. Frontal	47	4.55	128
6	4	9	Sub-Cortical	Caudate		4.13	96
-29	-30	-12	Temporal	Parahippocampal	36	4.37	192
24	-29	-16			35	4.06	496
26	-5	-15		Amygdala / Insula		5.29	992
-27	-5	-11				4.55	1400
45	-5	-8		Sup. Temporal	21	4.42	128

Table 6

Neuroimaging Foci for Later Not Recognized Words (ER)

x	y	z	Lobe	Foci	BA	Z Value	Cluster Size (mm^3)
26	-5	-16	Temporal	Amygdala		4.86	352
-29	-32	-14		Parahippocampal	36	4.59	136
-24	4	-18			34	4.43	208

Figure Captions

Figure 1: Diagram of the Papez Circuit[1]; [1]From "Memory and the brain," by Canadian Institutes of Health Research, September 2002, In *The brain from top to bottom* (How memory works; Neurological; Advanced). Retrieved March 26, 2009, from http://thebrain.mcgill.ca/flash/a/a_07/a_07_cr/a_07_cr_tra/a_07_cr_tra.html. Reprinted with permission of the author.

Figure 2: Semantic List Learning Task[2]; [2]From "Disrupted Verbal Encoding in Cushing's Disease Explored Using Functional MRI," by S. A. Langenecker, L. M. Guidotti, E. M. Anderson, S. L. Wright, B. Giordani, D. E. Schteingart et al., 2006, *Biological Psychiatry*, *59*, p. 715. Reprinted with the permission of the author.

Figure 3: Serial Position Curve for Memory Performance in Recall and Recognition.

Figure 4: Encoding Activation for Correctly Recalled Words (ER) and Correctly Recognized Words (ER); Recalled = Red, Recognized = Blue; Imaging figures shown in radiological format, Right = Left.

Figure 5: Hippocampus ROI Analysis, Encoding Activation for Recalled Words – Not Recalled Words (ER); Imaging figures shown in radiological format, Right = Left.

Figure 1

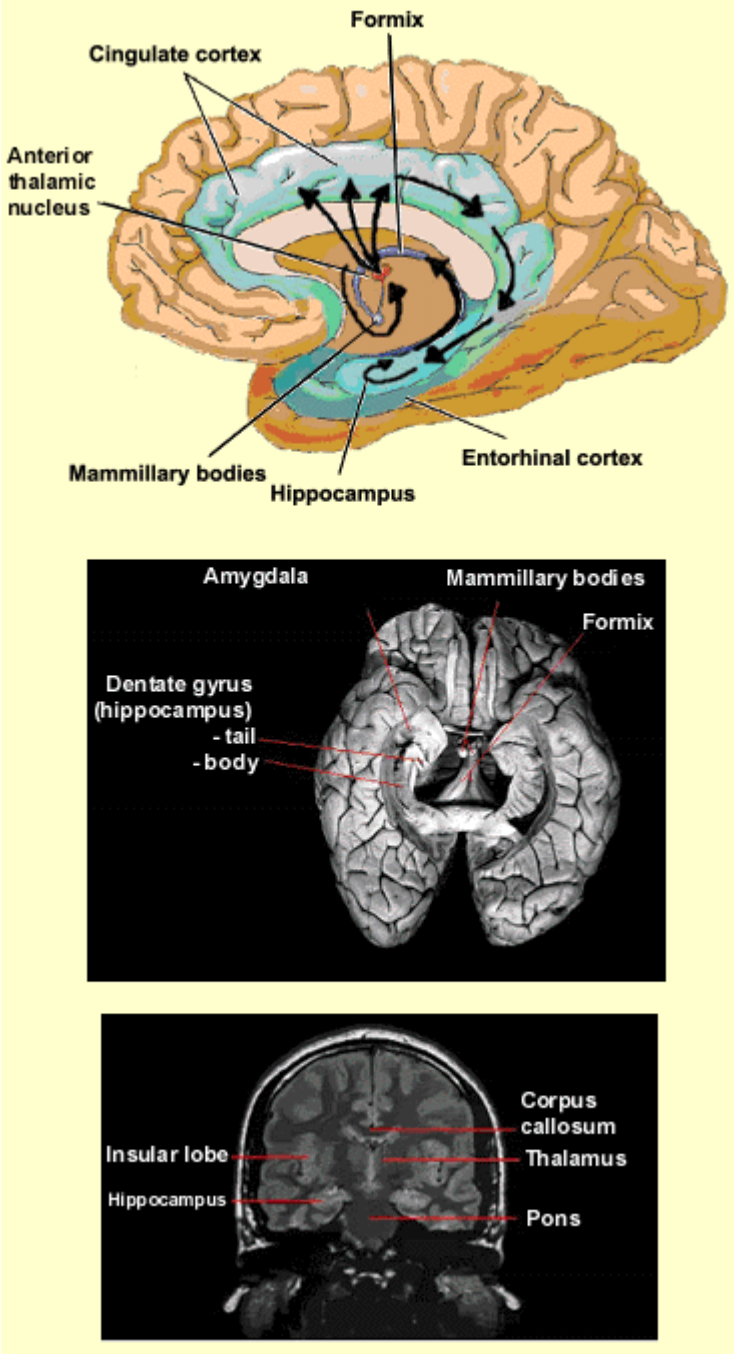
Formix
Cingulate cortex
Anterior thalamic nucleus
Mammillary bodies
Hippocampus
Entorhinal cortex
Amygdala
Mammillary bodies
Formix
Dentate gyrus (hippocampus)
- tail
- body
Corpus callosum
Insular lobe
Thalamus
Hippocampus
Pons

Figure 2

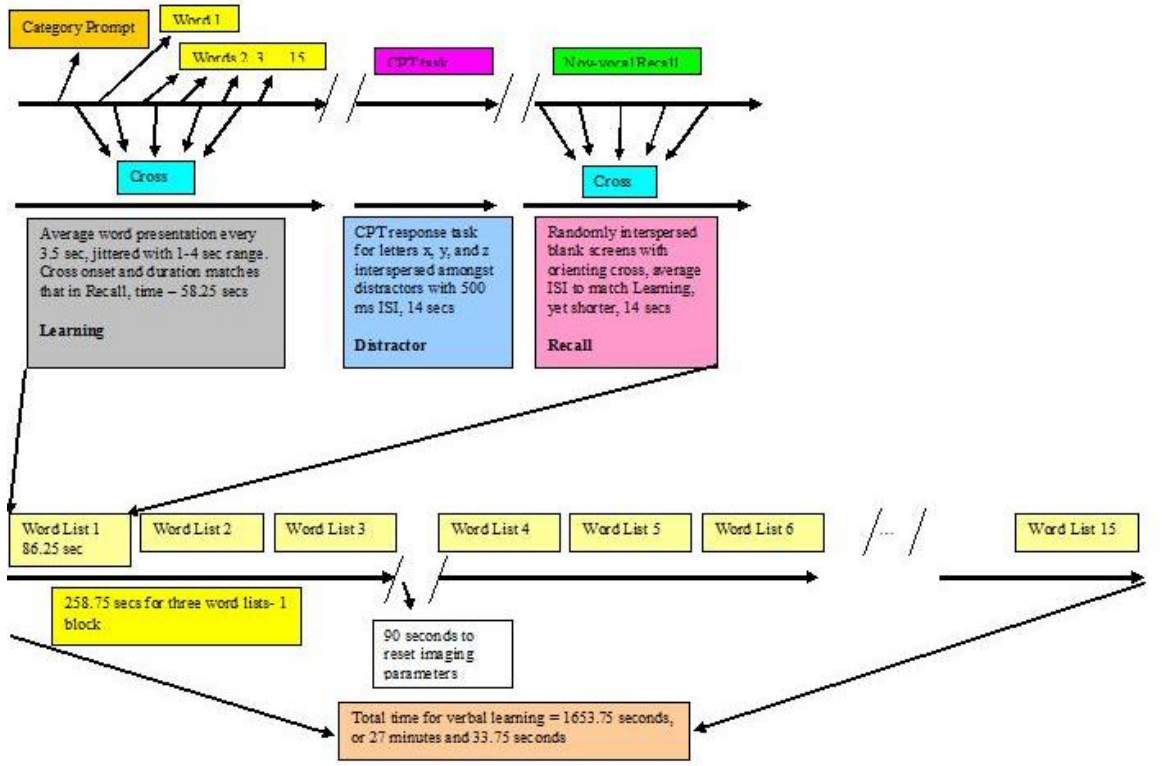
Category Prompt
Word 1
Words 2, 3 ... 15
CPT task
Non-vocal Recall
Cross
Cross
Average word presentation every 3.5 sec, jittered with 1-4 sec range. Cross onset and duration matches that in Recall, time – 58.25 secs
Learning
CPT response task for letters x, y, and z interspersed amongst distractors with 500 ms ISI, 14 secs
Distractor
Randomly interspersed blank screens with orienting cross, average ISI to match Learning, yet shorter, 14 secs
Recall
Word List 1 86.25 sec
Word List 2
Word List 3
Word List 4
Word List 5
Word List 6
...
Word List 15
258.75 secs for three word lists- 1 block
90 seconds to reset imaging parameters
Total time for verbal learning = 1653.75 seconds, or 27 minutes and 33.75 seconds

Figure 3

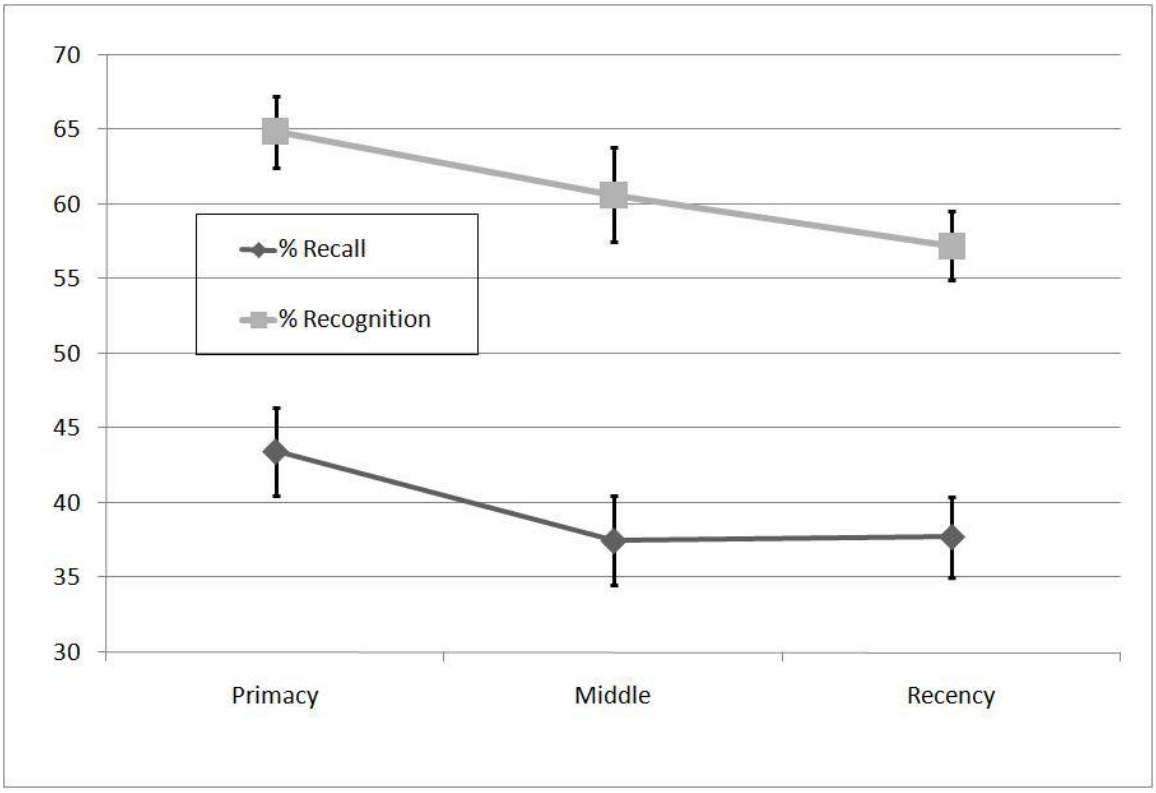
70
65
60
55
50
45
40
35
30
% Recall
% Recognition
Primacy
Middle
Recency

Figure 4

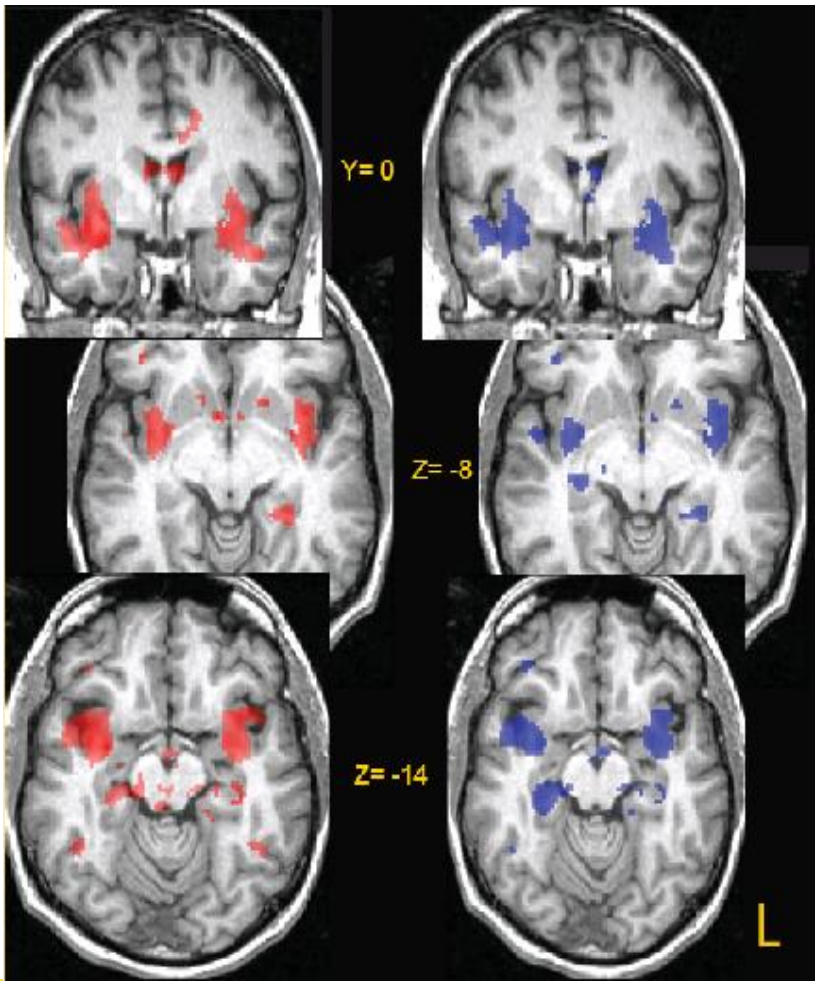

Figure 5