

**Activation of the Hippocampus During Emotional Learning**

A Thesis

Submitted to the Faculty

of

Drexel University

by

Matthew John Bellace

in partial fulfillment of the

requirements for the degree

of

Doctor of Philosophy

June 2005

## Dedications

I would like to dedicate my dissertation to everyone that has shown me love and support during this long process.

To my parents, Louise and Joseph Bellace, who supported me emotionally and at times financially during the past six years. I thank you for never insisting that I get a real job!

To my brother, Mike Bellace, thanks for your friendship and support.

To my grandmother, Rose Bellace, the true motivational speaker in the family, thank you for always being a positive influence.

To my mother and father-in-law, Carole and Richard Lucks, thank you for raising such a loving daughter and for your continued support.

To my closest cousins, John Bellace and Joe Matarese, and best friends, Doug Bratton, Billy Vogt and Paul Brown, thank you all for the laughs and being a healthy distraction.

Finally, to my wife, Dara. From our boring stats class at MCP Hahnemann to the final days of the dissertation process, you were always there for me. You helped give me perspective when I got carried away, picked me up off the floor when I wanted to quit and smiled with me when we realized we would make it. Thank you for never giving up.

## Acknowledgements

I would like to acknowledge the members of my dissertation committee, Drs. J. Michael Williams, Michael Lowe, Doug Chute, Mary Best and Gunner Furgueson. Your time and support are truly appreciated.

In addition, I wish to thank Dr. Feroze Mohamed for letting us use the fMRI scanner and teaching us how not to blow it up.

A special thanks to my mentor, Dr. Mike Williams, who saw something special in me back in 1999, but selected me for the Ph.D. program anyway. Without Dr. Williams, I would be just another guy reciting Seinfeld quotes. Dr. Williams was always there for me throughout this process, whether it was responding to questions over e-mail on a Saturday afternoon or just having long chats in your office; you were always there when it mattered most.

I would also like to thank Dr. Owen Floody at the Department of Psychology at Bucknell University. Your passion for teaching, whether it was physiological psychology, neuropsychology or research, was my inspiration to pursue neuropsychology. Thank you for the continued encouragement throughout my academic career.

## Table of Contents

LIST OF TABLES.....	vii
LIST OF FIGURES.....	viii
ABSTRACT.....	x
1. INTRODUCTION.....	1
1.1 Medial Temporal Lobe and Memory: Early Research.....	2
1.2 Hippocampal Involvement in Memory.....	3
1.3 Animal Model for Amnesia.....	5
1.4 Declarative and Nondeclarative Memory Systems.....	7
1.5 The Limbic System: Mediator of Emotion and Memory.....	8
1.5.1. Hippocampus.....	9
1.5.2. Amygdala.....	11
1.5.3. Interactions Between the Amygdala and Hippocampus.....	12
1.6 Localization of Visual and Verbal Memory Encoding.....	14
1.6.1. Encoding of visual information.....	14
1.6.2. Encoding of verbal information.....	17
1.7 Localization of Visual and Verbal Emotional Memory Encoding.....	20
1.7.1. Visual emotional encoding.....	20
1.7.2. Verbal emotional encoding.....	24
1.8 Hippocampal Activation and WADA Testing.....	26

1.9 Aims of the Current Study.....	29
1.10 Hypotheses.....	30
2. METHODS.....	32
2.1 Participants.....	32
2.2 Inclusion/Exclusion Criteria.....	32
2.3 Apparatus.....	33
2.4 Procedure.....	33
2.4.1. Stimuli Characteristics.....	33
2.4.2. fMRI Procedure.....	33
2.4.3. fMRI Paradigm.....	34
2.4.4. General Activation Design.....	35
2.5 Analysis of fMRI Data.....	35
2.5.1. Realignment, Normalization, and Smoothing.....	35
2.5.2. Activation Mapping.....	36
2.5.3. Direct Comparison of Emotional Versus Neutral Stimuli.....	37
3. RESULTS.....	39
3.1 Behavioral Results.....	39
3.2 Stimuli Ratings.....	40
3.3 Group BOLD Responses.....	40
3.4 Gender specific BOLD responses.....	42
4. DISCUSSION.....	43
4.1 Memory Recall.....	43
4.2 Hippocampal Activation During Encoding.....	44

4.3 Additional Areas of Activation During Encoding.....	46
4.4 Implications for an fMRI replacement of IAT.....	48
4.5 Additional Future Directions.....	49
List of References.....	51
Appendix A. Tables.....	60
Appendix B. Figures.....	74
Vita.....	90

## LIST OF TABLES

1. Imaging studies on encoding of visual information.....	60
2. Imaging findings for encoding of verbal information during medial temporal lobe.....	61
3. Imaging findings for encoding of emotional visual information.....	63
4. Imaging findings for encoding of emotional verbal information.....	64
5. Volunteer and normative stimuli ratings in mean valence and arousal with standard deviations in parenthesis.....	65
6. Brain regions where activation was present during the encoding of emotional pictures. Gender analysis examined only the hippocampus. Significance levels and T-scores are provided.....	66
7. Brain regions where activation was present during the encoding of neutral pictures. Significance levels and T-scores are provided.....	67
8. Brain regions where activation was present during the encoding of emotional words. Significance levels and T-scores are provided.....	68
9. Brain regions where activation was present during the encoding of neutral words. Significance levels and T-scores are provided.....	69
10. Brain regions that were activated during a direct comparison between emotional and neutral picture encoding.....	70
11. Brain regions that were activated during a direct comparison between emotional and neutral word encoding.....	71
12. Gender analysis of the hippocampus using ROI, showed regions that were activated during a direct comparison between emotional and neutral picture, as well as emotional and neutral word encoding.....	73

## LIST OF FIGURES

1. Schematic view of some of the medial temporal lobe structures important for declarative memory. S, subicular complex; DG, dentate gyrus; CA1, CA3, the CA fields of the hippocampus. Adapted from Burnwell, et al. 1996.....74
2. Taxonomy of Declarative and Nondeclarative Memory.....75
3. Schematic view of some of the limbic system structures. Adapted from Driesen (2005).....76
4. Direct and indirect cortical afferents of the hippocampus (reprinted from Nieuwenhuys, et al., 1992).....77
5. Subcortical afferents and intrinsic connections of the hippocampus.....78
6. Cortical afferents to the amygdala. Numbers indicate fields of Brodmann.....79
7. An interaction between emotionality and stimulus type for the memory recall data.....80
8. Glass brain images of the ROI analysis on group frontal lobe activation for all four conditions (All images were  $p < .05$ , extent threshold= 5). Neurological coordinates used.....81
9. Glass brain images of the ROI analysis on group temporal lobe activation for all four conditions (All images were  $p < .05$ , extent threshold= 5). Neurological coordinates used.....82
10. Glass brain images of the ROI analysis on group parietal lobe activation for all four conditions (All images were  $p < .05$ , extent threshold= 5). Neurological coordinates used.....83
11. ROI area of activation of the hippocampus during emotional picture encoding based on group analyses. Glass brain images showed marked activation ( $p < .09$ , extent threshold= 5) in the right hemisphere, but it did not reach  $p < .05$  level of significance. There was no significant activation for the other three conditions. Neurological coordinates used.....84
12. Glass brain images of whole brain activation for pictures and words. Images were derived from a direct comparison between emotional and neutral stimuli, where neutral stimuli served as the rest condition. Neurological coordinates used.....85

13. Glass brain images of hippocampal activation with ROI analysis for pictures ( $p < 0.01$ , extent threshold = 10) and words ( $p < 0.001$ , extent threshold = 10). Images were derived from a direct comparison between emotional and neutral stimuli, where neutral stimuli served as the rest condition. Neurological coordinates used. ....86
14. ROI area of activation of the hippocampus during emotional picture encoding based on the gender analysis of females. Glass brain images showed marked activation ( $p < .09$ , extent threshold = 5), although it did not reach the  $p < .05$  level of significance. There was no significant activation for the other three conditions. Neurological coordinates used.....87
15. Glass brain images of the ROI analysis direct comparison of emotional versus neutral words and pictures in females. Significant activation was seen in the hippocampus for pictures,  $p < .01$ , extent threshold = 5, and words  $p < .001$ , extent threshold = 5. There was no significant activation for males. Neurological coordinates used. ....88
16. Glass brain images of the ROI analysis direct comparison of emotional versus neutral words condition in females. Significant activation was seen in the amygdala,  $p < .01$ , extent threshold = 5. There was no significant activation for males. Neurological coordinates used.....89

**ABSTRACT**

Activation of the Hippocampus During Emotional Learning

Matthew Bellace

J. Michael Williams, Ph.D.

The current study examined the role of the hippocampus in emotional memory encoding using functional magnetic resonance imaging (fMRI). Previous studies suggested that the hippocampus plays a role in memory encoding, but consistent hippocampal activation remains elusive. There is intense clinical interest in using fMRI to evaluate memory functioning, especially in pre-surgical patients with intractable seizure disorder. Currently, these patients receive the intracarotid amytal test (IAT) to evaluate which hemisphere is more responsible for memory function. However, the IAT procedure is invasive and lacks reliability and consistency across treatment centers. An fMRI replacement for the IAT might well be a less invasive, more reliable alternative. The present study examined the activation patterns associated with words and pictures with high emotional tone and contrasted them with patterns associated with emotionally neutral stimuli. Twelve healthy participants (N= 12) were scanned while viewing the items and asked to try and remember them. Results revealed significant activation in the temporal and frontal lobes for emotional and neutral stimuli. Analysis of the temporal lobe showed greater activation in the left hippocampus for emotional words and the right hippocampus for emotional pictures compared to neutral stimuli. The increased activation was consistent with our hypothesis that emotional pictures and words would produce greater activation than neutral pictures and words. A gender analysis revealed that females showed significant activation for emotional pictures and words, while males did not.

## 1. INTRODUCTION

Emotional experiences are better remembered than neutral experiences, but the neural mechanisms involved in this contrast are unknown (Cahill and McGaugh, 1998; Cassasanto, Kilgore, Maldjian, et al. 2002). Lesion studies have shown that the hippocampus is integral to the encoding of verbal and visual information (Milner, Squire and Kandel, 1998). Similar to the amygdala, the hippocampus is directly innervated by sensory cortical regions and could be independently involved in the processing of emotional memory. The current study utilized emotional information to increase levels of hippocampal activation.

There are clinical implications for producing consistent hippocampal activation. Epilepsy is one of the most widespread pathologies of the human brain, affecting approximately 1% of the world population. Temporal lobe epilepsy (TLE) with hippocampal sclerosis is probably the most common human epilepsy (Sloviter, 2005). Despite the development of new antiepileptic drugs (AEDs), the number of non-responding patients may be as high as 30% (Trojnar, Wojtal, Trojnar, et al., 2005). Patients with intractable epilepsy are then considered for brain surgery to remove the seizure focus.

Prior to surgery, patients must undergo a procedure called the intracarotid amygdala test (IAT), also known as the WADA test. It is a general measure for localizing language and memory functioning to one hemisphere, yet important because it defines cerebral dominance for language and evaluates memory (Acharya and Dinner, 1997). The procedure involves anesthetizing one hemisphere of the brain, while the patient is given

language and memory tests. The WADA is invasive and lacks reliability, but recent attempts to develop an fMRI procedure to replace it have produced inconsistent results. The inconsistency in memory testing may be a result of lack of hippocampal stimulation in the unaffected tissue. An fMRI alternative to the WADA would be superior because it would be a less invasive procedure and the findings would be more specific in terms of locating active brain tissue. The current study presents healthy volunteers with verbal and visual emotional information in an attempt to produce greater activation in the hippocampus and allow it to be imaged using fMRI.

### **1.1 Medial Temporal Lobe and Memory: Early Research**

In the first half of the 20<sup>th</sup> Century, Karl Lashley attempted to localize brain regions in rats to examine the areas necessary for memory storage (Lashley, 1929). He explored the surface of the cerebral cortex, systematically removing parts of the neocortex and made knife cuts to nerve fiber pathways in an attempt to disrupt memory centers. After hundreds of experiments, Lashley was able to disrupt memory functioning, but was not able to identify any specific brain area responsible for memory storage. As a result, he formulated the law of mass action, which states that the efficiency of learning is correlated with the mass of intact cortex. In other words, the size of the memory defect is related to the size of the cortical area removed and not the location of the removal (Lashley, 1929).

In 1949, Donald Hebb argued that networks of neuronal circuits mediated memory storage. To explain Lashley's law that learning could not be localized to a single brain region, he suggested that individual cells worked together in groups to represent information across large areas of cortex. This occurred when individual cells

became active at the same time, grew synapses, strengthened and worked together as a functional unit. For example, when an axon of cell A is close enough to excite cell B and repeatedly participates in firing it, some metabolic change takes place in one or both cells. The change is such that cell A's efficiency, as one of the cells firing cell B, is increased. It was referred to as the "Hebb synapse", and these "reverberating circuits" became one model for the structural basis of memory (Kolb and Wishaw, 1996; Milner, Squire and Kandel, 1998).

Clinically, the link between the medial temporal lobe and memory functioning was reported in clinical case findings as far back as 1900 (Squire, Stark and Clark, 2004). In the 1950's, Brenda Milner's work with patient H.M. systematically detailed the profound effects of medial temporal lobe resection on human memory (Milner, 1972; Scoville & Milner, 1957). At the time of her research, little was known about the anatomy of the medial temporal lobe and the specific damage within that region that was responsible for H.M.'s memory impairment. Research that emerged from H.M.'s case would eventually help describe the functional anatomy of the medial temporal lobe, as well as two types of memory: explicit and implicit.

### **1.2 Hippocampal Involvement in Memory**

The importance of the hippocampus in human memory was revealed in a series of studies describing H.M. and several other patients. H.M. was described as having very specific impairment in memory following bilateral removal of the medial temporal lobes, including the hippocampus, for intractable epilepsy (Scoville and Milner, 1957). Following surgery, he had severe anterograde amnesia, a condition that persists to the present day.

In the years following his surgery, H.M. was employed in a state rehabilitation center and spent his days doing a very monotonous job. After six months, he was still unable to describe the events of his workday or the procedures of his job. A comprehensive neuropsychological evaluation showed that despite an above average IQ (117) and normal performance on perceptual tests, he was unable to retain new memories for facts and events (Milner, et al. 1998). He was able to recall information that was stored prior to his surgery. H.M.'s capacity for sustained verbal attention remained intact, as he was able to retain a three-digit number in mind for 15 minutes through constant rehearsal, once his attention was diverted by a new topic, however, the entire event was forgotten. H.M.'s non-verbal sustained attention was intact, but not as capable, information was lost in less than one minute (Milner, et al. 1998).

The hippocampus eventually became the focus of H.M.'s memory impairment. One theory was posited that the hippocampus was solely responsible for anterograde memory function (Kolb and Wishaw, 1996). Today, it is believed that not only the hippocampus, but adjacent tissue as well plays a crucial role in the encoding of information. For example, the perirhinal and entorhinal cortices are believed to be partially responsible for object- recognition memory (Squire, Zola-Morgan, 1991, Murray, 1996; 2000). Another theory was that H.M.'s impairment prevented all forms of new learning (Kolb and Wishaw, 1996). Researchers now believe there are several domains of new learning, and although H.M. was unaware of it, he was able to show learning of limited types of information through these other modalities (Squire, 1992; Milner, et al. 1998).

Neurosurgeon Wilder Penfield and Milner provided evidence supporting the temporal lobe's involvement in memory (Milner, et al. 1998). The two worked together at the Montreal Neurological Institute in the 1950's and found many cases of mild memory loss following unilateral temporal lobe removals. In a few cases they discovered profound and unexpected memory loss following left temporal lobectomy among seizure patients (Milner, et al. 1998; Penfield and Milner, 1958). They hypothesized that these severe cases must have been the result of a pre-existing, but undetected, hippocampal atrophy in the contralateral hemisphere to the seizure focus, which resulted in post-surgical anterograde memory deficits (Milner, et al. 1998; Penfield and Milner, 1958). This theory was confirmed when patient P.B., who had retractable epilepsy, received a two-staged resection and following the removal of the medial structures of the temporal lobe, experienced severe memory loss. Upon autopsy, it was revealed that P.B. had extensive right hippocampal atrophy, contralateral to the surgery site. It was believed that this right-sided atrophy was present prior to the surgery and the anterograde amnesia was a result of the bilateral damage (Penfield and Milner, 1958).

### **1.3 Animal Model for Amnesia**

An animal model of human amnesia became available in nonhuman primates during the 1980's. Despite tremendous difficulty in producing the model, it enabled researchers to systematically remove areas of the medial temporal lobe important for memory (Squire & Zola-Morgan, 1991). Through a combination of lesion and neurochemical studies, the system was identified as the hippocampal region (CA fields 1 and 3, the dentate gyrus and the subicular complex) and the adjacent entorhinal, perirhinal and parahippocampal cortices. Anatomical studies describe the hippocampus

as lying at the end of a “cortical processing hierarchy”, receiving most of its projections from the entorhinal cortex. Nearly two thirds of the cortical input to the entorhinal cortex originates in the adjacent perirhinal and parahippocampal cortices, which in turn receive widespread projections from the unimodal and polymodal areas in the frontal, temporal, and parietal lobes (Figure 1).

The difficulty in generating an animal model of human amnesia is related to an inability to demonstrate interference with the acquisition of declarative information, such as facts and events (Milner, et al., 1998). It was not until researchers expanded their concept of memory systems to include multiple memory modalities that tasks became more valid to administer. Mishkin (1978) performed the first monkey study involving deficits analogous to H.M.’s. The lesion damaged areas including the hippocampal formation, dentate gyrus, hippocampus proper, subicular complex, entorhinal cortex, amygdala, and the surrounding perirhinal and parahippocampal cortices. The lesion was termed  $H^+A^+$ , where the H refers to hippocampus, A the amygdala, and the plus signs indicate the cortical areas surrounding the hippocampus and amygdala. It was the first to demonstrate deficits in declarative memory in an animal model. Prior to the lesion surgery, and shortly after, animals were presented with a recognition memory task, called delayed nonmatching to sample. A single object was shown, followed by a delay and presentation of two objects, the original object and a novel object. The animal was rewarded with a food pellet for correctly selecting the novel object, demonstrating memory of what he viewed first and recognition that it was a different object. The result of the  $H^+A^+$  lesion was severe memory impairment, analogous to H.M. and other amnesic patients. The animals that were capable of discriminating novel from familiar objects

prior to the surgery were not capable after the surgery, but had a total sparing of skills-based learning. This suggested that medial temporal lobe structures were critical for declarative recognition memory and not skills based-learning.

A study by Alvarez and colleagues (1995) expanded on Mishkin's findings by using a stereotaxic approach to produce bilateral lesions limited to the hippocampal region (H only), sparing the adjacent perirhinal, entorhinal and parahippocampal cortex. In addition, the Alvarez study also produced lesions in separate animals that damaged the hippocampus and the adjacent cortex (H<sup>+</sup>). The amygdala was left completely intact on both sides. Monkeys with the H lesions exhibited long-lasting impairment on the delayed non-matching to sample task, but the monkeys performed better than those with H<sup>+</sup> lesions, who were also impaired. These findings suggested that the hippocampus alone is essential for memory encoding, but that the adjacent entorhinal, perirhinal and parahippocampal cortices, either alone or in combination, are also major components of the medial temporal lobe memory system.

#### **1.4 Declarative and Nondeclarative Memory Systems**

H.M. and other amnesic patients demonstrated that they could learn new information implicitly in other modalities, such as skills, habits, priming, simple classical conditioning and nonassociative learning, utilize unconscious, nonintentional memory systems (Milner, et al. 1998; Kolb & Wishaw, 1996). However, these modalities are in contrast with the conscious declarative memory system that encodes information about facts and events. They have been localized to various areas of the cortex, brain stem and limbic system, including the neocortex, striatum, amygdala and cerebellum (Figure 2).

In 1962, Brenda Milner showed that H.M. was capable of implicit learning in an elegant study of a mirror-drawing task. H.M. was required to trace a line between the double outline of a star while only seeing the star and the pencil in a mirror. This was not an easy task for the controls, but with practice they became more accurate and proficient. Despite initially performing worse than controls, H.M.'s drawings improved over a three-day period and eventually were at a similar level to that of the normal controls (Milner, 1962). Milner's study was replicated by Corkin, as she trained H.M. on various manual-tracking and coordination tasks. Again, H.M. began at an inferior level compared to controls, but improved from session to session without awareness of his improvement (Corkin, 1968). It was suggested that a dissociation exists between declarative and nondeclarative memory, further supporting the notion of multiple memory systems. The 'nondeclarative' memory system was hypothesized to be independent of the declarative memory system, since H.M. had such profound explicit memory deficits without implicit memory deficits.

### **1.5 The Limbic System: Mediator of Emotion and Memory**

The limbic area is a large horseshoe-shaped rim of cortex surrounding the junction between the diencephalon and each cerebral hemisphere (Figure 3). Since olfaction has direct input, the limbic system was first believed to be associated with only the sense of smell. Today, the role of the limbic system extends far beyond olfaction, as it is believed to play a role in the mediation of emotion and memory (Nolte, 2002). Although there is no complete agreement on the specific structures making up the limbic system, most authors include the cingulate and parahippocampal gyri, hippocampus, amygdala and septal nuclei (Nolte, 2002, Hanaway, 1998). The limbic system is believed

to be the highest level of autonomic control. Its connections to the autonomic nervous system are important for regulating the physical correlates of emotion, such as heart rate and respiration. Damage to the limbic system can result in a disturbance of emotion, seizure activity, aggression, and memory loss.

The limbic system contains numerous and complex interconnections. The portion of the system responsible for producing behaviors is a continuous core of neural tissue emanating from the septal area. This area extends through the hypothalamus and into the midbrain reticular formation. Two major subsystems feed into the septal area: one near the hippocampus, and the other near the amygdala. The hippocampal connection with the neocortex is within the cingulate and parahippocampal gyrus. In addition, it is closely associated with the anterior thalamic nuclei and mammillary bodies. The amygdalar system uses prefrontal and anterior temporal cortex as its connection with the neocortex, and is closely associated with the dorsomedial nucleus of the thalamus.

### *1.5.1 Hippocampus*

The word hippocampus literally means “seahorse”, which accurately defines its shape upon visual inspection. The curved nature of the hippocampus also conveys the evolutionary age of the structure, because as the brain expanded, the older structures were pushed into a circular formation. The structure of the parahippocampal formation is six-layered neocortex, which gradually changes to three-layered archicortex as it curves inward to become the hippocampus.

The hippocampus is a 5 mm structure that is a curved sheet of cortical tissue folded into the medial surface of the temporal lobe. It consists of three zones: the dentate gyrus, Ammon’s horn (cornu ammonis or CA) and the subiculum (Figure 4).

Ammon's horn and the dentate gyrus are three-layered with a superficial molecular layer and a deep polymorphic layer. The middle layer is made of granule cells in the dentate gyrus and pyramidal cells in the CA. The subiculum is a transitional zone, continuing from the CA at one of its ends to the parahippocampal gyrus at the other. The hippocampus receives virtually all types of sensory information. As shown in Figure 4 and described below, the hippocampus receives input from sensory neurons in the frontal, temporal, and occipital lobes. The projections include tertiary motor association areas, and secondary auditory and visual cortex (Kolb and Wishaw, 1996).

Input (afferents) enters the hippocampus from several surrounding cortices, such as the frontal lobe (Brodmann's areas 9 & 46), occipital lobe (area 19) and temporal lobe (areas 22) (Hanaway, 1998). The input arrives in the entorhinal cortex (parahippocampal area) and projects across the hippocampal fissure in the "perforant path" to Ammon's horn. The entorhinal cortex is the main source of input to the hippocampus via this pathway. The frontal and parietal lobes also have direct connections to Ammon's horn. In Ammon's horn, information is processed through local hippocampal circuits, the dentate gyrus and subiculum. In addition, fibers from the amygdala convey information to the hippocampus.

The hippocampal output (efferents) originates primarily from the subiculum, with contributions from Ammon's horn. Many fibers return to the entorhinal cortex and also other cortical areas, but the most prominent output area is the fornix. Most of the fornix fibers make their way to the cingulate cortex, while others extend to the anterior thalamic nucleus, hypothalamus and mammillary bodies.

Overall, the hippocampus is heavily innervated from cortical and subcortical neurons. These connections appear to bring all forms of sensory input into the hippocampus. On visual inspection, the hippocampus appears to be an interface for connections from the parietal, occipital, temporal and frontal areas. Thus, somatosensory, visual, auditory and many other forms of information are entering and exiting the hippocampus. In addition, the hippocampus is heavily innervated by subcortical structures, such as the thalamus, septal nuclei and the amygdala (Figure 5).

### *1.5.2 Amygdala*

In Latin, the word amygdala means “almond”, which describes the shape of the structure. The amygdala contains ten nuclei and is located beneath the uncus of the limbic lobe at the anterior end of the hippocampus and the inferior horn of the lateral ventricle (Nolte, 2001). In addition, it sits adjacent to the putamen and the tail of the caudate nucleus. The amygdala receives connections from diverse regions of the brain, including the forebrain, midbrain and brain stem, including a pathway from the hippocampus (Figure 6). The inputs bring somatosensory, visual, auditory and visceral information into the amygdala.

The amygdala sends projections to the cerebral cortex, hypothalamus and back to the hippocampus (Figure 6). Its fibers leave the amygdala through two major pathways. The first pathway is the stria terminalis, which connects mainly to the septal nuclei, hypothalamus and hippocampus. The second efferent route is the ventral amygdalofugal pathway, which contains afferents to and from the amygdala. The connections from this pathway spread out at the base of the brain and end in the septal nuclei and hypothalamus. Some of the connections reach the ventral striatum, which in turn projects

to the globus pallidus in the basal ganglia. This limbic connection with the basal ganglia is believed to be the route through which drive-related information can influence decisions about movement.

### *1.5.3 Interactions Between the Amygdala and Hippocampus*

The amygdala and hippocampal complex govern two independent memory systems that interact when emotion and memory come together. The first is attributed to the amygdala and involves the processing of emotion. This system is utilized for the acquisition and expression of fear conditioning, which occurs when a stimulus acquires aversive properties because it is paired with an aversive event. The second is attributed to the hippocampal complex and involves declarative and episodic memory. Recent studies have suggested a possible bi-directional relationship during emotional encoding (Richardson, Strange, Dolan, 2004), while others focused on each system's individual contribution.

In 1995, Bechara and colleagues showed that a double dissociation exists between these two memory systems (Bechara, Tranel & Damasio, et al., 1995). They studied patients with focal lesions to the amygdala or hippocampus. In a classical fear-conditioning paradigm, where a colored object was paired with an aversive shock to the wrist, patients with amygdala damage failed to show a normal physiological fear response, despite the fact that they could predict the shock. The patients with hippocampal damage showed the opposite reaction. They demonstrated a physiological arousal response to the object, but were not able to consciously recollect that it was paired with the shock. This study was able to show that the two systems can operate

independently and recent evidence suggests that the two systems can also influence each other.

Most studies of amygdala-hippocampal interactions have focused on how the amygdala influences encoding of episodic memory for emotional stimuli. As discussed earlier, the amygdala has reciprocal connections with sensory cortical processing regions. An fMRI study showed that there was an enhanced amygdala response to emotional stimuli and that the response was similar to the response seen in sensory cortices (Amaral, Behnia, Kelly, 2003). It was also suggested that the amygdala receives information about the emotional significance of a stimulus very early in stimulus processing and could enhance later perception, resulting in enhanced encoding for emotional events (Davis & Whalen, 2001).

There is also evidence that hippocampal-dependent memory can influence the amygdala. In an fMRI study, participants were told that they would receive mild shocks to the wrist, but only when a colored object was presented (Phelps, O'Conner, Gatenby, et al., 2001). The shocks were never received, but when the objects were shown it produced activation in the left amygdala. A similar study with patients that had damage to the left amygdala showed an impaired physiological fear response to the colored object, despite reporting knowledge of the pairing (Funayama, Grillon, Davis, et al., 2001). This suggested that having an imagined representation of an emotionally significant stimulus mediates the fear response and demonstrated how the hippocampus can have an influence on the amygdala.

There is more known about the amygdala's role on the hippocampal-dependent encoding than the reverse. Similar to the amygdala, the hippocampus has extensive

connections with sensory cortex. It would seem logical that the hippocampus could process emotional information, perhaps to a lesser extent than the amygdala, but enough to increase its activation in the presence of emotional stimuli. Presented below is a thorough review of encoding of visual and verbal information, both neutral and emotional, to examine the influences of the hippocampus, amygdala or surrounding areas.

### **1.6 Localization of Visual and Verbal Memory Encoding**

Since the hippocampal region was deemed necessary for the storage of declarative memories, it has been the focus of many neuroimaging investigations. Recent studies have shown medial temporal lobe activation, including the hippocampus, during the encoding of verbal (Wagner, Schacter, Rotte et al., 1998; Fernandez, Weyerts, Schrader-Bolsche, et al., 1998; Kelley, Miezin, McDermott, et al., 1998; Saykin, Johnson, Flashman, et al., 1999; Luebe, Erb, Grodd, et al., 2001; Dolan and Fletcher, 1997; Hunkin, et al., 2002; Golby, et al., 2001; Cassanto, et al., 2002; Martin, Wiggs, Weisburg, et al., 1997; Davachi and Wagner, 2002) and visual information (Garbieli, et al. 1997; Stern, et al. 1996; Frey and Petrides, 2000; Rombouts, Barkof, Witter, et al., 2001; Luebe, et al., 2001; Martin, et al. 1997; Kelly, et al. 1998). Several of these studies also found activation in the prefrontal cortex (Kelley, et al., 1998; Saykin, et al., 1999; Luebe et al., 2001; Hunkin, Mayes, Gregory et al., 2002; Casasanto, Killgore, Maldjian, et al., 2002) for verbal and visual information.

#### *1.6.1 Encoding of visual information*

During the early 1990's, imaging studies were able to show medial temporal lobe contributions to visual memory encoding. Initially, there was little evidence of hippocampal activation (Shallice, Fletcher, Frith, et al., 1994; Buckner and Koutstaal,

1998), but later studies were able to demonstrate activation in the hippocampus in response to objects and faces (Stern, et al. 1996; Gabrieli, et al., 1997; Frey & Petrides, 2000; Wright, Martis, Shin, Fisher & Rauch, 2002; Canli, Desmond, Zhao & Gabrieli, 2002; Rombouts, et al., 2001; Luebe, et al., 2001; Kelley, et al., 1998).

Stern (1996) was the first study to show robust signal changes in the human hippocampal region using functional MRI (fMRI) techniques. Healthy participants were imaged while being given a 'sequential task-activation paradigm' involving switching between novel visual stimuli (40 complex colored pictures) and familiar (1 color picture shown continuously). During the scanning, participants were asked to examine the photos carefully for later recognition. The novel visual encoding trials produced activation in the posterior portion of the hippocampus and adjacent parahippocampal gyrus, bilaterally, compared to the control condition. The participants were able to identify the pictures with 86% accuracy following the scan, suggesting that they were attending to the task. Thus, the evidence suggested that novelty plays an important role in the activation of the hippocampus and that the structure makes a comparison between novel and familiar that guides the formation of new representations.

Gabrieli and colleagues (1997) also found posterior hippocampal activation in a study of visual memory encoding. Participants were asked to remember several pictures of complex indoor and outdoor scenes, again with novel and familiar conditions. Significant activation was seen in the posterior medial temporal lobe (e.g. parahippocampal cortex), bilaterally, and right frontal lobe for novel pictures compared to the familiar pictures. The retrieval task subsequent to the encoding showed that 88.5% of the visual material was accurately retrieved. The findings were consistent with a more

recent study that showed faces activate the parahippocampal cortex (Luebe, et al., 2001). Perhaps the only limitation of the study, as with many visual encoding studies, is that one does not know if the activation for encoding is exclusively visual, especially since the task was so amenable to verbal identification.

In a 2000 study using PET, participants were presented with 20 novel abstract images and asked to commit them to memory (Frey & Petrides, 2000). The images were chosen for their abstractness, to prevent participants from verbally organizing the material. As a control task, participants viewed three familiar abstract images presented in random order with no memorizing requirements. They found an increase in regional cerebral blood flow (CBF) compared to controls in the right orbitofrontal cortex, fusiform gyrus, as well as the entorhinal and perirhinal cortex. In addition, the recognition task showed an 83.3% accuracy rate at identification. This study was the first to show orbitofrontal activation, in addition to medial temporal, during visual encoding, despite several failed attempts (Tulving, Kupar, Craik, et al., 1994; Haxby, Ungerleider, Horowitz, et al. 1996; Courtney, Ungerleider, Horowitz, et al. 1996).

*Summary.* Overall, neuroimaging studies of visual memory showed that the hippocampus and parahippocampal gyrus were involved in the encoding process. However, the location of the activity appeared to vary depending on the stimuli presented. Novel pictures and scenes generated bilateral posterior hippocampal activation, while abstract images generated entorhinal and perirhinal activation. Familiar images also activate these regions, but not to the same extent. In addition, novel pictures were also shown to activate orbitofrontal cortex, and faces generated right posterior involvement.

### *1.6.2 Encoding of verbal information*

The first neuroimaging studies of verbal memory encoding were designed to study language function. They required participants to generate meanings of words while being imaged (Petersen, Fox, Posner, et al., 1988; Wise, Chollet, Hadar, 1991), but also proved to be useful for measuring encoding. Subsequent studies showed activation in the left prefrontal areas, the anterior cingulate and the right-lateral cerebellum during encoding (Shallice et al. 1994; Petersen et al. 1988; Kapur, Craik, Tulving, et al. 1994; Gabrieli, Desmond, Demb, et al., 1996). In contrast, few findings supported the medial temporal lobe's involvement in verbal encoding. It was even suggested as recently as 1998 that "certain aspects of medial temporal lobe contributions to memory may simply be invisible to present human neuroimaging techniques (Buckner & Koutstaal, 1998)." More recently, several studies found hippocampal activation following successful verbal memory encoding (Fernandez, et al. 1998; Wagner, et al. 1998; Kelley, et al. 1998; Saykin, et al. 1999; Luebe, et al. 2001; Baker, Sanders, Maccotta et al., 2001; Dolan and Fletcher, 1997; Hunkin, et al. 2002; Golby, et al., 2001; Casasanto, et al. 2002; Golby, Poldrack, Illes et al. 2002; Davachi and Wagner, 2002; Martin, et al. 1997; Alkire, Haier, Fallon et al., 1998) (Table 2).

The early studies included a word generation task, where participants were asked to process information in a shallow (e.g., deciding whether a word has the letter "a" in it) or deep (e.g., deciding if a word refers to something "living" or "nonliving") fashion (Kapur, et al., 1994). Following the task, participants showed strong recognition for both PET images and results revealed significant activation in the left prefrontal cortex (Brodmann's areas 45, 46, 47 and 10) during the deep processing task compared to the

shallow. A more directed study followed by Gabrieli and colleagues (1996), which supported the findings of the first showing activation of a left prefrontal cortex (Brodmann's areas 45, 46 and 47) during a deep encoding task compared to a shallow.

Several studies have investigated medial temporal involvement in verbal memory encoding, but results were variable. Dolan and Fletcher (1997) were the first to show medial temporal activation using fMRI in a study that manipulated the novelty of verbal material. Their task involved learning category-exemplar word pairs (e.g., food-biscuit) in which the novelty and category were independent variables. Participants showed increased activity in the region of the left medial temporal lobe, especially the hippocampus, when degree of novelty was manipulated. In addition, the left prefrontal cortex was active during manipulation of category. The results suggested dissociable roles for the prefrontal cortex and hippocampus, where the left prefrontal cortex is sensitive to changes in category-exemplar, while the left hippocampus is sensitive to changes in the novelty of the information. The authors also commented that previous studies might have had difficulty reproducing hippocampal activation because of "too much novelty." Fletcher, Frith and Rugg (1997) proposed that the hippocampus might be continuously engaged in encoding information, which would lead to little activity relative to the baseline.

Other studies supported Dolan and Fletcher's (1997) findings for the medial temporal processing of novel and familiar words (Saykin, et al. 1999; Hunkin, et al. 2002). Saykin and colleagues (1999) asked participants to listen to a 48-word list of nouns, 10 of which they heard prior to the scanning, the remaining 38 heard for the first time. The familiar words were randomly scattered throughout the word list and were

always separated by a novel word. Familiar words produced activations in the right prefrontal cortex and posterior left parahippocampal gyrus, while novel words activated the anterior left hippocampal region, suggesting a possible dissociation between the structures.

A comparison of the Gabrieli (1997) and Saykin (1999) studies showed a nearly inverse relationship between the activation patterns of visual and verbal encoding. Gabrieli and colleagues found that novel visual information activated the posterior MTL (parahippocampal gyrus), bilaterally, while Saykin (1999) found novel verbal information activated the anterior MTL. Familiar information had a similar pattern, as familiar visual images activated the anterior hippocampal formation, while the verbal activated posterior hippocampal gyrus. The Gabrieli (1997) study acquired slices in an oblique coronal plane through the hippocampus. Overall, the differences between the two studies highlighted the different activation patterns for visual and verbal stimuli.

Luebe and colleagues (2001) combined verbal and visual encoding using a word and face memory task. Neuroimaging revealed a widespread network of common activations, including right posterior hippocampal activation for faces, and bilateral anterior hippocampus and left prefrontal cortex activation for words. Thus, the regions of the hippocampus are activated differentially depending on the type of stimuli. Face encoding activated the right posterior region of the hippocampus and word encoding activates the anterior region. The frontal lobe was activated during encoding regardless of the type of stimuli. The results were consistent with previous imaging studies (Gabrieli et al., 1997; Saykin et al., 1999).

*Summary.* Despite the inconsistencies, it appears that the hippocampal region, including the parahippocampal gyrus and fusiform gyrus, is activated during verbal encoding. A few studies had difficulty demonstrating laterality, but most studies showed either left or bilateral hippocampal activation. In addition, several studies supported prefrontal cortex activation during verbal encoding, perhaps as evidence of the cortex attempting to organize the information.

### **1.7 Localization of Visual and Verbal Emotional Memory Encoding**

There is considerably less evidence for the role of the hippocampus in the encoding of verbal and visual emotional information when compared to the encoding of non-emotional information. There is some support for the role of the hippocampus in emotional encoding, despite evidence that it may simply be modulated by the amygdala (Cahill, Haier, Fallon et al., 1996; Lane, Reiman, Bradley et al., 1997; Hamann & Mao, 1997; Canli, Zhao, Desmond, et al., 1999). There is recent evidence, however, that both the amygdala and the hippocampus play a role in the encoding of both verbal and visual emotional information (Crosson, Cato, Sadek, et al., 2002; Beauregard, Chertkow, Bub, et al., 1997; Hamann, 2001; Wright, Martis, Shin, Fischer and Rauch, 2002).

#### *1.7.1 Visual emotional encoding*

Wright and colleagues (2002) examined the processing of emotional facial expressions. Participants were given an fMRI while viewing simple line drawings of happy, sad and neutral faces. There were significant increases in responsiveness to emotional versus neutral schematic faces within the left amygdala and hippocampus, as well as the left inferior and bilateral medial prefrontal cortex and right anterior temporal cortex. In addition, angry faces alone appeared to activate the right occipitotemporal

cortex. These results supported a previous lesion study that suggested the amygdala plays a role in the processing of human emotional facial expressions (Adolphs, Tranel, Damasio, & Damasio, 1994).

Several studies examined participants while viewing emotionally provocative film clips and pictures (Cahill et al., 1996; Lane et al., 1997; Hamann et al., 1999). One study defined *a priori* two regions of interest, the amygdala and hippocampal/ parahippocampal region, to examine the relationship between the two structures during memory encoding (Hamann, Ely, Grafton, Clinton, 1999). Participants viewed four types of pictures while being scanned, including pleasant, aversive, neutral and interesting, which served as a control for emotional pictures without being emotionally arousing. They also underwent an unexpected recognition test at 10-minutes and 4-weeks after the viewings to monitor the quality of encoding. The data suggest that pleasant or aversive pictures were remembered better than neutral events and PET scans revealed that bilateral amygdala activity during memory encoding was correlated with enhanced episodic recognition memory for the pleasant and aversive stimuli. In addition, the data suggest that the amygdala modulates the strength of memory for events according to their emotional importance and enhances episodic memory through the modulation of the hippocampus. The findings regarding the amygdala's modulation of the hippocampus were consistent with previous studies (Cahill and McGaugh, 1998; McGaugh, Cahill & Roozendaal, 1996).

There is evidence that memory for emotional stimuli and experiences differ between the sexes (Canli, et al., 2002). The fMRI study measured visual encoding differences in twelve healthy male and female participants. The individuals were

scanned while being shown 96 neutral to highly negative pictures selected from the International Affective Picture Series (Lang, Greenwald, Bradley, & Hamm, 1993). The participants rated their emotional experiences on a three-point scale (0, “not emotionally intense” to, 3, “extremely emotionally intense”). Three weeks later, they completed an unexpected recognition memory test, which involved previously seen pictures (targets) and unseen pictures (foils).

The results were consistent with Hamman, et al. (1999), as the pictures rated as the most emotionally arousing were more likely to be remembered. Women had better memory for emotional pictures than men, but rated more pictures as emotionally arousing. When subjective ratings of arousal were equated, women still had superior memory for emotional pictures.

The fMRI data revealed that only pictures rated most intensely produced any correlation between amygdala activation and later memory. In fact, the most arousing pictures were correlated with greater left amygdala activation in woman and right amygdala for men. Both sexes showed correlation clusters in the left anterior cingulate gyrus and the left precentral gyrus. A conjunction analysis was performed to identify regions in which greater activation correlated with both emotional intensity and subsequent memory accuracy. There were conjunctions of activation found for woman in nine regions, including the left amygdala, bilateral hippocampus and left anterior cingulate cortex. In contrast, men showed such conjunctions in only two frontal regions and none of the medial temporal regions.

The data provided evidence for the neural basis of sex differences between men and women. Behaviorally, woman rated more pictures as highly negative and

remembered the pictures better than the men. The women also had more brain areas activated by subjective emotional experience and had more successful encoding of that experience into long-term memory. The hippocampus was one of two structures activated in woman and not men. Since woman had greater level of encoding, however, it could be argued that the hippocampus is necessary for successful encoding of emotional information, while the amygdala only responds to emotional valence, and does not have direct influence on encoding. The absence of hippocampal activation in men may be a result of the stimuli not being sufficiently emotionally arousing for men.

Overall, activation of medial temporal lobe structures, such as the amygdala, can be elusive. In an earlier study by Canli et al. (1998) on the hemispheric asymmetry of emotional stimuli, the authors could not produce activation in the amygdala in response to negative stimuli, despite its well-documented role in the processing of other emotional visual stimuli (Aldophs, et al., 1994). Canli et al. (1998) provided several possible explanations, including small statistical power, lack of arousal from their stimulus set or that the amygdala may not play a role in the experience of negative affect.

*Summary.* Research on visual emotional encoding has shown activation in both the amygdala and hippocampus. Lateralizing the activation appeared to be the greatest challenge, since studies have reported activity in the right and left hemisphere alone, and bilaterally. The wide range of stimuli may also contribute to the variation. One study used line drawings of faces, while others used film clips or photos. There were also differences between men and woman. Women tend to have a lower threshold for rating emotional pictures than men; they also tend to remember pictures better. Interestingly,

women also have more hippocampal activation than men for these emotional pictures, which may provide a neural explanation for the poor performance.

### *1.7.2 Verbal emotional encoding*

A 1995 case study suggested the amygdala was responsible for verbal emotional encoding (Cahill, Babinsky, Markowitsch, & McGaugh, 1995). Patient B.P. suffered from Urbach-Wiethe disease, a rare genetic disorder that produces bilateral brain damage to the amygdaloid complex. B.P. tested in the normal range for cognitive functions, including attention, intelligence and short-term memory. However, when B.P. was presented with an emotional story in slide show format, his memory for the emotional events was worse than the non-emotional events and worse than controls. B.P.'s self-reported emotional reaction to the story was consistent with the control participants, suggesting that he could react to emotional events but not retain them. These results were consistent with previous findings from another Urbach-Wiethe patient (Markowitsch, et al., 1994), but inconsistent with findings that suggested a dissociation between the hippocampus and amygdala (Richardson, et al., 2004; Bechara, Tranel & Damasio, et al., 1995).

A recent study used fMRI to examine the response to emotional information (Hamann & Mao, 2001). The fourteen male participants were imaged while they read 50 'high-arousal' positive words (e.g. ecstasy, thrill, etc.), 50 'high-arousal' negative words (e.g. gangrene, morgue, etc.) and 50 neutral words (e.g. lamp, fabric, etc.). To ensure that the words would have the intended emotional content, nouns with emotional connotations were selected from the Affective Norms for Emotional Words (Bradley & Lang, 1998). In addition, the participants rated the positive and negative words as equally emotionally

arousing. The data suggested left amygdala activation for both positive and negative words compared to neutral words, which was consistent with a previous study (Tabert, Borod, Tang, et al., 2001). In addition, positive words activated dorsal and ventral striatal regions, perhaps because it engaged reward centers. No activation was seen in the hippocampal or parahippocampal regions, as they did not perform a memory paradigm.

Crosson and colleagues (2002) investigated the brain areas involved in the monitoring of words with emotional connotation. The words included nouns with emotional content (e.g., vomit and tornado), implement names (e.g., spatula), and animal names (e.g., puppy) and were rated for emotional valence and arousal from a large population. During the semantic monitoring task, participants were instructed to press a button when the item was a nonliving thing and had a negative emotional connotation. For the monitoring of emotional words, there appeared to be activation in the left anterior frontal cortex and the superior temporal gyrus, which was consistent with a previous study (Beauregard, et al., 1997). There was no activity found in the left frontal and temporal lobes for monitoring of animal names: however, There was, however, activity in the anterior left frontal lobe and the posterior temporal pole for implement names. The results implicated the anterior left frontal and portions of the temporal lobe in semantic processing of emotional connotation compared to monitoring a simple tone.

In a more recent study, Richardson and colleagues (2004) utilized patients with left hippocampal and amygdala damage to examine the impact of pathology on verbal emotional encoding. They imaged 16 right-handed patients, all with left hippocampal sclerosis of variable severity, with or without additional left amygdala sclerosis, and 12 normal controls. During the fMRI, the participants viewed words on a screen, of which

12.5% were emotionally aversive (e.g., “rape” or “terrorist”), while performing a deep-encoding task. Subsequently, all participants performed an unexpected recognition test, which actually showed no enhanced recognition for emotional items in the patient or control groups. The imaging data revealed that severity of left hippocampal pathology predicted memory performance for all items (neutral and emotional). The severity of amygdala pathology, however, only predicted memory performance for emotional items. The authors concluded that the amygdala and hippocampus are interdependent during the encoding of emotional memories, which contributes to greater level of encoding. These results were consistent with a study on normal controls that showed emotional memory enhancement for arousing information depended on the amygdalar-hippocampal network (Kensinger and Corkin, 2004).

*Summary.* Overall, there have been few imaging studies of verbal encoding and emotional information. Recent evidence has linked the amygdala and hippocampus in emotional encoding, suggesting that the hippocampus is necessary in this role. In addition, the anterior frontal lobe has been suggested to play a role in emotional encoding.

### **1.8 Hippocampal Activation and WADA Testing**

There is intense clinical interest in using the fMRI to detect activation of the hippocampus during memory tasks, especially in the treatment of patients with temporal lobe epilepsy (TLE). Thirty percent of individuals with intractable TLE (i.e. fail pharmacological treatment) have memory decline. This, in turn, requires surgical intervention and risks further memory damage (Engel, 1996). The surgical procedure is

known as anterior temporal lobectomy (ATL) and it provides patients with an 80-90% chance of becoming seizure-free (Engel, 1992).

Patients considered for the surgery receive the intracarotid amytal test (IAT), also known as the WADA test, which attempts to localize language and memory functioning (Wada, Rasmussen, 1960). The IAT was initially used for the lateralization of language, but later found to have a role in the evaluation of memory functioning. The IAT involves the injection of sodium amytal into one internal carotid artery (ICA), which transiently anaesthetizes the ipsilateral cerebral hemisphere and allows for testing of the contralateral hemisphere. The protocol and criteria for IAT vary considerably from center to center, particularly in regard to memory testing.

Numerous controversies exist in the use of the IAT for memory assessment. Since the procedure is invasive and requires the insertion of a carotid catheter and injection of iodinated medium, there is a possibility of a thromboembolic complication or errors due to insufficient or excessive anesthesia (Deblaere, Backes, Hofman, et al., 2002). Patients may develop confusion, inattention and/or somnolence during the initial phase following injection (Malmgren, Bilting, Hagberg, 1992). The injection temporarily paralyzes perisylvian speech and language areas and renders the patient aphasic, which may play a role in verbal recall errors on subsequent memory testing.

There are also more basic criticisms of the IAT procedure for memory testing involving concerns about its ability to test hippocampal memory functioning. In ninety percent of individuals, the mediotemporal lobe blood supply comes from the posterior cerebral artery, not the middle cerebral artery. This means that a sodium amytal injection into the ICA, which travels into the middle cerebral artery, will not directly perfuse the

hippocampal formation and the parahippocampal gyrus (Nolte, 2002). Typically, the injection perfuses the frontal, parietal and lateral temporal lobes, but not the medial temporal lobes (Petersen, Sharbrough, & Jack, 1993).

In defense of the IAT, an EEG study showed that hippocampal functioning ipsilateral to the injection was slowed by the procedure (Gotman, Bouwer, Jones-Gotman, 1992). The contralateral hippocampus, however, also showed slowing that lasted for a short duration. Their conclusion was that the hippocampus is clearly affected by the IAT due to the “functional deafferentation” that occurs secondary to the inactivation of adjacent structures. This may explain findings that the IAT is valid and can identify true-positives (i.e., patients who fail the test and subsequently became amnesic after unilateral temporal lobectomy) (Rausch, Silfvenius, Wieser, et al., 1993). There have been instances of false-negatives, however, where the IAT has missed patients at-risk for postoperative amnesia (Rausch, et al., 1993), and false-positives, where patients failed the IAT and underwent temporal lobectomy only to have no postoperative amnesia (Loring, et al., 1990). Thus, an accurate estimate of the usefulness of the IAT in predicting postoperative amnesia is difficult, and its validity for this purpose continues to be a concern.

Functional MRI (fMRI) was recently introduced as a non-invasive alternative to the IAT. The fMRI technique uses the blood oxygenation level-dependent response to measure physiological changes that coincide with neuronal activity. There have been a number of studies that addressed the reliability of the fMRI for lateralization of language and memory in healthy individuals and patients with epilepsy (Detre, Macotta, King et al., 1998; Stern et al., 1996; Deblaere, et al., 2002; Bullock, 2000). The Deblaere study

was the first pilot study using fMRI to suggest a paradigm including both language and memory (2002). The memory portion of the test included two portions, a test of naming and a test of complex scene encoding. They examined nine right-handed healthy volunteers and found bilateral hippocampal, parahippocampal and fusiform gyrus activation following the memory tests. The results were encouraging, but lacked a verbal memory encoding condition. The current study attempted to extend these findings by presenting emotional verbal information, as well as visual, to activate the hippocampus.

One of the challenges of an fMRI study is producing enough activation within small structures, such as the hippocampus, to be quantifiable. The use of stimuli with emotional content is believed to increase the level of activation in the hippocampus, as well as the amygdala and inferior frontal lobe (Crosson, et al., 2002; Beauregard, et al., 1997; Hamann, et al., 2001). Several recent studies have used non-emotional information to produce hippocampal activation in an attempt to create an fMRI alternative to the IAT (Aldenkamp, Boon, Deblaere, et al., 2003; Golby, Poldrack, Illes, 2002; Rabin, Narayan, Kimberg, et al., 2004). Ultimately, the goal would be to assist in the creation of an alternative test the IAT that would consistently produces activation using fMRI.

### **1.9 Aims of the Current Study**

The current study examined the effects of emotional and neutral stimuli, both verbal and visual, on the hippocampus and related memory structures in healthy participants. The verbal stimuli were made up of words taken from the Affective Norms for English Words (Bradley and Lang, 1988), while the visual stimuli were pictures taken from the International Affective Picture Series (Lang, Greenwald, Bradley, & Hamm, 1993). It was believed that the salience of standardized emotional pictures and words

would increase activation of the structures involved in memory compared to neutral pictures and words.

### **1.10 Hypotheses**

1. Based on the extensive input to the hippocampus from sensory cortex and previous literature (Kelley et al., 1998; Saykin et al., 1999), it is expected that words with emotional content will activate the left hippocampus, greater than neutral words.
2. Based on the extensive input to the hippocampus from sensory cortex and previous literature (Stern et al., 1996; Gabrieli et al., 1997), it is expected that emotional pictures will activate the hippocampus, bilaterally, greater than neutral images.
3. Based on previous research (Canli, et al., 2002), women are expected to produce greater activation in the hippocampus (bilaterally) following exposure to emotional words and pictures when compared to men.
4. Women are expected to have greater recognition memory for the words and images with emotional content than men.
5. Activation is expected to be greater in the left amygdala for both emotional words and pictures (Hamann & Mao, 2002; Canli et al., 2002; Lane et al., 1997). Neutral words and pictures are not expected to produce activations in the amygdala.

The comparisons presented above are important because they would provide further evidence that a standardized set of emotional words and images enhance activation of the hippocampus. In addition, they could further the creation of an fMRI alternative

to the IAT by overcoming the problem of poor activation in the hippocampus for visual, and more importantly verbal, information.

## 2. METHODS

### **2.1 Participants**

Participants included twelve adult volunteers (N= 12), seven female and five male, with no history of neurological illness or memory deficits. All participants were right-handed, native English speakers who ranged in age from 26-37. They were recruited through the Drexel University Department of Psychology via local advertisement on and off campus. All participants provided informed consent and the study was approved by the Institutional Review Board of Drexel University.

### **2.2 Inclusion/Exclusion Criteria**

All participants who responded to the advertisements were given a self-report handedness examination. There were no left-handed or mixed individuals included. A semi-structured interview protocol was used to screen participants for personal and familial medical history and symptoms, including neurological, psychiatric and substance abuse. None of the participants reported past or present symptoms of a major psychiatric (Axis I) disorder or neurological disorder, such as a head injury with loss of consciousness for more than five minutes. None of the participants were taking psychoactive or cardiovascular medications.

### **2.3 Apparatus**

The participants wore headphones, connected to an amplifier that was connected to a Macintosh I-Book laptop computer. The computer contained the SoudEdit 16 (version 2) program used to record and play back the sound samples. Visual images were

presented through goggles with a video screen inside. The video images were projected from the Macintosh I-book computer.

## **2.4 Procedure**

### *2.4.1 Stimuli Characteristics*

During scanning, participants were presented with 80 items, 40 neutral and emotional words, and 40 neutral and emotional pictures. All the items were presented three times to facilitate memory. The words were selected from over 1000 standardized words from the Affective Norms for English Words (Bradely & Lang, 1988). The emotional words included “abuse, cruel, and terrible”, the neutral words included, “bus, book, and table.” Normative ratings for all stimuli were available on a 9-point scale for the dimensions of emotional valence and (1, most unpleasant, and 9, most pleasant) and arousal (1, calm/dull, and 9, most arousing or intense). The emotional words were selected based on their normative ratings of valence and arousal, which ranged from 1.0 to 3.0 for valence and 5.5 to 9.0 for arousal. The pictures were selected from over 750 images in the Affective Norms for and the International Affective Picture Series (Lang, Greenwald, Bradley, & Hamm, 1993). The emotional pictures included scenes of crying, natural disasters and pollution, and the neutral pictures included pictures of a chair, building or watch. The emotional pictures were selected based on their normative ratings of valence and arousal, which ranged from 1.5 to 4.5 for valence and 5.5 to 7.5 for arousal.

### *2.4.2 FMRI Procedure*

FMRI was performed using the Blood Oxygen Level Dependent (BOLD) contrast method as an indirect marker of neuronal function. Images were acquired using a clinical

1.5 Tesla Siemens Vision (Siemens, Erlangen, Germany) whole body scanner capable of high-speed echo-planar imaging. Prior to scanning, linear shims were used to optimize the images. Participants were placed in the supine position in the MRI scanner. Their heads were immobilized using cushions to reduce motion artifacts. Partial brain scans were conducted with 26 contiguous no-gap 5-mm axial oblique image planes to cover the cerebrum. Slice planes were positioned and aligned parallel to an imaginary line passing through the anterior-posterior commissures (AC-PC line). The orientation relative to the AC-PC line was selected in order to assist a spatial transformation of the volumes into a standard anatomical space.

Anatomical references were acquired with high-resolution T1-weighted images. The imaging parameters of the spin-echo sequence used to acquire the images were as follows: TR = 500 msec, TE = 14 msec, matrix size =  $256^2$  pixels, FOV = 22 X 22 cm<sup>2</sup>, flip angle 90°, slice thickness = 5 mm; NEX = 1, and in-plane resolution = 0.86 x 0.86 mm<sup>2</sup>. The T1-weighted images were collected with an echo-planar imaging free induction decay (EPI-FID) single-shot pulse sequence. The positions of the T1-weighted images were identical to those of the anatomical reference images. EPI-FID image parameters were as follows: TR = 4000 msec, TE = 54 msec, matrix size =  $128^2$  pixels, FOV = 22 X 22 cm<sup>2</sup>, flip angle = 90°, slice thickness = 5 mm, NEX = 1, band-width = 1470 Hz/pixel, and in-plane resolution = 1.72 X 1.72 mm<sup>2</sup>. Shimming was performed for each data set as a way to reduce artificial fluctuations and in homogenities across images.

#### *2.4.3 fMRI Paradigm*

Participants were placed in the fMRI scanner and instructed to get comfortable because once the testing began they had to remain as still as possible. The participants

were then instructed to keep their eyes open during the picture presentation and their eyes closed during the word presentation. Participants were asked to “try and remember” each of the 40 words. For verbal encoding, participants listened to items at a rate of one item every 2 seconds with a 10 second inter-trial interval. For visual encoding, participants were given a similar paradigm and asked to remember each of the 40 pictures.

Approximately ten minutes after the scan, participants completed a recognition memory test, in which they heard all of the previous words (targets) and 80 new words (foils).

The test served as a measure of their attention to the task and ability to encode the information.

#### *2.4.4 General Activation Design*

The general design for all stimuli was a conventional on-off boxcar design. The sequence consisted of 20 seconds of rest followed by 20 seconds of the activation condition. Scans of the whole brain were acquired every four seconds. The activation sequence alternated six times, and resulted in a set of 60 whole-brain volumes.

### **2.5 Analysis of fMRI Data**

Functional images were analyzed using statistical parameter processing software package, SPM '99 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, University College of London, UK), run under Matlab® (The Mathworks, Inc., Natick, MA) environment. Region of interest (ROI) analyses were conducted using the WFU Pick Atlas version 1.02 (Maldjian, Luarienti, Burdette & Kraft, 2003). This software allowed for the generation of ROI masks based on the Talairach database (Talairach & Tournoux, 1988).

#### *2.5.1 Realignment, Normalization, and Smoothing*

All collected images were converted from the Siemens format in which they were initially stored into the ANALYZE (AnalyzeDirect, Inc., Lenexa, KY) format adopted in the SPM package. A slice timing correction was performed to compensate for delays associated with acquisition time differences between slices during the sequential imaging. This was done to adjust the magnetic resonance signal's phase shift so that each volume had the signal values that would have been obtained had each slice been acquired first.

The second step, a three-dimensional automated image registration routine (six-parameter rigid body, sinc interpolation; second order adjustment for movement) was applied to the volumes to realign them with the first volume of the series used as a spatial reference. All functional and anatomical volumes were then transformed into the standard anatomical space (Talairach & Tournoux, 1988) using the T2 EPI template and the SPM normalization procedure (Ashburner & Friston, 1999). This procedure used a sinc interpolation algorithm to account for brain size and position with a 12 parameter affine transformation, followed by a series of non-linear basic function transformations and nonlinear basic functions for the x,y, and z directions, respectively, with 12 nonlinear iterations to correct for morphological differences between the template and the given brain volume. Next, all volumes underwent spatial smoothing by convolution with a Gaussian kernel of  $3.44 \times 3.44 \times 10 \text{mm}^3$  full width half maximum (FWHM) (two times the voxel size), to increase the signal-to-noise ratio (SRN) and account for residual intersession differences (Mohammed, 2002).

### *2.5.2 Activation Mapping*

The response by visual cortex neurons to luminance-graded stimulation was characterized by two independent functions of the luminance intensity: the spatial extent

of the cortex activation, and the amount of local BOLD signal from the activation areas. The changing signal extent of the activation would imply a varying degree of neuronal activation in a particular area of neuronal enhancement is an indicator of the regional cerebral blood flow (rCBF) rate, and could be manifested by the magnitude of the regional BOLD signal.

To determine the spatial extent of the recruited neurons and subsequently calculate the BOLD signal, SPM general linear model (GLM) procedures were used to identify the voxels associated with the auditory and visual stimulation. This was achieved by administering a series of voxel-based t-tests and creating so-called statistical parametrical maps (SPM{t}), a visual representation of the areas wherein statistically significant differences between BOLD contrast responses elicited during the activation and rest conditions were present. Then the quantitative analyses of changes in the activation extent and the magnetic resonance signal was carried out using a set of these maps produced for each participant's trial (Mohamed, 2002). The criteria chosen for all images in the cluster analyses was at least  $p < 0.05$ , with the ROI analysis of the hippocampus meeting the  $p < .01$  criteria.

### *2.5.3 Direct Comparison of Emotional Versus Neutral Stimuli*

The initial analysis of emotional versus neutral words and pictures was an indirect comparison. The data from the active condition, words or pictures, was compared to the rest condition. The rest condition consisted of a blank screen. The direct comparison of emotional versus neutral stimuli utilized the same data, but the active condition consisted of emotional stimuli directly compared to the neutral stimuli. Removing the initial rest condition files, replacing them with neutral condition files and reanalyzing the data,

allowed us to perform the direct comparison. In total, there were 30 volumes of rest condition data replaced by 30 volumes of neutral condition data. The data were realigned, normalized and smoothed and analyzed similar to the procedure described above.

### 3. RESULTS

#### **3.1 Behavioral Results**

A one-way ANOVA was conducted to evaluate the relationship between stimulus type, emotionality and gender on recall of information. The three independent variables, stimulus type, emotionality and gender, included two levels each. The dependent variable was the raw number of items recalled by the participants. The ANOVA indicated a significant main effect for stimulus type (i.e., pictures, words), as picture recall was superior to words  $F(1, 48) = 70.17, p < .05$ . The strength of relationship between stimulus type and recall, as assessed by  $\eta^2$ , was strong, with the stimulus type factor accounting for 15% of the variance of the dependent variable. In addition, there was a main effect for emotionality (i.e., emotional, nonemotional), as emotional item recall was superior to nonemotional items,  $F(1, 48) = 7.31, p < .05$ . The strength of relationship between emotionality and recall, as assessed by  $\eta^2$ , was strong, with the stimulus type factor accounting for 64% of the variance of the dependent variable. Figure 7 depicts a significant interaction between emotionality and stimulus type,  $F(1, 48) = 9.09, p < .05$ . Pictures were recalled significantly better than words [ $t(1, 46) = 7.59, p < .05$ ], and emotional words were recalled significantly better than non-emotional words [ $t(1, 48) = 3.13, p < .05$ ]. The strength of relationship between the interaction and recall, as assessed by  $\eta^2$ , was strong, with the stimulus type factor accounting for 19% of the variance of the dependent variable. There were no gender differences in memory recall [ $t(1, 46) = 0.75, p < .05$ ]. Overall, participants remembered emotional items (87%) significantly better than non-emotional items (77%). Emotional pictures (96%) and

neutral pictures (97%) were significantly better recalled than emotional words (79%), and neutral words (60%).

### **3.2 Stimuli Ratings**

Prior to the scanning, a separate group of volunteers rated the emotional words and pictures on a similar scale (Table 5). There were no significant differences between the normative and volunteer ratings for emotional words valence  $F(1, 40) = 1.10, p = .31$  or arousal  $F(1, 40) = 1.36, p = .71$ , emotional pictures valence  $F(1, 40) = 0.27, p = .61$  or arousal  $F(1, 40) = .06, p = .81$ , nonemotional words valence  $F(1, 40) = .35, p = .56$  or arousal  $F(1, 40) = 1.3, p = .26$  and nonemotional pictures valence  $F(1, 40) = .11, p = .74$  or arousal  $F(1, 40) = .09, p = .77$ . Arousal and valence ratings were highly correlated ( $r = -0.81$ ), which was consistent with a previous study (Canli, et al, 2002).

### **3.3 Group BOLD Responses**

Compared to the resting state, the encoding of pictures and words produced significant blood oxygenation changes in multiple areas of the cerebral hemispheres. Specifically, activation was observed in the frontal, temporal and parietal lobes (Figures 8-10). Each lobe was isolated using Pick Atlas, and all regions that survived the  $p < .05$  threshold are presented below (Table 6-9). Frontal lobe activation was seen for emotional pictures in the dorsolateral prefrontal cortex (Brodmann's area 9 and 45), lateral premotor cortex, precentral gyrus (Brodmann's area 6) and frontal eye fields. Neutral pictures activated the frontal eye fields. Emotional and neutral words produced bilateral activation in the middle and inferior frontal gyrus, respectively. Temporal lobe activation was seen for emotional pictures in the middle temporal gyrus and cerebellum. Neutral pictures activated the transverse temporal gyrus. Emotional and neutral words

produced activation in the superior temporal gyrus (area 38). Parietal lobe activation was seen for emotional pictures in the supramarginal gyrus (Brodmann's area 40), while neutral pictures only activated the primary somatosensory cortex (Brodmann's area 2). Emotional and neutral words produced activation in the postcentral gyrus. The hippocampi were isolated as a Region of Interest (ROI) using the PickAtlas program. This ROI analysis revealed marked activation in the right hippocampus ( $p < 0.09$ ) for emotional picture encoding, but it did not reach the  $p < .05$  level of significance (Figure 11). There was no significant activation for emotional words, neutral pictures or neutral words.

In a direct comparison of emotional versus neutral pictures, significant blood oxygenation changes were seen in all areas of the cerebral hemispheres. Specifically, activation was seen in the frontal, temporal, parietal and occipital lobes (Figure 12). Occipital lobe activation was found in all conditions, but was not included in Table 10. A cluster analysis was performed and all regions that survived the  $p < .05$  threshold are presented below (Table 10). Frontal lobe activation was found in the left middle frontal gyrus, inferior frontal gyrus (Brodmann's area 47), corpus callosum and sub-cortical white matter. Parietal lobe activation was found in the left cingulate gyrus, superior parietal lobe (BA 7) and left and right precuneus. An ROI analysis revealed activation in the right hippocampus (Figure 13).

In a direct comparison of emotional versus neutral words, significant blood oxygenation changes were seen in all areas of the cerebral hemispheres (Figure 12). A cluster analysis was performed and all regions that survived the  $p < .05$  threshold are presented below (Table 11). Frontal lobe activation was seen in the left cingulate gyrus,

right cingulate gyrus, left and right anterior cingulate gyrus (BA 32), left and right medial frontal gyrus (BA 9), left inferior frontal gyrus (Brodmanns area 47) and subcortical white matter. Parietal lobe activation was seen in the left inferior parietal lobe.

Temporal lobe activation was seen in the left insula (BA 13). The ROI analysis revealed temporal lobe activation in the left hippocampus and parahippocampal gyrus (Table 11; Figure 13), and the left amygdala (Table 11; Figure 16) and uncus.

### **3.4 Gender specific BOLD responses**

The gender specific analysis showed significant activation across several brain regions for pictures and words. The ROI analysis of the hippocampus in females was consistent with the ROI analysis of the group data. In the initial analysis, females showed marked activation in the right hippocampus during encoding emotional pictures (Figure 14), but the activation did not reach the  $p < 0.05$  threshold. When the direct comparison was performed using neutral stimuli as the rest condition, there was significant activation for females in the right hippocampus for emotional pictures,  $p < .01$ , (Figure 15, Table 12) as well as significant activation in the left hippocampus for emotional words,  $p < .01$ , (Figure 15, Table 12). There was also significant activation in the left amygdala for females when comparing emotional versus neutral words,  $p < .01$ , (Figure 16, Table 12). There was no significant activation in the hippocampus for the males in either the picture or word condition.

## 4. DISCUSSION

The present study used functional MRI to examine the differences in hippocampal activation during the encoding of emotional versus neutral information. Several brain areas, including the frontal, parietal and temporal lobes, showed activity during these tasks. When each condition was examined in isolation, there was no significant hippocampal activation for pictures or words. When the direct comparison method was used, comparing emotional versus neutral pictures, the right hippocampus showed greater activation for emotional pictures. The opposite was true for the direct comparison of words, as there was significantly more left hippocampus and parahippocampal gyrus activation for emotional than neutral words. Additional findings also showed activation in the left amygdala for emotional words. The gender analysis showed a similar pattern of activation for females, but not males. The recall data suggested that participants recalled pictures better than words, and emotional items better than non-emotional items. There were no gender differences in memory recall.

### **4.1 Memory Recall**

The differences found between picture and word memory recall supported the consistent empirical finding known as the picture superiority effect (Shepard, 1967; Standing, Conezio & Haber, 1970). This theory asserts that pictures are remembered better than words because pictures evoke two memory traces, verbal and visual. In addition, relative to words, pictures have highly distinctive visual features that allow them to be uniquely encoded in memory. Similarly, the differences found between emotional and non-emotional information supports the ample evidence that emotional

information is better recalled than non-emotional (Hamann, 2001; Kensinger & Corkin, 2004). It has been referred to informally as “flashbulb memory,” as it is a highly vivid form of memory for an emotionally intense event (i.e. learning about the death of a family member). From an evolutionary perspective, the emotional valence and arousal of an event signals that the event might have some future importance for survival. It is adaptive to have superior recall for emotional events, so that information will be available to the individual for future events.

Studies of emotional perception have shown a similar response distribution for emotional pictures, words and acoustic stimuli (Bradley & Lang, 1999). There is an overall boomerang-shaped distribution of the stimuli, with two arms that extend from a calm, non-affective base toward either the high-arousal pleasant or the high-arousal unpleasant quadrant (Lang, Bradley, & Cuthbert, 1998). It would seem consistent that the picture superiority effect would hold for emotional information, in that emotional pictures would be remembered better than emotional words.

Based on the Canli study (2002), we hypothesized that females would have superior emotional memory recall for words and pictures. The discrepancy in our findings may be explained by a small sample size. The Canli study used twenty-four participants, twelve of each gender, where the current study only used seven females and five males. There was also a ceiling effect for recall, as the participants recalled over three-quarters of the emotional items.

#### **4.2 Hippocampal Activation During Encoding**

Prior studies suggested that pictures, both emotional and non-emotional, produced bilateral activation of the hippocampus (Stern, et al., 1996; Gabrieli, et al., 1997;

Kensinger & Corkin, 2004; Richardson, et al., 2004; Canli, et al., 2002; Wright, et al., 2002). We hypothesized similar findings, but also that emotional pictures would produce greater hippocampal activation compared to neutral pictures. We were not able to show significant activation in the hippocampus when we analyzed the pictures in isolation, but the direct comparison revealed greater activation in the right hippocampus for emotional pictures. This finding supported the notion that the hippocampus plays a role in emotional memory processing.

The lack of activity in the hippocampus during the initial analysis of emotional memory was unexpected. One explanation for this could have been due to the rest task. In between each stimuli presentation, participants were shown a blank screen and asked simply to keep their eyes open and prepare for the next image. When the data was analyzed, each active condition was compared to the blank screen rest condition. A recent study suggested that these types of rest periods result in activation of the medial temporal lobe, including the hippocampus and parahippocampal cortex (Stark and Squire, 2001). Thus, our rest task may have produced hippocampal activation, offsetting the activity produced by the emotional images. This would also explain why the neutral images did not produce hippocampal activation. When we replaced the data from the rest condition data with data collected with the active phase of the neutral pictures condition, we found significant hippocampal activation.

We hypothesized that words would activate the left hippocampus with greater activation for emotional words than neutral words. Using the initial analysis, we were not able to demonstrate significant activation of the hippocampus for neutral or emotional words. When we performed a direct comparison between emotional versus neutral words

we found significantly greater activation in the left hippocampus for emotional rather than neutral words. Thus, our initial hypothesis was supported and emotional memory was relatively greater for emotional words.

Based on previous research, we hypothesized that females would have greater hippocampal activation, bilaterally, than males to emotional words and pictures (Canli, et al., 2002). Using the direct comparison analysis, females demonstrated significant activation in the right hippocampus for emotional pictures and the left hippocampus for emotional words. Males did not demonstrate significant hippocampal activation in either condition. This is consistent with the Canli study, which also found hippocampal activation in only females.

One explanation for the gender differences in encoding affective experiences is the “cognitive-style” hypothesis. This hypothesis states that there are sex differences in the amount of detail encoded for emotional experiences, which serves to improve memory recall. Thus, females have better memory for emotional information because they experience life events more intensely (Seidnitz & Diener, 1998). The Canli study supported this hypothesis by controlling for affect intensity at encoding and the sex-based difference remained. As a result, they concluded that females possess a greater integration of brain processes associated with encoding of emotional experiences. The current study supports this notion and extends the findings for the encoding of emotional words, as well as emotional pictures.

### **4.3 Additional Areas of Activation During Encoding**

Based on previous research, we hypothesized left amygdala activation for emotional word and picture encoding. The initial comparison revealed no activation in

any condition, but using the direct comparison method we found significant activation in the left amygdala for emotional versus neutral words. This finding was also seen during the gender analysis with females. We did not expect activation in the left amygdala for only emotional words, especially with the considerable support for a reciprocal dependence between the amygdala and hippocampus during the encoding of emotional memory (Richardson, et al., 2004; Hamann & Mao, 2002; Canli, et al., 2002; Lane et al., 1997). The only explanation for this discrepancy could be related to the stimuli. The pictures selected from the International Affective Picture Series were not the most emotionally arousing of the set, and may not have produced enough activity in the amygdala.

Emotional pictures and words also showed activation in the middle and inferior frontal gyrus. Activation in this area is consistent with anatomical evidence suggesting the middle and inferior frontal gyri send afferents containing sensory information to the hippocampus (Hanaway, 1998), and that the pathway is important for emotional responses. The right middle frontal gyrus has been shown to be active during emotion-related events (Lane, et al., 1997; Prohovnik, Skudlarski, Fulbright, et al., 2004). Prohovnik and colleagues (2004) used emotional faces from the IAPS to evoke emotional responses and asked participants to indicate at the onset of an emotional reaction. Significant activation was detected in the middle frontal gyrus and hippocampus using this paradigm.

Emotional picture encoding also revealed extensive activation of the precuneus. This parietal lobe structure has been shown to be involved in memory-related imagery and is believed to play a key role in the neural substrate of visual imagery in conscious

memory recall (Fletcher, Frith, Baker, et al., 1995). Participants in the current study were most likely utilizing this structure in their attempt to retain the visual information.

Analyses of emotional words showed activation in the medial frontal gyrus, and superior temporal gyrus, both areas reportedly involved in verbal processing (Jancke, Buchanan, Lutz, Shah, 2001; Prohovnik, et al., 2004; Ochsner, Knierim, Ludlow, et al., 2004). The Jancke study (2001) used fMRI to identify cortical regions involved in emotional dichotic listening. The superior temporal region was activated when the participants focused on words with emotional tone.

#### **4.4 Implications for an fMRI replacement of IAT**

Considering the current and previous studies on emotional memory, there is reason to believe that the fMRI can replace IAT as a memory functioning task. However, the current findings should be viewed with caution. The participants of the current study were young, healthy adults with no prior history of the neurological disorders. Epilepsy patients tend to be older and often have co-morbid psychiatric symptoms. This study should be replicated on a population of epilepsy patients, perhaps in conjunction with a WADA test for comparison. In addition, the current findings on hippocampal activation do not appear to generalize to males. This suggests that different sets of stimuli need to be created for men and woman that take their emotional arousal into account.

A recent fMRI study addressed gender differences in emotional responsiveness by factoring out differences in emotional arousal. Females still produced significantly greater activation of the hippocampus for emotional pictures when compared to men. Thus, future studies must address how to significantly activate the male hippocampus with emotional information. Perhaps instead of increasing the emotional arousal of the

images, increase the novelty of the stimuli. Previous studies of non-emotional encoding have shown that the hippocampus may be responsible for encoding of novel information (Saykin, et al., 1999). This could also be accomplished by presenting environmental sounds with emotional content, which has been shown to activate the hippocampus (Bradley & Lang, 2000). Emotional environmental sound have also been shown to have a similar pattern of memory recall as emotional pictures (Bradley & Lang, 2000). Either way, findings from previous studies of emotional encoding should also be viewed with caution if the of gender was not taken into account.

#### **4.5 Additional Future Directions**

Future studies of hippocampal activation and emotional encoding should continue to use unpleasant emotional stimuli. Previous studies examining the neuroanatomical correlates of pleasant and unpleasant emotional encoding found unique components mediating each of them in healthy woman (Lane, et al., 1997). Unpleasant emotional pictures were distinguished from pleasant pictures because they activated the left parahippocampal gyrus and hippocampus, while pleasant emotional pictures activated the medial prefrontal cortex (Brodmann's area 9), thalamus, hypothalamus and midbrain, but not the hippocampus. However, future studies of the amygdala should consider using both positive and negative emotional stimuli, as both elicited left amygdala activation (Hamman & Mao, 2002).

Future studies should consider using an event-related design instead of the block design used in the current study. An event-related design would enable data to be collected on the activation of many brief sets of items. Therefore, the stimuli to be alternated in terms of emotional content and hippocampal activation could be measured

in a more dynamic fashion. In addition, future studies should consider examining the hippocampus after simply presenting emotional information without a memory component. It may be possible to stimulate the hippocampus in this fashion because of its role bi-directional relationship with the amygdala.

### List of References

- Adolphs, R., Tranel, D., & Damasio, A. (1998). *Nature (London)*, 393, 470-474.
- Adolphs, R., Tranel, D., Damasio, H. & Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature*, 372,669-672.
- Aldenkamp, A., Boon, P., Deblaere, K., Achten, E., Backes, W., Boon, P., Hofman, P., Troost, J., Vandemaele, P., Vermeulen, J., Vonck, K., & Wilmink, J. (2003). Usefulness of language and memory testing during intracarotid amobarbital testing: observations from an fMRI study. *Acta Neurologica Scandinavia*, 108, 147-152.
- Alkire, M., Haier, R., Fallon, J., & Cahill, L. (1998). Hippocampal, but not amygdala, activity at encoding correlates with long-term, free recall of nonemotional information. *Proceedings of the National Academy of Sciences, USA*, 95, 14506-14510.
- Alvarez, P., Zola-Morgan, S., & Squire, L. (1995). Damage limited to the hippocampal region produces long-lasting memory impairment in monkeys. *The Journal of Neuroscience*, 15 (5), 3796-3807.
- Amaral, D., Behniea, H., & Kelly, J. (2003). Topographical organization of projections from the amygdala to the visual cortex in the macaque monkey. *Neuroscience*, 118, 1099-1120.
- Ashburner, J. & Friston, K. (1999). Nonlinear spatial normalization using basis functions. *Human Brain Mapping*, 7 (4), 254-266.
- Baker, J., Sanders, A., Maccotta, L., & Buckner, R. (2001). Neural correlates of verbal memory encoding during semantic and structural processing tasks. *Brain Imaging*, 12 (6), 1251-1256.
- Beauregard, M., Chertkow, H., Bub, D., Murtha, S., Dixon, R., & Evans, A. (1997). The neural substrate for concrete, abstract, and emotional word lexica: A positron emission tomography study. *Journal of Cognitive Neuroscience*, 9 (4), 441-461.
- Bechara A., Tranel D., Damasio, H., Adolphs, R., Rockland, C., & Damasio, A. (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science*, 269, 1115-1118.

- Blair, J. & Spreen, O. (1989). Predicting premorbid IQ: A revision of the National Adult Reading Test. *The Clinical Neuropsychologist*, *3*, 129-136.
- Bradley, M. & Lang, P. (2000). Affective Reactions to acoustic stimuli. *Psychophysiology*, *37*, 204-215.
- Bradley, M. & Lang, P. (1999). *Affective Norms for English Words (ANEW)*. Gainesville: NIMH Center for the Study of Emotion and Attention, University of Florida.
- Buckner, R.L., Petersen, S.E.M., Ojemann, J.G., Miezin, F.M., Squire, L.R., & Raichle, M.E. (1995). *Journal of Neuroscience*, *15*, 12-29.
- Buckner, R. & Koutstaal, W. (1998). Functional neuroimaging studies of encoding, priming, and explicit retrieval. *Proceedings of the National Academy of Sciences*, *95*, 891-898.
- Bullock, J. (2000). Beyond speech lateralization: A review of the variability, reliability, and validity of the intracarotid amobarbital procedure and its nonlanguage uses in epilepsy surgery candidates. *Neuropsychology Review*, *10*, 41-74.
- Burnwell, R., Suzuki, W., & Amaral, D. (1996). Some observations on the perirhinal and parahippocampal cortices in the rat, monkey and human brains. In *Perception, Memory and Emotion: Frontiers in Neuroscience*, ed. T Ono, BL McNaughton, S Molotchnikoff, ET, Rolls, H, Nishijo, pp. 95-110. New York: Elsevier. 620 pp.
- Cahill, L. & McGaugh, J. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends in Neuroscience*, *21*, 294-299.
- Cahill, L., Haier, R., Fallon, J., Alkire, M., Tang, C., Keator, D., Wu, J., & McGaugh, J. (1996). *Proceedings of the National Academy of Sciences, USA*. *93*, 8016-8021.
- Cahill, L., Babinsky, R., Markowitsch, H. & McGaugh, J. (1995). The amygdala and emotional memory. *Nature*, *377*, 295-296.
- Canli, T., Desmond, J., Zhao, Z., & Gabrieli, J. (2002). Sex differences in the neural basis of emotional memories. *Proceedings of the National Academy of Sciences*, *99* (16), 10789-10794.
- Canli, T., Zhao, Z., Desmond, J., Glover, G., & Gabrieli, J. (1999). FMRI identifies a network of structures correlated with the retention of positive and negative emotional memory. *Psychobiology*, *27*, 441-452.

- Canli, T., Desmond, J., Zhao, Z., Glover, G., & Gabrieli, J. (1998). Hemispheric asymmetry for emotional stimuli detected with fMRI. *NeuroReport*, 9 (14), 3233-3239.
- Carretie, L., Hinojosa, J., & Mercado, F. (2003). Cerebral patterns of attentional habituation to emotional visual stimuli. *Psychophysiology*, 40, 381-388.
- Casasanto, D., Killgore, W., Maldjian, J., Glosser, G., Alsop, D., Cooke, A., Grossman, M., & Detre, J. (2002). Neural Correlates of successful and unsuccessful verbal memory encoding. *Brain and Language*, 80, 287-295.
- Cohen, N., & Squire, L., (1980). Preserved learning and retention of pattern analyzing skill in amnesia: dissociation of knowing how and knowing that. *Science*, 210, 207-209.
- Corkin, S. (1968). Acquisition of motor skill after bilateral medial temporal-lobe excision. *Neuropsychologia*, 3, 339-351.
- Crosson, B., Cato, M., Sadek, J., Gokcay, D., Bauer, R., Fischler, I., Maron, L., Gopinath, K., Auerbach, E., Browd, S., & Briggs, R. (2002). *Journal of the International Neuropsychological Society*, 8,607-622.
- Courtney, S., Ungerleider, L., Keil, K., & Haxby, J. (1996). *Cerebral Cortex*, 6, 39-49.
- Davachi, L. & Wagner, A., (2002). Hippocampal contributions to episodic encoding: Insights from relational and item-based learning. *Journal Neurophysiology*, 88, 982-990.
- Davis, M., & Whalen, P., (2001). The amygdala: vigilance and emotion. *Molecular Psychiatry*, 6, 13-34.
- Deblaere, K., Backes, W., Hofman, P., et al., (2002). Developing a comprehensive presurgical functional MRI protocol for patients with intractable temporal lobe epilepsy: a pilot study. *Neuroradiology*, 44, 667-673.
- Detre, J., Macotta, B., King, D., et al., (1998). Functional MRI lateralization of memory in temporal lobe epilepsy. *Neurology*, 50, 926-932.
- Dolan, R., & Fletcher, P. (1997). Dissociating prefrontal and hippocampal function in episodic memory encoding. *Nature*, 7,582-585.
- Driesen, J.L. (2005). The limbic system- 2.  
[http://www.driesen.com/the\\_limbic\\_system\\_-\\_2.htm](http://www.driesen.com/the_limbic_system_-_2.htm)

- Engel, J. (1996). Surgery for Seizures. *New England Journal of Medicine*, 334, 647-652.
- Engel, J. (1992). Outcome with respect to epileptic seizures. In: Engel J, ed. *Surgical treatment of the epilepsies*, 2<sup>nd</sup> ed. New York: Raven Press 609-621.
- Fernandez, G., Weyerts, H., Schrader-Bolsche, M., et al., (1998). Successful verbal encoding into episodic memory engages the posterior hippocampus: A parametrically analyzed functional magnetic resonance imaging system. *The Journal of Neuroscience*, 18 (5), 1841-1847.
- Fletcher, P., Frith, R. & Rugg, M. (1997). The functional neuroanatomy of episodic memory. *Trends in Neuroscience*, 20, 213-218.
- Fletcher, P., Frith, C., Baker, S., et al. (1995). The mind's eye- precuneus activation in memory-related imagery. *Neuroimage*, 2, 195-200.
- Frey, S., & Petrides, M. (2000). Orbitalfrontal cortex: A prefrontal region for encoding information. *Proceedings of the National Academy of Science*, 97 (15), 8723-8727.
- Funayama, E., Grillon, C., Davis, M., & Phelps, E. (2001). A double dissociation in the affective modulation of startle in humans: effects of unilateral temporal lobectomy. *Journal Cognitive Neuroscience*. 13:721-729.
- Gabrieli, J., Fleischman, D., Keane, M., Reminger, S., & Morrell, F. (1995). Double Dissociation between memory systems underlying explicit and implicit memory in the human brain. *Psychological Science*, 6 (2), 76-82.
- Gabrieli, J., Desmond, J., Domb, J., et al., (1996). Functional magnetic resonance imaging of semantic memory processes in the frontal lobe. *Psychological Science*, 7, 278-283.
- Gabrieli, J., Brewer, J., Desmond, J., et al., (1997). Separate neural basis of two fundamental memory processes in the human medial temporal lobe. *Science*, 276(5310), 264-266.
- Golby, A., Poldrack, R., Brewer, J., Spencer, D., Desmond, J., Aron, A., & Gabrieli, D. (2001). Material-specific lateralization in the medial temporal and prefrontal cortex during memory encoding. *Brain*, 124, 1841-1854.
- Golby, A., Poldrack, R., Illes, J., Chen, D., Desmond, J., & Gabrieli, J. (2002). Memory lateralization in medial temporal epilepsy assessed by functional MRI. *Epilepsia*, 43 (8), 855-863.

- Gotman, J., Bouwer, M., & Jones-Gotman, M., (1992). Intracranial EEG study of brain structures affected by internal carotid injection of amobarbital. *Neurology*, 42, 2136-2143.
- Hamman, S., Ely, T., Grafton, S., & Clinton K. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nature Neuroscience*, 2 (3), 289-294.
- Hamann, S. (2001). Cognitive and neural mechanisms of emotional memory. *Trends in Cognitive Sciences*, 5, 394-400.
- Hamann, S. & Mao, H. (2002). Positive and negative emotional verbal stimuli elicit activity in the left amygdala. *NeuroReport*, 13 (1), 15-19.
- Hanaway, J., Woolsey, T., Gado, M., & Roberts, M. (1998). The Brain Atlas: A visual guide to the human central nervous system. Fitzgerald Science Press, Inc., Bethesda, MD.
- Haxby, J., Ungerleider, L., Horwitz, B., Maisog, J., Rapoport, S., & Grady, C. (1996). *Proceedings of the National Academy of Science, USA* 93, 922-927.
- Hebb, D., & Penfield, W. (1949). The Organization of Behavior: A Neuropsychological Theory. Wiley, New York.
- Holmes, A., & Friston, K. (1998). Generalisability, random effects and population inference. *Neuroimage*, 7(4), S754.
- Hunkin, N., Mayes, A., Gregory, L., Nicholas, A., Nunn, J., Brammer, M., Bullmore, E., & Williams, S. (2002). Novelty-related activation within the medial temporal lobes. *Neuropsychologia*, 40, 1456-1464.
- Janke, L., Buchanan, T., Lutz, K., & Shah, N. (2001). Focused and nonfocused attention in verbal and emotional dichotic listening: An fMRI study. *Brain and Language*, 78, 349-363.
- Kapur, S., Craik, F., Tulving, E., Wilson, A., Houle, S., & Brown, G. (1994). *Proceedings of the National Academy of Science*, 91, 2008-2011.
- Kelley, W., Miezin, F., McDermott, K., Buckner, R., Raichle, M., Cohen, N., Ollinger, J., Akbudak, E., Conturo, J., Snyder, A., & Petersen, S. (1998). Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. *Neuron*, 20, 927-936.
- Kolb, B., & Wishaw, I. (1996). *The Fundamentals of Human Neuropsychology*. W.H Freeman and Company, New York.

- Lane, R., Reiman, E., Bradley, M., Lang, P., Ahern, G., Davidson, R., & Schwartz, G. (1997). *Neuropsychologia*, 35(11), 1437-1444.
- Lang, P., Greenwald, M., Bradley, M., & Hamm, A. (1993). *Psychophysiology*, 30, 261-273.
- Lang, P., Bradley, M., & Cuthbert, B. (1998). Emotional and Motivation: Measuring Affective Perception. *Journal of Clinical Neurophysiology*. 15(5): 397-408.
- Lashley, K. (1929). *Brain Mechanism and Intelligence*. Chicago Illinois: University of Chicago Press (pp 27-70).
- Loring, D., Lee, G., Meador, K., et al. (1990). The intracarotid amobarbital procedure as predictor of memory failure following unilateral temporal lobectomy. *Neurology*. 40, 605-610.
- Luebe, D., Erb, M., Grodd, W., Bartels, M. & Kircher, T. (2001). Differential activation in parahippocampal and prefrontal cortex during word and face encoding tasks. *Brain Imaging*, 12(12), 2773-2777.
- Maldjian, J., Laurienti, P., Kraft, R. & Burdette, J. (1993). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*. 19(3), 1233-1239.
- Malmgren, K., Bilting, M., Hagberg, I., et al., (1992). A compound score for estimating the influence of inattention and somnolence during the intracarotid amobarbital test. *Epilepsy Research*. 12, 253-259.
- Markowitsch H.J., Calabrese P., Wurker M., et al., (1994). The amygdala's contribution to memory: a study on two patients with Urbach-Wiethe disease. *NeuroReport*, 5, 1349-1352.
- Martin, A., Wiggs, C., & Weisburg, J. (1997). Modulation of human medial temporal activity by form, meaning and experience. *Hippocampus*, 7, 587-593.
- McGaugh, J., Cahill, L., & Roozendaal, B. (1996). Involvement of the amygdala in memory storage: interaction with other brain systems. *Proceedings of the National Academy of Science*, 93, 13508-13514.
- Milner, B. (1962). Les troubles de la memoire accompagnant les lesions hippocampiques bilaterales. *In Physiologie de l'Hippocampe, Colloques Internationaux No. 107* (Paris C.N.R.S.), pp. 257-272.
- Milner, B. (1972). Disorders of learning and memory after temporal lobe lesions in man. *Clinical Neurosurgery*, 19, 421-466.

- Milner, B., Squire, L., & Kandel, E., (1998). Cognitive Neuroscience and the Study of Memory. *Neuron*, 20, 445-468.
- Mishkin, M. (1978). Memory in monkeys severely impaired by combined but not separate removal of amygdale and hippocampus. *Nature*, 273, 297.
- Mohamed, F., Pinus, A., Faro, S., Patel, D., & Tracy, J. (2002). BOLD fMRI of the visual cortex: quantitative responses measured with a graded stimulus at 1.5 Tesla. *Journal of Magnetic Resonance Imaging*, 16, 128-136.
- Murray, E. (1996). What have ablation studies told us about the neural substrates of stimulus memory? *Seminars in Neuroscience* 8, 13-22.
- Murray, E. (2000). Memory for objects in nonhuman primates. In: Gazzaniga MS, editor. *The New Cognitive Neurosciences*. Cambridge, MA: MIT Press, p.753-763.
- Nieuwenhuy, R., & Voogd, J., vanHuijzen, C. (1992). *The Human Central Nervous System*, A Synopsis and Atlas. Third Edition. Springer-Verlag, Berlin.
- Nolte, J. (2002). *The Human Brain*. Fifth Edition. Mosby, St. Louis, MO.
- Penfield, W., & Milner, B. (1958). Memory deficit produced by bilateral lesions in the hippocampal zone. *Archives of Neurology and Psychiatry*, 79,475-497.
- Petersen, S., Fox, P., Posner, M., et al., (1988). Positron emission tomographic studies of the cortical anatomy of single word processing. *Nature (London)*, 372, 543-546.
- Petersen, R., Sharbrough, F., & Jack, C. (1993). *Intracarotid amobarbital testing*. In: Wyllie E, ed. *The treatment of epilepsy: principles and practice*. Philadelphia: Lea & Febiger, 1993: 1051-61
- Phelps, E., O'Conner, K., Gatenby, J., Grillon, C., Gore, J., & Davis, M. (2001). Activation of the left amygdala to a cognitive representation of fear. *Nature Neuroscience*, 4, 437-441.
- Phillips, M., Bullmore, E., Howard, R., et al. (1998). Investigation of facial recognition memory and happy, sad facial expression perception. *Psychiatry Research*, 83 (3), 127-138.
- Rabin, M., Narayan, V., Kimberg, D., et al. (2004). Functional MRI predicts post-surgical memory following temporal lobe epilepsy. *Brain*, 127, 2286-2298.
- Rama, P., Martinkauppi, S., Linnankoski, I., Koivisto, J., Aronen, H. & Carlson, S. (2001). *Neuroimage*, 13, 1090-1101.

- Rausch, R., Silfvenius, H., Wieser, H., et al. Intraarterial amobarbital procedures. In: Engel J Jr., ed. *Surgical treatment of the epilepsies*. 2<sup>nd</sup> ed. New York: Raven Press, 1993:341-357.
- Richardson, M., Strange, B., Dolan, R. (2004). Encoding of emotional memories depends on amygdala and hippocampus and their interactions. *Nature Neuroscience*, 7 (3), 278-285.
- Rombouts, S., Barkof, F., Witter, M., Machielsen, C. & Scheltens, P. (2001). Anterior medial temporal lobe activation during attempted retrieval of encoding visuospatial scenes: An event-related fMRI study. *Neuroimage*, 14, 67-76.
- Saykin, A., Johnson, S., Flashman, L., et al. (1999). Functional differentiation of medial temporal and frontal regions involved in processing novel and familiar words: an fMRI study. *Brain*, 122, 1963-1971.
- Scoville, W., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, 20, 11-21.
- Schmahmann, J., & Sherman, J. (1998). The cerebellar cognitive affective syndrome. *Brain*. 121, 561-579.
- Seidlitz, L. & Diner, E. (1998). Sex differences in the recall of affective experiences. *Journal of Personality and Social Psychology*, 74(1), 262-271.
- Shallice, T., Fletcher, P., Frith, C., Grasby, P., Frackowlak, S. & Dolan, R. (1994). Brain regions associated with acquisition and retrieval of verbal episodic memory. *Nature*, 386, 633-635.
- Shepard, R. (1967). Recognition memory for words, sentences, and pictures. *Journal of Verbal Learning and Verbal Behavior*, 6, 156-163.
- Squire, L. (1992). Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychological Review*, 99 (2), 195-231.
- Squire, L, Stark, C & Clark, R. (2004). The medial temporal lobe. *Annual Review of Neuroscience*, 27,279-306.
- Squire, L. & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science*, 253,1380-1386.
- Standing, L., Conezio, J. & Haber, R. (1970). Perception of memory for pictures: Single trial learning of 2560 visual stimuli. *Psychonomic Science*, 19, 73-74.

- Stark, C. & Squire, L. (2001). When zero is not zero: The problem of ambiguous baseline conditions in fMRI. *Hippocampus*, *10*, 329-337.
- Stern, C., Corkin, S., Gonzalez, G., Guimares, A., Baker, J., Jennings, P., Carr, C., Sugiura, R., Vedantham, V., & Rosen, B. (1996). The hippocampal formation participates in novel picture encoding: Evidence from functional magnetic resonance imaging. *Proceedings of the National Academy of the Sciences*, *93*, 8660-8665.
- Tabert, M, Borod, J, Tang, C, Lange, G, Wei, T, Johnson, R, Nusbaum, A, Buchsbaum, M. (2001). Differential amygdala activation during emotional decision and recognition memory tasks using unpleasant words: an fMRI study. *Neuropsychologia*, *39*, 556-573.
- Talairach, J. & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: An approach to cerebral imaging*. New York: Thieme.
- Tulving, E., Kapur, S., Craik, F., Moscovitch, M. & Houle, S. (1994). *Proceedings of the National Academy of the Sciences USA*, *91*, 2016-2020.
- Wada, J. & Rasmussen, T. (1960). Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. *Journal of Neurosurgery*, *17*, 266-282.
- Wagner, A., Schacter, D., Rotte, M., et al. (1998). Building Memories: Remembering and Forgetting of Verbal Experiences as Predicted by Brain Activity. *Science*, *281*, 1188-1191.
- Weiss, K.L., Figueroa, R.A., and Allison, J. (1998). Functional MR imaging in patients with epilepsy. *MRI Clinics of North America*, *6*, 95-112.
- Wise, R., Chollet, F., Hadar, U., et al. (1991). Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain*, *114*(4), 1803-1817.
- Wright, C., Martis, B., Shin, L., Fischer, H. & Rauch, S. (2002). Enhanced amygdala responses to emotional versus neutral schematic facial expressions. *NeuroReport*, *13* (6), 785-790.

## Appendix A. Tables

Table 1. Imaging studies on encoding of visual information.

Author(s)	Stimuli	Findings
Stern et al., 1996	Novel pictures	Encoding: Bilateral, posterior hippocampus, parahippocampal gyrus, and lingual/fusiform gyrus Retrieval: Bilateral, Anterior hippocampus
Gabrieli et al., 1997	Novel & familiar images	Novel: Bilateral, posterior MTL (e.g., para-Hippocampal cortex), right frontal (inferior frontal sulcal region) Familiar: anterior temporal lobe (subiculum)
Frey and Petrides, 2000; (PET)	Abstract images	Entorhinal and perirhinal cortex Right rostral, orbitalfrontal cortex, fusiform gyrus, and LPFC areas
Rombouts et al., 2001	Novel and Familiar pictures	Novel: Left posterior MTL (parahippocampal gyrus), Fusiform gyrus and frontal cortex
Luebe et al., 2001	Faces	Faces: Right posterior hippocampal formation, Bilateral fusiform gyrus
Kelley et al., 1998	Unfamiliar faces	Right hippocampus, dorsal frontal cortex; bilateral Parietal and fusiform gyrus

Note: MTL, medial temporal lobe, LPFC, lateral prefrontal cortex; PFC.

Table 2. Imaging findings for encoding of verbal information during medial temporal lobe.

<b>Author (s)</b>	<b>Stimuli</b>	<b>Findings</b>
Tulving, et al., 1994	Series of words	Left ventrolateral PFC (BA 10, 46, 45, 47)
Fernandez et al., 1998	Word list	Posterior hippocampus (54% right, 46% left) Right precentral gyrus, left precentral gyrus, posterior transverse temporal gyrus
Kelley et al., 1998	Words and namable objects	Left hippocampus, dorsal frontal and fusiform gyrus, posterior parietal and posterior visual cortex
Wagner et al., 1998	Incidental word	Left parahippocampal, fusiform gyrus and PFC
Saykin et al., 1999	Novel and Familiar words	Novel: Anterior left hippocampus Familiar (learned): Right prefrontal cortex and superior temporal gyrus, left posterior parahippocampal gyrus and left parietal cortex
Luebe et al., 2001	Nouns	Left anterior hippocampal formation, left prefrontal, bilateral frontal, occipital, fusiform gyrus
Dolan and Fletcher, 1997	Novel and familiar words	Novel: Left hippocampal and prefrontal
Baker et al., 2001	Processing of words	Semantic (deep): Left inferior frontal, fusiform gyrus and right precentral gyrus, Structural (shallow): Medial and lateral parietal lobes, and anterior medial frontal lobe
Hunkin et al., 2002	Familiar and novel word association	Familiar: Posterior cingulate cortex Novel: MTL and posterior cingulate Single item: No significant differences
Golby et al., 2001	Nouns, Verbs and Adjectives	Left inferior prefrontal cortex and MTL
Casasanto, et al., 2002	4-word sentences	Left inferior prefrontal and MTL structures

Table 2. (*continued*)

<b>Author (s)</b>	<b>Stimuli</b>	<b>Findings</b>
Martin et al., 1997	Naming real and non-sense objects	Overall Left>Right activation MTL activation occurred greater when the activation depends on stimulus characteristics (word form and meaning)
Segar et al., 2000	Usual and unusual noun-verb	Usual: Left inferior prefrontal cortex and right cerebellum Unusual: Right middle and superior frontal gyri, left middle frontal gyrus and bilateral cerebellum
Davachi & Wagner, 2002	Item-based word associations	Relational-based processing: hippocampus Item-based: entorhinal and parahippocampal gyri
Dolan, 1999	Word	Left anterior hippocampus
Shallice et al, 1994	Dual-interference	Left prefrontal cortex
Alkire et al., 1998	Word List, recall	Left hippocampus activity at encoding highly correlated with free-recall; no correlation present with other MTL structures

Note: MTL, medial temporal lobe, PFC, prefrontal cortex.

Table 3. Imaging findings for encoding of emotional visual information

<b>Author(s)</b>	<b>Stimuli</b>	<b>Findings</b>
Cahill et al., 1996 (PET)	Emotionally neutral and arousing film clips	Emotional: Right amygdala; Neutral: bilateral parahippocampal cortex, Uncus
Hamann et al., 1999 (PET)	Pleasant and unpleasant visual stimuli	Pleasant: bilateral hippocampus Unpleasant: bilateral amygdala and hippocampus
Lane et al., 1997	Pleasant and unpleasant emotional pictures	Pleasant: left caudate nucleus Unpleasant: left amygdala, hippocampus, parahippocampal gyrus, and bilateral occipitotemporal cortex and cerebellum
Wright et al., 2002	Schematic emotional faces (angry, happy and neutral)	Emotional (i.e. happy & angry): Left hippocampus, amygdala, inferior and bilateral medial PFC, right anterior temporal cortex; Angry: left occipitotemporal
Canli et al., 2002	Emotional arousal through emotional pictures	Woman: left hippocampus, postcentral gyrus; Men & Woman: left amygdala, bilateral superior frontal gyrus, anterior cingulate
	Correlation: recognition memory, emotional pictures	Woman: left amygdala, hippocampus Men: right amygdala

Table 4. Imaging findings for encoding of emotional verbal information

<b>Author(s)</b>	<b>Stimuli</b>	<b>Findings</b>
Richardson, et al., 2004	Neutral and negative words	Negative: L hippocampus and amygdala
Kensinger and Corkin, 2004	Neutral and emotional words	Emotional: Amygdala & hippocampus
Crosson et al., 2002	Monitoring words with emotional connotations	Anterior left frontal lobe
Beauregard et al., 1997	Abstract or emotional words	Abstract: Left temporal and inferior frontal Emotional: Left anterior frontal
Tabert et al., 2001	Unpleasant words	Unpleasant: Right amygdala
Hamann, et al., 2001	Positive, negative and neutral words	Positive & Negative: Left amygdala, Dorsal; Striatum & ventral striatum (positive only)

Table 5. Volunteer and normative stimuli ratings in mean valence and arousal with standard deviations in parenthesis.

---

	<u>Normative Ratings</u>		<u>Volunteer Ratings</u>	
	Valence	Arousal	Valence	Arousal
Emotional Words	1.79 (1.28)	6.59 (2.51)	1.75 (1.30)	6.60 (2.50)
Non-emotional Words	4.55 (1.74)	4.37 (2.28)	4.60 (1.60)	4.30 (2.24)
Emotional Pictures	3.11 (1.79)	5.76 (2.12)	3.20 (1.80)	5.80 (2.10)
Non-emotional Pictures	5.45 (1.48)	3.66 (2.07)	5.50 (1.40)	3.75 (2.00)

---

Table 6. Brain regions where activation was present during the encoding of emotional pictures. Gender analysis examined only the hippocampus. Significance levels and T-scores are provided.

Structure	p-value	X,Y,Z Coordinates	T-score
<b>Group Analysis</b>			
Frontal lobe			
R inferior frontal gyrus	.05	50, 8, 28	8.83
R inferior frontal gyrus, BA 45		62, 18, 18	5.28
R inferior frontal gyrus, BA 9		62, 16, 22	4.58
R inferior frontal gyrus		58, 14, 20	2.99
R inferior frontal gyrus, BA 9		60, 16, 22	3.85
R middle frontal gyrus		34, 10, 30	2.87
R precentral gyrus, BA 6		40, 2, 28	5.12
R precentral gyrus		54, 4, 34	4.24
Temporal lobe			
R hippocampus	.086	32, -18, -14	1.88
R middle temporal gyrus	.01	36, -58, -20	7.95
R cerebellum		42, -62, -20	5.29
R cerebellum posterior lobe		46, -52, -24	6.58
R cerebellum posterior lobe		44, -60, -24	4.63
R cerebellum posterior lobe		52, -62, -18	4.24
R cerebellum anterior lobe		38, -46, -24	4.18
		36, -24, -40	5.36
Parietal lobe			
R inferior parietal lobe, BA 40	.05	38, -36, 40	2.10
R inferior parietal lobe		40, -40, 34	1.81
<b>Female</b>			
R hippocampus	.086	32, -18, -14	1.97

Table 7. Brain regions where activation was present during the encoding of neutral pictures. Significance levels and T-scores are provided.

Structure	p-value	X,Y,Z Coordinates	T-score
Group Analysis			
Temporal lobe			
R transverse temporal gyrus	.05	66, -14, 10	2.49
Frontal lobe	.05	34, 24, 54	3.37
Parietal lobe			
L postcentral gyrus, BA 2	.05	-36, -38, 62	2.12

Table 8. Brain regions where activation was present during the encoding of emotional words. Significance levels and T-scores are provided.

Structure	p-value	X,Y,Z Coordinates	T-score
Group Analysis			
Temporal lobe			
R supratemporal gyrus, BA38	.05	-44, 18, -24	1.82
Frontal lobe			
R middle frontal gyrus	.05	-26, 30, -6	1.89
R subgyral	.05	-26, 26, 8	1.76
Parietal lobe			
L postcentral gyrus	.05	-52, -22, 16	2.07

Table 9. Brain regions where activation was present during the encoding of neutral words. Significance levels and T-scores are provided.

Structure	p-value	X,Y,Z Coordinates	T-score
Group Analysis			
Temporal lobe			
R subgyral	.05	32, -36, 10	2.16
R subgyral	.05	34, -36, 6	2.09
Frontal lobe			
R inferior frontal gyrus	.05	-34, 10, 26	2.04
Parietal lobe			
L postcentral gyrus	.05	-58, 16, 18	1.88

Table 10. Brain regions that were activated during a direct comparison between emotional and neutral picture encoding.

Structure	p-value	X,Y,Z Coordinates	T-score
Group Analysis			
Frontal Lobe			
L middle frontal gyrus	.01	32, 48, -8	2.85
L middle frontal gyrus		38, 44, -12	2.87
L middle frontal gyrus		34, 44, -4	3.48
L middle frontal gyrus		34, -14, -14	3.59
L inferior frontal gyrus, BA 47		34, 26, 0	3.11
L corpus callosum		-10, 26, 12	6.79
L corpus callosum		10, 30, 8	5.82
L corpus callosum		16, 26, 10	5.18
L corpus callosum		16, 36, 4	5.07
L sub-gyral (white matter)		-12, 34, 8	6.11
R sub-gyral (white matter)		22, 30, 4	4.92
R sub-gyral (white matter)		24, 36, 2	4.54
R sub-gyral (white matter)		30, 30, 0	4.23
R sub-gyral (white matter)		24, 42, -2	3.70
R sub-gyral (white matter)		18, 44, 0	2.99
R limbic lobe (white matter)		10, 28, 12	6.09
R sub-lobar (white matter)		26, 24, 6	5.49
R extra-nuclear (white matter)		20, 26, 8	5.07
R extra-nuclear (white matter)		-18, 28, 4	4.96
L extra-nuclear (white matter)		-18, 26, 8	4.89
Temporal Lobe			
R hippocampus		32, -18, -14	2.51
Parietal Lobe			
L cingulate gyrus		-16, -44, 34	3.42
L superior parietal lobe, BA 7		-24, -64, 46	3.24
L superior parietal lobe, BA 7		-28, -66, 46	3.75
L precuneus		-16, -54, 38	5.45
L precuneus		-20, -52, 36	4.96
L precuneus		4, -70, 54	4.54
L precuneus		-6, -52, 38	4.53
L precuneus, BA 7		-10, -62, 46	4.15
L precuneus, BA 7		-20, -66, 46	3.92
L precuneus, BA 7		4, -56, 44	3.70
L precuneus		-16, -62, 44	3.78
L precuneus		-14, -58, 44	3.59
L precuneus, BA 7		-6, -62, 46	3.24
R precuneus		4, -62, 48	2.78
R precuneus, BA 7		10, -54, 50	4.03
R precuneus		10, -56, 44	3.97

Table 11. Brain regions were activated during a direct comparison between emotional and neutral word encoding.

Structure	p-value	X,Y,Z Coordinates	T-score
Group Analysis			
Frontal Lobe			
L cingulate gyrus	.001	-14, 28, 28	7.43
R cingulate gyrus		10, 28, 28	4.39
L anterior cingulate, BA 32		-2, 34, 22	4.12
L anterior cingulate		0, 32, 18	4.05
L anterior cingulate		-10, 38, 24	6.09
R anterior cingulate		20, 30, 22	5.24
R anterior cingulate		16, 26, 20	4.61
R anterior cingulate, BA 32		6, 30, 22	5.24
R anterior cingulate, BA 32		8, 36, 16	3.55
R inferior frontal gyrus, BA 46		38, 36, 12	5.54
L medial frontal gyrus, BA 9		-20, 36, 18	4.35
L medial frontal gyrus, BA 9		-4, 40, 22	4.62
R medial frontal gyrus, BA 46		42, 34, 14	5.15
R medial frontal gyrus, BA 9		14, 38, 20	4.92
R medial frontal gyrus		24, 38, 18	4.32
R medial frontal gyrus, BA 9		8, 44, 14	3.67
R medial frontal gyrus		-44, 42, -8	3.46
L inferior frontal gyrus, BA 47		-32, 16, -30	6.25
L inferior frontal gyrus		-42, 34, 6	7.56
L inferior frontal gyrus		-44, 30, -8	6.26
L inferior frontal gyrus, BA 47		-48, 34, -4	5.68
L inferior frontal gyrus		-48, 34, 12	5.49
L inferior frontal gyrus		-46, 26, 2	3.77
L sub-gyral (white matter)		-22, 26, 18	4.16
L sub-gyral (white matter)		-24, 38, 16	3.55
R sub-gyral (white matter)		26, 30, 18	5.81
R sub-gyral (white matter)		34, 28, 12	4.63
R sub-gyral (white matter)		34, 44, 4	3.80
Parietal Lobe			
L inferior parietal lobule		-60, -28, 30	3.96
Temporal Lobe			
L hippocampus		-26, -38, -4	5.49
L hippocampus		-28, -38, 0	2.88
L parahippocampal gyrus		-20, -10, -12	4.17
L parahippocampal gyrus		-26, -6, -20	3.69
L superior temporal gyrus		-44, 16, -22	8.72
L insula		-35, 14, -18	6.39
L insula, BA 13		-38, 16, -2	5.37
L insula, BA 13		-44, 10, -2	3.92
L insula		-46, 6, 0	4.02

Table 11. (*continued*)

Structure	p-value	X,Y,Z Coordinates	T-score
L insula		-50, 14, 0	3.99
L insula		-44, 14, 0	3.75
L amygdala		-20, -8, -18	4.67
L amygdala, BA 34		-18, -8, -16	4.58
L amygdala		-26, -6, 20	3.69
L amygdala/ uncus		-22, -6, -22	3.67
L amygdala/ uncus		-18, -6, -20	3.56

Table 12. Gender analysis of the hippocampus using ROI, showed regions that were activated during a direct comparison between emotional and neutral picture, as well as emotional and neutral word encoding.

Structure	p-value	X,Y,Z Coordinates	T-score
Female- Pictures			
L hippocampus	.01	32, -18, -14	2.51
R hippocampus	ns		
L amygdala	ns		
R amygdala	ns		
Female- Words			
L hippocampus	.01	-26, -38, -4	5.49
L hippocampus		-28, -38, 0	2.88
R hippocampus	ns		
L amygdala		-20, -8, -18	4.67
L amygdala, BA 34		-18, -8, -16	4.58
L amygdala		-26, -6, 20	3.69
L amygdala		-22, -6, -22	3.67
L amygdala		-18, -6, -20	3.56
R amygdala	ns		
Male- Pictures & Words			
R hippocampus	ns		
L hippocampus	ns		
R amygdala	ns		
L amygdala	ns		

## Appendix B. Figures

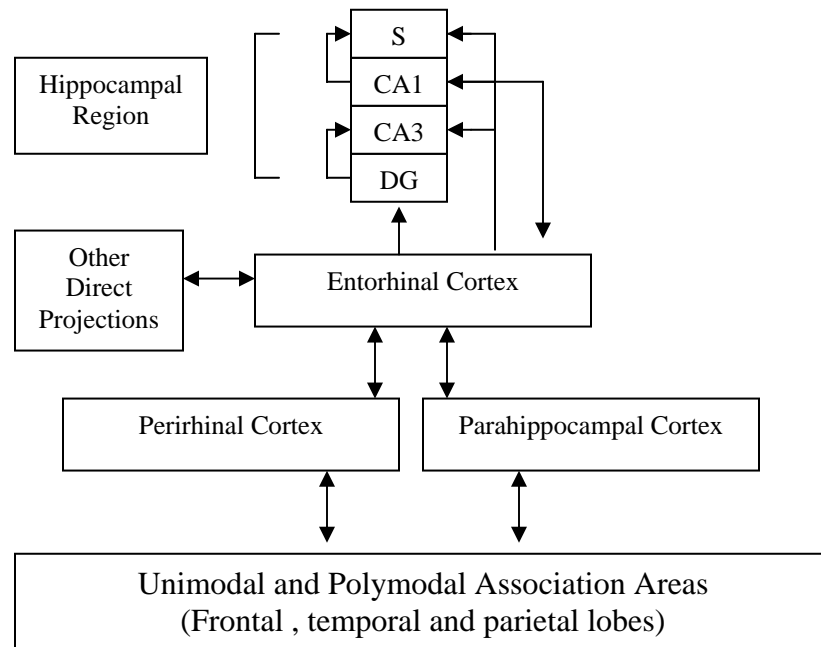


Figure 1. Schematic view of some of the medial temporal lobe structures important for declarative memory. S, subicular complex; DG, dentate gyrus; CA1, CA3, the CA fields of the hippocampus. Adapted from Burnwell, et al. 1996.

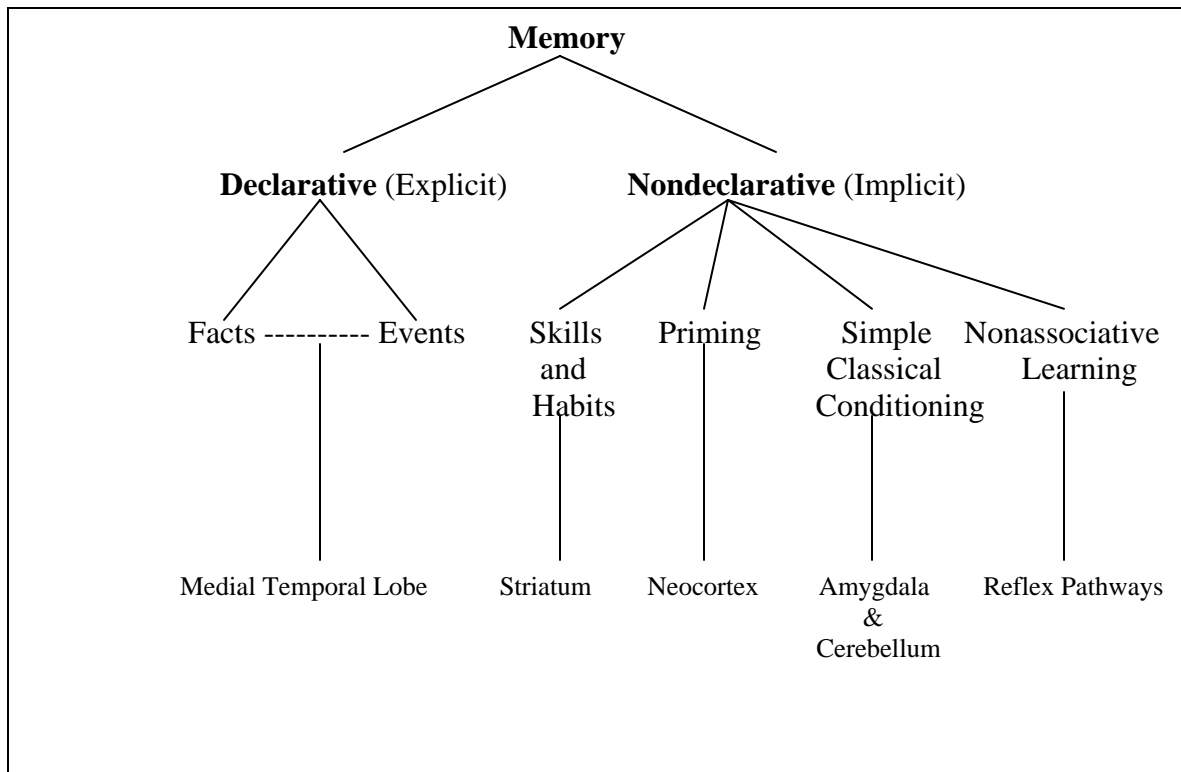


Figure 2. Taxonomy of Declarative and Nondeclarative Memory.

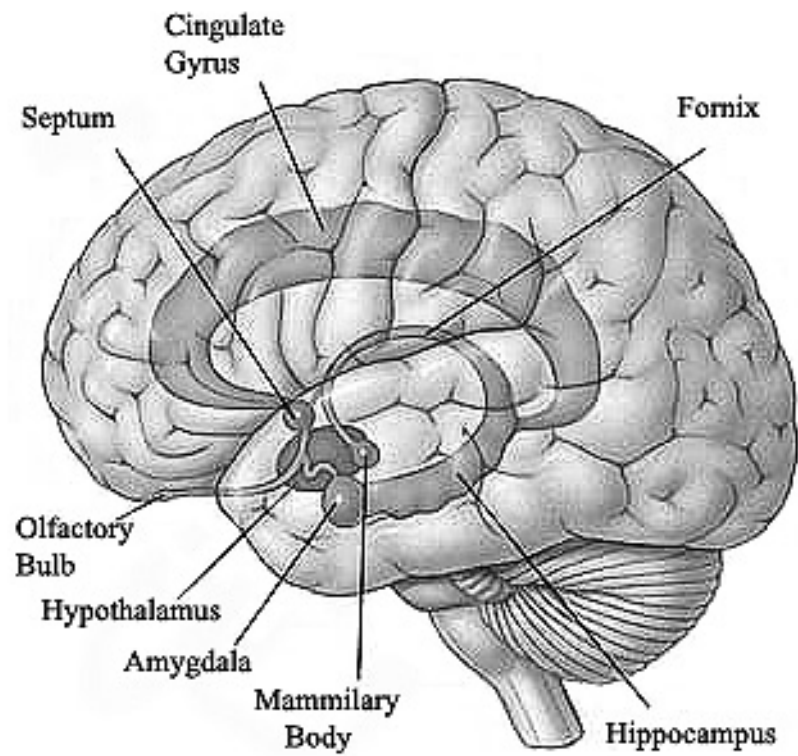


Figure 3. Schematic view of some of the limbic system structures. Adapted from Driesen (2005).

IMAGE INCLUDED IN  
BOUND COPY ONLY

Note:

I	Insula	fd	Fascia dentata
Cam	Cornu ammonis or CA (Ammon's Horn)	sub	Subiculum

Figure 4. Direct and indirect cortical afferents of the hippocampus (reprinted from Nieuwenhuys, et al., 1992).

IMAGE INCLUDED IN  
BOUND COPY ONLY

Note:

- |                              |  |
|------------------------------|--|
| 1. Cingulum                  | 8. Regio supramammillaris              |
| 2. Fornix                    | 9. Fascia dentate                      |
| 3. Anterior Thalamic Nucleus | 10. Cornu ammonis (Ammon's Horn)       |
| 4. Medial Thalamic Nucleus   | 11. Subiculum                          |
| 5. Anterior Commissure       | 12. Nucleus basalis + lateral amygdala |
| 6. Septal Medialia Nucleus   | 13. Perforant pathway                  |
| 7. Gyri Diagonalis Nucleus   | 14. Entorhinal Cortex                  |

Figure 5. Subcortical afferents and intrinsic connections of the hippocampus.

IMAGE INCLUDED IN  
BOUND COPY ONLY

Figure 6. Cortical afferents to the amygdala. Numbers indicate fields of Brodmann.

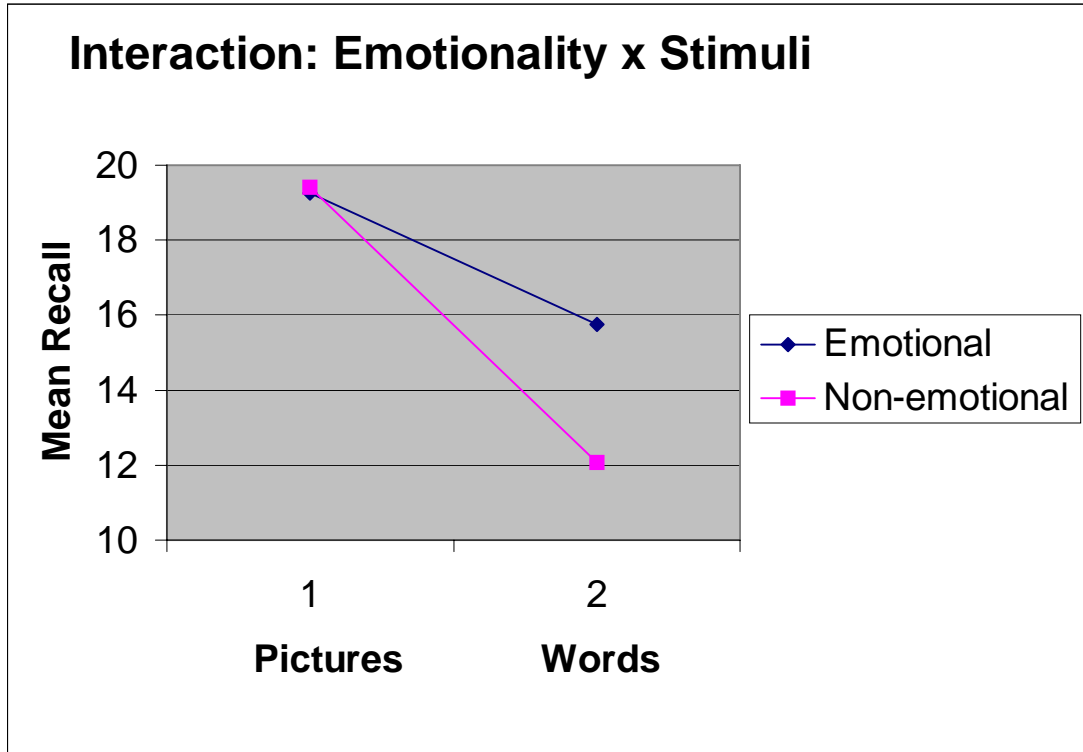


Figure 7. An interaction between emotionality and stimulus type for the memory recall data.

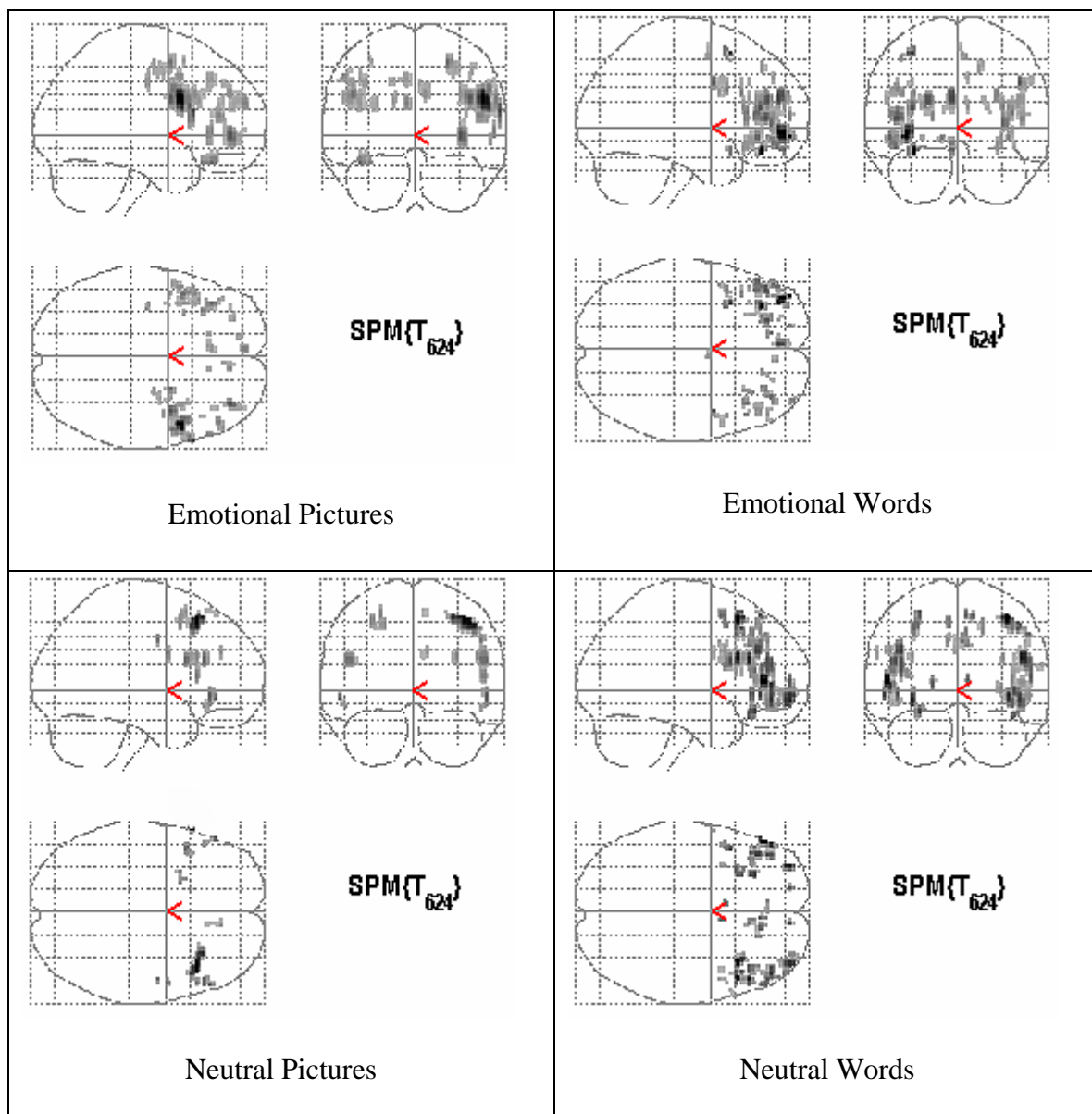


Figure 8. Glass brain images of the ROI analysis on group frontal lobe activation for all four conditions (All images were  $p < .05$ , extent threshold = 5). Neurological coordinates used.

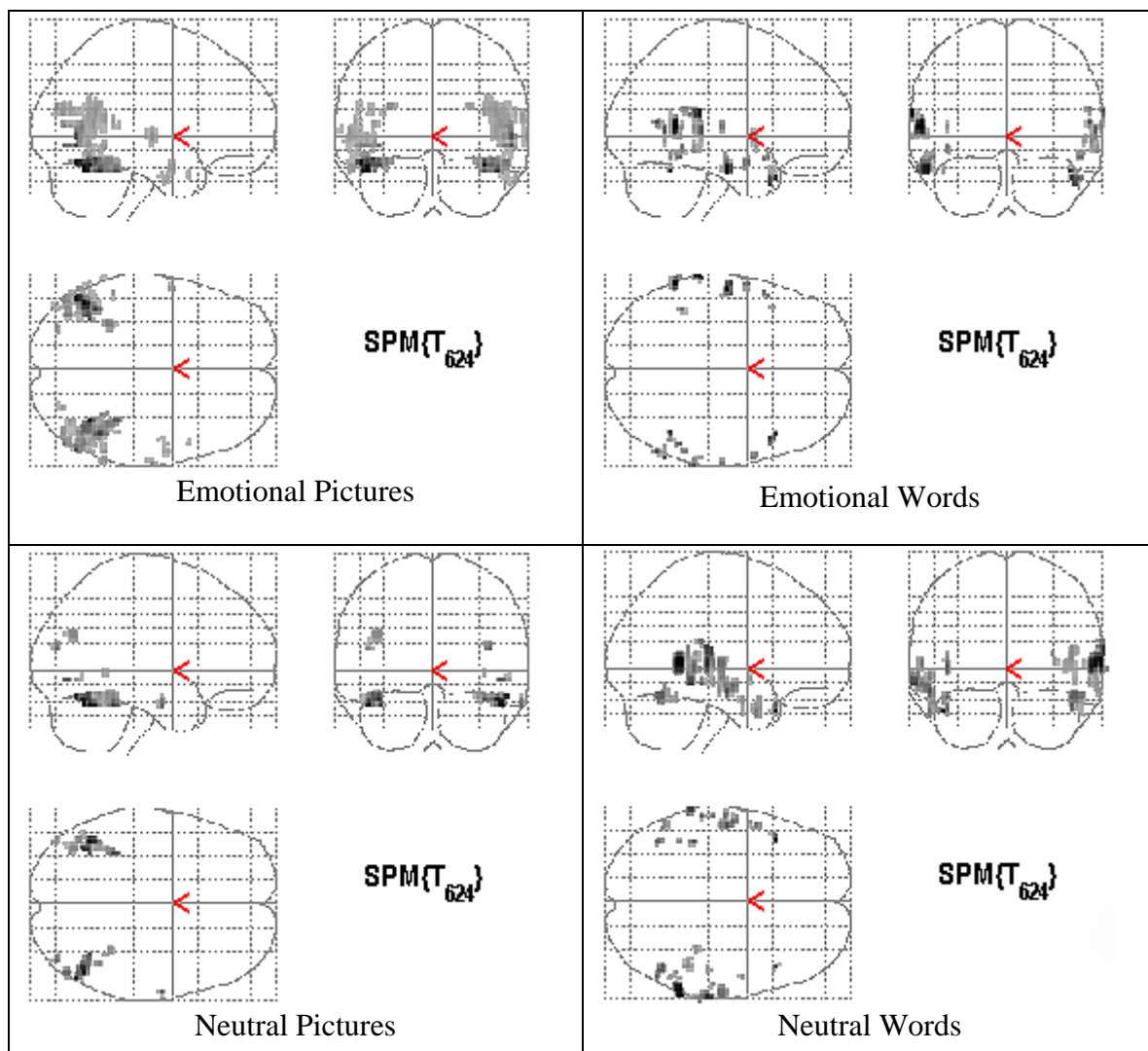


Figure 9. Glass brain images of the ROI analysis on group temporal lobe activation for all four conditions (All images were  $p < .05$ , extent threshold = 5). Neurological coordinates used.

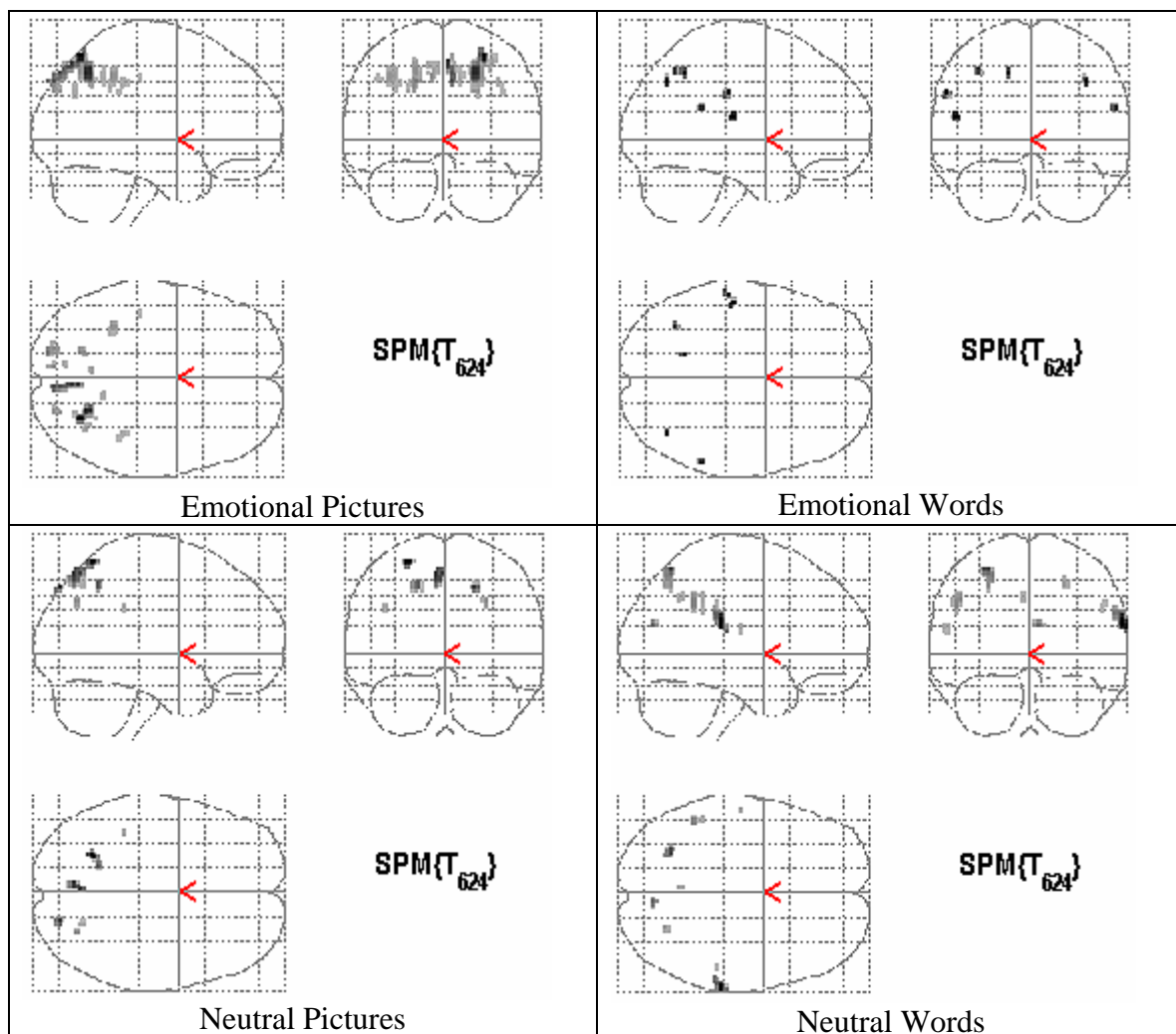


Figure 10. Glass brain images of the ROI analysis on group parietal lobe activation for all four conditions (All images were  $p < .05$ , extent threshold = 5). Neurological coordinates used.

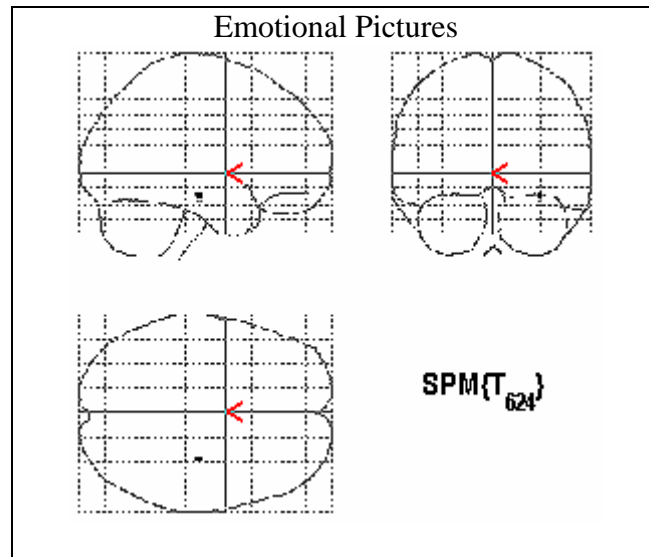


Figure 11. ROI area of activation of the hippocampus during emotional picture encoding based on group analyses. Glass brain images showed marked activation ( $p < .09$ , extent threshold = 5) in the right hemisphere, but it did not reach  $p < .05$  level of significance. There was no significant activation for the other three conditions. Neurological coordinates used.

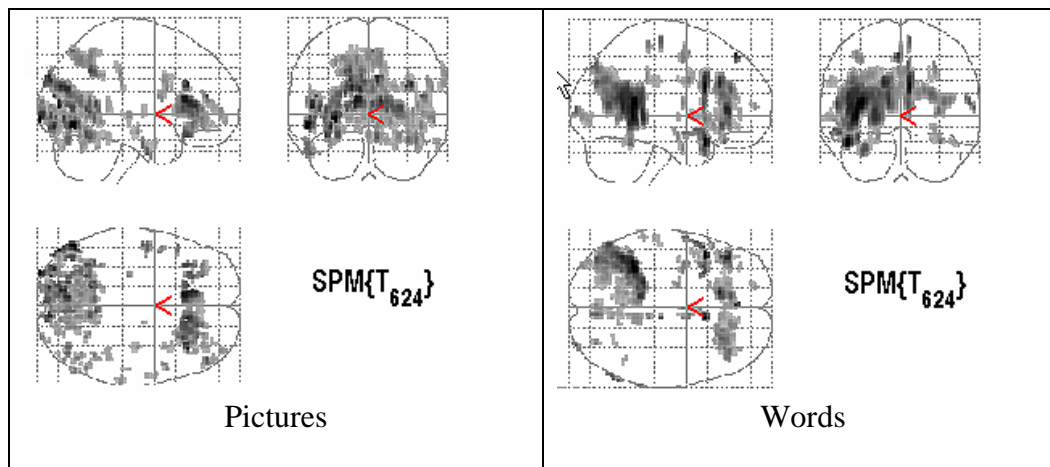


Figure 12. Glass brain images of whole brain activation for pictures ( $p < 0.01$ , extent threshold = 10) and words ( $p < 0.001$ , extent threshold = 10). Images were derived from a direct comparison between emotional and neutral stimuli, where neutral stimuli served as the rest condition. Neurological coordinates used.

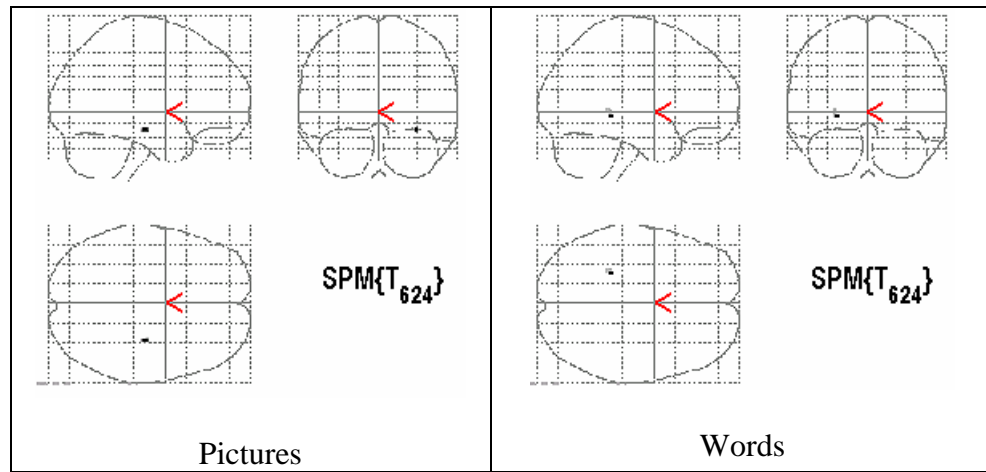


Figure 13. Glass brain images of hippocampal activation with ROI analysis for pictures ( $p < 0.01$ , extent threshold = 10) and words ( $p < 0.001$ , extent threshold = 10). Images were derived from a direct comparison between emotional and neutral stimuli, where neutral stimuli served as the rest condition. Neurological coordinates used.

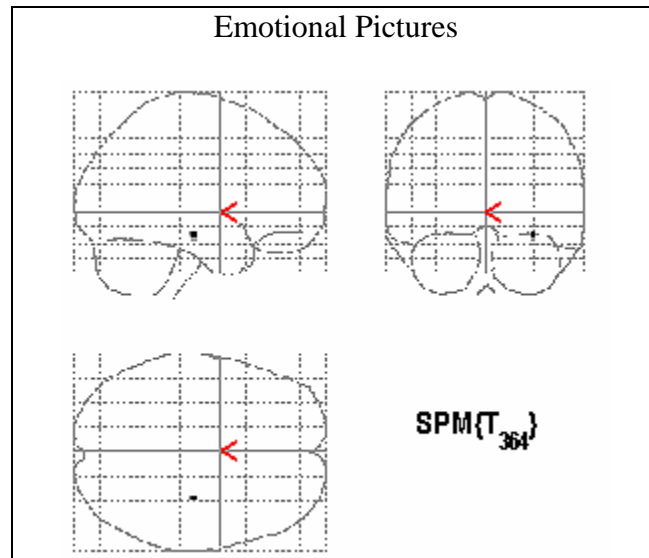


Figure 14. ROI area of activation of the hippocampus during emotional picture encoding based on the gender analysis of females. Glass brain images showed marked activation ( $p < .09$ , extent threshold = 5), although it did not reach the  $p < .05$  level of significance. There was no significant activation for the other three conditions. Neurological coordinates used.

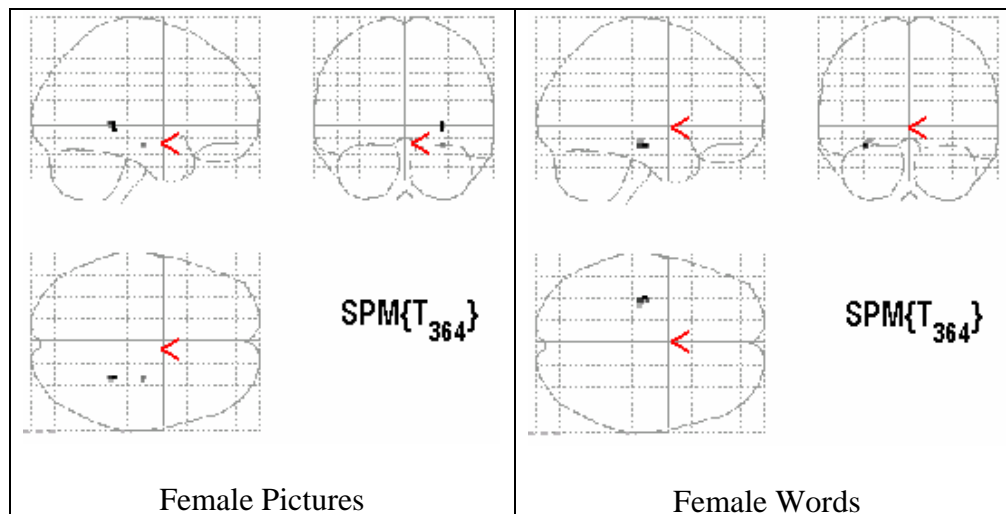


Figure 15. Glass brain images of the ROI analysis direct comparison of emotional versus neutral words and pictures in females. Significant activation was seen in the hippocampus for pictures,  $p < .01$ , extent threshold = 5, and words  $p < .001$ , extent threshold = 5. There was no significant activation for males. Neurological coordinates used.

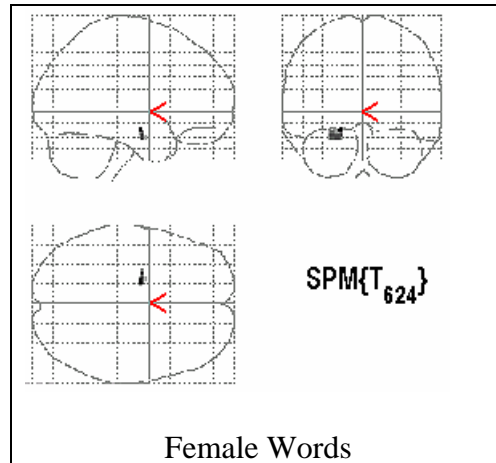


Figure 16. Glass brain images of the ROI analysis direct comparison of emotional versus neutral words condition in females. Significant activation was seen in the amygdala,  $p < .01$ , extent threshold = 5. There was no significant activation for males. Neurological coordinates used.

## Vita

Matthew John Bellace graduated from Montclair High School in 1992. He attended Bucknell University in Lewisburg, PA and graduated with a Bachelors of Science in Biology and Psychology in 1996. As a senior, Matt was awarded the Thelma Johnson Showalter Prize for his accomplishments in the field of public and community affairs. After graduation, he remained at Bucknell and completed a Masters of Science in Biology with a concentration in Neuroscience in 1998. Matt then moved to Philadelphia, PA to begin his doctoral studies in Clinical Neuropsychology at Drexel University. During his first four years of the program, Matt was involved in neuropsychology research with J. Michael Williams, Ph.D. at Drexel University and in the Laboratory of Neuropsychology at the National Institutes of Mental Health in Bethesda, MD. He also obtained clinical neuropsychology experiences at the Comprehensive Epilepsy Center at Thomas Jefferson University Hospital, and in a pediatric neuropsychology at a private practice run by Barbara Malamut, Ph.D. and Ed Moss, Ph.D. Matt obtained psychotherapy training working as a staff therapist at the Drexel University- Hahnemann Campus Student Counseling Center. He then completed a one-year clinical internship in Clinical Neuropsychology and Rehabilitation Psychology at The Mount Sinai Medical in New York, NY. Matt is currently living with his wife, Dara, in New York, NY.