

AGING, EMOTIONAL MEMORY AND THE HIPPOCAMPUS

By

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Purpose: The purpose of the present study was to investigate the effects of emotional arousal on memory in individuals with amnesic mild cognitive impairment and healthy controls. Additionally, this study sought to examine the relationship between hippocampal volume and memory for emotionally arousing material.

Background and hypotheses: Emotional arousal is known to enhance memory, presumably due to the influence of the amygdala, an important emotional region of the brain, on the hippocampus, a brain region involved in memory consolidation. The effects of emotional arousal on memory have not yet been investigated in mild cognitive impairment (MCI), a condition characterized by impaired memory in the context of preserved general cognition and normal activities of daily living. We presented MCI patients and normal controls with a set of emotional and neutral photographs, followed by four recognition tests at increasing time delays. We hypothesized that a) patients with MCI would demonstrate poorer performance than controls on the recognition tests, b) controls, and to a lesser extent MCI patients, would have better recognition memory for

arousing than neutral pictures, and c) hippocampus volumes would be positively correlated with memory for arousing but not neutral photographs. Due to concerns about accurate group classification, we also examined the first two hypotheses using a continuous indicator of memory status rather than the between-groups classification.

Methods: Twelve MCI patients and 13 age and education-matched healthy controls were presented with a set of emotional and neutral photographs, followed by four recognition tests 10 minutes, 1 hour, 2 weeks, and 3 months later. The percentage of correctly recognized pictures was calculated for pictures classified in low, medium, and high arousal categories.

Results: The control and MCI groups did not differ in their overall picture recognition performance and neither group showed enhanced recognition performance for emotionally arousing pictures. However, upon removal of the between-groups classification, memory status was significantly associated with 2-week recognition memory performance for high arousing pictures. Additionally, hippocampal volume was positively correlated with recognition memory performance for arousing but not neutral stimuli.

Conclusions: This study suggests that individuals with better memory status benefit more from emotional arousal on memory than those with poorer memory status. Additionally, the hippocampus appears to be involved in this enhanced consolidation of emotional information. Therefore, the use of emotionally arousing stimuli may represent a promising memory aid for older individuals, particularly those with good memory status and larger hippocampal volumes.

CHAPTER 1 INTRODUCTION

Recently, there has been increasing interest in a subgroup of older individuals who present with mild memory complaints but are not demented. Amnesic mild cognitive impairment, a variant of this condition characterized by impaired memory in the context of preserved general cognition and normal activities of daily living, may represent a transitional state between normal aging and Alzheimer's disease (Petersen et al., 2001). Although a multitude of investigations have examined performance on tests of memory and of other cognitive functions in amnesic MCI, there have been no studies of emotional memory in MCI. Memory for emotional material is often enhanced in healthy individuals and this effect has been attributed to the response of the amygdala, a small almond-shaped structure within the brain, to emotionally arousing stimuli (McGaugh, 2004). However, it is not clear whether the enhancement of memory by emotion is preserved in individuals with amnesic MCI. Determining whether emotional arousal enhances memory for individuals with amnesic MCI will have tremendous theoretical and practical importance. Regardless of the outcome, this investigation will help to elucidate the influence of emotional content on memory in older adults with and without memory impairments as well as to provide greater insight into the role of certain brain structures in emotional memory. If emotional arousal is shown to enhance memory for individuals who have amnesic MCI, it may be possible to design memory improvement strategies based on this form of memory. Before presenting the specific aims and hypotheses of this study, I will review the following aspects of mild cognitive

impairment: (1) characterization, (2) neuropathology, and (3) issues in the classification of MCI. Additionally, I will review the following issues pertaining to emotional memory: (1) the predominant current theory explaining emotional memory, (2) evidence supporting this theory in human studies, (3) studies of emotional memory in normal older adults, and (4) studies of emotional memory in Alzheimer's disease.

Mild Cognitive Impairment

Characterization

Mild cognitive impairment (MCI) may represent a transitional state between normal aging and dementia (Petersen et al., 2001). However, not all cases of MCI necessarily progress to dementia, and MCI may be caused by heterogeneous conditions. For example, certain medications and other medical conditions can lead to reversible MCI (Morris, 2005). Given the variability of the very early clinical signs and their overlap with the normal changes of aging, various subtypes of MCI have been identified (Petersen et al., 2001). The present study focuses on the subtype of amnesic MCI, which is characterized by slightly abnormal memory compared to same-aged peers in the context of intact general cognitive abilities and activities of daily living (Petersen et al., 2001; Petersen et al., 1999). The syndrome of amnesic MCI is of great theoretical interest, and it may be relevant to the study of early detection of Alzheimer's disease (AD) because of the high rates at which people who present with the syndrome go on to develop AD. Subjects who present with amnesic MCI have an increased risk of developing diagnosable AD at rates of 12 to 15% per year, in contrast to 1 to 2% per year in age-matched normals (Petersen et al., 2001).

Neuropathology

The medial temporal lobe limbic structures, particularly the hippocampus, play a central role in memory formation. Indeed, the hippocampus is one of the earliest brain regions affected by neurofibrillary pathology in Alzheimer's disease (Arriagada, Marzloff, & Hyman, 1992). Studies of normal older adults, individuals with mild cognitive impairment and patients with AD have shown correlations between memory performance and size of the hippocampus, with smaller hippocampal volumes associated with worse memory scores (Golomb et al., 1993; Petersen et al., 2000; Soininen et al., 1994). Additionally, hippocampal pathology has been observed in MCI. Reduced hippocampal glucose metabolism and hippocampal atrophy have been reported in individuals with MCI compared to normal controls (Convit et al., 1995; Convit et al., 1997; Du et al., 2001; Mosconi et al., 2005). Furthermore, premorbid MRI-based volume measurements of hippocampal atrophy in individuals with MCI have been shown to be predictive of subsequent conversion to AD (de Leon et al., 1997; Jack et al., 1999; Visser, Verhey, Hofman, Scheltens, & Jolles, 2002). Rate of change of hippocampal volume measurements is also significantly associated with conversion from a stable control group to MCI status and from MCI status to AD diagnosis over the course of one to 5 years (Jack et al., 2004). Thus, the hippocampus, a structure crucially involved in memory formation, undergoes significant atrophy and metabolic changes in MCI and these changes may be associated with subsequent conversion to AD.

Like the hippocampus, the amygdala is also known to be atrophic in AD. The amygdala is a limbic structure located anterior to the hippocampus, which appears to play a critical role in the emotional enhancement of memory. MRI investigations have demonstrated smaller amygdala volumes in Alzheimer's patients compared to controls

(Callen, Black, Gao, Caldwell, & Szalai, 2001; Hensel et al., 2005; Horinek et al., 2006; Ishii et al., 2006; Krasuski et al., 1998). Although few studies have examined the amygdala in MCI, one such investigation found that the volume of the left amygdala was significantly smaller in individuals with mild cognitive impairment than in normal controls (Bottino et al., 2002). Thus, it is not entirely clear at what stage of AD amygdala atrophy develops or whether amygdala pathology is consistently present in MCI.

Issues in the Classification of Mild Cognitive Impairment

Classification of MCI, while supported by neuropsychological data, ultimately rests on clinical judgment. Given the heterogeneity of MCI, there exists the possibility of “contaminating” the MCI group with healthy individuals, or vice versa, when conducting research studies comparing these two groups. Some subjects classified as having MCI may actually have had long-standing poor memory function that may not progress to dementia (Petersen et al., 1999). Additionally, healthy subjects experiencing transient memory problems due to medication or other factors may be inaccurately classified in the MCI group (Morris, 2005). Accurate group classification is vital for the study of MCI; however, there is evidence that some studies have significant levels of misclassification. For instance, Visser and colleagues (Visser, Scheltens, & Verhey, 2005) retrospectively applied the MCI diagnostic criteria used by six clinical drug trials in a cohort of 150 non-demented subjects from a memory clinic. They found that the diagnostic accuracy of MCI criteria used in these trials was low to moderate, suggesting the possibility of inclusion of many patients who do not have MCI or to exclusion of many who do.

Some scholars have questioned the use of the MCI classification, suggesting that this classification “pathologizes” features of normal aging and creates “artificial...boundaries” within the aging process (Whitehouse & Juengst, 2005, p.1419).

These authors argue instead for consideration of “a continuous spectrum of normal aging” (p. 1419).

In summary, the syndrome of amnesic mild cognitive impairment, characterized by impaired memory in the context of preserved general cognitive abilities and activities of daily living, has generated much research interest. Although some investigators have argued against the use of this classification, others have found it theoretically useful. MCI is associated with pathology of the hippocampus, a vital medial temporal lobe memory structure. However, it is not known for certain whether the amygdala, an important structure for the formation of emotional memory, is affected in MCI.

Emotional Memory

Most people vividly remember their first kiss and what they were doing when they first heard about Princess Diana’s death or the Challenger disaster. Such events are thought to be vividly preserved in memory because of their emotionally arousing nature. A large body of research suggests that moderate levels of emotional arousal enhance memory consolidation, the process by which short-term memories are strengthened and maintained as long-term memories.

The Modulation Hypothesis: Involvement of the Amygdala

One of the most clearly articulated models of the biological basis of emotional memory is the “modulation” hypothesis of McGaugh and colleagues (McGaugh, 2004; McGaugh, Cahill, & Roozendaal, 1996; Roozendaal, Nguyen, Power, & McGaugh, 1999). According to this hypothesis, the amygdala plays a critical role in the enhancement of memory for emotional material. First explicated using animal research, this model specifies that (a) stress hormones and certain neurotransmitters released in response to emotional stimuli enhance long-term memory formation, (b) the amygdala

mediates the memory-enhancing effects of these substances, and (c) the amygdala modulates memory consolidation via its influence on other brain regions that are intrinsically involved in learning and maintenance of memories (e.g., hippocampus, caudate nucleus, and nucleus accumbens).

The premises outlined by the modulation model are supported by several lines of research. First, post training injections of the rat adrenal stress hormones, epinephrine and corticosterone, produce dose- and time-dependent enhancement of memory in rats (McGaugh, 2004). Second, the amygdala appears necessary for mediating the effects of these hormones, since lesions of the amygdala effectively block their memory enhancing effect (Cahill & McGaugh, 1998). Similarly, the amygdala appears to mediate the memory-modulating effects of several classes of neurotransmitters, including glutamate and acetylcholine (McGaugh, 2004). Interestingly, several findings have indicated that intra-amygdala infusions of drugs enhance memory retention in rats tested after 24 hours but not in those tested within a few hours of the intervention (Barros, Pereira, Medina, & Izquierdo, 2002; Bianchin, Mello e Souza, Medina, & Izquierdo, 1999; Schafe & LeDoux, 2000). This suggests that these hormones and neurotransmitters selectively affect the consolidation of long-term memory.

Third, although the amygdala is an important site for bringing together memory-modulating influences of stress hormones and certain neurotransmitters, the actual memory encoding and consolidation takes place elsewhere in the brain. One key memory area that receives direct input from the amygdala is the hippocampus (Petrovich, Canteras, & Swanson, 2001; Pitkanen, Pikkarainen, Nurminen, & Ylinen, 2000). Electrophysiological evidence strongly suggests that influences from the amygdala

modulate memory consolidation processes in the hippocampus (Cahill & McGaugh, 1998; Frey, Bergado-Rosado, Seidenbecher, Pape, & Frey, 2001). Thus, extensive research with rats provides a model for emotional memory formation that implicates the amygdala in this process. Once activated by stress-related hormones and neurotransmitters, the amygdala enhances long-term memory consolidation in other brain regions, particularly the hippocampus.

Evidence Supporting the Modulation Hypothesis in Humans

Findings from memory studies in humans provide additional support for the modulation hypothesis of emotional memory, forming parallels with the animal research. First, the results of several human studies indicate a critical role of stress hormones in memory consolidation. Some investigators have found that the administration of the stress hormone cortisol prior to presentation of words or pictures results in improved recall performance (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003). Additionally, epinephrine administered after subjects viewed emotionally arousing slides enhanced their long-term memory of the slides (Cahill & Alkire, 2003).

Consistent with the animal research, the amygdala also appears to be critical in mediating the memory-enhancing effects of these hormones in humans. Human subjects with selective bilateral lesions of the amygdala do not demonstrate the enhanced memory for emotionally arousing material that normal subjects do (Adolphs, Cahill, Schul, & Babinsky, 1997; Cahill, Babinsky, Markowitsch, & McGaugh, 1995). Functional brain imaging studies provide additional evidence that the influence of emotional arousal on memory involves amygdala activation. For instance, amygdala activity during encoding is correlated with long-term memory of emotionally arousing but not neutral material (Cahill et al., 1996). This relationship between amygdala activity at encoding and long-

term memory performance appears to be greatest for stimuli rated as most emotionally intense (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000).

Finally, functional neuroimaging studies provide evidence that amygdala activation in humans influences memory consolidation in other brain regions, particularly the hippocampus. Hamann and colleagues (Hamann, Ely, Grafton, & Kilts, 1999) presented emotional and neutral photographs to normal participants while they underwent positron emission tomography (PET) scanning. Subjects had better memory for emotional than neutral pictures upon 4-week recognition testing. This enhanced emotional recognition memory was correlated with bilateral activity in the amygdala and hippocampus measured at encoding. Additionally, amygdala activity was significantly correlated with hippocampal activity for emotional pictures. Similar results were obtained in a functional magnetic resonance imaging (fMRI) study by Dolcos, LaBar and Cabeza (2004). Consistent with the animal research, the results of these studies suggest that the amygdala's influence on other brain regions – particularly the hippocampus - is critical for creating lasting memories in humans.

Emotional Memory in Older Adults

Because no studies have yet examined emotional memory in amnesic MCI, it is helpful to first review emotional memory in the context of normal aging and Alzheimer's disease. To some extent, the demonstration of the emotional enhancement effect in older adults depends on the type of memory test used, i.e. recognition versus recall. There is general support for the preservation of emotional enhancement of memory in aging with the use of recall tests, and some support for the preservation of this effect with use of recognition tests.

Studies employing recall tests have demonstrated emotional enhancement of memory in older adults tested at various time intervals. For instance, Kensinger and colleagues (Kensinger, Brierley, Medford, Growdon, & Corkin, 2002) reported that older adults showed a similar degree of emotional memory enhancement for words and pictures upon immediate recall testing as did younger adults. According to Charles and colleagues (Charles, Mather, & Carstensen, 2003), middle-aged adults (41-53 years) and older adults (65-80 years) remembered more positive than negative or neutral photographs when tested with a recall probe 15 minutes after stimulus presentation. Hamann, Monarch and Goldstein (2000) found that older adults had better recall for negative and positive compared to neutral pictures one minute and two weeks after stimulus presentation. Finally, Denburg and colleagues (Denburg, Buchanan, Tranel, & Adolphs, 2003) presented young (35-51 years), middle-aged (52-69 years), and older (70-85 years) adults with positive, negative, and neutral photographs accompanied by a one-sentence narrative description. The authors found that although older adults showed a decline in memory relative to young adults, the groups showed similar patterns of emotional influence on memory, including enhanced free recall of negative and positive compared to neutral pictures. This pattern of emotional enhancement was observed at 24 hours and 8 months after stimulus presentation.

Several studies employing recognition tests have demonstrated enhanced emotional memory in older adults, although there have been some studies that have not shown this effect. Abrisqueta-Gomez and colleagues (Abrisqueta-Gomez, Bueno, Oliveira, & Bertolucci, 2002) found that upon 30-minute recognition testing, older adults recognized significantly more emotional than neutral pictures. According to Hamann et al. (2000),

two-week recognition discrimination ability for a group of older adults was enhanced for negative compared to positive and neutral photographs. On the other hand, Charles et al. (2003) did not find an emotional enhancement effect with the use of recognition testing. In their study, young adults correctly recognized a greater proportion of negative than positive or neutral pictures, while middle and older adults recognized equal proportions across emotional valence categories. Thus, most studies employing recall tests have demonstrated emotional enhancement of memory in older adults while some studies employing recognition tests have demonstrated this effect.

Emotional Memory in Alzheimer's Disease

Findings from the Alzheimer's disease literature on the effects of emotionally arousing material on memory have been contradictory. While some studies have demonstrated a preserved emotional enhancement effect on memory in Alzheimer's disease (Kazui et al., 2000; Moayeri, Cahill, Jin, & Potkin, 2000), others have not (Abrisqueta-Gomez et al., 2002; Hamann et al., 2000). Differences in the types of emotional stimuli used and the types of memory tests used may help to explain this discrepancy.

In general, emotional enhancement of memory is more likely to be preserved in Alzheimer's disease when stimuli are presented within a semantic context. For instance, Alzheimer's patients have demonstrated better memory for an emotional compared to a neutral passage in a story when memory was tested by recall (Kazui, Mori, Hashimoto, & Hirono, 2003; Kazui et al., 2000) or by recognition (Moayeri et al., 2000). Although overall memory was worse for Alzheimer's patients than controls, the magnitude of enhancement by emotional arousal was similar in the Alzheimer's patients and controls (Kazui et al., 2000). However, semantic context does not always allow for the

preservation of emotional enhancement in individuals with Alzheimer's disease. In a study by Kensinger and colleagues (Kensinger, Anderson, Growdon, & Corkin, 2004), older adults had higher recognition scores for the negative portion of a story than the neutral portion after 10 minutes, while individuals with Alzheimer's disease showed no effect of emotion.

On the other hand, presentation of stimuli in the absence of a semantic context (i.e., a series of unrelated pictures) has been less likely to be associated with preservation of the emotional enhancement effect in Alzheimer's disease. For instance, Abrisqueta-Gomez et al. (2002) presented AD patients and older controls with emotional and neutral photographs. Upon 30 minute recognition testing, controls recognized significantly more emotional than neutral pictures, but AD patients showed no benefit for emotional picture recognition.

As with normal older adults, the type of memory test used affects the pattern of memory performance for AD patients presented with a series of unrelated stimuli. When tested with a one minute free recall test following the presentation of 60 positive, negative, and neutral photographs, patients with Alzheimer's disease had enhanced memory for positive compared to negative and neutral pictures. When tested with a recognition test, Alzheimer's disease patients demonstrated no emotional enhancement of memory (Hamann et al., 2000). However, recall tests have not always yielded an emotional enhancement effect in AD patients who are presented with unrelated stimuli. In a study by Kensinger et al. (2002), AD patients did not show memory enhancement for emotional words or pictures on immediate recall tasks, although young and older controls did show emotional enhancement for these items.

Therefore, there is some evidence for emotional enhancement of memory in AD when stimuli are presented within a semantic context but little evidence of this effect when unrelated stimuli are presented in the absence of a semantic context. When patients with AD are presented with unrelated stimuli, they may be more likely to show an emotional enhancement effect if memory is tested using a recall rather than a recognition test.

CHAPTER 2 STATEMENT OF THE PROBLEM

Memory problems are among the most prominent age-related cognitive changes, possibly due to their influence on activities of daily living. Not all aspects of memory are equally affected by normal aging. Retrieval of old remote memories remains relatively stable well into the 70's and 80's. In contrast, the ability to learn and retain new episodic memories is particularly susceptible to aging and is the primary symptom of the memory variant of amnesic MCI. Many researchers have attempted to characterize the types of memory disturbances associated with aging in an effort to design effective rehabilitation techniques and memory management strategies.

The overall focus of the present study is to determine whether the memory problems displayed by older individuals, particularly those with amnesic MCI, extend to emotionally arousing materials. Specifically, does the memory performance of individuals with amnesic MCI benefit from emotionally arousing information? If so, is this emotional enhancement effect similar in magnitude to that of healthy peers? Moreover, is there any relationship between volumetric measures of medial temporal regions involved in memory (i.e., hippocampus) and this enhancement effect?

It is vital to address these questions for two primary reasons. First, a wealth of literature indicates that emotional memory modulation is mediated by the very brain regions (i.e., amygdala, hippocampus) that seem to be involved early in Alzheimer's disease. To date, findings from the Alzheimer's literature on the effects of emotionally arousing materials in memory have been contradictory. Virtually no studies have

examined emotional memory among patients with amnesic MCI, who are at particular risk for transitioning into Alzheimer's disease. Based on the pathophysiology of brain changes in MCI and early Alzheimer's disease, one might hypothesize that MCI patients will show less robust effects of emotional arousal on memory performance than normal age peers. Second, if emotional arousal is shown to enhance memory for individuals who have amnesic MCI, it may be possible to design memory improvement strategies based on this form of memory. Even if the enhancement is reduced relative to peers, this might nevertheless present an opportunity to structure memory tactics and strategies for remembering salient events.

Research into the modulation hypothesis of emotional memory suggests that the amygdala exerts its modulatory effects on memory consolidation over long-term intervals. While most studies investigating emotional memory have been short-term, we chose to examine emotional memory in the present study using a "rate of forgetting" task that probed memory over extended periods of time. Specifically, recognition testing occurred at 10 minutes, 1 hour, 2 weeks, and 3 months after initial stimulus presentation. The rate of forgetting procedure used in our study is modeled after that of Huppert and Piercy (1979) who found that the famous bitemporal amnesic H.M. exhibited an abnormally rapid forgetting rate, relative to controls, over a 7 day period. In contrast, patients experiencing amnesia due to alcoholic Korsakoff's disease (i.e., diencephalic amnesics) showed a normal forgetting rate when initial level of encoding was equated with that of controls. These findings illustrate the utility of rate of forgetting as a sensitive measure of medial temporal memory dysfunction in humans. The use of extended testing intervals in the context of the rate of forgetting paradigm therefore

allows us to test the long-term emotional memory consolidation processes thought to be mediated by the amygdala and hippocampus.

In order to examine the effects of emotional arousal on memory, pictures from the International Affective Picture Set were used as stimuli in the rate of forgetting memory task. While most studies of emotional memory have classified pictures according to valence categories (positive, negative, neutral), we expected that arousal categories would be more helpful for investigation of emotional memory, given that amygdala activity is related more to emotional arousal than to valence (Kensinger & Corkin, 2004). We therefore selected pictures according to low, medium, and high arousal categories based on normative arousal ratings. The specific aims and hypotheses of the study are outlined below.

Specific Aim I

To test the hypothesis that individuals with MCI will exhibit greater forgetting for all picture stimuli (regardless of emotional content) than normal age-matched controls. To examine this hypothesis, we compared information loss between the MCI and control groups across each of the memory time delays (10 minutes, 1 hour, 2 weeks, 3 months). Additionally, given the difficulty of accurately identifying individuals with MCI and the suggestion by some investigators that the MCI classification be replaced by a “spectrum of aging,” we next examined picture recognition performance as an outcome of a continuous indicator of memory status. We hypothesized that individuals with better memory status would perform better on the picture recognition task at all time points.

Specific Aim II

To examine the effects of emotional arousal on memory performance in individuals with amnesic MCI and normal peers. Given the relatively well-established emotional enhancement effect, we hypothesized that controls will show better recognition memory performance for high arousing stimuli compared to medium and low arousing stimuli. While emotional memory has not yet been investigated in MCI, studies suggest that emotional enhancement of memory is preserved in some instances for individuals with Alzheimer's disease, although not as frequently as controls. It is therefore hypothesized that MCI patients will also benefit from arousal but to a lesser extent than controls.

We also examined self-reported and physiological reactivity to emotional stimuli of MCI patients and controls in the context of this aim. This was done in order to determine whether emotional reactivity at the time of initial presentation (encoding) of the pictures was similar for the MCI and control groups.

Finally, as with specific aim I, we examined picture recognition performance for the low, medium, and high arousal conditions as an outcome of a continuous memory status variable. We hypothesized that individuals with better memory status would benefit more from emotionally arousing pictures than people with poorer memory status.

Specific Aim III

To investigate the relationship between hippocampus volume and (1) overall memory performance on the rate of forgetting task and (2) memory performance for emotional items on the rate of forgetting task. Because the rate of forgetting task has been shown to be sensitive to hippocampal pathology, we hypothesized that hippocampal volume would be positively correlated with overall picture recognition memory performance on this task. Additionally, because the hippocampus interacts intimately

with the amygdala in enhancing memory for emotional material, we hypothesized that hippocampal volume would be correlated with recognition memory for the medium and high arousal conditions but not the low arousal conditions.

CHAPTER 3 METHODS

Figure 3-1 displays a flowchart of the study design. In the following pages, each element will be discussed in detail.

Subject Recruitment and Screening

Potential participants were initially recruited from advertisements, from previous MCI studies conducted by colleagues at the University of Florida, and from an existing research registry for older adults. All underwent an initial screening evaluation by telephone in order to address inclusion/exclusion criteria. To be included, participants had to be over 55 years of age. Exclusion criteria included history of a recent heart attack, presence of neurological disease, history of head injury or stroke, psychiatric disturbance sufficient to warrant hospitalization, substance abuse, and adverse reaction to prescription medication. A total of 58 individuals underwent screening. Of these, 32 individuals did not meet initial eligibility criteria or were no longer interested in participating after learning more about the study. Reasons for exclusion included being below the minimum age, history of stroke, and presence of neurological conditions. Twenty-six subjects passed initial screening and underwent additional testing of neuropsychological and mood status, including tests of memory, intellectual functioning, language, attention, and executive functioning.

Neuropsychological/Mood Testing

All participants underwent neuropsychological testing in order to rule out dementia and to obtain data which would assist in group classification at the consensus conference.

Intellectual Assessment and Dementia Screening

Mini-Mental State Examination (MMSE). The MMSE (Folstein, Folstein, & McHugh, 1975) has been used for detecting dementia for over 25 years. The maximum score on the MMSE is 30 points. We employed a cut-off score of 24, considering scores of 24 or below to be indicative of probable dementia. The MMSE includes measures of memory, attention, formation, orientation, figure copying, reading and writing. Factor analysis of the MMSE administered to a community-dwelling population revealed dimensions that corresponded directly to the MMSE sections articulated by the developers of the instrument, supporting the construct validity of the MMSE (Jones & Gallo, 2000).

Wechsler Abbreviated Scale of Intelligence (WASI). The Vocabulary and Matrix Reasoning subtests from the WASI were administered in order to obtain an estimate of intellectual functioning (Psychological Corporation, 1999) yielded an estimated two-scale IQ. The Vocabulary subtest assesses the ability to define words and the Matrix Reasoning subtest is a measure of non-verbal abstract reasoning.

North American Adult Reading Test (NAART). We administered the NAART in order to obtain an estimate of premorbid intellectual ability. The NAART (Blair & Spreen, 1989) is a word reading test used for this purpose. The NAART is thought to primarily index prior (rather than current) intellectual ability (Crawford, Deary, Starr, & Whalley, 2001). Additionally, Utzl (2002) demonstrated that the NAART is a reliable and valid measure of verbal intelligence.

Memory

Hopkins Verbal Learning Test-Revised (HVLT-R). The HVLT-R (Benedict, Schretlen, Groninger, & Brandt, 1998) is a three-trial list learning and free recall task

comprising 12 words, 4 words from each of three semantic categories. The Total Recall score refers to the total number of words recalled after all three list presentations. The delayed recall test is administered 20 minutes after completion of the first three recall trials. The Percent Retention score is determined by dividing the total number of correct items recalled after the delay by the number of items recalled on the third learning trial prior to the delay. The HVLTR also includes a 24-item delayed recognition test, from which a discrimination index can be calculated. All raw scores obtained on the HVLTR were converted to z-scores based on the age-based norms of Benedict et al. (1998).

Test-retest correlations of the HVLTR are similar to those of other verbal memory tests (Rasmussen et al., 1995). Other studies of the HVLTR support its alternate form and test-retest reliability (Benedict et al., 1998) and its construct and content validity (Shapiro, Benedict, Schretlen, & Brandt, 1999).

Language

Boston Naming Test-Short Form. We administered the 30-item short form of the Boston Naming Test (Fastenau, Denburg, & Mauer, 1998). In this version, either odd or even items from the standard 60-item test (Kaplan, Goodglass, & Weintraub, 1983) are given. Fastenau et al. (1998) demonstrated adequate reliability and validity for each form. Fisher, Tierney, Snow, and Szalai (1999) found support for criterion-related validity of the short forms. For the present study, raw scores obtained on the short form of the Boston Naming Test were converted to z-scores based on age-based norms (Fastenau et al., 1998).

Phonemic fluency. The total number of words generated in 1 minute for the letters F, A, and S was obtained. The instructions were identical to those used by Spreen and Benton (1977). Participants were instructed that proper nouns and multiple words

using the same stem with a different suffix (e.g., friend, friends, friendly) were not acceptable. The total number of words generated in all three trials was converted to a scaled score according to age-based norms (Ivnik, Malec, Smith, Tangalos, & Petersen, 1996). Scaled scores were then converted to z-scores for the purposes of consistency throughout the neuropsychological test battery.

Semantic fluency. Following the instructions of Rosen (1980), participants were asked to say the names of as many animals that they could think of in a one-minute period. The total number of animals named was converted to a z-score based on age and education-based norms (Tombaugh, Kozak, & Rees, 1999).

Attention, Psychomotor Speed, and Executive Function

Stroop Color and Word Test. The Stroop Color and Word Test (Golden, 1978) consists of three trials, one in which the participant is asked to read color words printed in black ink (Word Reading), one requiring the naming of printed colors (Color Naming), and one in which reading focuses on color words printed in ink of incongruent colors (Interference). The Stroop technique has satisfactory reliability (Franzen, Tishelman, Sharp, & Friedman, 1987; Spreen & Strauss, 1991). Scores obtained on the Stroop test for each of the three trials were converted to scaled scores according to age-based norms (Ivnik et al., 1996). Scaled scores were then converted to z-scores for the purposes of consistency throughout the neuropsychological test battery.

Trail Making Test. The Trail Making Test (Army Individual Test Battery, 1944) is given in two parts. In Part A the subject must first draw lines to connect consecutively numbered circles on a worksheet. In Part B, the subject must connect consecutively numbered and lettered circles by alternating between letters and numbers. Part A is a measure of visuospatial attention, motor speed, and numerical sequencing, while Part B

has the additional requirement of mental flexibility. The Trail Making Test generally yields reliability coefficients above 0.60, with most in the 0.80s (Spren & Strauss, 1991). Scores obtained on the Trail Making Test were converted to scaled scores according to age-based norms (Ivnik et al., 1996). Scaled scores were then converted to z-scores for the purposes of consistency throughout the neuropsychological test battery.

Self-Report Measures

Geriatric Depression Scale (GDS-15). The GDS-15 (Sheikh & Yesavage, 1986) is a 15-item self-report instrument designed specifically for older adults that assesses depressive symptoms without focusing on physical complaints. It is scored dichotomously (yes/no) and inquires into subjective depression experienced during the prior week. The GDS-15 has been widely recommended as a brief screening instrument for late-life depression and has been found to be useful in detecting late-life major depression in primary care settings (Lyness et al., 1997; Watson & Pignone, 2003).

State Trait Anxiety Inventory (STAI). The STAI was developed to gauge two measures of anxiety: state anxiety, defined as a transitional emotional response, and trait anxiety, referring to enduring personality differences in anxiety. Stanley, Beck and Zebb (1996) found strong test-retest reliability for the STAI-trait and slightly weaker reliability for the STAI-state, as might be expected. Additionally, they found adequate convergent validity with other anxiety measures.

The Instrumental Activities of Daily Living Scale (IADL). The IADL scale (Lawton & Brody, 1969) assesses functional ability to perform several activities, including using the telephone, managing personal finances, and preparing food. The score ranges from 15 to 45, with a score of 15 representing no impairment.

Memory Functioning Questionnaire (MFQ). The MFQ (Gilewski, Zelinski, & Schaie, 1990) assesses the self-appraisal of everyday memory functioning in adults. It consists of 64 items rated on 7-point scales. For the purposes of this study, we report the response to the following question: “How would you rate your memory in terms of the kinds of problems that you have?” Answers are given on a 7-point scale, with “1” representing “major problems” and “7” representing “no problems.”

Consensus Conference

After completion of the neuropsychological and mood testing, participant profiles were discussed at a case conference and classified into MCI and control groups. Members of the consensus conference committee included Ann Mikos (author), Dr. Dawn Bowers, PhD (neuropsychologist), Dr. Catherine Price, PhD (neuropsychologist), and Ida Kellison (graduate student). Participants were classified as belonging to the MCI group if they had a memory impairment of at least 1.5 standard deviations below the mean on the Hopkins Verbal Learning Test-Revised, intact performance on other cognitive tests, and in tact activities of daily living.

Twenty-six participants passed the initial screening, underwent neuropsychological and mood assessment, and were discussed at a consensus conference meeting. A decision was made to exclude one of these participants, because this individual scored below the MMSE cut-off of 24 (MMSE = 23) and displayed impairment in several other cognitive domains besides memory (e.g., language, executive function, attention). According to consensus conference classifications, 12 of the remaining individuals were assigned to the MCI group and 13 to the normal control group.

MRI

A subset of 13 participants underwent MRI scanning at the University of Florida McKnight Brain Institute. Of the 25 participants that were enrolled in the study, 12 had contraindications for MRI (claustrophobia, presence of metal implants in the body) or were unwilling to complete the MRI scan. MRI scans were obtained for 7 individuals in the MCI group and 6 controls. Images were obtained on a Siemens 3T Allegra scanner. The imaging protocol consists of a series of gradient echo scans (MPR3D: TR = 10 ms, TE = 4 ms, 10 degree flip angle, matrix = 130 by 256, 160 mm volume, and section thickness = 1.25 to 1.40 mm), producing a gapless series of high quality images. Volume of the hippocampus was traced in the program “Measure” by a trained and blinded rater who previously attained inter-rater reliability of >0.90.

Emotional Memory Task

Participants first viewed a set of 120 emotional and neutral target pictures (study phase). Pictures were presented in two blocks of 60 pictures each, with a short break in between blocks. Participants then underwent several recognition tasks at increasing time delays (test phases), modeled after the rate of forgetting task of Huppert and Piercy (1979) in order to assess their rate of forgetting over time.

Study Phase

During the study phase of the picture task, subjects sat quietly in a darkened electrically and sound attenuated chamber where they viewed a series of emotional and neutral pictures. This testing took place in the Cognitive Neuroscience Laboratory at the McKnight Brain Institute. Visual stimuli were presented on a 21” computer monitor. During testing each picture was shown for 6 seconds, followed by an intertrial interval of 8 seconds.

Following presentation of each picture, participants verbally rated each picture using two independent 1-9 ordinal rating scales (one for valence and one for arousal). The scales were vertically arrayed on a slide as cartoon figures and were presented on the computer screen following each picture.

Test Phases

Subjects participated in four test phases in order to evaluate rate of forgetting over time. Recognition testing occurred 10 minutes, 1 hour, 2 weeks, and 3 months after completion of the study phase. During each test phase, a unique set of 30 target pictures from the initial presentation were shown in conjunction with an equal number of distracters. Subjects were asked to indicate whether or not each picture was one of the initial targets.

Picture Stimuli

The stimuli presented in the study phase of the emotional memory task consisted of 120 pictures selected from the International Affective Picture Set (Lang, Bradley, & Cuthbert, 2001) on the basis of normative valence and arousal ratings. For the purpose of analysis, pictures were divided into low, medium, and high arousal categories. Normative arousal ratings differed significantly among the low, medium, and high arousal categories. Low arousal pictures had a mean normative arousal rating of 3.08, medium arousal pictures had a mean normative arousal rating of 4.79, and high arousal pictures had a mean normative arousal rating of 6.14. For each recognition memory test, target pictures were matched to distracter pictures on the basis of content and of normative valence and arousal ratings. Low, medium, and high arousal targets did not differ significantly from their distracters in terms of valence or arousal. One-way

ANOVAs also revealed that the stimuli did not differ within the four testing blocks in terms of valence or arousal.

Skin Conductance Response (SCR)

The skin conductance response was assessed in this study because it is an index of sympathetic arousal, correlates with self-reports of emotional arousal, and is relatively independent of valence (Bradley & Lang, 2000). The SCR was measured from electrodes attached to the palms with adhesive collars. Prior to beginning the study phase of the emotional memory task, the skin from both hands was cleaned and dried thoroughly. Two 12 mm Ag/AgCl were filled with conducting gel (K-Y Brand Jelly, McNeil-PPC, Inc.) and were attached adjacently using electrode collars on the thenar and hypothenar surfaces of each palm in order to obtain measures of skin conductance during picture presentation.

Skin conductance data were sampled at 20 Hz using two Colbourn Isolated Skin Conductance Couplers. The SCR was defined as the difference between the peak conductance during the 6-second viewing period and the mean conductance achieved during the last pre-stimulus second, derived independently for each hand. SCR was represented in microsiemens (μS) units. The SCR was averaged for both hands, unless data from one hand contained excessive artifact or did not contain enough valid trials (i.e., less than 3 out of 20) to generate acceptable averages. In these cases, the data from the other hand were used in place of the composite data.

Due to concerns about habituation, only skin conductance data obtained during presentation of the first block of 60 pictures were analyzed. Because skin conductance habituates relatively quickly, data from the first 30 trials of this block were analyzed separately.

Statistical Analyses

To test the first aim (comparison of rate of forgetting for pictures between the MCI and control groups), a mixed ANOVA consisting of a between-subjects factor of *group* (control, MCI) and a within-subjects factor of *recognition test delay* (10 minutes, 1 hour, 2 weeks, 3 months) was conducted. The dependent variable was the percentage of correct responses on the picture recognition tests.

Given the concerns discussed earlier about the heterogeneity of MCI and potentials for misclassification, data were also examined using a continuous indicator of memory status as a predictor of performance on the picture recognition task. The percent retention z-score on the HVLT-R was used as the continuous variable, because it represents loss of information over time. Next, a series of regression analyses was conducted with memory status (as indicated by the HVLT-R retention z-score) as the predictor and recognition memory performance as the dependent variable. Separate regression analyses were conducted for each of the four recognition testing sessions.

In order to test the second aim (examination of the effect of emotional arousal on recognition memory performance at increasing time delays in MCI patients compared to controls), a mixed factorial ANOVA was conducted. The ANOVA consisted of a between-subjects factor of *group* (control, MCI) and within-subjects factors of *arousal* (low, medium, high) and *recognition test delay* (10 minutes, 1 hour, 2 weeks, 3 months).

Within this second aim, a comparison of the MCI and control groups' ratings and skin conductance responses to emotional stimuli was carried out using two separate mixed ANOVAs. The ANOVAs consisted of a between-subjects factor of *group* (control, MCI) and a within-subjects factor of *arousal* (low, medium, high). For one

ANOVA, the dependent variable was self-reported picture ratings. For the second ANOVA, the dependent variable was skin conductance response.

As with the previous aim, the data for aim 2 were also examined using a continuous indicator of memory status instead of the between-groups classification. We conducted a series of regression analyses with memory status (as indicated by the HVLT-R retention z-score) as the predictor and recognition memory performance as the dependent variable. Separate regression analyses were conducted for the low, medium, and high arousal conditions at each of the four recognition testing sessions.

In order to test the third aim (examination of the relationship between hippocampus volume and recognition memory performance), two-tailed Pearson correlations were conducted between hippocampal volumes and recognition scores on the picture test. Correlations were conducted both for overall recognition scores at each of the four testing sessions and for recognition scores within the low, medium, and high arousal categories for each of the four testing session.

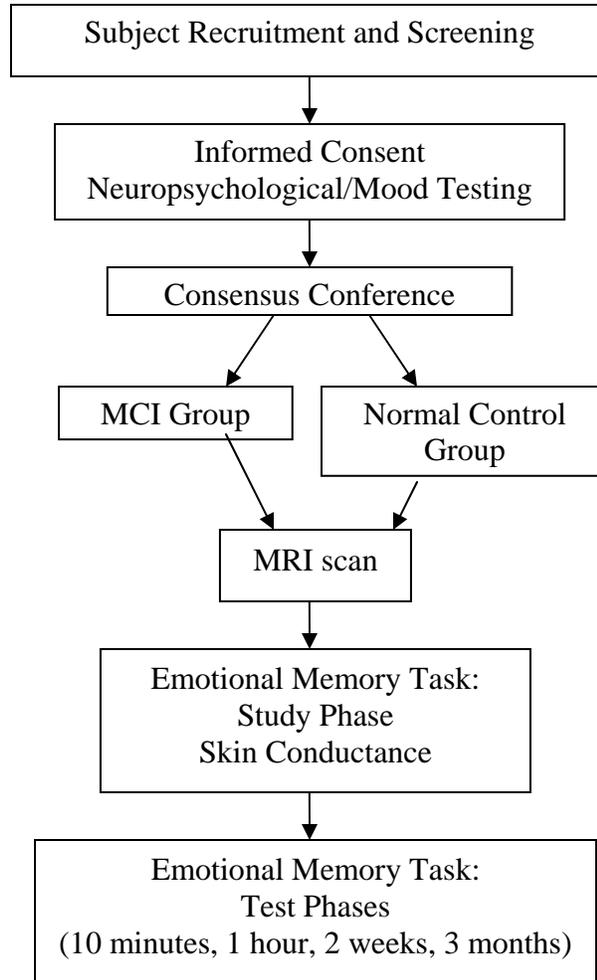


Figure 3-1. Study design flowchart.

CHAPTER 4 RESULTS

Table 4-1 displays the demographic characteristics of the control and MCI groups. As a whole, participants ranged in age from 55 to 88 (mean = 75.6), were well educated (mean = 15.9 years, range 12-20) and included approximately twice as many males as females (ratio of 16:9). As shown in Table 4-1, the two groups did not differ significantly in terms of age, education, or ratio of males to females.

Neuropsychological and Mood Performance: MCI versus Control Groups

Results of the neuropsychological and mood evaluation are shown in Table 4-1. As indicated in the table, the MCI group attained significantly lower scores across the various indices of recent memory from the Hopkins Verbal Learning Test-Revised. This included measures of overall learning, delayed recall after 20 minutes, percent retention, and the recognition discrimination index. On average, these memory scores ranged from 1.6 to 2.2 standard deviations below normative standards and are in line with those reported in the literature for MCI classifications. The MCI group did not differ from the control group on any other measures, including tasks of language (Boston Naming, phonemic and semantic fluency), attention and processing speed (Trailmaking and Stroop Color and Word Naming), and executive functioning (Stroop interference). The MCI group attained a mean IQ estimate of 113 (high average) and performed in the nondemented range on the MMSE. Taken together, performance by the MCI group across the neurocognitive screening measures was largely intact, with the exception of relatively impaired scores on tests of recent memory.

In terms of mood, the MCI group did not differ from the control group on the Geriatric Depression Scale or the State Trait Anxiety Inventory. Additionally, the two groups did not differ in their abilities to perform activities of daily living. However, individuals with MCI did report significantly more memory problems than did controls.

Aim 1: Comparison of Overall Rate of Forgetting

One participant from the MCI group had missing data for the one hour picture recognition task and was therefore not included in the rate of forgetting analyses. Figure 4-1 shows the overall recognition performance at the 4 testing sessions for each group. To test the first hypothesis that MCI patients would show an increased rate of forgetting over time for all stimuli, we conducted a repeated measures ANOVA consisting of a between-subjects factor of *group* (control, MCI) and a within-subjects factor of *recognition test delay* (10 minutes, 1 hour, 2 weeks, and 3 months). There was a significant effect of delay, $F(3,66) = 201.056, p < 0.001$. Bonferroni-adjusted post hoc tests revealed that subjects correctly recognized significantly more pictures at 1 hour (mean = 93.05%) than at 2 weeks (mean = 72.11%; $p < 0.001$), and at 2 weeks than at 3 months (mean = 59.83%; $p < 0.001$). There was no significant difference between the percentage of correctly recognized items at 10 minutes (mean = 93.32%) and 1 hour (mean = 93.05%; $p = 1.0$). There was no significant group by delay interaction [$F(3,66) = 1.934, p = 0.133$], and no main effect of group [$F(1,22) = 0.528, p = 0.475$].

We then ran a series of regressions with memory status (as indicated by the percent retention z-score on the HVLTR) as the predictor variable and overall picture recognition memory performance as the dependent variable. Memory status was a significant predictor of picture recognition performance at 10 minutes ($R^2 = 0.377, p =$

0.001) and 2 weeks ($R^2 = 0.214$, $p = 0.012$), but not at 1 hour ($R^2 = 0.018$, $p = 0.210$) or at 3 months ($R^2 = 0.032$, $p = 0.193$).

Aim 2: Effects of Emotional Arousal on Recognition Memory Performance

Emotional Memory Performance: MCI versus Control Group

In order to investigate the effects of arousal on memory performance we conducted a repeated measures ANOVA consisting of a between-subjects factor of *group* (control, MCI) and within-subjects factors of *recognition test delay* (10 minutes, 1 hour, 2 weeks, 3 months) and *arousal category* (low, medium, high). Figure 4-2 shows the rate of forgetting for low, medium, and high arousal pictures over the four testing sessions for the two groups. There was no significant main effect of arousal [$F(2,44) = 0.902$, $p = 0.413$], no significant main effect of group $F(1,22) = 0.597$, $p = 0.448$], no significant group by arousal interaction [$F(2,44) = 0.686$, $p = 0.509$], and no significant arousal by delay interaction [$F(6,132) = 0.715$, $p = 0.509$].

Arousal Ratings

After examining memory performance for the various arousal conditions, we wanted to verify whether participants' subjective arousal ratings at the time of encoding were consistent with our predetermined arousal categories (low, medium, high). Figure 4-3 shows the mean picture arousal ratings given by participants in both groups as a function of predetermined arousal category. To determine whether individuals in the two groups rated stimuli differently, a 2 X 3 mixed factorial ANOVA was conducted. *Group* (MCI, control) was the between-subjects factor, *arousal* (low, medium, high) was the within-subjects variable, and mean picture arousal ratings was the dependant variable. There was a significant main effect of arousal, $F(1.559,35.858) = 170.050$, $p < 0.001$. Bonferroni-adjusted post hoc tests revealed that pictures in the low arousal category

(mean rating = 6.0) were rated as significantly less arousing than pictures in the medium arousal category (mean rating = 5.0; $p < 0.001$), and that pictures in the medium arousal category were rated as significantly less arousing than pictures in the high arousal category (mean rating = 3.2; $p < 0.001$). There was no significant arousal by group interaction [$F(1.559,35.858) = 1.752, p = 0.193$] and no main effect of group [$F(1,23) = 0.997, p = 0.328$]. In summary, there were no differences between the MCI and control groups in their arousal ratings of emotional pictures at the time of encoding.

Skin Conductance Response (SCR)

Next, we evaluated the skin conductance response, a measure of sympathetic arousal, to determine whether subjects reacted physiologically to arousing stimuli. Because skin conductance habituates relatively quickly, data from only the first 30 trials of this block were analyzed first. The data from 11 participants were excluded from the analysis of the first 30 trials because they had too few valid trials (i.e., less than 3 out of 20) to generate valid averages. To assess whether the control and MCI groups had similar physiological responses to the photographic stimuli, a 2 X 3 mixed factorial ANOVA was conducted with *group* (control, MCI) as the between-subjects factor and arousal (low, medium, high) as the within-subjects factor. There was a significant main effect of arousal, $F(2,24) = 7.480, p = 0.003$. Bonferroni-adjusted post hoc tests revealed that SCRs were significantly lower for pictures in the low arousal category than pictures in the high arousal category ($p = 0.010$), and significantly lower for pictures in the medium arousal category than pictures in the high arousal category ($p = 0.050$). There was no significant arousal X group interaction [$F(2,24) = 0.154, p = 0.858$], and no main effect of group [$F(1,12) = 0.503, p = 0.492$].

A second similar mixed factorial ANOVA was conducted in order to analyze skin conductance data from the entire first block of 60 trials. The data from 4 participants were excluded from the analysis because they had too few valid trials to generate valid averages. For this analysis, there was no significant main effect of arousal [$F(2,38) = 2.539, p=0.092$], no significant arousal X group interaction [$F(2,38) = 2.078, p = 0.139$], and no main effect of group [$F(1,19) = 0.867, p = 0.363$].

Emotional Memory Performance: Spectrum of Aging

Next, we ran a series of regressions with memory status (as indicated by the percent retention z-score on the HVL-T-R) as the predictor and recognition memory performance as the dependent variable for the low, medium, and high arousal conditions at each of the four testing sessions. Table 4-2 shows the regression coefficients for each condition. At the 10 minute picture recognition testing session, memory status was a significant predictor of picture recognition performance for all arousal conditions. Memory status was not a significant predictor of recognition performance at the 1 hour session for any of the arousal conditions. At the 2-week picture recognition testing session, memory status was a significant predictor of picture recognition performance for only the high arousal condition. At the 3-month testing session, memory status was not a significant predictor for any of the arousal conditions.

Aim 3: Relationship Between Hippocampus Volumes and Recognition Memory Performance

Hippocampal Volume and Overall Rate of Forgetting

To test the third hypothesis that hippocampal volume would be positively correlated with picture recognition memory performance, Pearson correlations were conducted between hippocampal volume and overall recognition performance at each of

the four testing sessions. Hippocampal volume was significantly correlated with picture recognition performance at 10 minutes ($R^2 = 0.715, p = 0.006$), at 1 hour ($R^2 = 0.637, p = 0.026$), at 2 weeks ($R^2 = 0.67, p = 0.012$), and at 3 months ($R^2 = 0.690, p = 0.009$).

Hippocampal Volume and Rate of Forgetting for Emotional Material

Additionally, to test the hypothesis that hippocampal volume would be correlated with recognition memory for the medium and high arousal conditions but not the low arousal condition, Pearson correlations were conducted between hippocampal volume and recognition memory test performance for each arousal condition at each testing session. As shown in Table 4-3, hippocampal volume was significantly correlated with recognition memory performance for high arousal pictures at 10 minutes, 1 hour, and 2 weeks. Additionally, hippocampal volume was significantly correlated with recognition memory performance for medium arousal pictures at 10 minutes, 1 hour, and 3 months.

Table 4-1. Demographic characteristics and performance on neuropsychological tests.
Means (\pm standard deviation) are shown.

	Controls (N=13)	MCI (N=12)	t	p
Demographic characteristics				
Age (years)	77.92 (7.11)	73.08 (11.29)	1.270	0.220
Education (years)	16.23 (3.14)	15.50 (2.39)	0.650	0.522
Male/Female	8/5	8/4		
Dementia Screening				
MMSE	29.23 (1.17)	28.25 (1.49)	1.845	0.078
Intellectual Estimates				
WASI 2-scale IQ	121.92 (11.59)	113.42 (10.39)	1.926	0.067
NAART estimated IQ:				
Verbal	112.95 (6.97)	113.86 (4.24)	-0.426	0.674
Performance	111.97 (2.91)	112.44 (1.96)	-0.465	0.646
Full-Scale	114.00 (5.01)	114.85 (3.74)	-0.455	0.653
Memory (Hopkins Verbal Learning Test-Revised; z-scores shown)				
Total Recall	0.75 (0.97)	-1.81 (0.70)	3.122	0.005
Delay Recall	-0.30 (0.98)	-2.23 (0.69)	5.630	<0.001
% Retained	-0.066 (0.89)	-1.64 (1.51)	3.142	0.006
Discrimination Index	-0.16 (1.0)	-2.12 (0.87)	5.237	<0.001
Language (z-scores displayed)				
Boston Naming Test	-0.40 (1.73)	-0.57 (1.64)	0.243	0.811
Phonemic fluency	0.53 (0.83)	0.48 (0.86)	0.152	0.880
Semantic fluency	0.20 (1.28)	-0.28 (1.15)	0.965	0.345
Attention / Psychomotor Speed / Executive Function (z-scores displayed)				
Trails A	0.30 (0.77)	0.28 (0.82)	0.064	0.949
Trails B	0.64 (0.87)	0.11 (0.55)	1.805	0.084
Stroop Word	0.069 (0.78)	-0.09 (1.03)	0.421	0.678
Stroop Color	0.27 (1.09)	-0.06 (0.81)	0.817	0.423
Stroop Interference	0.47 (1.01)	0.30 (0.88)	0.431	0.671
Self-Report Questionnaires				
GDS-15	2.31 (2.56)	3.67 (2.67)	-1.298	0.207
STAI Standard Score				
State	42.69 (6.54)	47.17 (7.42)	-1.603	0.123
Trait	45.85 (11.067)	48.42 (9.26)	-0.627	0.537
IADL scale	15.67 (1.073)	16.00(1.48)	-0.632	0.534
MFQ self-memory assessment	4.58 (1.17)	3.60 (0.97)	2.127	0.046

Table 4-2. Regression coefficients (R^2) for individual regression equations with memory status as the predictor of recognition memory performance for the low, medium, and high arousal conditions (N=25). *Indicates significance at the $p < 0.001$ level. +Indicates significance at the $p < 0.05$ level.

	Low Arousal	Medium Arousal	High Arousal
10 minutes	0.362*	0.294 ⁺	0.261 ⁺
1 hour	-0.036	0.070	0.033
2 weeks	-0.019	-0.034	0.403*
3 months	-0.042	0.027	0.029

Table 4-3. Correlations between hippocampal volume and recognition memory performance for each arousal condition at each testing session (N=13). *Indicates significance at the $p < 0.001$ level. +Indicates significance at the $p < 0.05$ level.

	Low Arousal	Medium Arousal	High Arousal
10 minutes	0.530	0.708*	0.679 ⁺
1 hour	0.163	0.737*	0.750*
2 weeks	0.511	0.327	0.549 ⁺
3 months	0.174	0.705*	0.523

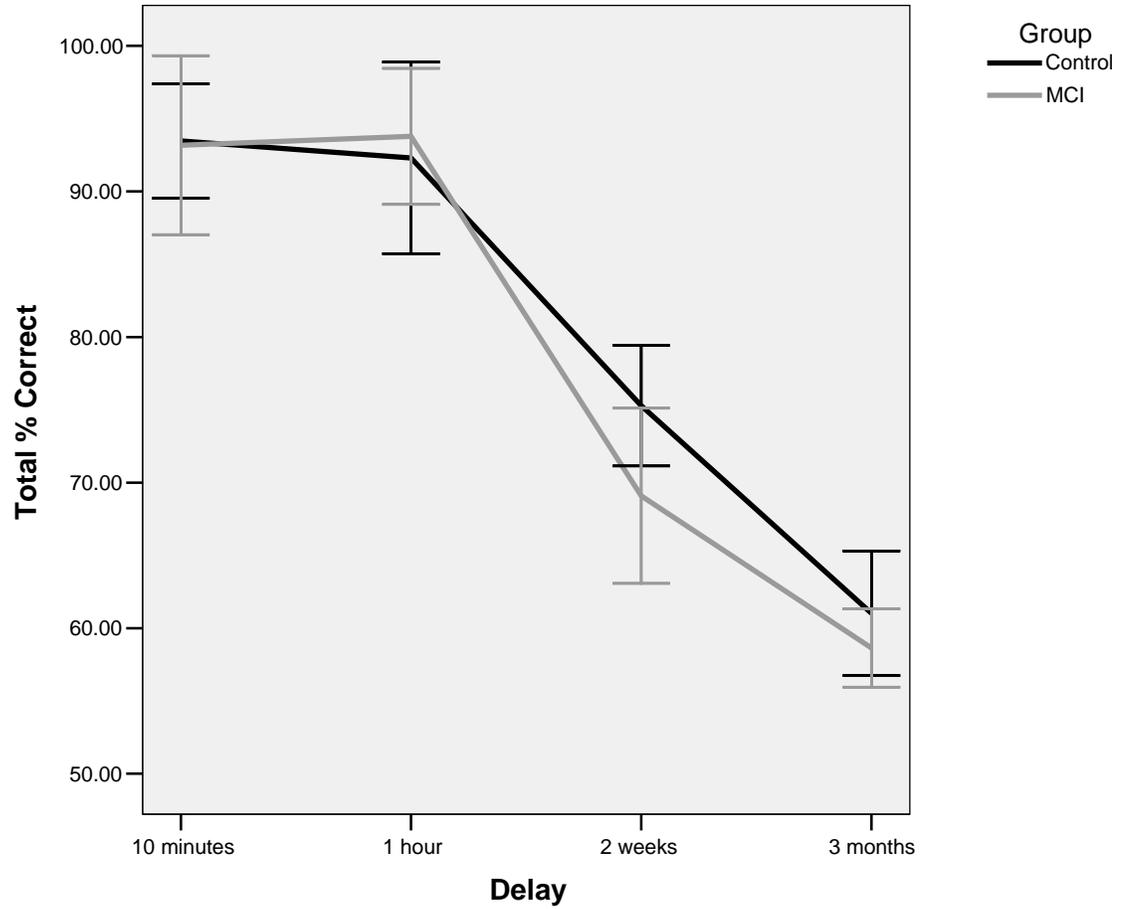


Figure 4-1. Recognition performance at the 4 testing sessions for the MCI (N=11) and control groups (N=13).

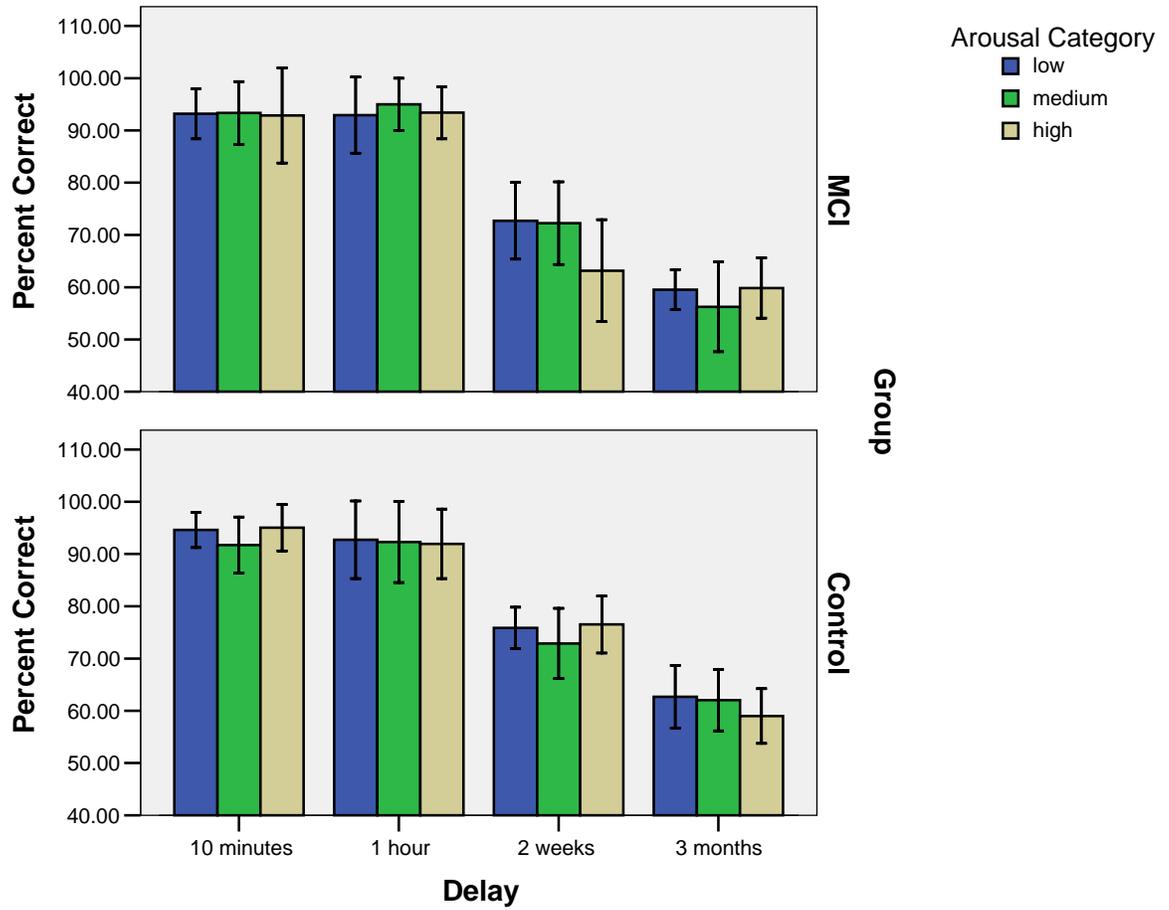


Figure 4-2. Percent correct picture recognition for low, medium, and high arousal pictures over the four testing sessions for the MCI (N=11) and control groups (N=13).

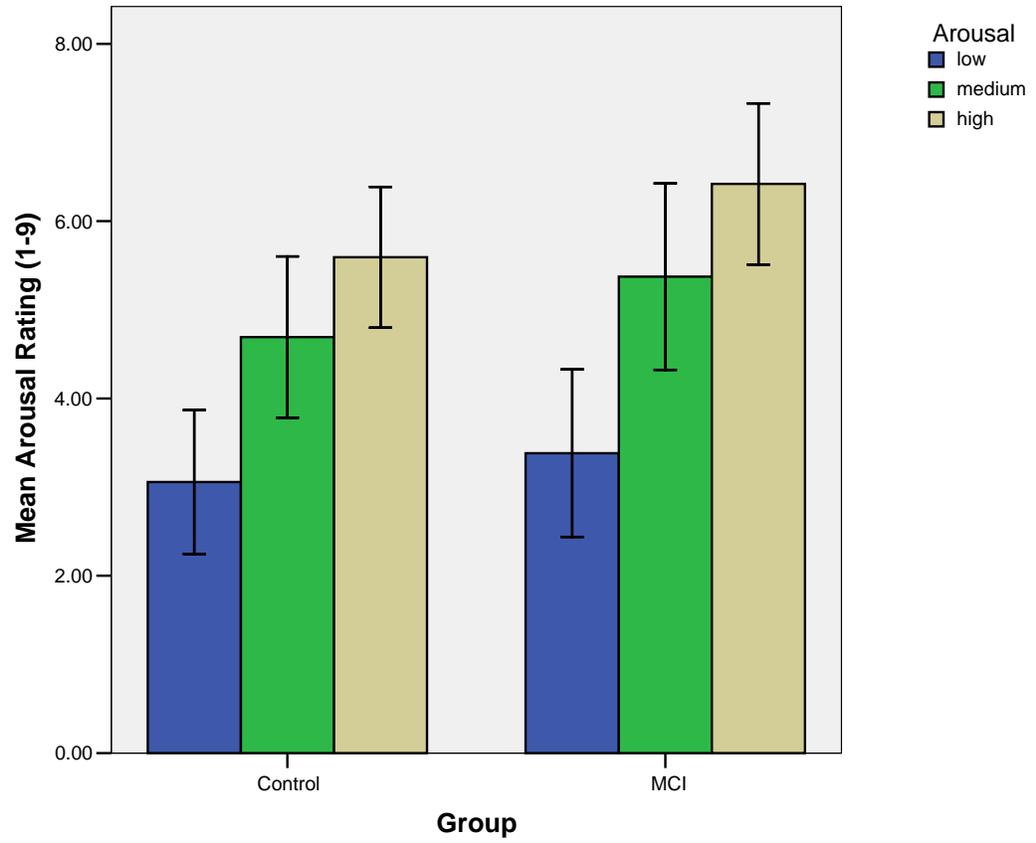


Figure 4-3. Mean arousal ratings ($\pm 95\%$ confidence limits) for low, medium and high arousal pictures by control subjects (N=13) and MCI subjects (N =12).

CHAPTER 5 DISCUSSION

The present study examined three major aims. The first hypothesis was that patients with mild cognitive impairment would demonstrate increased rates of forgetting for a picture recognition task compared to controls, as demonstrated by their recognition memory performance at increasing time delays. This prediction was based on the findings that performance on memory retention tasks at increasing time delays is dependent on an intact hippocampus (Huppert & Piercy, 1979) and that the hippocampus is pathologically involved in MCI. In follow-up analyses for this aim, the MCI versus control group classification was removed and memory status was entered as continuous predictor of picture recognition performance in a series of regression equations. These analyses were conducted because of increasing concerns with the accuracy and utility of the MCI group classification.

The second aim examined whether the picture recognition memory performance of controls and MCI subjects benefited from emotional arousal. Based upon a review of the available emotional memory literature in aging and in Alzheimer's disease, we hypothesized that controls would show better recognition memory performance for high arousing stimuli compared to medium and low arousing stimuli and that MCI patients would also benefit from arousal but to a lesser extent than controls. In assessing the second aim, we next investigated whether MCI patients differed from controls in their arousal ratings of neutral and emotional stimuli and in their physiological reactivity (as assessed by skin conductance responses) to these stimuli. These analyses were necessary

in order to verify whether individuals in both groups had similar levels of arousal (both subjective and physiological) to emotional stimuli at the time of encoding. Finally, we examined this aim using memory status as a continuous predictor of picture recognition performance for the various arousal conditions.

The third hypothesis was that hippocampus volumes would be positively correlated with overall recognition memory performance at each of the four testing sessions and that hippocampus volume would be more strongly related to memory of medium and high arousal pictures than of low arousal pictures. This prediction was based on the hypothesized role of the hippocampus in processes mediated by the amygdala that lead to enhanced memory for emotionally arousing materials.

Summary and Interpretation of the Findings

The first hypothesis was not supported when the data were examined using the dichotomous group classification (MCI versus control). That is, there were no group differences in recognition memory performance at any of the four recognition testing sessions. There are several potential explanations for this finding. It is possible that a ceiling effect at the first two testing sessions (10 minutes and 1 hour) and a floor effect at the last testing session (3 months) may have masked group differences. Additionally, our MCI group may have contained individuals who performed poorly on memory testing at screening but later reverted to normal. Thus, contamination of our MCI group with normal controls may have confounded our results. Several factors led us to question the consistency and accuracy of consensus conference classifications, lending support to this explanation. For instance, a linear discriminant function analysis with measures from the HVLT-R (total recall, delayed recall, and percent retention) as the independent variables classified two cases (one MCI and one control) differently from the consensus conference

classifications. Additionally, one of the participants that we classified as a control participant had been referred to us by another investigator who had previously classified that person as an MCI participant. Finally, two participants who were classified by us as MCI cases were later classified as controls by another clinician who was conducting a separate research study.

Given the difficulty of accurately identifying individuals with MCI, we next examined the rate of forgetting data using a continuous indicator of memory status rather than group classifications. Using this approach, we found a relationship between memory status and performance on the rate of forgetting task at some of the testing intervals. That is, memory status predicted picture recognition performance at 10 minutes and 2 weeks, but not at 1 hour or 3 months. It is unclear why memory status was related to recognition memory performance at 10 minutes and 2 weeks but not 1 hour. However, it is possible that memory status was not correlated with recognition memory performance at 3 months due to a floor effect in picture recognition performance at this time.

In summary, the regression analyses revealed some significant relationships between memory status and picture recognition performance on the rate of forgetting task while the between-groups analyses revealed no relationship between group status and performance on the rate of forgetting task. This indicates that using the dichotomous group classification masked an important relationship between memory status and performance on the picture rate of forgetting task.

The second aim examined the effect of emotional arousal on memory performance. The hypothesis that control subjects, and MCI subjects to a lesser extent, would

demonstrate better recognition memory performance for highly arousing pictures was not supported when data were examined using a dichotomous MCI versus control classification. In fact, neither controls nor MCI patients showed an emotional enhancement effect for memory at any of the four recognition testing sessions. The finding that controls did not show an emotional enhancement effect for memory is somewhat surprising given the reasonably well-established enhancing effect of emotion on memory. Potential explanations are discussed below.

Next, we examined subjective arousal ratings and physiological arousal levels at encoding in order to determine whether both groups responded similarly to the emotional stimuli. Across all subjects, high arousal pictures were rated as significantly more arousing than medium arousal pictures, and medium arousal pictures were rated as significantly more arousing than low arousal pictures. There was no significant group difference or group by arousal interaction, suggesting that MCI patients and controls had similar arousal ratings of the low, medium, and high arousal pictures.

The skin conductance data were generally consistent with this pattern of arousal ratings. Due to concerns about habituation, skin conductance data were examined for only the first 30 pictures and then for the entire first block of 60 pictures. When data from the first 30 trials were examined, all subjects showed significantly greater physiological reactivity to high than to low arousal pictures. There were no group differences, indicating that both groups showed this pattern of enhanced physiological reactivity to high arousal pictures. However, when data from the first 60 trials were examined, there were no differences in physiological reactivity across arousal categories for the entire set of subjects. There was no significant group effect, suggesting that both

groups showed a similar pattern of habituation when all 60 trials were considered together. Thus, there do not appear to be differences in self-reported arousal rating or in physiological reactivity to arousing stimuli between MCI patients and controls. Both groups rated high arousal pictures as more arousing than low arousal pictures and had higher levels of physiological reactivity to pictures in the high arousal than the low arousal categories. This suggests that the absence of a demonstrated emotional memory enhancement effect in the previous analysis cannot be explained by a lack of emotional arousal at encoding.

However, when the group classification was removed and memory status was used as a continuous predictor of recognition memory performance, we found evidence indicating that higher memory status is associated with more of a benefit from emotional arousal on subsequent memory performance. Memory status predicted picture recognition performance for all arousal categories at the first recognition session (10 minutes). At 1 hour, memory status was not a significant predictor of recognition performance for any arousal categories, but at 2 weeks memory status was a significant predictor of recognition performance for the high arousal category. At 3 months, memory status was not a significant predictor of recognition for any of the arousal categories. Thus, the relationship observed at 10 minutes between memory status and picture recognition memory performance was not specific to emotional arousal category. Because the literature on the modulation hypothesis of emotional memory suggests that the amygdala's enhancement of memory consolidation for emotional material is a long-term process, this result is not surprising. However, at 2 weeks, people with better general memory status benefited more from arousal on picture recognition performance

than did people with poorer memory status. The fact that this emotional enhancement effect was demonstrated at 2 weeks but not at 1 hour is also consistent with the notion that the amygdala's enhancement of emotional memory consolidation in the hippocampus is a long-term process. In fact, research from the animal literature suggests that this process takes place over the course of days and weeks, and that emotional enhancement effects on memory are not yet evident after a few hours (Barros et al., 2002; Bianchin et al., 1999; Schafe & LeDoux, 2000). The lack of relationship between memory status and picture recognition performance at 3 months may be due to a floor effect.

The third aim investigated the relationship between hippocampus volume and rate of forgetting performance on the picture recognition task. Our hypothesis that hippocampal volume would be positively correlated with overall recognition memory performance at each of the four testing sessions was supported by the data. Specifically, hippocampal volume was significantly correlated with picture recognition performance at each of the four testing sessions.

Additionally, our hypothesis that hippocampus volume would be more strongly related to recognition memory for medium and high arousal pictures than for low arousal pictures was generally supported by the data. Hippocampal volume was not correlated with recognition of low arousal pictures at any of the testing sessions. Hippocampal volume was significantly correlated with recognition memory performance for medium arousal pictures at 10 minutes, 1 hour, and 3 months, and hippocampal volume was significantly correlated with memory for high arousal pictures at 10 minutes, 1 hour, and 2 weeks.

Interpretation and Relationship to the Literature

Huppert and Piercy (1979) demonstrated that a patient suffering from amnesia due to bilateral hippocampal ablation had impaired memory performance as assessed by his rate of forgetting at increasing time delays. Our study adds to this observation by demonstrating that rate of forgetting over time is sensitive to hippocampal pathology in older adults. While performance on the rate of forgetting task, assessed at four time points, did not differ between individuals classified as belonging to an MCI group and those classified as controls, the task was sensitive to a continuous indicator of memory status as well as to hippocampal volume. That is, memory status and hippocampal volume were each significantly associated with picture recognition performance at some of the recognition testing sessions. Interestingly, hippocampal volume was significantly correlated with picture recognition performance at all four testing sessions, while memory status was significantly associated with picture recognition performance at only the 10 minute and 2 weeks testing sessions. This suggests that the rate of forgetting may be more sensitive to hippocampal pathology than to a neuropsychological memory measure.

Our finding that normal older controls did not demonstrate enhanced recognition memory performance for highly arousing pictures is not entirely unprecedented in the literature. While some investigators have demonstrated enhanced recognition performance for emotional pictures in older adults (Abrisqueta-Gomez et al., 2002; Hamann, Monarch, & Goldstein, 2002), others have not (Charles et al., 2003). In general, tests of recall have been more likely to elicit emotional enhancement effects for normal older adults than have recognition tests (Denburg et al., 2003; Kensinger et al., 2002). However, the decision to use recognition tests in the present study was based on

the risk of encountering floor effects with the use of recall tests at the long-term testing intervals.

The dual process theory of memory (Jacoby, 1991) may help to explain the lack of observed emotional enhancement for memory when comparing MCI and control groups. This theory posits that recollection involves a ‘controlled’ process in which there is conscious retrieval of a prior learning episode, while familiarity is a fast and automatic process requiring few cognitive resources which occurs when prior exposure or processing lead to a feeling of familiarity or ‘perceptual fluency.’ Interestingly, recollection and familiarity have been found to be differentially affected by emotional arousal in both laboratory (Ochsner, 2000) and autobiographical memory studies (Reisberg, Heuer, McLean, & O’Shaughnessy, 1988). Ochsner (2000) found that recollection, but not familiarity, was boosted for negative or highly arousing and, to a lesser extent, positive stimuli. The authors concluded that greater recollection for affective events leads them to be more richly experienced in memory.

In an elegant study employing the dual process theory, Dolcos LaBar, and Cabeza (2005) examined memory for emotional and neutral pictures one year after encoding, and they used fMRI to measure neural activity during the recognition test. Participants included nine healthy young adult females. The authors found that memory performance was better for emotional than for neutral pictures, but that this emotional enhancement was limited to recollection-based memory. Successful retrieval of emotional pictures elicited greater activity than successful retrieval of neutral pictures in the amygdala, entorhinal cortex, and hippocampus. Moreover, in the amygdala and hippocampus, the emotion effect was greater for recollection than for familiarity, whereas in the entorhinal

cortex, it was similar for both forms of retrieval. Thus, emotion selectively enhanced recollection-based activity in both the amygdala, a prototypical emotion region, and the hippocampus, a prototypical memory region thought to be involved in recollection. The co-activation of the amygdala and hippocampus in the recollection of emotional items is consistent with the modulation hypothesis (McGaugh, 2004). Importantly, the findings of Dolcos et al. (2005) and Ochsner (2000) suggest that emotional arousal enhances recollection but not familiarity. Therefore, recognition tests that rely on familiarity process might not detect any emotional enhancement effect on memory.

Our recognition task likely involved a substantial familiarity component, because subjects were asked to make quick decisions about whether or not they had seen each stimulus but were not asked to effortfully retrieve details of the original learning experience. Because emotional arousal appears to have negligible effects on familiarity-based memory, the fact that we did not observe an emotional enhancement effect may be due to the reliance of our recognition tests on familiarity rather than recollection. However, we did find a relationship between emotional arousal and picture recognition performance when we used a continuous predictor of memory performance rather than the between-groups classification. This suggests that our group classification may be a more important factor than the issue of recollection versus familiarity.

When we used a continuous predictor of memory performance rather than the between-groups classification, memory status (represented by percent retention z-score on the HVLT-R) significantly predicted picture recognition performance at 10 minutes for all arousal categories, and at 2 weeks only for high arousal categories. This indicates that memory status seems to be associated with the degree to which people benefit from

emotional arousal at long-term delays (2 weeks). This relationship did not hold at three months, perhaps due to a floor effect. These findings suggest the importance of examining a “spectrum of aging,” because the relationship between emotional arousal and memory performance was masked when the data were examined using a between-groups classification. This may have been due to inaccurate classifications of MCI and/or control subjects, which is difficult to avoid given the heterogeneity of MCI and its overlap with memory changes associated with normal aging.

Finally, the finding that hippocampal volume was associated with memory performance for medium and high arousal pictures but not for low arousal pictures is consistent with the modulation hypothesis of emotional memory. This hypothesis posits that the amygdala enhances memory consolidation for emotionally arousing stimuli through its modulatory effects on other brain structures, including the hippocampus. It appears that larger hippocampal volumes were associated with a greater memory benefit from emotionally arousing stimuli. Therefore, having an intact hippocampus may be necessary for exhibiting emotional enhancement of memory.

Limitations of the Present Study

One limitation of the study to which I have already referred relates to the difficulty distinguishing MCI subjects from control subjects. Our examination of emotional memory performance using a between-groups classification (MCI versus control) indicated that neither group benefited from emotional arousal. On the other hand, our examination of emotional memory performance using a continuous predictor of memory status revealed a relationship between memory status and the degree to which individuals benefit from emotional arousal. This discrepancy indicates that our classification of MCI and control subjects may not have been entirely accurate. This may be due to the fact

that group classifications were based on performance at a single testing session. Classification accuracy may have been improved by basing the consensus conference judgments on performance at multiple testing sessions rather than a single session and by using more memory measures.

It is also possible that the three month testing interval was too long. Some participants, particularly those with poorer memory status, may have demonstrated a floor effect at this time. It may have been more useful to perform the final recognition test at one month. This would have allowed us to examine long-term consolidation processes before the likelihood of encountering floor effects became too great.

Additional limitations of the study relate to the emotional stimuli employed. The static photographs may be of limited ecological validity. It will be important to investigate memory for real-life emotional stimuli and events that have personal relevance.

Finally, this study included no imaging measure of amygdala pathology (either structural or functional). This makes it difficult to draw definitive conclusions about the role of the amygdala in the emotional enhancement effects observed, and prevents us from investigating the status of the amygdala in MCI or in individuals with poor general memory performance.

Directions for Future Research

It appears likely that the recognition format of the picture memory tests employed in this study required familiarity processes rather than recollective processes. The findings in the literature that normal controls and Alzheimer's patients are more likely to demonstrate emotional enhancement of memory with the use of recall tests than the use of recognition tests suggests that emotional arousal serves to enhance recollective rather

than familiarity processes. Thus, future studies should investigate emotional memory in MCI using tasks that tap recollective processes. In fact, we intend to assess the one-year recognition memory performance of subjects from this study using a paradigm that distinguishes between recollection and familiarity. Based on the previously discussed literature, we expect that these individuals will be more likely to demonstrate emotional memory enhancement for items of which they have a conscious “recollection” rather than for items that they perceive as “familiar.” We will investigate whether MCI diagnosis or memory status has any influence on the effect of emotional enhancement of recollective processes.

Future studies should continue to address the difficulty of accurately distinguishing MCI subjects from controls. Longitudinal studies may examine the fluidity of the MCI classification over time. Additionally, studies should investigate the utility of examining performance along a “spectrum of aging” rather than relying solely on the MCI versus control classification.

Given the limited ecological validity of emotional and neutral photographs, emotional memory should be examined further in MCI using other tasks, such as emotional narratives, or using other paradigms, such as fear conditioning.

Because it is not known with certainty whether or not the amygdala undergoes significant pathology or atrophy in MCI, future studies should investigate the status of the amygdala in this condition. Studies investigating amygdala volumetrics and functional activation are especially relevant for studies of emotional memory in MCI, given the central role of the amygdala in the emotional enhancement of memory.

In conclusion, this study sought to investigate the effects of emotional arousal on memory for individuals with mild cognitive impairment and normal controls and to examine the relationship between hippocampal volume and this enhancement effect. Although we did not demonstrate the expected emotional enhancement effect with the use of an MCI versus control group classification, we did show that emotional enhancement of memory is related to memory status as well as to hippocampal volume. That is, individuals with better memory status benefited more from emotional arousal at a long-term memory testing delay (2 weeks), and larger hippocampal volume was associated with better memory recognition performance for arousing stimuli. This study suggests that memory function in older adults should be assessed not only according to MCI versus normal classifications but also along a “spectrum of aging”. Additionally, this study suggests that the use of emotionally arousing stimuli may be a promising memory aid for older individuals – at least for those with good memory status and larger hippocampal volumes. However, the emotional stimuli employed in this study included static photographs which may have had limited ecological validity and little personal relevance to the participants. Therefore, it is entirely possible that emotionally meaningful stimuli with autobiographical relevance could also be helpful for individuals who have isolated memory impairments.

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BIOGRAPHICAL SKETCH

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