

ITEM AND ASSOCIATIVE MEMORY IN NORMAL AGING AND INDIVIDUALS WITH
MILD COGNITIVE IMPAIRMENT

By

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To my parents, for their love and support

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TABLE OF CONTENTS

	<u>page</u>
ACKNOWLEDGMENTS	4
LIST OF TABLES.....	8
LIST OF FIGURES	9
CHAPTER	
1 INTRODUCTION	13
Item versus Associative Memory	13
Association Memory and Its Neural Correlates	15
Frontal lobe and associative memory.....	15
Hippocampus and associative memory	16
Can Item Memory and Associative Memory be Disproportionately Impaired?	20
Aging and Memory	24
Individual Difference among Older Adults.....	26
Mild Cognitive Impairment.....	27
Associative Memory in Normal and Pathological Aging.....	28
2 PURPOSES AND AIMS OF THE PRESENT STUDY	32
3 METHODOLOGY	35
Participants	35
Mild Cognitive Impairment Participants	35
Healthy Older Control Participants	38
Differential Contributions of the Frontal and Medial Temporal lobes.....	39
General Procedure	42
Standardized Clinical Neuropsychological Measures	42
Neuropsychological and Questionnaire Data	45
4 THE EFFECT OF INCIDENTAL VERSUS INTENTIONAL LEARNING ON THE RETRIEVAL OF ASSOCIATION INFORMATION	48
Introduction.....	48
Methods	49
Participants	49
Design.....	49
Materials and Procedure	50
Hypotheses and Predictions	52
Results.....	53
Analyses on the HY, HO, and MCI Groups.....	53
Analyses on Groups Divided by MTL-FL Status.....	58

Discussion.....	61
5 MEMORY OF ASSOCIATIONS BETWEEN ITEMS OF THE SAME KIND USING SEMANTIC RELATED OR UNRELATED WORD PAIRS.....	64
Introduction.....	64
Methods	65
Participants	65
Design.....	65
Materials and Procedure	66
Hypotheses and Predictions.....	67
Results.....	68
Discussion.....	72
6 ASSOCIATIONS BETWEEN DIFFERENT KINDS OF INFORMATION - CROSS-REGION ASSOCIATIONS	73
Associations between Objects and Locations.....	73
Introduction	73
Methods	74
Participants	74
Design.....	74
Materials and Procedure.....	75
Hypotheses and Predictions.....	75
Results	76
Analyses on HY, HO, and MCI groups	76
Analyses on groups divided by MTL-FL status.....	79
Associations between Faces and Houses--Relational Information.....	82
Introduction	82
Method.....	82
Participants	82
Design.....	83
Materials and procedure	83
Hypotheses and Predictions.....	84
Results	85
Analyses on the HY, HO, and MCI groups.....	85
Analyses on groups divided by MTL-FL status.....	86
Association between Temporal Information and Novel Faces.....	89
Introduction	89
Methods	90
Participants	90
Design.....	90
Materials and procedure	90
Hypotheses and Predictions.....	92
Results	92
Analyses on the HY, HO, and MCI groups.....	92
Analyses on groups divided by MTL-FL status.....	93

Association between Temporal Information and Historical Events	96
Methods	96
Participants	96
Design.....	96
Materials and procedure	96
Hypotheses and Predictions.....	97
Results	97
Analyses on the HY, HO, and MCI groups.....	98
Analyses on groups divided by MTL-FL status.....	98
Correlations between temporal order test and neuropsychological measures.....	99
Discussion.....	100
7 CONCLUSIONS AND DISSCUSIONS	106
Disproportionate Impairment on the Associative Memory Compared to Item Memory	107
Semantic Memory versus Episodic Memory.....	111
Frontal Lobe Involvement in Associative Memory and the Heterogeneity Among Older Adults	113
Study Limitations.....	114
Future Direction.....	116
Conclusions.....	117
LIST OF REFERENCES	118
BIOGRAPHICAL SKETCH	129

LIST OF TABLES

<u>Table</u>		<u>page</u>
3-1	Mean characteristics of groups based on cognitive status	38
3-2	Mean characteristics of groups based on frontal lobe (FL) function and medial temporal lobe (MTL) function.....	41
3-3	Numbers of people classified as normal old or MCI in each of the four groups.....	42
3-4	Neuropsychological measures included in the present study	43
3-5	Means and standard deviations for neuropsychological non-memory measures.....	46
3-6	Means and standard deviations for neuropsychological memory measures.....	46
3-7	Means and standard deviations for subjective mood and memory questionnaires.....	47
4-1	Data for the incidental and intentional learning conditions in three groups.....	54
5-1	Means and standard deviations for the variables obtained on the semantic related or novel word pair list in both immediate and delayed conditions on the young, healthy old, and MCI groups.....	70
6-1	Means and standard deviations of variables obtained on the Object Location Test on the three groups.....	77
7-1	Effect sizes for all associative measures	109

LIST OF FIGURES

<u>Figure</u>		<u>page</u>
3-1	Frequency distribution of medial temporal lobe composite scores for total elderly sample (n=35)	40
3-2	Frequency distribution of frontal lobe composite scores for total elderly sample (n=35).....	40
4-1	Data of the immediate item recognition hits for the three groups.	55
4-2	Data for the immediate and delayed recognition of the pairs (hits) in the incidental and intentional learning conditions for the three groups.	57
4-3	Data for the immediate and delayed recognition false alarms (false positive) errors of the pairs in the incidental and intentional learning conditions for the three groups.	58
4-4	Data for the immediate and delayed recognition of the pairs (hits) in the incidental and intentional learning conditions for the four groups divided by their MTL-FL function levels.....	60
4-5	Data for the immediate and delayed recognition false positive score of the pairs in the incidental and intentional learning conditions for the four groups divided by their MTL-FL function levels.	60
5-1	Data for free recall, cued recall, and recognition test on the semantic related or novel word pair list in both immediate and delayed conditions for the young, healthy old, and MCI groups.	71
6-1	The display of the namable objects and their locations for the object-location test.	76
6-2	Data for object recognition hit and object-location recognition tests in both immediate and delayed conditions for the young, normal old, and MCI groups.....	78
6-3	Data for object, location, and object-location free recall tests in both immediate and delayed recall for the young, normal old, and MCI groups.	79
6-4	Data for object, location, and object-location free recall tests in both immediate and delayed recall for the four groups divided based on their function on MTL and FL factors.....	81
6-5	Data for object recognition hit and object-location recognition tests in both immediate and delayed conditions for the four groups divided based on their function on MTL and FL factors.....	81
6-6	An example of the stimuli and the task for the face –house association test.....	84

6-7	Data for immediate and delayed recall on the face-house association test across three groups.....	86
6-8	Data for face-house association test in both immediate and delayed conditions for the four groups divided based on their function on MTL and FL factors.	87
6-9	Data for face-house association test in both immediate and delayed conditions for the two groups divided based on their function on medial temporal lobe factor.....	88
6-10	Data for face-house association test in both immediate and delayed conditions for the two groups divided based on their function on frontal lobe factor.....	88
6-11	Data of the between-list and within-list trials at two time points for the young, healthy old, and the MCI groups.....	94
6-12	Data of the recency task for the four groups divided by their frontal and medial temporal lobe function levels.....	95
6-13	Data of the difference scores on the historical event temporal order test for the young, healthy old, and the MCI groups.....	98
6-14	Data of the difference scores on the historical event temporal order test for the four groups divided by their medial temporal lobe and frontal lobe function levels.	99

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Efficient and accurate prediction of dementia in the preclinical stage is important for social and medical reasons. The foregoing literature review suggests that associative memory may serve as a tool for early detection of individuals who may develop dementia later in life. Individuals with mild cognitive impairment (MCI) may be in a transitional stage between normal aging and dementia. The primary goal of the current study was to systematically investigate associative memory in healthy younger adults, healthy older adults, and individuals with Amnestic MCI. We further examined heterogeneity in frontal functioning documented in literature and its relationship with the performance on associative memory among older individuals. Thirty-five older adults (11 with Amnestic MCI) and 20 younger adults completed a series of associative memory experiments which assessed associations between information of the same kind (word-word pairs), associations between different kinds of information (e.g., object-location pairs), and relational associations (an association established between two items through a third item). Additionally, each participant completed a neuropsychological screening battery which served the purpose of classification into different groups (Amnestic MCI or healthy control). Results revealed that older adults with Amnestic MCI demonstrated the greatest and a disproportionate impairment of associative memory with relatively spared item memory. Second, the impaired

associative memory was found in all kinds of associative memory tasks. Third, the results suggest that normal healthy old adults, but not MCI individuals, benefited from explicit encoding instruction when performing associative memory. Furthermore, free recall compared to recognition was a more sensitive paradigm when examining the associative memory. Finally, a parallel analysis on groups established by the older individuals' functional level (high vs. low) in the frontal /executive functioning and medial temporal lobe functioning revealed that the medial temporal lobe function is critical for associative memory. The level of frontal/ executive function became important only when the integrity of the medial temporal lobe was compromised. Overall, our results suggest that associative memory functioning may serve as a reliable and sensitive indicator for early detection of people who may develop dementia later in life.

CHAPTER 1

INTRODUCTION

Item versus Associative Memory

Complex events consist of multiple kinds of information that are related or “bound” together as a unitary whole. An event can include the semantic content, information about the time in which the event took place, the place in which it occurred, the acting agents and their characteristics, and so on. All of these aspects integrated with the internal cognitive state of the person are encoded as an episode. Remembering such an episode requires that at least some of the bound components be retained, as well as their relationships with each other. As people age, their memory for recent events tends to become less precise. Although they might know that a particular event occurred or have the knowledge of a particular fact, they may be less likely to recall other information associated with the event (e.g., where or when the event took place).

The distinction between item and associative information has a long history in psychology and has been supported by several experiments that yielded different patterns of results for the two types of information (Hockley, 1991, 1992; Hockley & Cristi, 1996). The items in question are typically well-integrated stimuli such as words, letters, numbers, or pictures, whereas associative information refers variously to the information of new items by binding features together, to the links among several items, or to the integration of an event with its context of occurrence. It could be argued that vast areas of memory research, including contextual aspects of memory and memory for source, basically involve the study of associative memory. For example, the relationships of two messages can be conceptualized within a classic paired-association paradigm. The relationships of a message and the characteristics of the acting agents (e.g., the voice or the face) can be probed as memory for context. Memory for a message in a specific time and space is investigated as memory for source. All of these examples constitute

the establishment of connections (associations) among single representational units at one level or another.

Although the distinction between item and associative information is well supported in the literature, methodological issues have raised questions concerning the interpretation of many of the existing studies of item and associative memory. First, because retrieving associations is commonly more difficult than retrieving single items, individuals with poor memories, such as amnesic patients and older adults, may show associative memory impairments because of task difficulty, rather than because of differential impairment in associative memory capacity per se. Second, memory for associative information has usually been assessed only for those items that are remembered. Thus, item and associative memory tests have not been independent. Third, the forms of the tests for item and associative information are not often equated. For example, in some studies, item memory has been tested in recognition, whereas associative memory has been tested in recall. In general, studies have shown impaired associative memory when item memory is either normal or equated across groups, but have not shown impaired item memory with normal associative memory. Typically, recognition of single items is matched between patient and control groups by giving the patients extended study time or by testing them following shorter delays than control subjects. The ability to remember the associative information is then investigated under the equivalent item memory conditions and, if it is impaired, it can be concluded that memory for this kind of information is disproportionately impaired, relative to item recognition. The validity of this conclusion, however, depends on insuring that the matching procedure does not affect one kind of memory more than the other in normal subjects (Mayes, Meudell, & Pickering, 1985).

Association Memory and Its Neural Correlates

The actual mechanisms of integration or binding are still poorly understood, although we know that content and context must be integrated at encoding, and information about their co-occurrence must be stored in memory. Integrative encoding processes that often involve conscious attentional processes may depend on the frontal lobe (Stuss & Benson, 1986). Alternatively, the binding of multiple components of a stimulus event into an integrated trace, which is often considered as an automatic process may be a key function of the hippocampal-medial temporal lobe memory system (Cohen & Eichenbaum, 1993; Cohen, Poldrack & Eichenbaum, 1997).

Frontal lobe and associative memory

Previous research has clearly established that certain types of frontal lesions can produce deficits in associative memory, particularly in temporal or source context memory tasks, when compared to lesions of the temporal lobe (Butters, Kaszniak, Glisky, Eslinger, & Schacter, 1994; Milner, 1982; Milner, Corsi & Leonard, 1991). This pattern is also seen in certain spatial context memory tasks (Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Owen, Sahakian, Semple, Polkey, & Robbins, 1995). Cabeza et al. (1997) used positron emission tomography (PET) to directly contrast the neural correlates of items and temporal order memory. In their study, subjects studied a list of words and were then scanned while retrieving information about what words were in the list or when they occurred within the list (recency judgment). They found item retrieval was related to increased neural activity in medial temporal and basal forebrain regions, whereas temporal-order retrieval was associated with activations in dorsal prefrontal, cuneus/precuneus, and right posterior parietal regions. The dissociation between temporal and frontal lobe regions confirms and extends previous lesion data. Although historically important, these results leave some gaps. First, the double dissociation between temporal lobe and frontal

lobe patients has been difficult to replicate. Milner, Corsi, & Leonard (1991) showed that frontal patients were more impaired in recency than on recognition judgments, but the opposite pattern in temporal lobe patients was not clearly observed. Patients with temporal lobe lesions were surprisingly unimpaired in recognition memory for words or representational drawings, and although temporal lobe patients were significantly impaired on recognition of abstract pictures compared to control subjects, they also showed a decrement in recent memory for these items.

Hippocampus and associative memory

The discovery that the medial temporal brain regions, particularly the hippocampal formations, are essential for human memory provided the basis for neuroscientific theories and experimental practice during the past several decades. In the years following this discovery, research with amnesic patients led to the finding that memory is not a unitary system but is divided into subsystems, each supported by different but partially overlapping neuronal networks. The hippocampus is thought to be primarily involved in declarative memory, though its specific function has been variously described as involving consolidation (Squire & Zola-Morgan, 1991) episodic memory (Vargha-Khadem et al., 1997), novelty detection (Tulving et al., 1994, 1996), and spatial learning (Maguire et al., 1998). At the same time, learning experiments with rats (Cohen & Eichenbaum, 1993; Eichenbaum et al., 1994; Eichenbaum, 1997) as well as with amnesic patients (Kroll et al., 1996; Mayes et al., 2001; Vargha-Khadem et al., 1997) indicated that the hippocampal formation is important for the establishment of associations between components of episodes in memory. Neuroimaging evidence in younger adults also suggests that medial-temporal regions are critically involved in associative-recognition tasks for words, both at encoding (Jackson & Schacter, 2004) and at retrieval (Giovanello, Schnyer & Verfaellie, 2004; Heckers et al., 2004; Preston et al., 2004; Yonelinas et al., 2001).

The experience of an episode typically involves the simultaneous processing of diverse sensory inputs, bodily sensations, thoughts, and emotions in distributed cortical regions, creating patterns of coactivations in the cortex. The composition and temporal contiguity of these coactivations needs to be stored in memory for the later recovery of some or all aspects of that episode. The anatomy and physiology of the hippocampal system lends itself to store such patterns of neuronal coactivations temporarily (Cohen & Eichenbaum, 1993; Eichenbaum, 1997; Squire & Zola-Morgan, 1991). Inputs from the various sensory association cortices are channeled through the perirhinal and parahippocampal cortices to the entorhinal cortex (or directly to the entorhinal cortex) and, from there, to the hippocampal formation. The hippocampus is reciprocally connected with these sensory areas and therefore can reactivate them. This suggests that the hippocampus performs the most complex mnemonic computations such as associating the different inputs with one another and reactivating the involved cortical sites for consolidation and retrieval of information. Moscovitch and Winocur (1995) also suggested that medial temporal areas are at the core of an associative system that automatically binds together what is consciously apprehended. They indicated that at any point in time a number of distinct neural networks/ pathways are activated via both internally generated and/or externally available stimuli. The medial temporal system has been viewed as binding these distinct patterns (activation patterns) in a relatively automatic/modular manner to produce a record of the conscious experience.

Although the hippocampal system seems to be important for the process of binding information from different inputs, it is unclear whether hippocampal damage impairs all kinds of associative memory to the same extent. Three types of associative memories have been described commonly across studies, although the terms in different studies are slightly different:

1) intra-item association. An example of such type of associations is the associations among parts or components within a face. 2) associations between the same kinds of items or within-region associations, i.e., associations between information stored in the same cortical region. Examples of this kind of association include word-word or face-face associations. 3) associations between different kinds of information or cross-region associations, i.e., associations between information represented in distinct cortical regions. Examples for this kind of associations are associations between objects and their location, words and their temporal information, and faces and names etc. Describing this three-level taxonomy of associative memory is not meant to imply that associative memories cannot be categorized in other meaningful ways (e.g., intramodal vs. cross-modal associations, etc.).

Kroll et al. (1996) examined recognition memory for associations between components of schematic faces or syllables of known words (e.g., study “valley” and “barter” and test either with these target words, new words, or the syllabic recombination “barley”). They found their patient with bilateral hippocampal damage could discriminate between studied words or faces and completely novel foils, but was significantly impaired at discriminating between studied items and recombined foils for both the word and face items. Their results suggest that hippocampal lesions disrupt the ability to form intra-item associative memory. In contrast, Vargha-Khadem et al. (1997) found that early hippocampal lesions in childhood impairs the recognition of associations between different kinds of information (e.g., face-voice and object-place associations) but spares the recognition of associations between the same kinds of items (e.g., word-word or face-face associations). Similarly, Mayes et al. (2001, 2004) reported the case of an adult amnesic patient with bilateral hippocampal atrophy who showed normal intra-item associations and associative recognition of word or face pairs but failed in the recognition

of associations between different kinds of information after controlling the difficulty level between different tasks. Based on these findings, the suggestion has been made that hippocampal damage disrupts memory for cross-region associations but spares memory for single items and memory for intra-item and within-region associations. The Kroll et al. (1996) study did not control for task difficulty; in their study, normal subjects found the recombination task harder than discriminating targets from novel foils. Furthermore, their patient was impaired at discrimination of studied patterns comprising several components from recombination foils. It is unclear whether this test required memory for intra-item associations or inter-item association because the patterns may not have been perceived as items. Interestingly, Turriziani et al. (2004) found that patients with hippocampal lesions performed more poorly than the normal controls on associations between the same kinds of items and associations between different kinds of information, and there was no indication that the impairment was relatively more severe for the latter than for the former kind of association.

Deficits in source memory (association between content and context) have been occasionally reported in patients with diencephalic or temporal lobe lesions, though it is controversial as to whether such deficits should be attributed to concomitant frontal pathology. On the basis of correlational data and also comparisons with patients with frontal lobe lesions, various authors have taken the view that association memory for temporal order and source are dependent upon frontal function (Janowsky, Shimamura, & Squire, 1989; Schacter, 1987; Schacter, Harbluk, & McLachlan, 1984; Shimamura & Squire, 1987; Shimamura, Janowsky, & Squire, 1990). However, Kopelman (1989), Parkin, Leng, & Hunkin (1990), Kopelman, Stanhope, & Kingsley (1997), and Mayes et al. (2001) found that temporal association memory was more strongly correlated with target memory performance in amnesic patients than with

performance on tests of frontal lobe function. Pickering, Mayes and Fairbairn (1989) reported a similar finding for modality context, and Shoqeirat & Mayes (1991) and Holdstock et al. (2002) had similar findings for spatial context. Likewise, Chalfonte, Verfaellie, Johnson and Reiss (1996) failed to find a correlation between frontal function and spatial location memory. These latter findings indicate that associative memory impairment seems to be more closely associated with a “core” memory deficit in amnesic patients than with concomitant executive or frontal dysfunction per se.

In summary, although the precise roles of hippocampus and frontal lobe in associative memory are still unclear, available evidence suggests that both brain regions are needed for successful coding and storage of an entire event. The frontal lobe is needed to initiate and carry out cognitive control processes to ensure that all aspects of an experience are encoded; the medial temporal lobe-hippocampus is critical for the rapid formation of associative memories and may serve to physiologically integrate information recorded in many different areas of the brain. Although there is insufficient evidence to indicate that hippocampus damage impairs one type of associative memory over the other, available data suggests that the hippocampus may play a more important role in item-item associations (involving both same and different items) than it does in intra-item association (i.e., linking parts of items together). This latter function may be more likely handled by modality-specific association cortex and may be computed prior to hippocampal processing.

Can Item Memory and Associative Memory be Disproportionately Impaired?

As suggested by the findings reviewed above, hippocampus may have as its most important function the rapid formation of associative memories. However, the literature on the effects of relatively selective hippocampal lesions on item memory in humans is also well documented (Reed & Squire, 1997), although the effects on item recognition vs. recall are

conflicting (Mayes et al., 2002). One issue that remains unresolved is whether any impairment in associative memory following amnesic patients with selective hippocampal lesions is disproportionate to their deficit in memory for individual items (Cave & Squire, 1991; Mayes et al., 2004; Squire, 1982; Vargha-Khadem et al., 1997).

Although studies have consistently shown that amnesic patients are impaired at list discrimination and temporal sequencing tests, performance on these tests has not always been found to be disproportionately impaired relative to item recognition in patients with medial temporal lobe (MTL) damage. Early work by Squire et al. (1981, 1982) reported a disproportionate deficit in memory for temporal context in patients with Korsakoff's syndrome, whereas the performance of MTL patients was no worse than would have been predicted by their poor recognition memory. Based on such findings, these authors suggested that hippocampal, more extensive MTL, and midline diencephalic lesions should each disrupt temporal order memory and item recognition to equivalent extents. This "unitary" view predicts that temporal order memory will be more impaired than item recognition when any of these lesions is accompanied by frontal cortex damage that further impairs temporal order memory in a relatively selective way. However, some caution in accepting the conclusions of Squire et al. (1981, 1982) is warranted because their MTL group was recruited from a sample of depressed patients who had recently undergone ECT, in whom it was claimed would be likely to suffer a functional disturbance of MTL structures. Also, a matching procedure was not used in their study.

Despite these limitations, several further studies have also supported the contention that disproportionate deficits in list discrimination memory seen in patients with Korsakoff's syndrome need not be related to frontal lobe dysfunction (Hunkin & Parkin, 1993; Hunkin,

Parkin, & Longmore, 1994). For example, Hunkin, Parkin, & Longmore (1994) found that although amnesics with Korsakoff's syndrome and those with MTL damage were similarly impaired in their recognition memory for target items, the Korsakoff amnesics were more impaired than the MTL patients on a test of list discrimination. The disproportional impairment found in Korsakoff amnesia did not correlate with performance on tests associated with frontal lobe functioning. Based on the results, Parkin et al. (1992) argued that retrieval of contextual information, defined as spatiotemporal and other information that allows memories for events to be differentiated, plays a role in the recall/recognition of target (or attended) information and that encoding of contextual information into memory is disrupted by the kind of damage to diencephalic structures that is found in Korsakoff patients. In contrast, the role of the MTL is postulated to be that of consolidating target information, context information, and presumably the associations between them, into memory.

According to this hypothesis, patients with MTL damage would therefore be equally impaired at consolidating target (item) and temporal as well as other kinds of contextual and associative information into memory. MTL lesions of any kind should, therefore, disrupt these different forms of memory to the same degree. Their hypothesis differs from the unitary view in predicting that midline diencephalic lesions will disrupt context information more than item recognition even when there is no additional impairment of context memory caused by frontal cortex damage. The results found in Hunkin, Parkin, & Longmore (1994) support their argument, however, as was the case with the Squire et al. (1981, 1982) study, Hunkin et al. (1994) did not use matching procedure and therefore the results may be confounded by difficulty issues.

Several recent studies based on matching procedures have found that patients with selective hippocampal lesions displayed disproportional associative memory impairment relative to their item memory. For example, Vargha-Khadem et al. (1997) found that patients with selective hippocampal lesions showed fairly normal item recognition, but that their recognitions of object-location and face-voice associations were impaired. Kroll et al. (1996) also examined recognition memory for associations between syllables of known words (e.g., study “valley” and “barter” and test either with these target words, new words, or the syllabic recombination “barley”) or components of schematic faces. They found their patient who reportedly had bilateral hippocampal damage following an anoxic episode could discriminate between studied words or faces and completely novel foils, but was significantly impaired at discriminating between studied items and recombined foils for both the word and face items.

Similarly, Mayes et al. (2004) found that a patient who suffered a selective bilateral lesion to the hippocampus showed relatively preserved verbal and visual item recognition memory. However, this patient demonstrated disproportional impairment at recognition of associations between different kinds of information (e.g., association between objects and their location, words and their temporal order, and faces and voices, etc.). The views of Squire and his colleagues (1981, 1982), and Parkin et al. (1992) cannot explain the above findings. Alternatively, those results seem to fit with the hypothesis, forwarded by Aggleton and Brown (1999), that the role of the extended hippocampal system (hippocampus, fornix, mammillary bodies, anterior thalamus, and possibly parts of the cingulate cortex) is to link target information with contextual information such as spatial, temporal, and source information in memory so that particular episodes are uniquely characterized. As such, the extended hippocampal system is postulated to mediate memory for all kinds of associations that underlie the process of

recollection (item-context retrieval) on which free recall and associative recognition are based. On the other hand, perirhinal cortex of the MTL and its projection to the dorsomedial nucleus of the thalamus (DM) are postulated to mediate the process of familiarity on which recognition of single-item information is based. Their view predicts that both hippocampal and more extensive MTL lesions would disrupt temporal order memory to a greater extent than item recognition even when there is insignificant damage to the frontal lobes. Furthermore, hippocampal lesions will not disrupt item recognition at all if this mainly depends on item familiarity rather than recollection. It also predicts that midline diencephalic lesions will have the same effect as hippocampal lesions if they only affect structures in the “extended hippocampal system,” and the same effect as more extensive MTL lesions if they additionally damage structures in the perirhinal cortex-DM system.

In summary, the review of the literature reveals conflicting results with regard to the issue of whether associative memory is more impaired than item memory following selective hippocampal lesions, although several recent studies found the associative memory is disproportionately impaired when compared to item memory based on the careful use of procedures that match for initial level of learning.

Aging and Memory

Memory loss is one of the main complaints of normal aging. Older adults often experience substantial difficulty compared with young adults in remembering many types of event details. For example, there is evidence of age-related memory deficits for spatial information (Kirasic, 2001), voices (Kausler & Puckett, 1981), color (Park & Puglisi, 1985), temporal information (Parkin, Hunkin, & Walter, 1995; Schacter et al., 1991), and persons (Ferguson, Hashtroodi, & Johnson, 1992). Several hypotheses have been attempted to explain the relatively poor memory performance of old adults, including a deficit in semantic processing, a failure of metamemory, a

failure of deliberate recollection, a reduction in processing resources (Light, 1991), impaired processing speed (Salthous, 1996), and a failure of inhibitory processes (Hasher & Zacks, 1988). Although all of the above relate to older adults' episodic memory deficits, none of them alone can provide an explanation for the full range of phenomena associated with age-related declines in memory.

Lesion (Pruall, Gabrieli, & Bunge, 1999) and imaging (Cabeza & Nyberg, 2000) studies indicate that episodic memory draws on a widespread network of brain structures, including the hippocampus and related regions, diencephalon, basal forebrain, anterior cingulate gyrus, precuneus and other parietal structures, cerebellum, and frontal lobe. The susceptibility of episodic memory to aging may thus reflect that performance could be disrupted because of changes at multiple sites in a large distributed network. Brain structures that may be particularly relevant to episodic memory are known to be affected by aging. Specifically, moderate age-related atrophy of hippocampus (Golomb et al., 1994) and a more sizable loss of frontal volume in old age (Raz et al., 1997) have been reported. In general, attempts to link volumetric measurements of these structures to age-related episodic memory deficits have been successful, with most studies reporting moderate to strong relationships.

The pattern of outcome from studies in which the brain activity of young and older adults is compared during encoding and retrieval is less consistent, likely reflecting differences across studies in tasks, methods, and subject selection procedures. Many studies additionally suffer from small sample sizes. Nevertheless, there are several findings that may contribute to our understanding of age-related episodic memory deficits. Grady et al. (1995) found an age-related decrease in hippocampal activity during encoding of faces. Such a decrease was not observed during recognition. This suggests that age-related functional changes in the hippocampus are

more likely to occur at encoding than at retrieval. There is also evidence of age-related decreases of activity in left inferior frontal cortex during episodic encoding (Cabeza et al., 1997). This region has been implicated in semantic elaboration during encoding in imaging research with young adults (Kapur et al., 1994). Also of interest is the finding that young adults show decreased activity in left frontal cortex under conditions of divided attention (Idaka et al., 2000). In addition, in young adults prefrontal activation is lateralized for episodic memory, such that left prefrontal activity dominates during encoding and right prefrontal activity dominates at retrieval (Nyberg, Cabeza & Tulving, 1996). Several studies demonstrate that this encoding-retrieval asymmetry is markedly reduced in old age (Backman et al., 1997; Cabeza et al., 1997), possibly reflecting age-related decreases in specificity of neural processing during episodic remembering (Cabeza, 2001).

Individual Difference among Older Adults

Although older adults, in general, perform more poorly than young adults in episodic memory tasks, there is great variability within the older population with regard to the size of the impairment. Many researchers have focused on demographic, lifestyle, and health-related factors to explain these individual differences (Backman et al., 1999). However, knowledge of these factors is not very useful in determining the sources of age-related performance deficits, although it is informative in understanding late life variability in memory performance.

As suggested by literature, there are data suggesting dysfunction of both medial temporal and frontal lobe regions in older adults. Moreover, the link between volumetric measurements of these structures to age-related episodic memory deficits has been successful.

Recently, Glisky, Polster & Routhieaux (1995) divided their older adults into groups based on two dimensions of functioning- frontal lobe functioning and medial temporal functioning to address the individual difference issues in the topic of source memory. Their data suggested that

source memory is deficient only in a subset of older adults, who had lower frontal lobe functioning compared to younger adults. Although their measures of FL and MTL function were based on neuropsychological, not neuroanatomical, evidence, and so they could provide only indirect indication of the involvement of specific brain regions, their study actually demonstrated an effective way to explain the variable results among literatures and the individual differences among older population.

Mild Cognitive Impairment

In the past several years, there has been considerable debate in the aging literature surrounding what appears to be a continuum of memory performance between normal aging and pathological aging. Mild cognitive impairment (MCI) is a controversial concept which is generally referring to persons who do not fulfill criteria for Alzheimer's disease (AD) or dementia, but who exhibit some form of cognitive impairment. Evidence from both neuropsychological and neuroimaging studies have suggested that MCI may represent a clinical prodrome to degenerative dementias such as AD. For example, both cross-sectional and longitudinal neuropsychological research has suggested that people with MCI have significant memory impairment beyond what is expected in normal aging, but less than that seen in dementia syndromes, and that such cognitive deficits may increase the likelihood that dementia will develop later (Bischkopf, Busse & Angermeyer, 2002). In addition, significant hippocampal and entorhinal cortex volume reductions, which are well-established risk factors for the development of AD, are consistently found in subjects with MCI as compared with cognitively unimpaired controls (Wolf et al., 2003).

Although criteria have been specified for the classification of MCI, these criteria differ across studies, and the potential of misclassification is high (Busse & Angermeyer, 2002, Petersen et al., 2001). It has been suggested that MCI may represent a highly heterogeneous

group, the members of which cannot be classified perfectly by current criteria. With the subclassifications of MCI, which includes ‘MCI-amnestic’, ‘MCI-multiple domains slightly impaired’, and ‘MCI-single non-memory domain’, proposed at the Current Concepts in MCI Conference in 1999 (Petersen et al., 2001) a number of shortcomings of the classical MCI concept was addressed. Cognitive impairment in MCI is now clearly related to age and education-specific norms and is not limited exclusively to isolated memory impairment.

Although the subclassifications of MCI by Petersen et al. (2001) was a further step for scientists to understand the inherent nature of MCI, Busse et al. (2003) recently found that none of the three subclassifications alone proved to have significant relative predictive power in the prediction of dementia. Thus, further population-based studies addressing the heterogeneous nature of MCI are needed, as is the development of cognitive test and biological markers. If persons with MCI are in a prodromal or “at risk” stage for developing dementia, we will need to develop criteria with a high sensitivity and specificity for identifying these individuals so that they can be offered effective pharmacological and behavioral interventions for delaying the onset and progression of the disease.

Associative Memory in Normal and Pathological Aging

Chalfonte and Johnson (1996) have suggested that part of older adults’ deficient memory performance stems from their difficulty in binding new information into complex memories. Similarly, Naveh-Benjamin (2000) has proposed an associative deficit hypothesis that states that older adults have poorer memory because of a deficiency in creating and retrieving links between single units of information. The basic units can be two items, an item and its context, two contextual elements, or more generally, the representation of two mental codes.

Age differences in associative memory appear quite consistent. For example, in comparison with their young counterparts, normal older adults experience difficulties in

remembering the source of information (Spencer & Raz, 1995) and the temporal order of information (Fabiani & Friedman, 1997; Newman et al., 2001). Older adults also tend to forget specific contextual details such as the case format of stimulus text (Kausler & Puckett, 1980), the color of stimulus material (Park & Puglisi, 1985), or the spatial location of items (Park, Puglisi & Lutz, 1982). Meta-analytic evidence suggests that although frontal dysfunction has been observed in older adults, intentional encoding instructions do not necessarily put healthy older adults at a disadvantage on memory tasks as we see in patients with significant frontal lobe lesion (Verhaeghen et al., 1993). Both content memory and context memory were actually enhanced by intentional encoding strategies (Kausler et al., 1985; Kausler & Phillips, 1989; Schmitter-Edgecombe & Simpson, 2001), and age differences seem to remain stable across manipulations that affect the overall level of performance. Manipulations of study time and of the delay between study and test also show the same pattern for young and old adults (Perlmutter et al., 1981). Overall, the existing literature indicates that age difference represent a quantitative rather than a qualitative decrease in associative memory.

However, the important question is not only whether older adults are less adept in associative memory than young adults, but also whether this impairment is disproportionately greater than age-associated impairment in memory for items (or content). The literature yields conflicting answers to this question. Some research has suggested that normal older adults demonstrate a disproportionately greater deficit in the memory for associative relationships among items compared to their memory for the items themselves (Craik et al., 1990; Chalfonte and Johnson, 1996; Naveh-Benjamin, 2000). In other studies, however, differential age effects on associative memory are relatively small (Denney et al., 1991). A potential moderator of age effects is the type of associative information to be remembered. With the wide variety of

contextual details (e.g., perceptual, spatial and temporal), it is possible that age differences are not uniform across materials and encoding modalities. Unfortunately, there is practically no research on this question.

Research on age-related changes in the neural substrates of associative memory could bring new insight into the mechanisms of disproportionately different age-related declines in associative memory. Based on the frontal deficit hypothesis, many studies have concluded that age differences in the probability of associating items with relevant contextual information mainly result from the frontal lobe dysfunction in older people (Spencer & Raz, 1995). This conclusion is based on the idea that the frontal lobe is in charge of strategic information processing, including the implementation of elaborative and organizational schemes to help encode the associative information. However, as indicated earlier, not only functions mediated by frontal lobe system but also by medial temporal/hippocampus are affected by aging. Most of the literature does not discuss the relationship between medial temporal/hippocampus dysfunction and the performance in associative memory in healthy aging population. According to our literature review, we know that medial temporal/hippocampus has its important role in binding events together by simple temporal contiguity into memory traces and this system works in a rather automatic fashion under incidental conditions.

A recent study by Naveh-Benjamin, Hussain, Guez, & Bar-On (2003) demonstrated that dividing attention in younger adults fails to produce an impairment of associative memory equivalent to that seen in older adults performing the same task with full attention. Since dividing attention is thought to impair deliberate, elaborative encoding (e.g., the frontal contribution to learning), this study suggests that frontal impairment itself cannot account for the full degree of associative memory impairment in older adults and that another factor is involved.

One possibility is that although frontal lobe functions may be taxed during divided attention procedure, the binding capabilities of the hippocampus may not be taxed by this manipulation and may thus provide a means whereby younger adults can successfully process associative information in the memory task. If the literature reviewed above is correct, older adults may not succeed on the task because of incipient impairment in this binding mechanism.

MCI, characterized by substantial medial temporal/ hippocampus atrophy relative to healthy aging, is considered a transitional state between dementia and normal aging. Given the role of the hippocampus system in forming associations or integrating stimuli from multiple sensory sources into distinct episodes and events, it will be reasonable to expect to see the relatively poor performance on associative memory compared to healthy elders. Even if associative information is available to people with MCI, frontal dysfunction, as suggested in some aging literature, might impair their ability to strategically encode information and to oppose familiarity-based false recognition. To date, there is no research that addresses such hypotheses in people with MCI.

CHAPTER 2

PURPOSES AND AIMS OF THE PRESENT STUDY

The literature review suggests that associative memory may serve as an important gateway for researchers to understand age-related differences in episodic memory. Thus far, cognitive mechanisms of age-related differences as well as pathological aging in associative memory are poorly understood. To date, very few studies have dealt with these discrepancies by accounting for, or measuring, possible heterogeneity in the anatomical substrates (i.e., hippocampus and surrounding area) thought to underlie associative memory in aging. It is unknown whether pathological aging is characterized by disproportional impairment on associative memory (context memory) compared to item memory (content memory), since only item memory has been widely investigated across both cross-sectional and longitudinal studies. Moreover, it is unclear whether age effects on context recall are larger than those on recognition of contextual information, as is commonly found in memory for content. There is also a lack of data regarding whether age differences in memory for context are affected by intentional encoding instructions when context becomes another target and competes with content for attention resources.

Correlating behavioral performance on experimental tasks of associative memory with clinical neuropsychological measures as well as anatomic measures of hippocampus and surrounding area will provide important data to the associative memory literature, and to the memory and aging literature. Moreover, it can potentially yield new behavioral markers that will become useful for early detection of the pathological aging population.

This current study had several specific aims. First, we aimed to replicate the age-related declines in associative memory in other studies as well as to investigate whether patients with MCI showed impairment in associative memory compared to healthy older individuals. We also intended to determine whether such impairment was disproportionately impaired compared to

item memory. The performance of normal young individuals, normal aging individuals, and individuals with MCI on tasks of different types of associative memory was investigated. Specifically, performances on tasks investigating association between items of the same kind, association between different kinds of information, and relational association were investigated. In the tasks related to association between different kinds of information, we intended to include both verbal and visual (e.g., faces, objects, and spatial information), recent and remote information, as well as temporal information. We hypothesized that increasing associative memory impairment, particularly the associations between different kinds of information, would be found in the mild cognitive impairment population. In addition, we intended to investigate the effect of delayed recall on the associative memory, which was assumed to involve hippocampus function.

Second, we aimed to clarify the degree to which associative memory for novel and familiar or semantically related information depends on medial temporal lobe structures in a continuum of memory impairment represented by normal healthy aging and individuals with MCI. We hypothesized that performance on novel rather than semantically related association produced greater difference between MIC individuals and normal healthy aging individuals based on the widely-accepted view that the hippocampus was not needed for activation and retrieval of pre-existing (long-term) knowledge.

Third, we wanted to know whether age effects on associative information recall were larger than those on recognition. We expected larger age differences in free recall, a smaller one in cued recall, and still a smaller one in recognition. Fourth, we wanted to investigate whether performance on associative memory was affected by intentional encoding instructions, particularly when considering both frontal lobe functioning. Frontal lobe functioning is

associated with strategic information processing, while medial temporal functioning is thought to establish associations in an automatic way.

Finally, we aimed to determine the degree to which associative memory depended on medial temporal lobe functioning and frontal lobe functioning in a sense of considering the possible heterogeneity among individuals. We therefore would evaluate our data based on the Glisky et al. (1995) frontal-temporal classification scheme in both individual and group analyses.

CHAPTER 3

METHODOLOGY

Participants

Participants were 20 younger adults and 35 elderly individuals recruited from north-central Florida or from standing populations that exist through the Department of Neurology Memory Clinic at the University of Florida. Inclusion criteria were an age range of 18 to 25 for the younger individuals and age ≥ 60 for the elderly individuals. Exclusion criteria include: 1) past history of central nervous system disease (e.g., cerebrovascular accident, Parkinson's disease or Alzheimer's disease), 2) history of head injury with loss of consciousness, 3) history of self-reported substance use with adverse social, medical, or occupational consequences, 4) history of significant psychiatric illness requiring hospitalization, 5) history of recent heart attack (i.e., within 6 months of participation), 6) history of learning disability or developmental disability. The mean age of the younger adults was 20.30 years with a standard deviation of 1.56 years. Mean education level was 13.70 years with a standard deviation of 1.26 years. Nine participants were male and eleven were female. Seventeen of the participants were Caucasian (85%) and three were African-American (15%). The mean age of the elderly individuals was 73.91 years with a standard deviation of 6.90 years. Mean education level was 15.23 years with a standard deviation of 2.40 years. Fourteen participants were female and 21 were male. All of the participants were Caucasian.

Mild Cognitive Impairment Participants

Diagnosis of MCI was made based on a formal consensus panel comprised of 11 professional raters including two board-certified neuropsychologists, one expert in cognitive aging, two post-doctoral fellows, and six graduate students in the Neuropsychology, Neurorehabilitation, and Clinical Neuroscience area of concentration in the APA-accredited

clinical psychology doctoral program at the University of Florida. The consensus conference was held after all data were collected, and thus diagnosis of MCI was made retrospectively. During the consensus conference, each rater was blinded to participant identity but was presented with demographic (age, gender, educational level) and neuropsychological test data for each elderly participant. Test data was presented in the form of both raw and standard scores (age and education corrected where available) on all psychological and clinical neuropsychological measures administered during the participants' laboratory sessions. Additionally, all raters were aware of, and were presented with the published criteria for Amnestic MCI and other subclassifications of MCI (Petersen et al., 1999, 2001). The criteria for Amnestic MCI-single or multiple domains included 1) Evidence of a subjective memory impairment which was demonstrated through use of the MAC-Q (Crook, Feher, & Larrabee, 1992) and through the Clinical Dementia Rating Scale (CDR) (Morris, 1993), 2) evidence of an objective memory impairment demonstrated through performance on the California Verbal Learning Test-Second Edition (CVLT-II, Delis et al., 2000) and the Wechsler Memory Scale (Logical Memory I & II, Visual Reproduction I & II, Verbal Pair Associates I & II, Visual Pair Associates, Wechsler, 1997), 3) Evidence of intact (for Amnesic MCI-single domain subtype) or impaired (for Amnesic MCI -multiple domains subtype) non-memory cognitive function demonstrated through performance on non-memory measures including the Wechsler Abbreviated Scale of Intelligence (WASI), language tests (e.g., Boston Naming test, Verbal Fluency, Controlled Oral Word Association), attention tests (e.g., Trail Making Test and Digit Span), 4) No evidence of impairment in Activities of Daily Living (ADL), demonstrated through the CDR (Morris, 1993), and 5) No evidence of dementia which was demonstrated through a score > 24 on the Mini Mental State Examination (MMSE, Folstein, 1975), and a CDR rating ≤ 0.5 . Criteria for the

diagnosis of probable Alzheimer's disease based on NINCDS-ADRDA criteria were also available for consensus conference participants. These included: 1) Dementia, established by clinical examination and documented by MMSE and Clinical Dementia Rating Scale, and confirmed by neuropsychological tests, 2) Deficits in two or more areas of cognition, 3) Progressive worsening of memory or other cognitive function, 4) No disturbance of consciousness, 5) onset between 40 and 90 years of age. The NINCDS-ADRDA criteria were provided to give participants specific information about the upper boundary between MCI and frank dementia. After viewing the data, each rater voted whether the participant qualified as: 1) healthy control, 2) MCI, or 3) probable AD. Consensus was established when the majority of the raters agreed. If there were more than two dissenting opinions, the dissenters explained the reasoning behind their vote, discussion ensued, and the voting was repeated until consensus was achieved.

The conference resulted in a diagnosis of four Amnesic MCI-single domain, seven Amnesic MCI-multiple domain, and one Non-Amnesic MCI of the 35 elderly participants. The age range of the MCI participants, which included all subtypes of MCI, was 66 to 88 years. The mean age was 77.50 years ($SD=6.43$), and mean education level was 15.42 years ($SD= 1.83$). Four of the participants were female and eight were male. All 12 participants were Caucasian. Because the main focus of the current study was to compare Amnestic MCI with normal aging, the one individual who was classified as Non-Amnesic MCI during the conference was excluded from the subsequent three-group (young, normal old control, and MCI) data analyses. The remaining 11 MCI individuals with diagnosis of either Amnestic MCI-single domain or Amnestic MCI-multiple domains were combined into a MCI group for subsequent data analyses.

The final MCI group had a mean age of 77.73 years (SD = 4.90) and mean education level of 15.73 years (SD = 1.56). Three of the participants were female and eight were male.

Healthy Older Control Participants

As a result of the consensus conference, 23 elderly individuals were classified as healthy elderly controls without memory difficulty. Compared to MCI individuals, the healthy elderly group was significantly younger [$t(32) = -2.24$, $p < .05$]. Therefore, 20 among the 23 healthy older individuals who were older than the age of 65 years were then selected to serve as a comparison group for the 11 MCI individuals to match the age, education, sex, scores on the Mini-Mental Status Examination (MMSE), and WASI Full Scale IQ scores of the two groups. The age range of the final healthy older control group was 65 to 82 years, with a mean age of 73.95 (SD = 6.25). The mean education level was 15.50 years (SD = 2.67). Eight were females and twelve were males. All twenty were Caucasian.

Table 3-1 shows the demographic information for the full older sample and each group. Compared to normal older and younger control, the MCI group demonstrated significantly lower scores on the MMSE [$F(2,48) = 11.80$, $P < .001$] but had equivalent Full-Scaled IQ scores ($p > .05$). The younger group demonstrated a lower educational level as a group compared to both normal old control and MCI groups ($p > .05$).

Table 3-1. Mean characteristics of groups based on cognitive status

Variable	Total older sample (n=35)	Total Non-MCI individuels (n=23)	Healthy elderly control (n=20)	MCI (n=11)	Younger control (n=20)
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Age	73.91 (6.90)	72.39 (7.13)	73.95 (6.25)	77.73 (4.90)	20.30 (1.56)
Education	15.23 (2.40)	15.13 (2.69)	15.50 (2.67)	15.72 (1.56)	13.70 (1.26)
MMSE	28.94 (1.42)	29.26 (0.81)	29.40 (0.68)	28.27 (1.42)	29.80 (0.52)
FSIQ	15.28 (13.74)	118.26 (12.42)	120.30 (11.52)	110.38 (13.11)	118.40 (7.81)
Gender (F/M)	14/21	10/13	8/12	3/8	11/9

Differential Contributions of the Frontal and Medial Temporal lobes

Each study participant was assigned two scores based on the work of Glisky, et al.(1995), one representing relative performance on a group of tests associated with frontal lobe (FL) executive function and the other representing relative performance on a group of tests thought to represent memory-relevant aspects of medial temporal lobe (MTL) function. The tests contributing on the FL factor included: 1) number of categories achieved on the Wisconsin Card Sorting Test, 2) the total number of words generated in a word fluency test, using initial letters F, A, and S (Spreen & Benton, 1997), 3) Mental Arithmetic from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1987), 4) Mental Control from WMS-R, and 5) Backward Digit Span from the WMS-R. The tests contributing to the MTL factor included: 1) Logical Memory I from the WMS-R, 2) Long-Delay Cued Recall measure from the CVLT (Delis et al., 1987), 3) Visual Paired Associates II from the WMS-R, 4) Verbal Paired Associates I from the WMS-R. In this present study, we used the latest version of these tests. For example, we used the Wechsler Memory Scale-third version (WMS-III) instead of the Wechsler Memory Scale-Revised version (WMS-R).

All elderly participants' performance, including the one Non-Amnestic MCI individuals, on each of these tests was converted to a z score based on available norms, such as Heaton norms, WMS-III norms, or the norms established by Glisky et al. (1995), wherever was available. The z scores were then averaged across the tests contributing to each factor. The resulting composite z scores thus represented an individual participant's relative performance on each factor. Based on these procedures described above, each individual was then assigned into one of the four different subgroups based on their scores on the two factors were above or below the group composite means. The resulting distribution of composite z scores on the frontal lobe factor was approximately normal with a mean z score of .06 (SD= .65); 16 of the 35 participants

had scores above the mean. The distribution of scores on the medial temporal lobe factor was somewhat negatively skewed with a mean z score of .24 ($SD = .71$) and 19 participants scored above the mean. Figure 3-1 displays the frequency distribution of composite frontal lobe scores and Figure 3-2 shows the frequency distribution of composite temporal lobe scores for the total elderly sample.

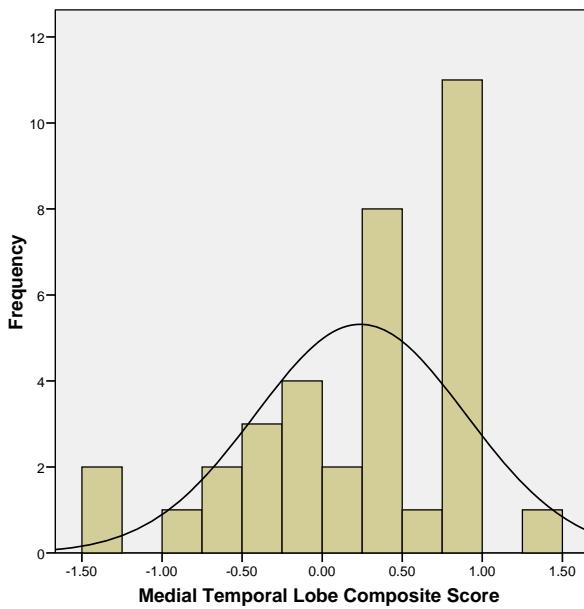


Figure 3-1. Frequency distribution of medial temporal lobe composite scores for total elderly sample (n=35)

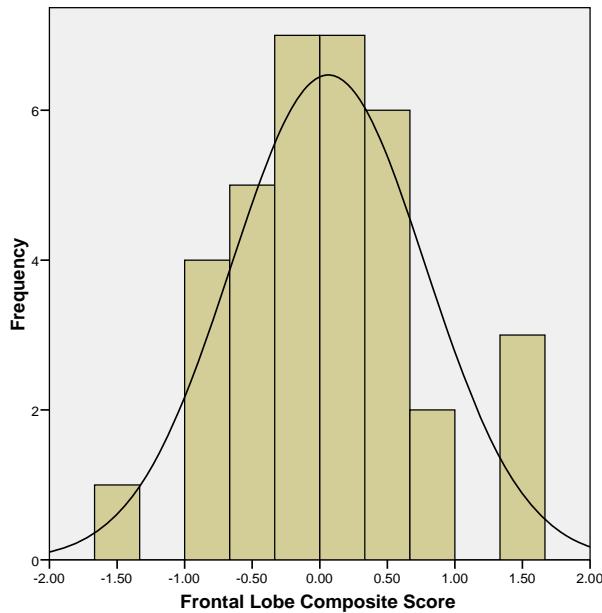


Figure 3-2. Frequency distribution of frontal lobe composite scores for total elderly sample (n=35)

Classifying participants according to their scores on the two composite measures yielded a distribution of twelve who were above the mean on both factors, ten who were below on the mean on both factors, four who were above the mean on the FL factor and below the mean on the MTL factor, and nine who were above the mean on the MTL factor and below the mean on the FL factor. Characteristics of the four groups are presented in Table 3-2. Table 3-3 indicates the actual number of people in each of four groups who were previously identified as normal healthy old individuals, Amnestic MCI, or Non-Amnestic MCI. Separate one-way between-subject analyses of variance (ANOVAs) indicated that there were no differences in age [$F(3,31) = .98, P >.05$], education [$F(3,31) = 1.87, P >.05$], or scores on the MMSE [$F(3,31) = 2.46, P >.05$] among the four groups. However, the Full Scale IQ scores were significantly higher in the High-MTL-High FL group when compared to the Low MTL-Low FL group [$t(17) = -3.35, p <.005$]; no other group differences involving FSIQ were found. The High and Low FL groups differed significantly on their composite FL scores [$t(33) = -6.74, p < .001$] but not on their MTL scores ($p >.05$), whereas the High and Low MTL groups differed on MTL scores [$t(33) = -8.58, p < .001$] but not on FL scores ($p >.05$).

Table 3-2. Mean characteristics of groups based on frontal lobe (FL) function and medial temporal lobe (MTL) function

Variable	High FL function				Low FL function			
	High MTL function (n=12)		Low MTL function (n=4)		High MTL function (n=9)		Low MTL function (n=10)	
	M	SD	M	SD	M	SD	M	SD
Age	72.83	5.67	78.00	3.74	71.89	8.42	75.40	7.57
Education	15.33	2.87	17.50	1.91	14.22	2.11	15.10	1.79
MMSE	29.33	0.65	29.00	0.82	29.22	0.83	28.20	1.55
FSIQ	122.67	10.33	122.50	11.70	110.00	14.14	105.29	11.91
FL score	0.62	0.50	0.75	0.63	-0.24	0.31	-0.60	0.48
MTL score	0.76	0.31	-0.03	0.20	0.57	0.26	-0.58	0.45

Table 3-3. Numbers of people classified as normal old or MCI in each of the four groups

	Low FL	High FL
Low MTL	3 Normal old	1 Normal old
	2 Amnestic MCI-single domain	2 Amnestic MCI-single domain
	5 Amnestic MCI-multiple domains	1 Amnestic MCI-multiple domains
High MTL	7 Normal old	
	1 Amnestic MCI-single domain	12 Normal old
	1 Non-Amnestic MCI	

Data analyses described below were based on one of the two described methods of grouping subjects. In some analyses, three clinical groups (younger adults, healthy elderly, MCI) were used. In others, the four groups resulting from the Glisky, et al. (1995) approach (i.e., High MTL-High FL, Low MTL-High FL, High MTL-Low FL, and Low MTL-Low FL) were used.

General Procedure

All participants were tested in a quiet clinic or laboratory room at the Department of Clinical Psychology at the University of Florida. Each person completed the standardized clinical neuropsychological measures first. A return visit was scheduled for completion of the experimental tasks. Each participant provided informed consent, and was given the opportunity to decline participation prior to, during, or after administration of the neuropsychological and experimental measures. Participants were reimbursed 10 dollars per hour for their participation.

Standardized Clinical Neuropsychological Measures

Participants underwent a battery of neuropsychological tests that 1) broadly sampled a variety of cognitive domains and brain regions and 2) emphasized those cognitive domains (e.g., memory and executive functioning) that are sensitive to the earliest change in MCI. Measurement of non-memory domains provided the basis for ruling out (or in) alternative

hypotheses about the basis of early memory dysfunction in preclinical dementia. Whenever possible, normative standards that corrected for demographic characteristics (e.g., age, gender, education level, and race) were used. Neuropsychological tests administrated are outlined in Table 3-4, which provides a reference for each and a description of the cognitive construct/domain that each test was designed to measure.

Table 3-4. Neuropsychological measures included in the present study

Overall construct	Test name	Description of test measure	Dependent variables recorded
General mental status	Mini Mental State Exam (Folstein et al., 1975)	A brief screening of mental status	Total possible score=30
Observer/ interview ratings	Clinical Dementia Rating Scale (Morris, 1993)	Disease severity rating: includes informant & participants' subjective/objective elements	CDR rating (0-3); collected during semistructured interview
Intellectual functioning	WASI: Vocabulary, Similarities, Block Design, and Matrix Reasoning (Wechsler, 1999)	Together, these were used to predict general intelligence, verbal and performance abilities.	Predicted FSIQ, VIQ, and PIQ; Voc. & Info.
Memory functioning	Wechsler Memory Scale- III (Logical memory I & II; Visual Reproduction I & II; Verbal paired associates I & II) (Wechsler, 1997) California Verbal Learning Test- 2 nd Edition (Delis et al., 2000) Wechsler Memory Scale-R (Visual Paired Associates I & II, Wechsler, 1987)	Measure of verbal and visual/figure memory Verbal memory test that assesses learning strategy, immediate and delayed recall, recognition, interference, and errors Measure of paired verbal and visual memory	Scores for immediate and delayed recall Slop of learning trials, savings score, discriminability Index Total correct score
Language functioning	Boston Naming Test-2 nd Edition (Goodglass & Kaplan, 2001) Controlled Oral Word Association (COWA, Spreen & Benton, 1997) Category Fluency-Animals (Tombaugh et al., 1999)	Confrontation naming using large ink drawings Verbal fluency to alphabet letter Verbal fluency to a semantic category	Total correct score Total correct examples Total correct examples

Table 3-4. Continued

Overall construct	Test name	Description of test measure	Dependent variables recorded
Visuoperceptual/ visuoconstruction	WASI-Block Design (Wechsler, 1999)	Visuoconstruction measure requiring reproduction of two dimensional designs with blocks	Total score based on time limits
	Test of Facial Recognition (Benton & Van Allen, 1986)	Visual perception using facial matching paradigm	Total correct score
Frontal/executive monitoring functioning			
<i>Attention/ concentration</i>	WAIS-III Digit Span, (Wechsler, 1997) WMS-III Spatial Span	Auditory attention span Visual attention span	Total correct score and longest digits Total correct score and longest digits
<i>Working memory</i>	WAIS-III Letter-Number Sequencing WMS-III Mental Control	Ability to hold auditory information for a period of time and mental manipulation or numbers and letters Ability to manipulate familiar information	Total correct score
<i>Psychomotor speed</i>	Trail Making A & B Tests (Reitan, 1958)	Visuomotor speed, mental shifting between numbers and letters	Total time to completion; number of errors
<i>Abstract thinking/ problem solving</i>	WASI-Similarities (Wechsler, 1999) WASI- Matrix Reasoning (Wechsler, 1999) Wisconsin Card Sorting Test	Abstract thinking; requiring participant to tell how two words are alike Measure of visual reasoning ability Participants sort cards based on their own principle; measure of mental flexibility and problem solving.	Total correct score Number of categories achieved; errors; number to finish first category
Self-reported measures			
	Memory Assessment Clinic Questionnaire (MAC-Q; Crook et al., 1992)	Subjective memory complaints questionnaire	Total possible score=30, score >=25 as a cutoff.
	Lawton IADL scale (Lawton & Brody, 1969)	IADL; informant and participant self-reports on IADL abilities.	Sum of endorsed items from both participant and informant.
	Geriatric Depression Scale (Sheikh & Yesavage, 1986)	30- item self-evaluation questionnaire assessing elements of depression	Total number of items endorsed.
	Beck Depression Scale-II (Beck, Steer, & Brown, 1996)	21- item self-evaluation questionnaire assessing elements of depression	Total possible=24, conventional cutoff =10
	State Trait Anxiety Inventory (STAI; Speilberger, 1968)	40-item self-evaluation questionnaire assessing state and trait anxiety	Total number of items endorsed

Neuropsychological and Questionnaire Data

Tables 3-5 and 3-6 show mean performance on neuropsychological measures for all participants. The data for the total group of older individuals were also included. Raw neuropsychological scores were converted to standard scores using normative data appropriate for the participants whenever possible. Standard scores or raw scores if standard scores were not available for non-memory neuropsychological measures are present in Table 3-5, standard scores or raw scores if standard scores were not available for memory measures are presented in Table 3-6, and standard or raw scores for mood and memory questionnaires are presented in Table 3-7. ANOVAs were conducted between young, normal old control, and MCI using standard scores whenever possible followed by post-hoc t-tests. Compared to normal old control group, the MCI group demonstrated significantly lower scores on the WMS-III spatial span test, Trails A & B, number of category completed on the Wisconsin Card Sorting Test (WCST), Boston Naming Test, and animal fluency. The normal older control group completed fewer categories on the WCST test when compared to younger controls. Compared to normal old individuals, individuals with MCI demonstrated significantly lower scores on most of the memory measures, including Logical Memory I & II, Verbal Paired Associates II, Visual Reproduction I & II, CVLT-2 total recall, CVLT-2 short delayed free recall, and CVLT-2 long delayed free recall, which was not surprising given that these measures were used to classify individuals as “MCI”. Healthy old controls demonstrated significantly lower scores on Visual Paired Associates I when compared to younger controls. MCI subjects had lower CDR total scores than their healthy older counterparts.

Table 3-5. Means and standard deviations for neuropsychological non-memory measures

Measure	Total older adult sample (n=35)		MCI (n=11)		Normal old control (n=20)		Younger control (n=20)	
	M	SD	M	SD	M	SD	M	SD
Digit Span total (AcSS)	11.14	2.88	10.27	1.56	11.85	3.41	11.00	2.99
Spatial Span total (AcSS)	12.06	2.96	10.67*	1.87	13.45	2.67	12.65	1.98
Trails A (T-score)	45.51	12.03	36.73**	15.78	49.70	7.24	48.15	10.99
Trails B (T-score)	48.83	14.25	36.45**	15.23	55.50	10.15	51.70	7.65
Mental Control (AcSS)	12.11	2.74	11.73	3.61	12.90	2.00	11.20	1.85
Letter-Number Sequencing (AcSS)	10.71	2.27	9.82	2.14	11.50	2.06	12.25	3.02
Arithmetic (AcSS)	12.69	2.37	11.81	2.64	13.50	1.88	12.45	2.50
WCST-category Completed (raw)	3.86	1.91	2.82**	1.78	4.55 [#]	1.73	5.90	0.45
BFT (short version, raw)	21.39	2.54	19.33	3.30	22.05	1.96	23.70	1.81
BNT (T-score)	59.89	11.68	51.27*	8.39	64.75	9.80	50.80	9.20
COWA total (T-score)	50.49	10.76	48.45	9.81	52.55	11.68	51.35	10.61
Animal Fluency (T-score)	49.14	11.49	43.27*	11.69	53.65	9.80	51.35	10.74

Note: BFT=Benton Facial Recognition Test; BNT=Boston Naming Test; COWA= Controlled Oral Word Association; AcSS= Age-Corrected Scaled Score. ANOVAs conducted between groups using standard scores followed by t-tests post-hoc comparisons. * p<.05 for comparisons between MCI and old control group. ** p < 05 for comparisons between MCI and the other two control groups. # p<.05 for comparisons between old and young control groups.

Table 3-6. Means and standard deviations for neuropsychological memory measures

Measure	Total older adult sample (n=35)		MCI (n=11)		Normal old control (n=20)		Younger control (n=20)	
	M	SD	M	SD	M	SD	M	SD
LM I (AcSS)	11.97	2.86	9.18**	2.40	13.05	2.16	12.05	2.21
LM II (AcSS)	12.26	2.91	9.55**	2.62	13.35	2.27	12.45	2.28
Verbal PA I (AcSS)	10.51	2.70	9.27 [^]	2.76	11.25	2.69	13.05	2.28
Verbal PA II (AcSS)	11.49	2.81	9.64**	2.80	12.25	2.55	11.95	0.22
VR I (AcSS)	10.86	3.23	8.36**	2.91	12.30	2.62	11.65	2.16
VR II (AcSS)	12.66	3.39	9.82**	2.75	14.55	2.58	12.35	3.08
Visual PA I (raw)	13.38	4.71	9.09 [^]	4.13	12.05 [#]	4.74	17.35	1.04
Visual PA II (raw)	5.16	1.43	4.00 [^]	1.67	5.10	1.48	6.00	0.00
CVLT2-total recall (T-score)	53.23	10.06	43.91**	8.90	58.15	7.46	60.60	7.48
CVLT2-SDFR (Z-score)	0.03	1.28	-1.18**	0.72	0.65	1.08	0.68	0.82
CVLT2-LDFR (Z-score)	-0.20	1.18	-1.41**	0.83	0.43	0.88	0.53	0.85
CVLT2-recognition d' (Z-score)	-0.37	0.83	-0.86**	0.32	-0.50	0.94	0.33	0.54

Note: LM= Logical Memory; Verbal PA= Verbal Paired Associates; VR= Visual Reproduction; Visual PA= Visual Paired Associates; SDFR= short delayed free recall; LDFR=long delayed free recall; AcSS= Age-Corrected Scaled Score. All ANOVAs conducted between groups using standard scores, except for visual paired associated I & II tests in which raw scores were used, followed by t-tests post-hoc comparisons. ** p < 05 for comparisons between MCI and the other two control groups. # p<.05 for comparisons between old and young control groups. ^ p<.05 for comparisons between MCI and young control groups.

Table 3-7. Means and standard deviations for subjective mood and memory questionnaires

Measure	Total older adult sample (n=35)		MCI (n=11)		Normal old control (n=20)		Younger control (n=20)	
	M	SD	M	SD	M	SD	M	SD
BDI-2 (raw score)	---	---	---	---	---	---	5.15	4.34
GDS (raw score)	3.09	2.92	3.60	3.34	2.85	2.70	---	---
STAI-state (z score)	-0.49	0.72	-0.19	1.15	-0.48	0.60	-0.65	0.58
STAI-trait (z score)	-0.51	0.78	-0.51	0.84	-0.78	0.56	-0.26	0.90
MAC-Q (raw score)	22.94	5.09	25.36 [^]	4.65	23.30	5.58	19.92	3.80
CDR (total score)	0.21	0.25	0.50*	0.00	0.08	0.18	---	---

Note: BFT-Benton Facial Recognition Test; BNT=Boston Naming Test; COWA= Controlled Oral Word Association. ANOVAs conducted between groups using standard scores followed by t-tests post-hoc comparisons.
 * p<.05 for comparisons between MCI and old control group. ^ p<.05 for comparisons between MCI and young control groups.

CHAPTER 4
THE EFFECT OF INCIDENTAL VERSUS INTENTIONAL LEARNING ON THE
RETRIEVAL OF ASSOCIATION INFORMATION

Introduction

The purpose of this experiment was to examine the effect of incidental and intentional learning on the associative memory performance in healthy young (HY), healthy older (HO) individuals, and individuals with MCI. Based on the literature, we hypothesized that the medial temporal lobe (or more specifically, hippocampus) is important for the encoding of novel information (both item and associative information) into memory and that such a process proceeds in an automatic, rather than in a deliberate or controlled way. In contrast, neural systems of the frontal lobe have been recognized as important for controlled, strategic information processing, including the implementation of elaborative and organizational schemes to help encode to-be-remembered information. A generation of research in cognitive psychology has established that intentional encoding often produces better memory performance compared to incidental encoding in both young and healthy old individuals (Cherry & Park, 1993). However, results in normal aging studies are more mixed than in young people, in which giving intentional instruction to older people either has no effect or improves older adults' memory performance (Kausler et al., 1985; Kausler & Phillips, 1989; Schmitter-Edgecombe & Simpson, 2001).

One interesting question was whether disruption of hippocampal function would decrease the benefit derived from receiving intentional instruction in terms of encoding of associative information. Most studies of this issue have been based on studying item-based information rather than associative information. For example, we know that H.M.'s memory performance for items did not differ under incidental and intentional learning conditions (Smith, 1988), despite

extensive bilateral hippocampal damage. Whether similar results could be obtained in learning associative information has yet to be established.

In this experiment, we manipulated the encoding condition (encoding items or pairs) and the recognition tasks (item vs. pairs) to examine the effect of incidental versus intentional learning on the retrieval of associative information. We also examined the individual differences in neuropsychological correlates of temporal and frontal lobe functioning and how the differences could affect the performance on the specific tasks.

Methods

Participants

There were 51 participants, of which 20 were younger, 20 were healthy older and 11 were MCI individuals. The mean age and number of years of education appear in Table 3-1. For the second types of analyses based on the individual's frontal lobe and medial temporal lobe function level, 35 older adults were included. The details of demographic information and factor scores for each of the four groups can be found in Chapter 3.

Design

The design of this experiment is a 3 (Group; healthy young [HY], healthy old [HO], mild cognitive impairment [MCI]) \times 2 (Encoding Condition: items vs. pairs) \times 2 (Test Type: Items, Pairs) Repeated Measures Analysis of Variance. Group and Study Instructions are between-subject variables, while Test Type was a within-subject variable. Recognition memory was tested immediately following the learning phase as well as after a 30-minute delay for all tests. The design results in two conditions in which encoding and recognition are “matched” (Encode Item–Test Item, Encode Pair–Test Pair) and two conditions in which they are “mismatched” (Encode Item–Test Pair, Encode Pair–Test Item).

Materials and Procedure

Stimuli comprised from the Nelson Norms of Free Association (Nelson et al., 1998) and all of the words were high-frequency nouns. A total of 96 words were selected and 48 of them were used to create two lists of 12 novel word pairs. Pairing was done so that pairs reflected no semantic relationship. The association strength of the novel word pairs were very low or zero and therefore thought to be novel and unique, not accompanied by a pre-existing memory representation. Words belonging to different pairs were also unrelated to each other in any apparent way. Additionally, these word pairs were orthographically and phonemically unlike (avoiding perceptually and phonemically similar pairs, e.g., book–good). Within each list, the first and second word of each pair was balanced for length, frequency, and concreteness. Word pairs were also matched across lists for length, frequency, and concreteness. The remaining 48 words were used as foil trials for the immediate and delayed item recognition tests. In both learning conditions, recombination of pairs for the pair recognition tests was done randomly, with the constraint that no resulting pair had any obvious orthographic, phonemic, or semantic relationship.

All participants were given the incidental learning condition first, and then at least 45 minutes later, the intentional learning condition was given. The list used for intentional or incidental pair learning was counterbalanced between subjects with half of the participants using one list as the incidental list and half of the participants using the same list as the intentional list. All the stimuli were presented visually on a computer screen.

The procedures for the incidental and intentional learning conditions were identical except for the instructions during the study phase. In the incidental condition, participants were told to study the words in each pair individually (items) in preparation for an upcoming item recognition

test. In the intentional condition, participants were instructed to study the pairs in preparation for an upcoming paired associated recognition test.

After participants' questions were answered, the experimental phase started, in which participants were presented with the 12 experimental pairs visually on a computer, two words (one pair) at a time with a 400 ms pause between pairs. On each trial, the word pair was presented simultaneously in a horizontal left-right format. Presentation rate for each list was self-paced with a limit of seven seconds per pair. Each participant was given two learning trials in order to prevent floor effect and participants were asked to free recall words after each trial. After the end of the study phase, the item and pair recognition tests listed below were administered to all of the participants with the order of item recognition test first and then followed by the pair recognition test.

1) Item recognition test: In this test, 12 targets and 12 distracters were presented to participants one at a time. Participants were asked to give Yes/No responses to indicate if the word was one that appeared on the study list. Half of the targets were the words that appeared on the right side of the computer screen during the study phase, and half were words that appeared on the left side. No two words from the same pair were used as targets in the test.

2) Pair recognition test: In this test, 12 intact (targets) pairs from the study phase (i.e., the two words that appeared together on the computer screen in the study phase) and 12 recombined (distracters) pairs (i.e., they were composed of words taken from different study pairs) were presented. Participants were told that all of the items appeared in the study phase and that their task was to successfully identify those same pairs that appeared in the study phase. Participants had as much time as they needed to complete the two memory tests.

After a 30-minute delay, all participants were asked to perform the free recall, item recognition, and pair recognition tests in order to test their long-term memory. Similar to immediate recall condition, participants had as much time as they needed to complete these memory tests.

Hypotheses and Predictions

We predicted that the three groups (HY, HO, and MCI) would have comparable performance on the item memory (i.e., single word recognition) in both intentional and incidental encoding of association information conditions because item recognition could be achieved through familiarity recognition without heavy reliance on the hippocampus.

On the associative memory tests, we predicted that the HO group would demonstrate slightly poorer performance on the incidental learning condition and that giving intentional instructions would either have no effect or slightly improve the HO group's memory for associative information. The pattern of improvement in the performance, if there was any, should be similar between the HY and the HO groups. The memory decline over time (from immediate to delayed testing) should be minimal in the HO group.

Similarly, comparing the MCI group with the HO group, the MCI group should demonstrate poorer performance in learning associative information in both manipulated learning conditions due to compromise in hippocampus function, and the intentional instruction would not improve their performance to a significant degree. The MCI group would demonstrate significantly reduced recall for both item and associative information in the delayed recall condition when compared to the HO group.

A second set of analyses was conducted using the groupings derived from Glisky et al. (1995) frontal and temporal lobe factors. These analyses used a 4 (Group) \times 2 (Encoding Condition: items or pairs) \times 2 (Test Type: items, pairs) mixed factorial ANOVA. We predicted

that High MTL-High FL group would demonstrate the best performance on associative information compared to other groups for both learning conditions, and performance on the two conditions would be equivalent. Similarly, the High MTL-Low FL group should demonstrate good associative memory in both learning conditions, although a slight increase in performance in the intentional condition was expected. In contrast, the Low MTL-Low FL group should show poor associative memory on both learning conditions and performance on the two conditions should be equivalent. The Low MTL-High FL group would show poor associative memory on both conditions; however, they would show slightly better or equal performance in the intentional condition than in the incidental condition.

Results

For all analyses described in the current study, the level of statistical significance was set at $p = .05$. Tests for sphericity were carried out in each analysis. Huynh-Feldt or Greenhouse and Geisser corrected significance levels were reported for any effect for which the sphericity test was significant. Instead of running omnibus post-hoc tests, two planned contrast analyses were carried out on significant main effects of the between-subject variable (groups) and their interactions with time of test (immediate v. delay). These two planned contrast analyses served to accomplish two goals: 1) to examine differences between young adult group and normal older adults group, and 2) to compare differences between normal older adults and individuals with MCI. Similar analyses were also conducted by dividing individuals into four groups based on their FL-MTL function levels.

Analyses on the HY, HO, and MCI Groups

Table 4-1 describes the data for the two manipulated learning conditions in the three groups. A Group \times Learning Condition (immediate item recognition on the incidental and intentional conditions) repeated ANOVA was conducted to examine the item memory. A Group

× Learning Condition (incidental and intentional conditions) × Measures (pair hits and pair false positive) × Time (immediate and delayed recall) repeated ANOVA was conducted to examine the effect of encoding instruction on the associative memory.

Table 4-1. Data for the incidental and intentional learning conditions in three groups.

Measure	MCI (n=11)		Normal old control (n=20)		Younger control (n=20)	
	M	SD	M	SD	M	SD
Incidental learning						
<i>Immediate recall</i>						
Learning trial 1	3.09	1.58	6.80	3.38	11.95	3.49
Learning trial 2	5.90	2.88	10.9	4.47	18.15	3.48
Item recognition –hits	11.10	0.88	10.65	1.27	11.45	0.94
Item recognition-false positives	3.30	4.67	0.45	0.60	0.05	0.22
Item recognition- total	19.80	4.26	22.20	1.64	23.40	0.99
Pair association recognition-hits	9.60	1.96	9.85	1.57	11.45	0.10
Pair association recognition-false positives (recombined pairs)	7.30	2.54	4.75	2.65	0.55	0.83
Pair association recognition-total	14.30	1.16	17.10	3.51	22.90	1.62
<i>Delayed recall</i>						
Item free recall	2.70	2.36	8.80	5.21	16.90	5.17
Item recognition –hits	9.22	1.30	10.45	1.31	11.80	0.41
Item recognition-false positives	2.78	1.30	0.85	1.18	0.30	0.57
Item recognition- total	18.44	1.23	21.60	1.90	23.50	0.61
Pair association recognition-hits	8.67	1.73	9.75	2.38	11.70	0.57
Pair association recognition-false positives (recombined pairs)	4.78	1.64	4.20	2.88	0.60	1.05
Pair association recognition-total	15.89	1.36	17.55	3.99	23.10	1.48
Intentional learning						
<i>Immediate recall</i>						
Learning trial 1	3.60	2.63	5.50	3.53	10.35	3.79
Learning trial 2	6.33	2.24	13.20	4.94	19.00	3.21
Item recognition –hits	10.00	1.32	11.15	1.04	11.85	0.49
Item recognition-false positives	1.11	1.17	0.35	0.75	0.00	0.00
Item recognition- total	20.89	1.76	23.00	1.08	23.85	0.49
Pair association recognition-hits	9.56	1.42	10.95	1.50	11.70	0.57
Pair association recognition-false positives (recombined pairs)	3.44	3.17	1.35	1.95	0.30	0.66
Pair association recognition-total	18.11	3.86	21.60	3.05	23.50	0.76
<i>Delayed recall</i>						
Item free recall	2.80	2.90	8.00	4.84	15.05	5.38
Item recognition –hits	9.00	1.12	10.75	1.41	11.50	0.89
Item recognition-false positives	2.33	1.32	1.45	1.28	0.60	0.82
Item recognition- total	18.67	1.50	21.30	2.36	22.90	1.52
Pair association recognition-hits	9.22	1.56	10.55	2.11	11.70	0.57
Pair association recognition-false positives (recombined pairs)	4.89	2.57	1.90	2.15	0.15	0.37
Pair association recognition-total	16.33	3.28	20.65	4.13	23.55	0.76

We first conducted a Group x Learning Condition mixed factorial ANOVA to examine subjects' immediate item memory in both learning conditions. The analysis yielded a significant main effect for Group [$F(2, 46)=9.29, p < .001, \eta^2=.29$] and a significant Group \times Learning Condition interaction effect [$F(2,46)=4.17, p <.05, \eta^2=.15$]. Post-hoc planned contrast comparisons (HY vs. HO; HO vs. MCI) were conducted and revealed that the HY and the HO groups significantly differed in single word recognition in intentional [$t(47) = 2.351, p < .05$] and incidental learning [$t(46)=2.40, p < .05$] conditions, although the difference of the mean numbers of items recognized in the two groups was less than one item. When comparing the HO and the MCI group, the results demonstrated that the two groups did not differ significantly in item memory in the incidental condition [$t(47)=-1.08, p>.05$]. However, in the intentional learning condition, the MCI group demonstrated a significantly lower score on the item recognition [$t(46)=3.11, p <.005$]. Figure 4-1 demonstrates the data for the item memory for the three groups.

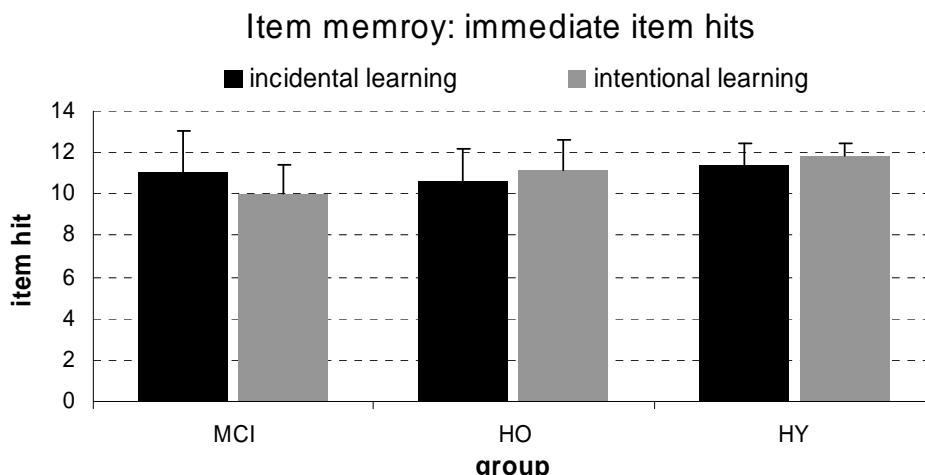


Figure 4-1. Data of the immediate item recognition hits for the three groups.

Due to the differences in item memory between groups, the subsequent analyses in the associative memory were conducted by entering the immediate incidental item hits as a covariate. A Group \times Measures (pair hits and false positives) \times Learning Condition (intentional

vs. incidental) \times Time (immediate and delayed) repeated ANOVA was conducted and the analysis yielded a significant main effect for Group [$F(2,45)=6.13, p < .01, \eta^2=.21$], and significant Group \times Learning Condition [$F(2,45)=4.03, p <.05, \eta^2=.15$], Group \times Measure [$F(2,45)=18.74, p <.001, \eta^2=.45$], Group \times Time \times Learning Condition [$F(2,45)=3.32, p <.05, \eta^2=.13$], and Group \times Learning Condition \times Measure [$F(2,45)=9.26, p <.001, \eta^2=.29$] interaction effects.

Further planned contrast comparisons were conducted on the two three-way interaction effects. The analyses between the HY and the HO groups showed that the HO group had significantly lower scores on the hits measure in the incidental learning condition compared to the HY group ($p <.05$); however, the difference disappeared when giving the intentional learning instruction, indicating that the HO group showed improvement on the pair recognition hits when giving intentional instruction while the HY group remained stable and showed high performance with or without the intentional instruction. In the delay recognition condition, the HO group demonstrated significantly lower performance compared to the HY group regardless whether under incidental ($p <.005$) or intentional ($p <.05$) learning condition.

In the analyses for the false positive measure, the HO group demonstrated higher numbers of false positives in the incidental condition during both immediate ($p <.001$) and delayed ($p <.001$) testing when compared to the HY group. However, in the intentional learning condition, the HO group significantly decreased the numbers of false positive errors during both immediate ($p <.005$) and delayed ($p <.001$) testing situations, and as a result, the differences in terms of numbers of false positive errors previously existed between the HO and HY groups disappeared under the intentional instruction. When comparing the HO and the MCI groups, the two groups did not differ significantly in the hits score under the incidental condition during either

immediate or delayed testing situations. However, when giving specific instructions to encode the pairs (intentional condition), the HO group, but not the MCI group, demonstrated significant improvement ($p < .05$) in the pair hits score, but only in the immediate testing situation. The analyses conducted on the false positive errors between the HO and the MCI groups showed that the MCI group had significantly higher number of false positive errors in both learning conditions (both $p < .05$) during the immediate testing situation, although both groups demonstrated the trend of decreasing numbers of false positive errors in the intentional condition compared to the incidental condition. During the delayed testing situation, the two groups did not differ significantly in terms of making false positive errors in the incidental condition; however, the intentional instruction helped the HO group to decrease numbers of false positive errors significantly ($p < .05$) while the MCI group made a similar number of false positive errors as in the incidental condition. The data for the pair recognition hits and false positive score in the two learning conditions at the two time points for the three groups is presented in Figures 4-2 and 4-3.

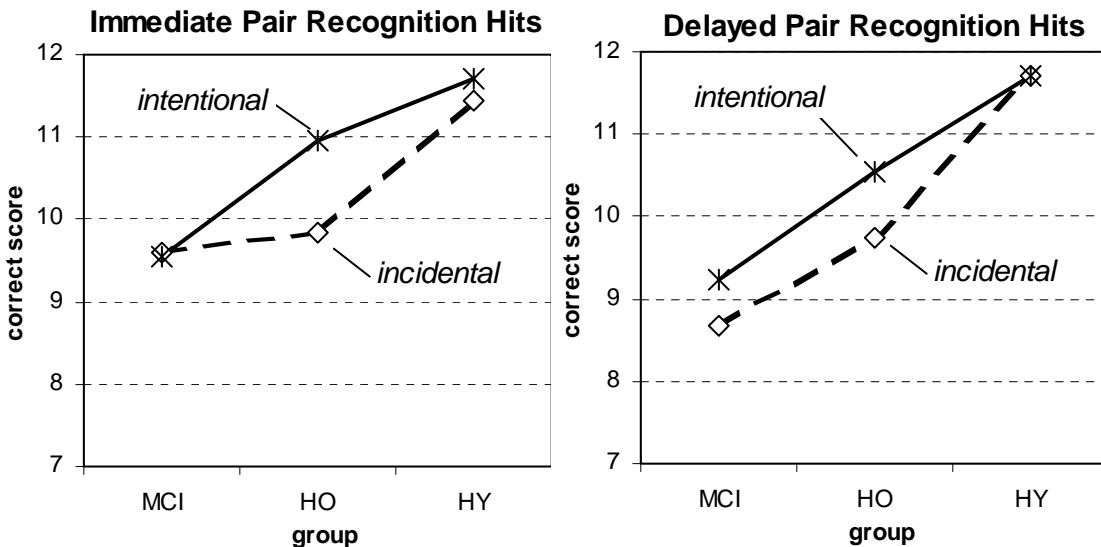


Figure 4-2. Data for the immediate and delayed recognition of the pairs (hits) in the incidental and intentional learning conditions for the three groups.

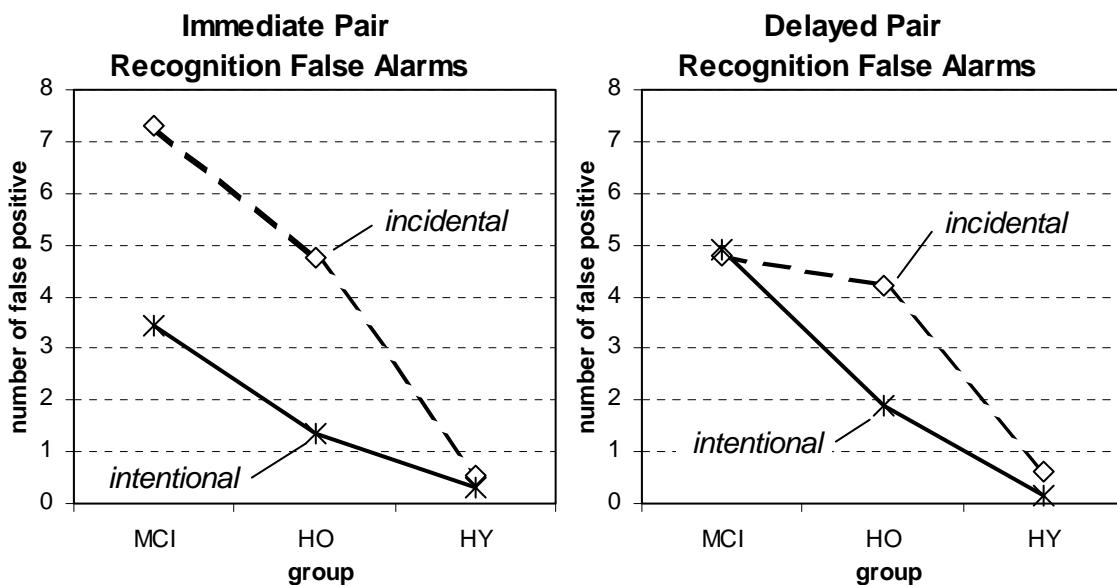


Figure 4-3. Data for the immediate and delayed recognition false alarms (false positive) errors of the pairs in the incidental and intentional learning conditions for the three groups.

Analyses on Groups Divided by MTL-FL Status

A second set of analyses was conducted by dividing individuals into four groups based on their FL-MTL function levels. It was hypothesized that the High MTL-High FL group would demonstrate the best performance on associative information compared to other groups for both learning conditions, and performance on the two conditions would be equivalent. Similarly, it was predicted that the High MTL-Low FL group would demonstrate good associative memory in both learning conditions, although a slightly increased performance in the intentional condition was expected. In contrast, the Low MTL-Low FL group should show poor performance of associative information on both learning conditions and performance on the two conditions should be equivalent. The Low MTL-High FL group would show poor associative memory on both conditions; however, they would show slightly better or equal performance in the intentional condition than in the incidental condition.

The analyses on item memory demonstrated that the four groups did not differ significantly on the single word recognition (hits) in either the intentional or the incidental learning condition [$F(3,29)=2.35$, $p > .05$, $\eta^2=.20$], indicating equivalent item memory.

In order to examine associative memory, a Group x Measures (pair hits and false positive) x Learning Condition (intentional vs. incidental) x Time (immediate and delayed) repeated ANOVA was conducted and the analysis yield significant main effects for Measure [$F(1,28)=207.09$, $p < .001$, $\eta^2=.88$] and Learning Condition [$F(1,28)=25.10$, $p < .001$, $\eta^2=.47$], and significant Group x Measure [$F(3,28)=8.62$, $p < .001$, $\eta^2=.48$], Learning Condition x Measure [$F(1,28)=28.86$, $p < .001$, $\eta^2=.51$], Time x Learning Condition x Measure [$F(1,28)=10.80$, $p < .005$, $\eta^2=.28$] interaction effects.

These interaction effects were examined further by conducting post-hoc comparisons. The results showed that the four groups did not differ significantly in the pair hits measure in either learning condition during the immediate or delayed testing condition. However, in the false positive measure, all four groups demonstrated a similar degree benefit from the intentional instructions and decreased the number of false positive errors during the immediate testing situation. During the delayed testing situation, the Low MTL-Low FL group did not benefit from the intentional learning instruction and made a similar number of false positive errors, while the High MTL-Low FL group showed a significantly lower number of errors ($p < .01$) and the Low MTL-High FL showed a marginal effect of decreasing number of errors ($p = .052$) in the intentional condition. The data of the pair recognition hits and false positive score in the two learning condition at the two time points for the four groups divided by their medial temporal lobe and frontal lobe function are presented in Figures 4-4 and 4-5.

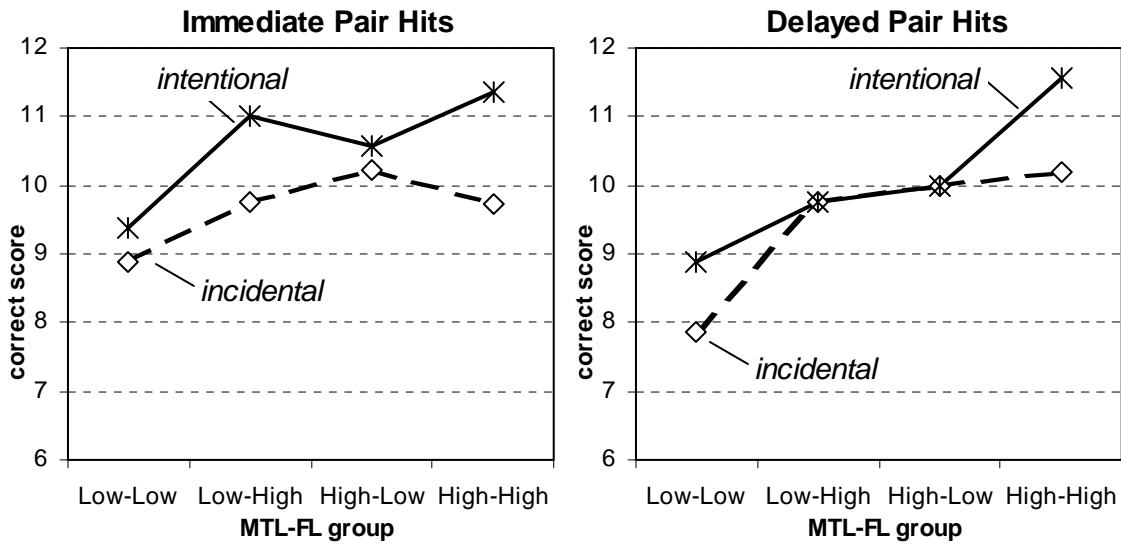


Figure 4-4. Data for the immediate and delayed recognition of the pairs (hits) in the incidental and intentional learning conditions for the four groups divided by their MTL-FL function levels.

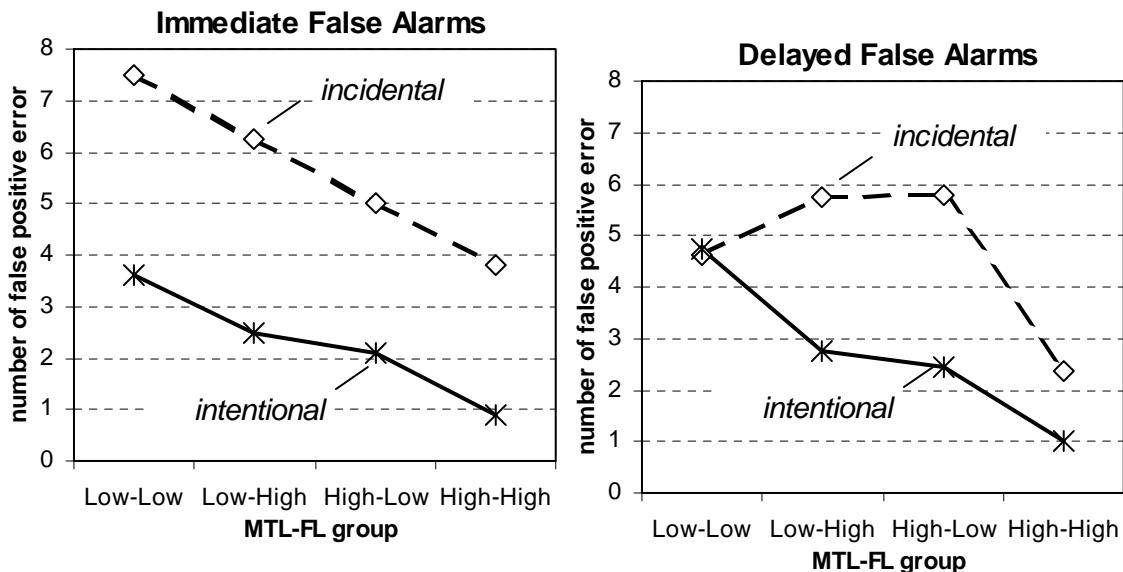


Figure 4-5. Data for the immediate and delayed recognition false positive score of the pairs in the incidental and intentional learning conditions for the four groups divided by their MTL-FL function levels.

Discussion

In this experiment, we manipulated the learning instructions (whether explicit instructions about learning the word pairs were given) and attempted to examine the relationship of encoding instructions and the performance on the associative memory using verbal materials. After controlling the item memory between groups, the overall findings indicated that healthy older adults have a decreased ability to encode associative information “automatically” when compared to younger adults. However, when their attention was directed to the associative information (intentional encoding), they demonstrated significant improvement in performance on the associative memory. The younger individuals maintained similar levels of performance regardless of the instruction types. The memory improvement evident in the intentional encoding condition in healthy older adults indicates that healthy older adults could use “strategic behavior” (controlled process) to help them encode associative information which was in accord with previous results on age-related difference in content and context memory (Kausler et al., 1985; Kausler & Phillips, 1989; Schmitter-Edgecombe & Simpson, 2001). Additionally, the results also corresponded to the notion that frontal lobe/ executive functioning is differentially affected by the normal aging process and the compromised frontal lobe system could impede the use of self-initiated strategic behavior during the incidental encoding condition (Stuss, 1986).

Despite the promising effect observed during the immediate recall condition for the healthy older adults, their performance on the delayed memory did not show a significant difference between the two encoding instructions. In contrast to the healthy older individuals, the MCI individuals did not benefit from the explicit encoding instruction and remained at a lower level of performance across instruction conditions during the immediate recall phase. Although a trend toward better memory under the intentional instruction condition was observed in both normal older group and the MCI group during the delayed recall phase, the healthy older adults

did not demonstrate a significantly larger performance gain under the intentional instruction condition compared to the MCI group.

The second major finding of the present study was the group difference in the occurrence of false positive errors. The findings indicated that the explicit encoding instructions not only improved the healthy old individuals' performance on the pair hits measure, but also effectively decreased their false positive errors. In other words, the instruction improved the healthy older adults' discrimination ability on this task, and such improvement could actually carry over to the delayed recall phase. In contrast, the MCI individuals did not benefit from the explicit encoding instruction as the healthy old individuals did and still displayed high numbers of false positive errors in both immediate and delayed recall conditions. Similar analyses were conducted on groups divided by their FL-MTL function levels, and the results suggested that while the explicit encoding instructions helped all four groups to decrease the occurrence of false positive errors on immediate recall, the benefit did not carry over to delayed recall for the Low MTL-Low FL group. Such benefits were carried over the delayed recall phase for the High MTL-Low FL group and Low MTL-High FL group, although the later group only demonstrated a marginal effect ($p = .05$). The High MTL-High FL group exhibited low error rates across conditions.

Overall, the collective results were consistent with the predictions. The findings obtained from the incidental encoding condition suggested that the healthy old adults showed a disproportionate impairment relative to younger adults in performance on the associative tests compared with performance on item tests when hippocampus was assumed to encode novel information in an automatic fashion. This replicated prior findings that older adults clearly have deficits in binding discrete units of information together. However, rather than a generalized decrement in associative memory across manipulations, the healthy older adults could overcome

the disadvantage and perform at the same level as the younger people did if provided specific encoding instruction, although the benefit did not last for long. On the other hand, the MCI individuals, as predicted, did not benefit from such instructions and showed lower performance and higher error rates when compared to the healthy old adults. This finding is consistent with the notion that the hippocampus is a key structure for binding information and forming the association. Even providing the explicit instruction during the encoding stage, individuals with putatively compromised hippocampal function were still unable to improve their memory for the associative information.

CHAPTER 5
MEMORY OF ASSOCIATIONS BETWEEN ITEMS OF THE SAME KIND USING
SEMANTIC RELATED OR UNRELATED WORD PAIRS

Introduction

In this current experiment, we wanted to test whether the less a task requires the creation of episodic associations between components, the less pronounced the associative deficits would be in healthy old and individuals with MCI. To test this prediction, we presented younger and older adults with pairs of words, either unrelated or related semantically, and tested them later with item and associative recognition tests. The two types of word pair materials have often been used to study verbal memory: one is material believed to pre-experimentally exist in memory stores (preexisting, or familiar information –semantic related pairs), and the other type of material is novel information (novel pairs). Bower and Schacter (1993) define “novel” information as material introduced to memory for the first time during a study phase of an experiment. This can include stimuli such as a nonword or a new association between previously unrelated words (island and broom). A large body of literatures indicates that context-rich episodic memories, but not context-free semantic memories, require processing provided by the hippocampal circuit (Squire & Zola-Morgan, 1991; Vargha-Khadem et al., 1997). Accordingly, we predicted that older adults and MCI individuals would show a relatively smaller deficit in the associative recognition test when semantic related pairs were used compared to the novel pairs, since this task allowed them to rely more on preexisting associations and less on establishing new associations.

Second, we wanted to investigate the effect of different test formats on recall of associative information. There is a large body of evidence suggesting that age-related difficulty in retrieval is a major reason for poorer memory performance in older adults. One might expect recognition performance, where the information is re-represent during the test phase and hence could help

induce the appropriate mental operations necessary for retrieval. This could not be affected by age as much as recall performance, where participants must generate their own cues because no retrieval cues are present (Craik & McDowd, 1987; Naveh-Benjamin, 2000). Some studies have demonstrated that contextual or associative memory plays a larger role in free recall than it does in recognition memory, which can rely on the retrieval of item representations involving minimal contextual elaboration (Jacoby, 1991). In this current experiment, the HY, HO, and MCI groups were given three formats of associative memory tasks: free recall, cued recall, and recognition by using word pairs as stimuli. On the free recall test, individuals had to generate their own cues because no retrieval cues were present. On the cued recall test, the first word of each word pair was given, and then the participant had to give the second word of the pair. On the recognition test, the word pairs were presented and participants had to answer yes/no for each pair to indicate whether the pair they saw was the same pair they were asked to remember during the study phase. According to previous literature, age-related decline in associative memory should be more closely related to age differences in the free recall than in the recognition tasks (Craik & McDowd, 1987; Naveh-Benjamin, 2000).

Methods

Participants

Participants were 20 young, 20 healthy old, and 11 individuals with MCI, who were taken from the same pools as those run in experiment 1. Their mean ages and other relevant demographic data appear in Chapter 3.

Design

The design was a 3 (Group) \times 2 (Pair Type; related, unrelated) \times 3 (Test Type; free recall, cued recall, recognition) \times 2 (Study-Test Interval; immediate, delay) Repeated Measures Analysis

of Variance. Group was a between-subject variable, while Pair Type, Test Type, and Study-Test Interval were within-subjects variables.

Materials and Procedure

The study phase for each of the tasks included the presentation of a list of 14 word-pairs shown on the computer screen as the experimental stimuli. For the word pair recognition test, 14 additional word pairs (seven semantically related and seven semantically unrelated pairs) were chosen. All of the words were high-frequency nouns. Half of the word pairs (e.g., seven pairs) in each of the lists were two words that were semantically unrelated. The other half of the word pairs were two semantically related words (e.g., cage-bird), which were considered as preexisting (or familiar) semantic associations because previous knowledge could support the creation of this kind of association. Previous work has provided the following guidelines for association: .40 (SD=.11) (strong), .17 (SD=.03) (moderate) and .07 (SD=.03) (weak) (Nelson, McEvoy, & Schreiber, 1998). Association strength for critical semantic pairs in the current study ranged from .17-.22, with a mean of .19 (SD=.02). Therefore, these semantically related word pairs were thought to reflect some preexisting semantic knowledge. Within the list, the semantically unrelated pairs and the semantically related pairs were matched for length, frequency, and concreteness. Additionally, among the list, the semantically related pairs and the semantically unrelated pairs were intermixed.

The list of 14 pairs was presented during the study phase at a rate of one pair every 7 seconds for all the participants. On each trial, the word pair was presented simultaneously in a horizontal left-right format. The task was run under intentional learning instructions. Participants were told that each trial consists of a cue word (on the left) and a target word (on the right) presented together on the computer screen. In all of the lists, participants were told to try to learn the cue-target pairs, but to pay special attention to the target word in each pair. They

were also told to pay attention to the cue word because it could help them memorize and retrieve the target word. Participants were told before the beginning of the study phase about the three upcoming memory tasks: 1) *Free recall task*: In this task, participants were asked to recall as many words as possible, particularly the target words (the second word in each pair). 2) *Cued-recall task*: In this task, participants were presented, in random order, each of the cue words from each pair and were instructed to recall the target word that was associated with each cue. 3) *Recognition task*: In this task, participants were shown 42 pairs of words, one pair at a time. Fourteen pairs were the intact pairs (those they studied during the study phase) with seven semantically related pairs and seven semantically unrelated pairs, 14 were recombined pairs (all words appeared during the study phase, but they are recombined, 7 were drawn from the semantically-related pairs, and 7 were from the unrelated pairs), and 14 were novel foil pairs. Participants were asked to answer “yes” if the pair was previously studied and “no” if it was not.

For all of the tests, participants had as much time as they needed to provide a response for each test item. The same measures were given again after 30- minute delay.

Hypotheses and Predictions

Semantically unrelated pairs (novel pairs): Due to previous findings that the establishment of novel associations depends upon hippocampal function, it was expected that HY participants would demonstrate the best performance on the novel pair tasks, and MCI participants should show the worst performance. We expected that the HO group would perform in an intermediate position. Also, we expected a large age effect in free recall, a smaller effect in cued recall, and a still smaller one in recognition. A similar pattern would carry over a 30-minute delayed recall condition.

Semantically related pairs: In the preexisting semantic related association condition, previous knowledge could support the creation of associations, which was assumed to not

depend on the hippocampus. We expected much smaller differences, if any, between HY, HO, and MCI groups across the three types of tasks (free recall, cued recall, and recognition) on learning and retention of semantically related pairs than was expected on semantically unrelated pairs. A similar difference would carry over a 30-minute delayed recall condition.

Results

In this experimental task, we predicted that group differences would appear for semantically unrelated pairs in which the HY group should demonstrate the best memory followed by the HO and MCI groups, respectively. Also, we expected a larger age effect in free recall, a smaller age effect in cued recall and in the recognition condition. In contrast to the semantically unrelated pairs (novel pairs), the three groups' memory of the semantically related pairs should be more equivalent. If there were any between-group differences, the differences should be much smaller than memory for the novel pairs, particularly in the recognition condition. A within-group difference between the semantically related and novel pairs should be stronger in the HO and the MCI groups than in the HY group. A similar difference would carry over a 30-minute delayed recall condition. To test this hypothesis, a mixed factorial Group × Material (semantic related or novel) × Task (free recall, cued recall and recognition) × Time (immediate and delayed recall) ANOVA was conducted. Group was a between-subject variable, and Material, Task, and Time were within-subject variables. Significant effects were further examined using planned contrast comparisons.

Table 5-1 presents the means and standard deviations for the variables obtained on the task in both immediate and delayed conditions for the three groups. The analysis yielded significant main effects for Group [$F(2,47)=36.17, p < .001, \eta^2=.61$], Task [$F(2,46)=421.59, p < .001, \eta^2=.95$], and Material [$F(1,47)=142.36, p < .001, \eta^2=.75$] as well as significant Group × Task [$F(4,94)=9.11, p < .001, \eta^2=.28$], Group × Material [$F(2,47)=22.32, p < .001, \eta^2=.49$], Time ×

Task [$F(2,46)=8.09$, $p < .005$, $\eta^2=.26$], Task \times Material [$F(2,46)=30.03$, $p < .001$, $\eta^2=.57$], and Group \times Task \times Material [$F(4,94)=6.50$, $p < .001$, $\eta^2=.22$] interactions.

The planned contrast comparisons on the interaction effects revealed that during the immediate recall condition, the HY group had better memory regardless the type of materials (semantically related or novel) than did the HO group in both free ($p < .005$) and cued ($p < .005$) recall conditions. However, in the recognition test, the HY group demonstrated a better memory for the novel materials compared to the HO group ($P < .01$), but for the semantically related materials, the two groups did not differ significantly. During the delayed recall condition, the age effect was significant for both types of materials in the free recall test ($p < .005$ in both materials). However, when giving a cued recall or recognition test, the HO group demonstrated similar performance as the HY group (Figure 5-1).

During the immediate recall condition, when comparing the HO and the MCI groups, the MCI demonstrated poorer memory on the semantic material ($p < .05$) but comparable memory on the novel materials on the free recall test. On the cued recall procedure, both the MCI and the HO groups demonstrated benefits from this procedure on the semantically related materials and the group difference found on the free recall procedure disappeared. In contrast to the performance gain on the semantically related materials, the MCI did not benefit significantly from the cued procedure while the HO group did when asked to recall the novel materials, resulting in a significant group effect ($p < .001$). The MCI and the HO groups did not differ significantly on the recognition tests for either type of materials. During the delayed recall condition, the HO group demonstrated better performance on both free recall and cued recall across both types of materials. On the recognition test, the MCI showed comparable

performance on the semantic related materials but poorer performance on the novel materials ($p<.001$).

Table 5-1. Means and standard deviations for the variables obtained on the semantic related or novel word pair list in both immediate and delayed conditions on the young, healthy old, and MCI groups.

Measure	MCI (n=11)		Normal old control (n=20)		Younger control (n=20)	
	M	SD	M	SD	M	SD
<i>Immediate recall:</i>						
Free recall (target word):						
Semantic word	0.80	1.03	1.90	1.12	3.60	1.14
Novel word	0.40	0.52	1.40	1.31	3.15	1.66
Cued recall :						
Semantic word	4.60	1.50	5.50	1.70	6.60	0.50
Novel word	0.80	0.79	3.30	1.95	5.90	1.12
Recognition:						
Semantic pairs	6.50	0.71	6.65	0.59	6.75	0.44
Novel pairs	4.40	1.65	5.20	1.47	6.70	0.66
<i>Delayed recall:</i>						
Free recall (target word):						
Semantic word	0.60	1.07	2.00	1.38	3.90	1.77
Novel word	0.20	0.63	1.75	1.29	3.40	1.39
Cued recall :						
Semantic word	4.90	1.91	5.95	1.28	6.65	0.59
Novel word	1.20	1.23	3.65	2.18	6.40	0.94
Recognition:						
Semantic pairs	6.30	1.06	6.75	0.44	6.80	0.41
Novel pairs	4.00	1.83	5.35	1.39	6.65	0.81

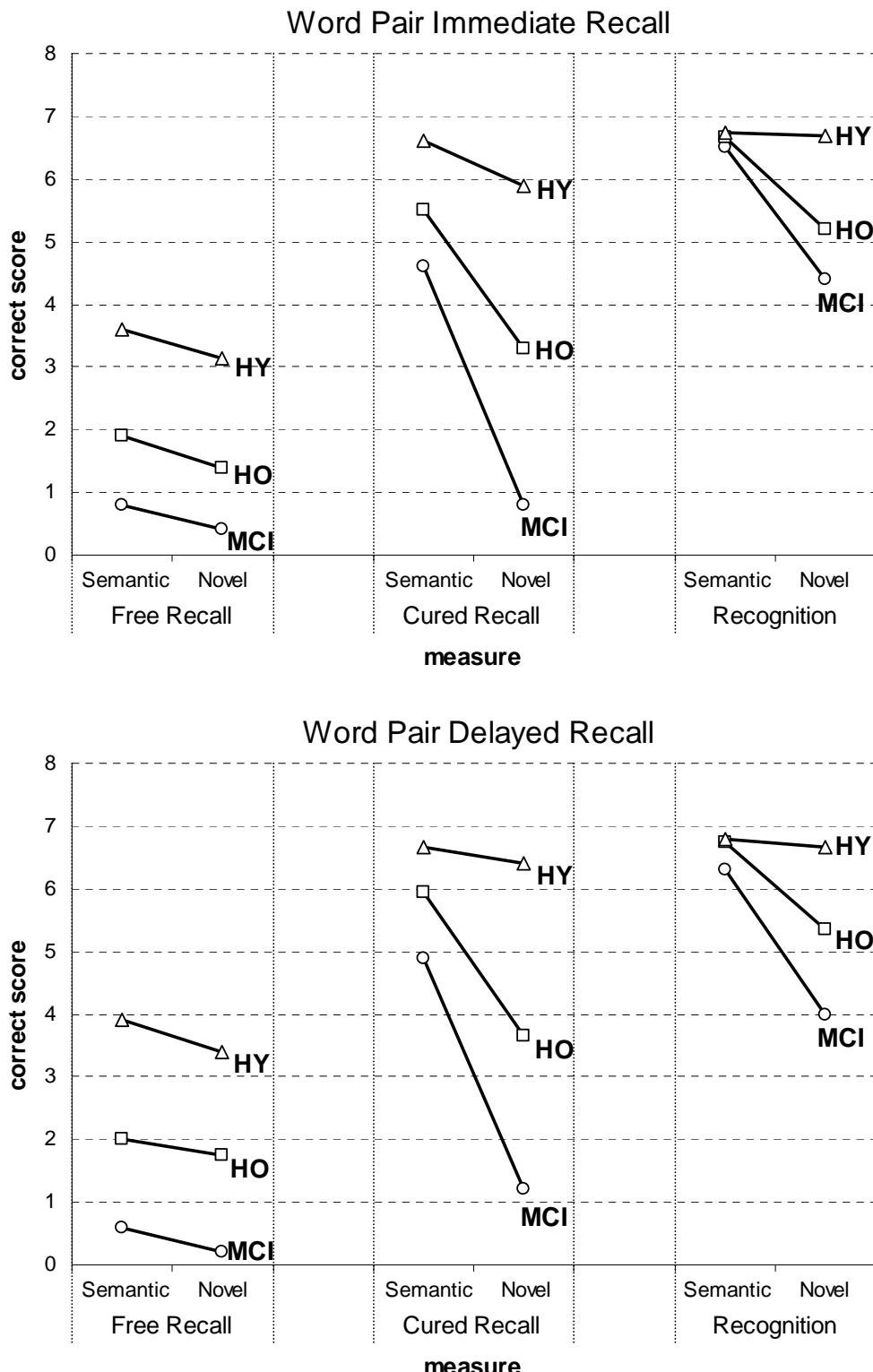


Figure 5-1. Data for free recall, cued recall, and recognition test on the semantic related or novel word pair list in both immediate and delayed conditions for the young, healthy old, and MCI groups.

Discussion

The major finding in this experiment demonstrated distinct group differences on different types of test recall (i.e., free recall, cued recall, or yes/ no recognition). In general, the three groups all followed the pattern with better performance on the recognition followed by the cued recall and then free recall on the same test, which was consistent with previous literatures (Craik and McDowd, 1987; Jacoby, 1991; Naveh-Benjamin, 2000). These evidences suggested that associative memory plays a larger role in free recall than it does in recognition memory. The pattern was particularly clear in the healthy old and the MCI groups: the MCI groups demonstrated the lowest level of performance compared to the healthy old adults and the impairment was particularly clear using the free recall and cued recall paradigms. Similarly, the healthy older individuals performed more poorly than younger participants on free recall of word pairs. A similar pattern was also shown in the delayed recall. Rather than a generalized decrement in memory across all manipulations, older adults showed specific deficits that were attenuated in certain conditions. Second, this memory deficit was mediated by the semantic relatedness of the pairs, in which inherent semantic structure in related word pairs lent cohesion to associative memory, and therefore, the group difference became smaller or even disappeared. In fact, even with substantial difficulty in learning the novel word pairs that did not have any semantic relatedness, the MCI group was able to achieve similar level of performance as the healthy older adults did on learning and recalling the semantically related pairs during the immediate recall condition. This finding was consistent with longstanding theories, which postulate that semantic memory or memory for semantic related materials is more “corticalized,” and thus less dependent on the medial temporal lobes which support the encoding and acquisition of memory for novel materials. (Squire & Zola-Morgan, 1991; Vargha-Khadem et al., 1997).

CHAPTER 6

ASSOCIATIONS BETWEEN DIFFERENT KINDS OF INFORMATION - CROSS-REGION ASSOCIATIONS

There is evidence that hippocampus damage does not impair all kinds of associations in an equal way. Vargha-Khadem et al. (1997) found that early hippocampal damage in childhood impairs the recognition of associations between items with different formats (e.g., face-voice and object-place associations) more than it does the recognition of associations between the same kinds of items (e.g., word-word or face-face associations). Associations between different kinds of information are different from associations of the same kinds in the sense that the components in the former associations were probably represented in distinct neocortical regions rather than represented within one neocortical region. Available evidence suggests that hippocampal damage preferentially disrupts associative memory that depends on the binding of information across cortical regions as compared to associations that depend on within-region binding. In this experiment, we investigated several types of associative information, including object-location, face-house, and item (pictures of faces and historical events) and temporal information association.

Associations between Objects and Locations

Introduction

The aim of the present task was to investigate object-location memory in young, healthy old, and MCI individuals. Object-location memory concerns knowledge of the exact position of objects and their relative relationship with each other (Kessels, Dehaan, Kappelle, & Postma, 2001). Previous literature has indicated that two major cortico-cortical processing pathways: the so-called dorsal and ventral processing streams (Ungerleider and Mishkin, 1982) are involved when performing such a test. The dorsal pathway is directed into the posterior parietal cortex and is important for spatial perception/ localization. The ventral pathway is directed into the inferior

temporal cortex and is important for visual object recognition (Ungerleider and Mishkin, 1982). Inputs from the two streams are integrated in hippocampal formation which bind these distinct components together and form new memory (Moscovitch & Winocur, 1995). Overall, we were interested to examine whether healthy old and individuals with MCI demonstrated disproportionate impairment on this task.

Methods

Participants

There were 51 participants, of which 20 were younger, 20 were healthy older and 11 were MCI individuals. The mean age and number of years of education appear in Table 3-1. For the second types of analyses based on the individual's frontal lobe and medial temporal lobe function level, 35 older adults were included. The details of demographic information and factor scores for each of the four groups can be found in Chapter 3.

Design

One set of 12 pictures of nameable natural and manmade objects presented on a 6 x 6 grid were used for this experiment. Memory for the studied objects was tested using free recall (object recall, subjects had to name them) and yes/no object recognition paradigms by presenting pictures of target and foil objects. Memory for studied locations on the grid was tested using free recall. Memory for the object and location association was tested by free recall (object-location recall) and forced-choice recognition tests (forced-choice object-location recognition). Memory was tested immediately following the study phase and again after a 30-minute delay for all tests. The design was a 3 (Group) \times 3 (Item Type, object, location, object-location) \times Study-Test Interval (immediate, delay) Repeated Measures Analysis of Variance. Group was a between-subject variable, and Item Type and Study-Test Interval were within-subject variables.

Materials and Procedure

One set of 12 pictures of nameable natural and manmade objects was placed in a predetermined random position on a 6×6 grid (12 grid positions were occupied by pictures, while 24 positions were blank). The participants had two minutes to study the entire display and they were instructed to remember both objects and their locations. After the two-minute study phase, subjects were given several types of tests in order: 1) *Object Free Recall and Recognition Tests*: subjects had to name as many as objects as they could remember from the study phase and then perform a yes/no object recognition test. If the participant did not reach a minimal criterion of 80% accuracy on the object recognition test, the study phase and recognition tests were repeated (before giving other tests) until 80% accuracy was achieved. 2) *Location Free Recall Test*: subjects were asked to place wood “dots” on those locations on the grid that were occupied by objects during the study phase. 3) *Object-Location Association Test (OLAT)*: In the OLAT recall test, subjects were provided with the pictures of 12 studied objects and they had to place the objects in their studied locations. Then, the subject were given the OLAT recognition test in which each picture were shown in its studied location and in three other locations (foils) which had been occupied by other studied pictures. Participants were asked to select the correct location for that individual picture. Memory was tested immediately following the study phase and also after a 30-minute delay for all tests. Figure 6-1 presents the stimuli used in this task.

Hypotheses and Predictions

Since establishment of associations between different kinds of information was believed to depend on the hippocampus, we expected that HO participants would demonstrate slightly reduced performance compared to HY, while participants with MCI would demonstrate worst performance compared to the other groups. Furthermore, by dividing individuals into four groups based on their FL-MTL function, we predicted that individuals with Low MTL would show

worst performance on the associative test. However, slight variation might be seen in those individuals with Low MTL depending on their FL function. Those Low MTL-High FL individuals would demonstrate slight better performance than those Low MTL- Low FL individuals.

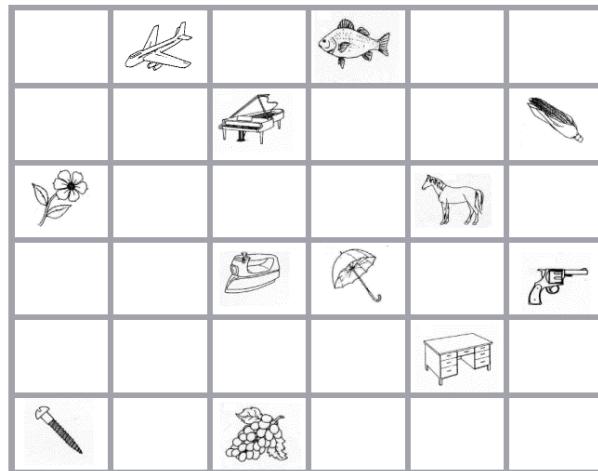


Figure 6-1. The display of the namable objects and their locations for the object-location test.

Results

Analyses on HY, HO, and MCI groups

In this experiment, we hypothesized that three groups (HY, HO, and MCI) should demonstrate equivalent memory for items indicated by their performance on the object recognition test, but that the MCI group should show disproportionate impairment in associating objects and locations in free recall and recognition tests of this ability. To test this hypothesis, three mixed factorial ANOVAs were conducted separately for object free recall and recognition, location free recall, and object-location free recall and recognition tests. Group was a between-subject variable, and Tasks and Time (immediate and delayed recall) were within-subject variables. Significant effects were further examined using planned contrast comparisons. Table 6-1 presents the means and standard deviations of the variables obtained on the Object Location Test in both immediate and delayed conditions on the three groups.

Table 6-1. Means and standard deviations of variables obtained on the Object Location Test on the three groups

Measure	MCI (n=11)		Normal old control (n=20)		Younger control (n=20)	
	M	SD	M	SD	M	SD
<i>Immediate recall:</i>						
Object free recall	6.00	1.90	8.70	1.92	10.55	1.50
Object recognition –hit	11.18	0.98	11.50	0.89	11.75	0.79
Object recognition-false positive	0.45	0.69	0.50	1.40	0.00	0.00
Object recognition-total	28.73	1.35	29.00	1.52	29.75	0.18
Location free recall	5.36	2.11	8.20	2.57	10.55	1.85
Object-location free recall	4.36	2.54	7.80	3.37	10.25	2.86
Object-location recognition	8.45	2.34	10.30	1.87	11.40	1.50
<i>Delayed recall:</i>						
Object free recall	6.60	2.99	9.35	2.28	11.70	0.66
Object recognition –hit	11.70	0.67	11.90	0.31	11.95	0.22
Object recognition-false positive	0.30	0.67	0.25	1.12	0.00	0.00
Object recognition-total	29.40	1.07	29.65	1.14	29.95	0.22
Location free recall	5.90	1.79	8.35	2.62	11.10	1.59
Object-location free recall	4.70	2.41	7.70	2.89	10.85	2.18
Object-location recognition	9.20	1.81	10.70	1.38	11.40	1.50

All participants used only one learning trial to reach 80% accuracy criteria. Analyses on the Object Free Recall and Recognition Tests (hits) revealed a significant main effect of Group [$F(2,47)=26.17$, $p < .001$, $\eta^2=.53$], Test [$F(2,47)=0.30$, $p < .05$, $\eta^2=.59$; all groups performed better on recognition than free recall] and Time [$F(1,47)=9.84$, $p < .005$, $\eta^2=.17$; all groups did better on delayed than on immediate recall]. A significant Test X Group interaction [$F(2,47)=26.23$, $p < .001$, $\eta^2=.53$] was also found and the post-hoc comparisons revealed that all groups had equivalent scores on the recognition tests (both immediate and delayed recall) which suggested an equivalent item memory. However, on the free recall tests, the younger control group had the best scores followed by normal old control and then MCI [$F(2,47)=28.25$, $p < .001$, $\eta^2=.55$]. On the Location Free Recall Test, a significant Group effect was found in which the younger control group has the best scores followed by normal old control and then MCI [$F(2,47)=27.70$, $p < .001$, $\eta^2=.54$]. No significant interaction effect was found [$F(2,47)=.17$, $p > .05$, $\eta^2=.01$]. Analyses on the Object-Location Free Recall and Recognition Test revealed a significant main effects of Group [$F(2,47)=13.89$, $p < .001$, $\eta^2=.37$] and Measure (free recall vs.

recognition) [$F(1,47)=153.94$, $p < .001$, $\eta^2=.76$] , in which all three groups demonstrated better performance on the recognition test compared to the free recall test. A Group x Measure interaction was also significant [$F(2,47)=21.69$, $p < .001$, $\eta^2=.48$]. The planned contrast analyses carried out on the Group and Group x Measure interaction showed that the HY group had significantly better performance on free recall tests (immediate: $t (48)=2.57$, $p <.05$ and delayed: $t(47)=3.94$, $p <.001$) but similar level of performance on the recognition tests ($p>.05$) when compared to the HO group. The HO group demonstrated significantly better performance on free recall (immediate: $t (48) = 3.04$, $p <.005$ and delayed: $t (47)=3.06$, $p <.005$) as well as recognition tests (immediate: $t(48)=2.66$, $p <.05$ and delayed: $t(47)=2.55$, $p <.05$) compared to the MCI group. Figure 6-2 shows scores of object recognition tests (item hits) and object-location recognition tests across group and two time points. Figure 6-3 shows that scores of each group on object, location, and object-location free recall tests.

Object-Location Test: Item and Associative Memory

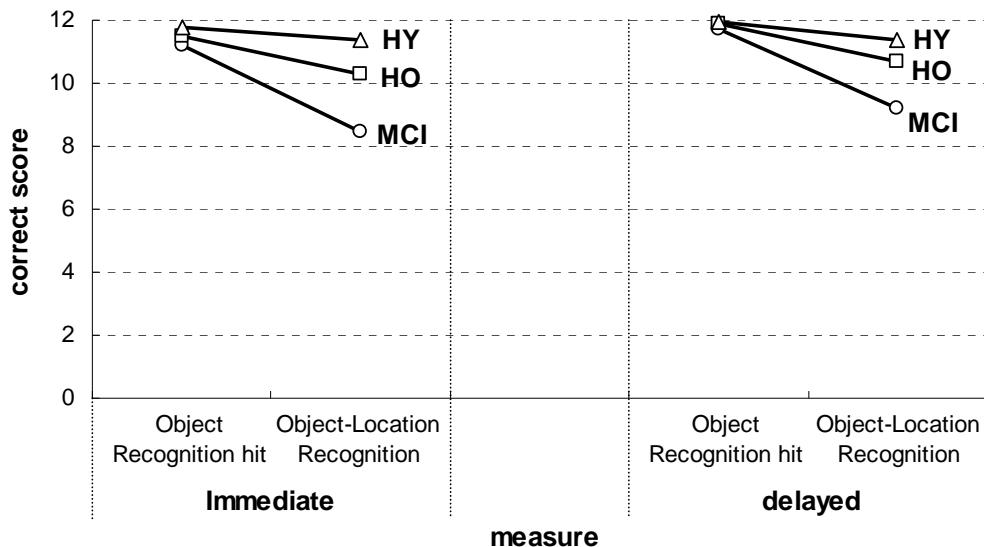


Figure 6-2. Data for object recognition hit and object-location recognition tests in both immediate and delayed conditions for the young, normal old, and MCI groups.

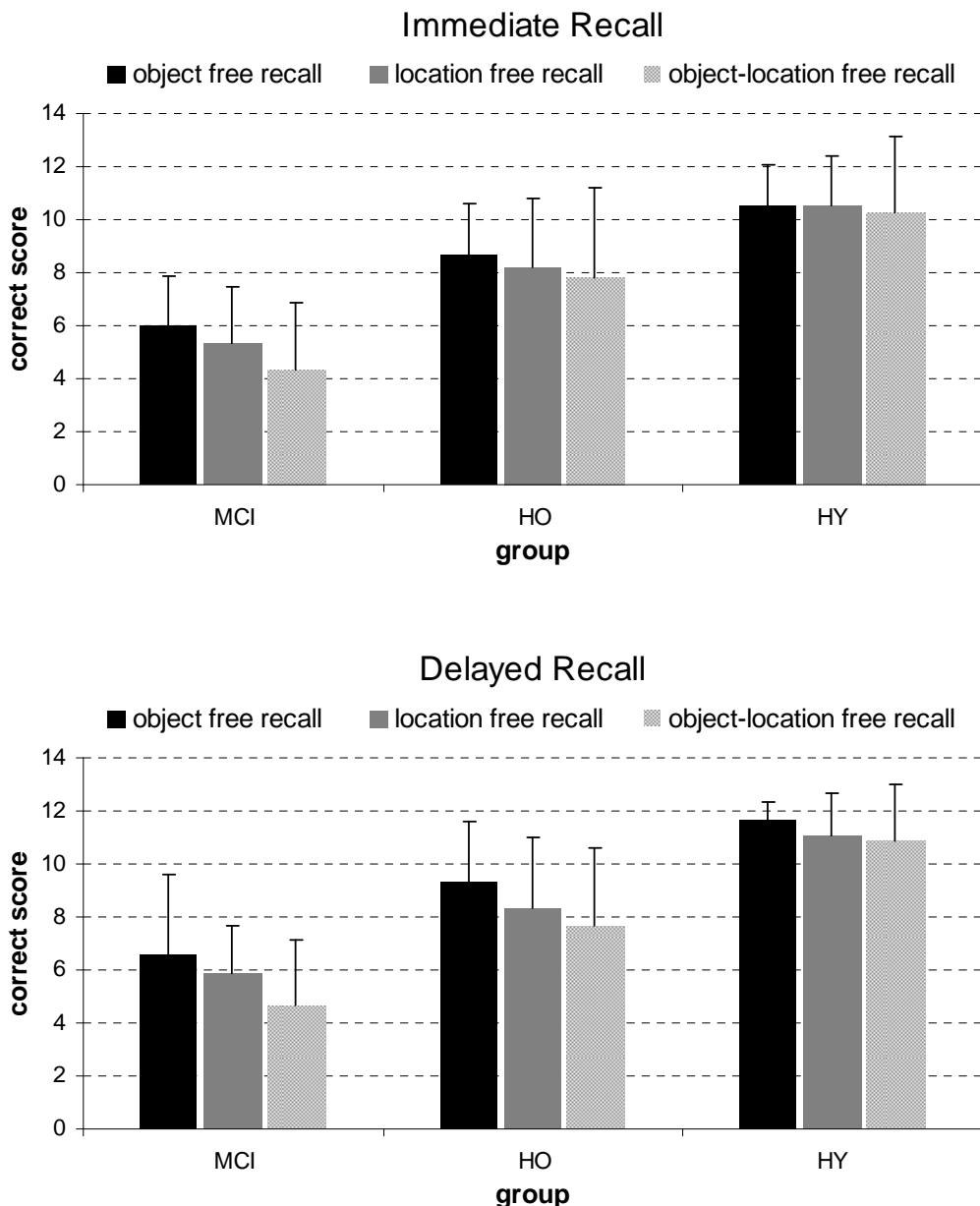


Figure 6-3. Data for object, location, and object-location free recall tests in both immediate and delayed recall for the young, normal old, and MCI groups.

Analyses on groups divided by MTL-FL status

A second analysis was conducted by dividing individuals into four groups based on their FL-MTL function levels. It was hypothesized that individuals with Low MTL should show worst performance on the associative test. However, slight variation might be seen in those individuals with Low MTL depending on their FL function. Those Low MTL-High FL

individuals would demonstrate slightly better performance than those Low MTL-Low FL individuals.

Analyses on the Object Free Recall and Recognition Tests (hit) revealed a significant main effect of Group [$F(3,31)=4.78$, $p <.01$, $\eta^2=.32$] and Test [$F(1,31)=84.66$, $p <.001$, $\eta^2=.73$] in which all groups showed a better performance on the recognition tests compared to the free recall tests. A significant Group x Test interaction [$F(3,31)=4.75$, $p <.01$, $\eta^2=.32$] was also found and the post-hoc comparisons revealed that all groups had equivalent scores on the recognition tests (both immediate and delayed recall), which suggested an equivalent item memory. However, on the free recall tests, the Low MTL-Low FL group, but not the Low MTL-High FL group, showed significantly poorer performance than the two groups with High MTL function. On the Location Free Recall Test, a significant Group effect was found in which the Low MTL-Low FL group had significantly lower scores compared to the two groups with High MTL function. No significant interaction effect was found.

Analyses on the Object-Location Free Recall and Recognition Test revealed significant main effects of Group [$F(3,31)=9.02$, $p <.001$, $\eta^2=.47$] and Measures (free recall vs. recognition) [$F(1,31)=112.37$, $p <.001$, $\eta^2=.78$], in which all groups demonstrated better performance on the recognition test than on the free recall test. A Group \times Measure interaction was also significant [$F(3,31)=3.73$, $p <.05$, $\eta^2=.27$]. The post-hoc contrast comparisons showed that the Low MTL-Low FL group had significantly lower performances on both free recall and recognition tests compared to the two groups with High MTL function. Compared to the Low MTL-High FL group, the Low MTL-Low FL group demonstrated a similar level of performance on the free recall tests, but on the recognition test, the former group had significantly better performance than the later group (Figures 6-4 and 6-5).

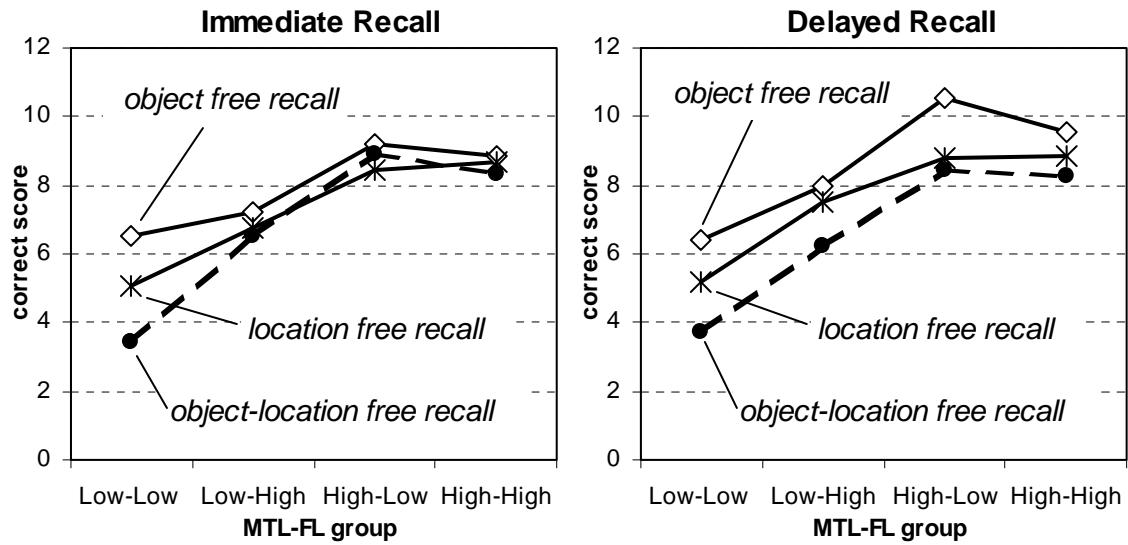


Figure 6-4. Data for object, location, and object-location free recall tests in both immediate and delayed recall for the four groups divided based on their function on MTL and FL factors.

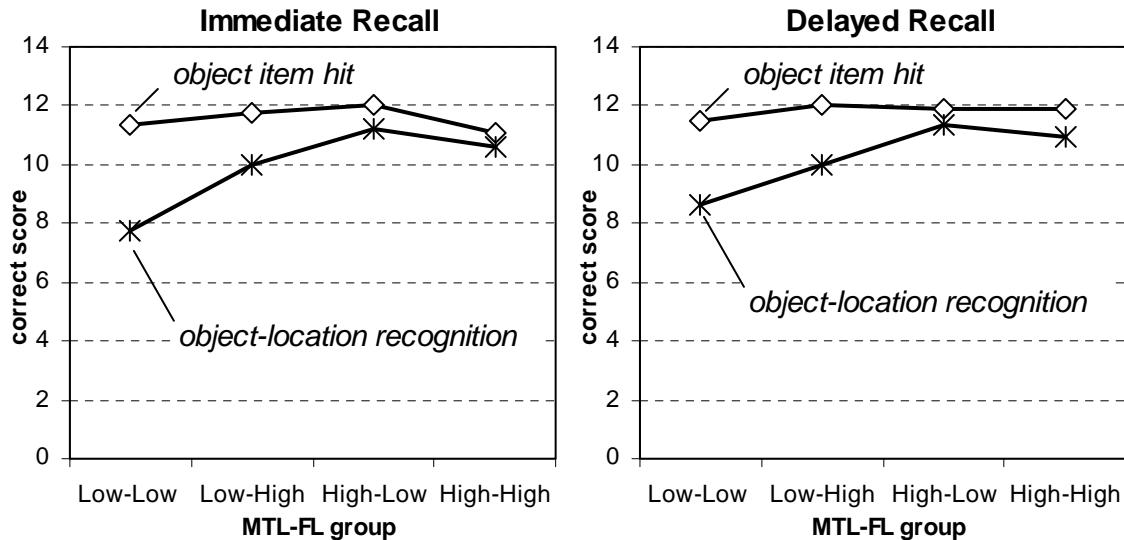


Figure 6-5. Data for object recognition hit and object-location recognition tests in both immediate and delayed conditions for the four groups divided based on their function on MTL and FL factors.

Associations between Faces and Houses--Relational Information

Introduction

Both animal and human functional imaging studies indicate a unique role for the hippocampus in the flexible expression of declarative memories because no other medial temporal region demonstrated a similar effect (Bunsey & Eichenbaum, 1996; Heckers et al., 2004; Preston et al., 2004). The memory for relational association is an ability to infer the relationships between indirectly related items that have not been presented together, based on previous learning of overlapping pairs (e.g., A and B are associated, if A is associated with C, then B is also associated with C) (Heckers et al., 2004). Although several studies have evaluated the relational association or transitive association in hippocampal lesion cases or normal individuals using functional imaging, to our knowledge, no study has examined the relational association in aging population as well as in individuals with mild cognitive impairment. Accordingly, the goal of the present experiment was to examine whether older adults and individuals with MCI demonstrated disproportionate impairment in relational association with relative sparing ability of the item memory.

Method

Participants

There were 51 participants, of which 20 were younger, 20 were healthy older and 11 were MCI individuals. The mean age and number of years of education appear in Table 3-1. For the second types of analyses based on the individual's frontal lobe and medial temporal lobe function level, 35 older adults were included. The details of demographic information and factor scores for each of the four groups can be found in Chapter 3.

Design

The design was a 3 (Group) \times 2 (Study-Test Interval; immediate, delay) Repeated Measures Analysis of Variance. Group was a between-subject variable, while Study-Test Interval was a within-subject variable.

Materials and procedure

The materials and design used by Preston, Shrager, Dudukovic, & Gabrieli (2004) was adapted in the current experiment. The stimuli consisted of 124 black and white photographs of faces (12 male, 12 female) obtained from yearbooks and 15 colorful pictures of real houses. Twenty-four photographs of faces and 12 photographs of houses were used to construct two sets of paired associates: two sets of face-house pairs and one set of face-face pairs. The first set of face-house pairs consisted of 12 faces (B, 6 men and 6 women) and 12 houses (A). The second set of face-house pairs consisted of a set of 12 different faces (C, 6 men and 6 women) and the same 12 houses (A) used in the first set. Therefore, the face-house pairings resulted in two faces that shared an association with the same house (A). Four of the remaining photographs of faces and three photographs of the houses were used to construct the practice trial and the other 96 faces served as foils for the item recognition tests. Figure 6-6 demonstrates an example of stimuli and the task for this experiment.

During the study phase, the set of face-house pairs was shown to subjects at a rate of one pair every six seconds. Participants were instructed to remember the single face, the relationship between the face and the house, and were particularly told to try and make the connection of the two faces that shared the same houses. The set of stimuli was presented to the subject three times on a computer to avoid a floor effect. Following the study phase, participants received a yes/no face recognition test to assess their learning of individual faces. In the recognition test, if the participant did not reach a minimal criterion of 80% accuracy on this test, the study phase

and recognition tests were repeated until 80% accuracy was achieved. If after repeating three more trials from the initial learning trials, the subject still could not reach 80% accuracy, s/he was excluded from the experiment. Following the face recognition test, subjects were asked to do an association recognition test in which there were five previously learned faces in each item (one target and four choices). They were asked to identify one face from the four choices that shared the same house as the target face. The picture of the shared house was not presented. A practice trial was given prior to the formal task to ensure that the participants understand the nature of the task. Both the face and association recognition tests were administrated again after a 30-minute delay.

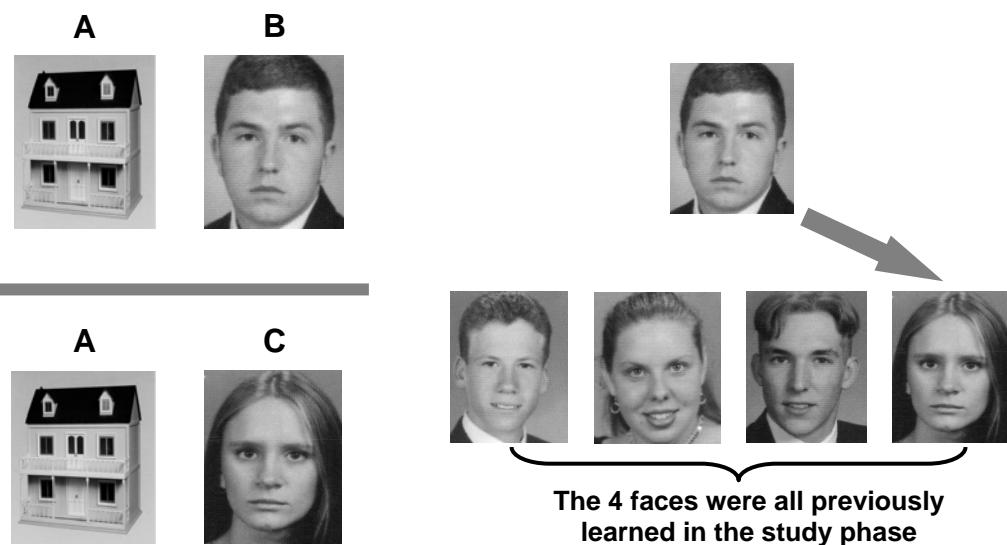


Figure 6-6. An example of the stimuli and the task for the face –house association test

Hypotheses and Predictions

Available evidence (Eichenbaum & Cohen, 2001; Heckers et al., 2004; Preston et al., 2004) suggests that the hippocampus contributes uniquely to the ability to infer relationships between elements of learned associations while other brain regions (e.g., prefrontal cortex and pre-supplementary motor area) also contribute to performance on this type of task. As a result,

we would predict individuals with MCI would demonstrate poorest performance compared to other subjects, following by HO, and then HY in the recognition tests. Furthermore, by dividing individuals into four groups based on their FL-MTL function, we would predict that individuals with low MTL (and possibly Low FL) function would show poorer performance on relational task compared to individuals with High MTL or/and FL function.

Results

Analyses on the HY, HO, and MCI groups

In this experimental task, with the manipulation of repeated learning trials, we predicted that three groups (HY, HO, and MCI) should demonstrate equivalent item memory as indicated by their performance on the face recognition test. However, the three groups should differ significantly on the face-house association test, in which HO participants would demonstrate slightly reduced performance compared to HY, while participants with MCI would demonstrate lower performance than HO. To test this hypothesis, we first examined the equivalence of the item memory and then conducted a mixed factorial ANOVA for the face-house association tests with group as the between-subject variable and time (immediate vs. delayed recall) as the within-subject variable. On the face recognition test (hit), a significant Group effect was found [$F(2,47)= 3.31, p<.05$] even after providing extra exposure to stimuli to people needed. Post-hoc comparisons were conducted and revealed that the MCI group had significantly lower scores on the face recognition test compared to the young control group, but no group differences were found between young control and old control groups, or old control group and the MCI group. Due to the difference in face recognition performance between MCI and HY group, the omnibus test was skipped and two planned Helmert contrast comparisons (HY vs. HO; HO vs. MCI) were conducted. For the HO vs. MCI comparisons, results revealed significant main effects for Time

[$F(1,28)= 6.39$, $P<.05$, $\eta^2=.19$], Group [$F(1,28)= 7.99$, $P<.01$, $\eta^2=.22$], and a significant Time x Group interaction [$F(1,28)= 4.57$, $P<.05$, $\eta^2=.14$]. The post-hoc comparisons showed that the MCI group and the NO group did not differ significantly on the immediate association test, although the p values was marginal [$t(48)=2.04$, $p =.052$]. After a 30 minutes delay, the MCI group showed significant decline on the same test compared to the NO group [$t(47)=4.37$, $p <.001$]. No significant main effects or interactions were seen in the HY vs. HO comparisons. Figure 6-7 shows the data of immediate and delayed association tests across the three groups.

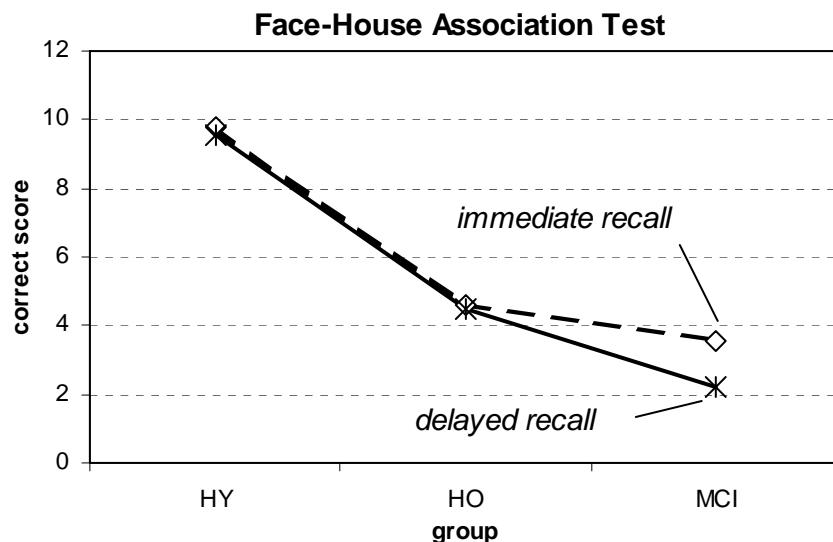


Figure 6-7. Data for immediate and delayed recall on the face-house association test across three groups.

Analyses on groups divided by MTL-FL status

A second analysis was conducted by dividing individuals into four groups based on their FL-MTL function levels. It was hypothesized that individuals with Low MTL or Low FL should have poorer performance on the associative test compared to individuals with High MTL or/and FL function.

On the face recognition test (hit), the four groups were found to have comparable performance [$F(3,30)= 1.36, p >.05$], indicating a similar level of item memory for the faces. The analyses on the Face-House association tests revealed that only the main effect for Group was significant [$F(3,31)= 3.09, p <.05, \eta^2=.23$]. However, when conducting post-hoc comparisons, the group differences were not revealed. The data of the four groups on the association tests are presented on Figure 6-8.

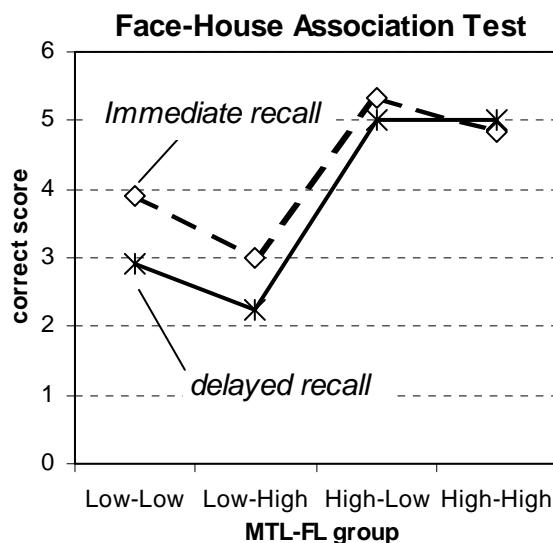


Figure 6-8. Data for face-house association test in both immediate and delayed conditions for the four groups divided based on their function on MTL and FL factors.

In order to further examine the relative involvement of frontal lobe and medial temporal lobe functioning, two separate analyses were also conducted by comparing Low MTL individuals with High MTL individuals regardless of their functional status on the frontal lobe factor, and Low FL individuals with High FL individuals regardless of their functional status on the MTL factor. The analyses revealed a significant Group main effect [$F(1,33)= 9.13, p <.01, \eta^2=.22$] when comparing the Low MTL group with the High MTL group, suggesting that the Low MTL group had lower scores compared to the High MTL group in both immediate and delayed recall of the face-house association test. No significant interaction effect was observed.

Figure 6-9 presents the data for Low MTL and High MTL groups on the association tests. When comparing Low FL and High FL individuals, no significant main effects or interaction effects were found. Figure 6-10 presents the data for Low FL and High FL groups on the association tests.

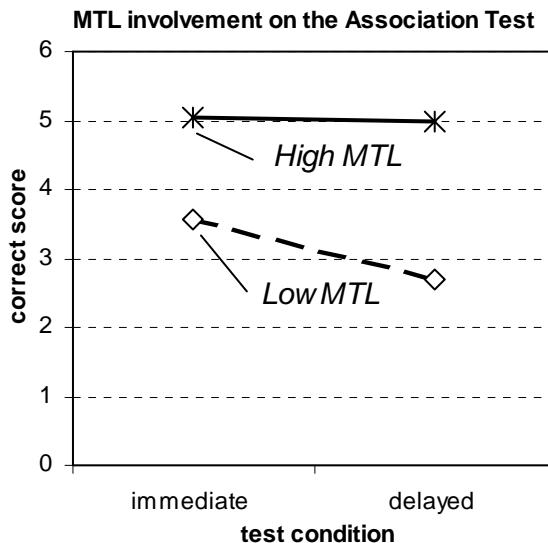


Figure 6-9. Data for face-house association test in both immediate and delayed conditions for the two groups divided based on their function on medial temporal lobe factor.

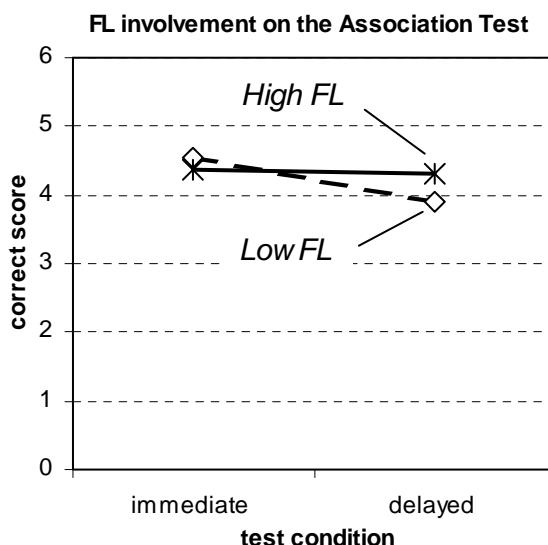


Figure 6-10. Data for face-house association test in both immediate and delayed conditions for the two groups divided based on their function on frontal lobe factor.

Association between Temporal Information and Novel Faces

Introduction

The purpose of the present task as well as the historical event temporal order test used in the next session was to assess healthy older adults and individuals with MCI's ability to process temporal information. Temporal memory is often associated with frontal lesions in humans (Shimamura et al., 1990). Similar to patients with frontal-lobe lesions, normally aging subjects show performance decrements (which are presumed to derive from diminished frontal lobe function) on tasks requiring the retrieval and organization of contextual information, such as the spatial and temporal source or context in which an item was initially learned. On the other hand, hippocampus has been heavily implicated in the modulation of associative memory and, consequently, is hypothesized to provide a memory mechanism for temporal events as well, particularly if these events involve novel materials (Eichenbaum et al., 1994). In fact, Floresco et al. (1997) found that the interaction between the hippocampus and medial prefrontal cortex (mPFC) was necessary for rats to perform integration of sequential responses with a 30-minute delay. Once a task requires prospective coding of a sequence of several spatial items during an intermediate-term delay (i.e., 30 min), based on memory of previously coded items, the interactive communication between the hippocampus and medial prefrontal cortex (mPFC) might become intensified (Floresco et al., 1997). Accordingly, temporal or sequence memory may be a function that depends on both mPFC and medial temporal lobe and the length of delay may be one of the critical factors in dissociating parallel coding between the hippocampus and PFC.

In the field of cognitive aging, several studies of temporal memory have been conducted, in which an age-related effect was reported on the temporal memory and the effect was often associated with frontal dysfunction, although its relationship with some frontal type tasks/executive tasks is still unsure (Cabeza et al., 2000; Fabiani & Friedman, 1997; Glisky et al.,

1995; Schmitter-Edgecombe & Simpson, 2001). However, similar studies conducted in MCI population are still lacking. Given the involvements of both hippocampus and frontal lobe systems in aging process, it was our goal to examine the temporal memory in healthy aging and individuals with mild cognitive impairment.

Methods

Participants

There were 51 participants, of which 20 were younger, 20 were healthy older and 11 were MCI individuals. The mean age and number of years of education appear in Table 3-1. For the second types of analyses based on the individual's frontal lobe and medial temporal lobe function level, 35 older adults were included. The details of demographic information and factor scores for each of the four groups can be found in Chapter 3.

Design

This task involves the presentation of two unfamiliar face lists for study followed by a forced choice recognition test comprised of three types of test trials: recognition, list discrimination, and within-list recency trials. The lags (the distances between the two items) between the list discrimination and within-list recency trials were matched. The design is a 3 (Group: HY, HO, MCI) \times 4 (Trials Type: recognition, list discrimination, within-list recency judgment, and recall) Repeated Measures Analysis of Variance.

Materials and procedure

The materials consisted of two 16- face lists. All faces were unfamiliar to subjects, having been derived from high school yearbooks from distant towns. Subjects first studied a list of 16 faces presented at a rate of 1 item every five seconds on a computer screen. After three repetitions of the first list, a second list was presented and repeated three times. The lag between the last item of the first list and the first item of the second list was fixed at 45 seconds. For all

participants, following presentation of one item, there was a blank interval (400 ms) before presentation of the next item. All of the stimuli were run under intentional learning instructions, in which participants were told that they would be shown two lists of faces, following which their memory for the temporal order relationship among these faces would be tested.

A recognition test with 124 trials was given to all participants. During the recognition test, two items appeared on the computer screen together and the subject's task was to indicate which of the two stimuli was presented most recently. In the case of recognition, only one item was previously seen and therefore was, by definition, the most recent. Subjects were instructed that in some test trials there was only one previously seen stimulus.

There were three types of test trials:

- 1) *Recognition trials* (32 trials): subjects were presented with a previously seen stimulus and a foil (i.e. a new stimulus) at the same time.
- 2) *Between-list discrimination trials* (44 trials): subjects were shown two faces that they had previously studied. One face was from the first list and one was from the second list.
- 3) *Within-list discrimination trials* (48 trials): subjects were shown with two stimuli from the same list (i.e., either from the first list or the second list).

The most recent stimulus (or the old stimulus for recognition trials) appeared equally frequently on the left and the right side of the screen, and relative positions were also counterbalanced across face-face lag. The three types of trials described above were intermixed randomly throughout the sequence. The advantage of this paradigm was that subjects did not need to be aware of whether the trial was testing recency or recognition memory, since the procedure was identical in the two cases and the trials were intermixed. Thus, any performance

difference observed between recency and recognition could not be attributed to difference in task requirements.

In the recency judgment trials, the lags (distances between two items) used in the within-list recency trials and list discrimination trials were matched. Thus, the performance difference observed between the two recency judgment tasks was not confounded by the lags between stimuli.

Hypotheses and Predictions

Previous findings suggested that hippocampal lesions can result in disproportional impairment (compared to item recognition) on temporal order memory, which included list discrimination task and within-list recency judgment. Based on such findings, we expected that HY would demonstrate best performance on the two temporal order tasks followed by HO. The MCI group would demonstrate poorest performance among these groups. It was also expected that a between-list discrimination would be easier than a within-list discrimination, leading to better performance for all three groups. In addition, by dividing individuals into four groups based on their FL-MTL function, we predicted that individuals with either Low MTL or/and Low FL would show poor performance based on past literature, in which both types of lesions have been suggested to impair memory for temporal information of novel information, compared to individuals in the High MTL-High FL group.

Results

Analyses on the HY, HO, and MCI groups

In this experiment, participants were asked to do a recency judgment test with novel pictures of faces as stimuli, it was predicted that the three groups would have similar levels of item memory performance (as seen in the item recognition score). We also predicted that the HY should perform better on the judgment of the temporal information compared to the HO

group, who would in turn show a better performance than the MCI group. The group effect should be larger after a 30-minute delay. In addition, it was expected that the between-list discrimination items would be easier than a within-list discrimination items for all three groups. To examine these predictions, item memory across groups was tested first and the result showed a significant Group effect [$F(2,47) = 12.59$, $p < .001$]. Two planned contrast comparisons indicated that the HY group and the HO group showed comparable item memory, but the MCI group had significantly lower score on the item memory than did the HO group.

Due to the group differences in item memory, a Group x Trial Type (between-list discrimination and within-list discrimination items) x Time (immediate and delayed recall) mixed factorial ANOVA was conducted with item memory (immediate item hit) as a covariate. The results revealed a significant main effect for Group [$F(2,46) = 5.35$, $p < .01$, $\eta^2 = .19$] and a significant Group \times Trial Type interaction [$F(2,46) = 5.36$, $p < .01$, $\eta^2 = .19$]. The planned contrast comparisons showed that, both immediately and after a delay, the HY outperformed the HO on the between-list items [immediate recall: $t(47) = 2.61$, $p < .05$; delayed recall: $t(47) = 3.52$, $p < .005$], but not on the within-list items.

When comparing the MCI and the HO groups, a similar pattern was revealed in which the HO group demonstrated a better performance on the between-list items in the immediate [$t(47) = 3.34$, $p < .005$] and delayed recall [$t(47) = 3.52$, $p < .005$] conditions. The two groups did not differ significantly on the within-list items. Figure 6-11 presents the data of the between-list and within-list trials for the young, healthy old, and the MCI groups.

Analyses on groups divided by MTL-FL status

A second set of analyses was conducted using groups divided by their frontal and medial temporal lobe function levels. It was hypothesized that individuals with either Low MTL or/and

Low FL would show poorer performance based on past literature compared to individuals in the High MTL-High FL group.

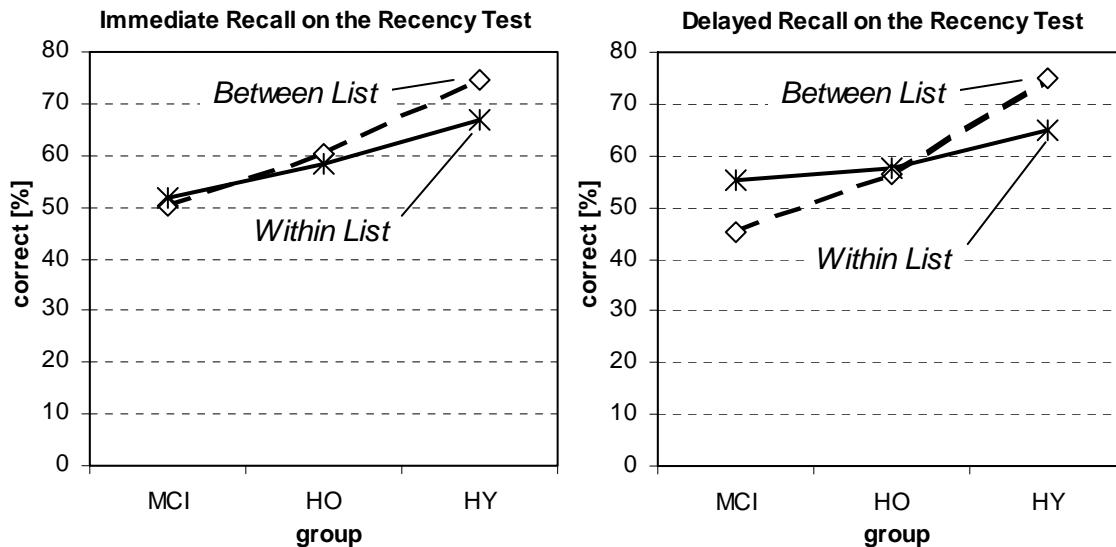


Figure 6-11. Data of the between-list and within-list trials at two time points for the young, healthy old, and the MCI groups.

Similar to previous three-group analyses, the item memory was first examined among the four groups and the results indicated that the four groups did not differ significantly on the item memory score [$F(3,30)= 2.35, p > .05$]. A Group x Trial Type (between-list discrimination and within-list discrimination items) x Time (immediate and delayed recall) mixed factorial ANOVA was conducted. The result demonstrated a significant main effect for Group [$F(3,30)=4.30, p <.05, \eta^2 = .30$] A Measure x Time interaction [$F(1,30)=5.28, p <.05, \eta^2 = .15$] indicated that memory for the between-list items declined more rapidly over time than did memory for the within-list items. Two separate analyses on the two frontal lobe groups regardless of their MTL function level (i.e. high frontal lobe group vs. low frontal lobe group) and the two MTL groups regardless of their FL function level (i.e., High MTL group vs. Low MTL group) were also conducted. The results showed that the Low and High FL groups differed significantly only on

memory for the within-list items during the immediate recall condition [$t(32) = -2.07$, $p < .05$], in which the High FL group showed a better memory on this measure. Comparing the Low and High MTL groups, the Low MTL group demonstrated significantly lower scores on the between-list during the delayed recall condition compared to the High MTL group [$t(30) = -2.58$, $p < .05$]. The effect on the memory for within-list items in the immediate recall condition was marginal ($p = .05$), in which the High MTL group demonstrated a better performance than the Low MTL group. Figure 6-12 displays the data on the recency task for the four groups divided by their frontal and medial temporal lobe function levels.

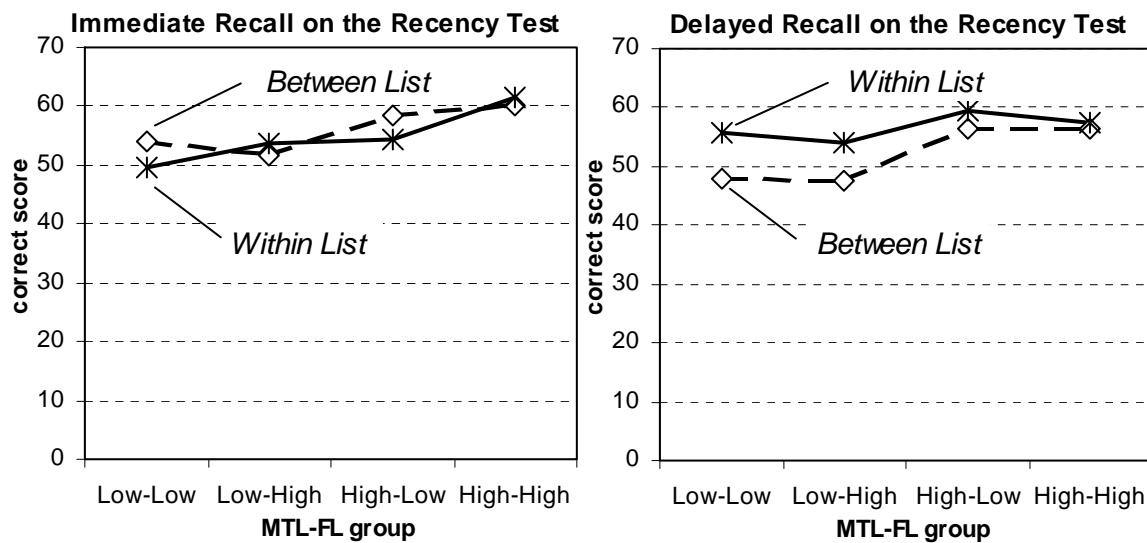


Figure 6-12. Data of the recency task for the four groups divided by their frontal and medial temporal lobe function levels.

Association between Temporal Information and Historical Events

Methods

Participants

There were 51 participants, of which 20 were younger, 20 were healthy older and 11 were MCI individuals. The mean age and number of years of education appear in Table 3-1. For the second types of analyses based on the individual's frontal lobe and medial temporal lobe function level, 35 older adults were included. The details of demographic information and factor scores for each of the four groups can be found in Chapter 3.

Design

This task involves the presentation of 15 historical events. The design is a one-way analysis by Group (HY, HO, and MCI).

Materials and procedure

This test was modified from Bauer (1984) & Shimamura, Janowski, & Squire (1990) and the events used for the experiment were selected based on pilot data. A total of 15 items were used, consisting of two to three events from each decade from the 1940's to the 2000's. Each item was presented on a separate card. The subject was presented with a set of 15 cards, arranged in a random order. The subject was then asked to order the events according to the time of occurrence, starting with the most remote event and completing the set with the most recent one. A global arrangement score, which was a vector score based on the distance between correct response and the subject's response, was obtained for each subject. For each item, the absolute difference was taken between the position given to the item by the subjects and its correct position. For example, a response (A1, A3, A2, A4, A5, A6, A7...assuming all correct responses after A7) would receive a score of $0+1+1+0+0+0+0+\dots=2$. The scores could range

between 0 (correct response) and 112 (total inversion of the correct order). The subject was allowed to use as much time as they needed to finish this task.

Hypotheses and Predictions

Due to the fact that knowledge of historical events was considered as one type of semantic memory stored in the semantic network and was believed not to rely on hippocampus or medial temporal lobe structures, the three groups (HY, HO, and MCI) would not be expected to show significant group difference on this measure. Furthermore, performance on this task was expected to correlate with the score on Glisky et al.'s frontal factor (since poor performance on this task would reflect source memory impairment or a failure in strategic processing). By dividing individuals into four groups based on their FL-MTL function, we expected that Low FL subjects would have poorer performance on this task compared to High FL subjects.

Results

In this experiment, we asked participants to arrange 15 historical events based on the chronological order. It was hypothesized that three groups (HY, HO and MCI) would not demonstrate significant group differences on this measure because semantic memory was believed not to rely on hippocampus or medial temporal lobe memory system. However, performance on this task was expected to correlate with the frontal function. To test this prediction, a correlational analysis between the task and clinical frontal measures as well as the frontal lobe composite scores was conducted. Additionally, by dividing individuals into four groups based on their medial temporal lobe and frontal lobe function levels, it was expected that subjects in the lower frontal function groups would have poorer performance on this task compared to subjects who were in the higher frontal lobe function groups

Analyses on the HY, HO, and MCI groups

An absolute difference score was calculated between the subject's answer and the actual order for the events. The higher scores indicated the poorer performance. A Group \times Task ANOVA was then conducted and yield a significant Group main effect [$F(2,48)=7.03, p<.005$]. The post-hoc comparison revealed that the MCI group showed significantly poorer performance on this measure than did the HY and HO groups, which did not differ from each other. Figure 6-13 presents the results for the three groups on the historical event temporal order test.

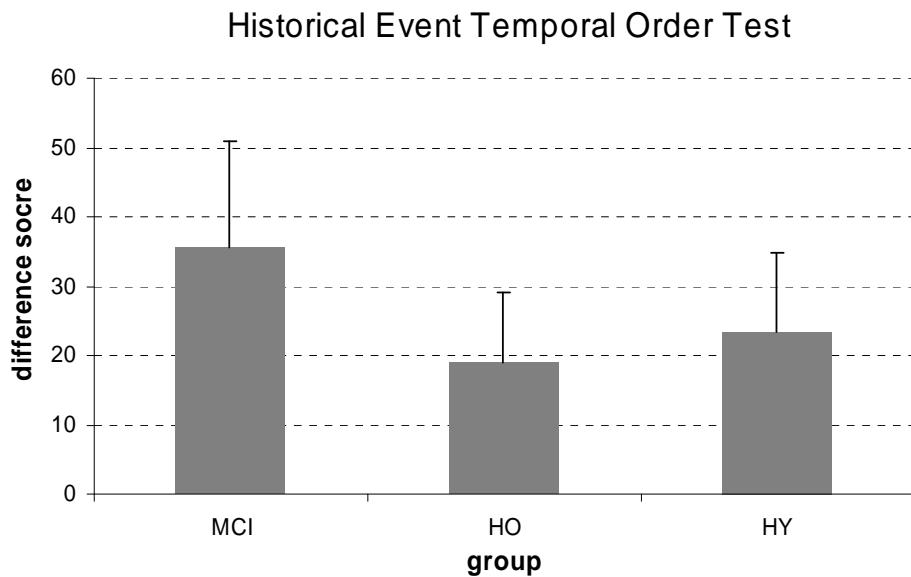


Figure 6-13. Data of the difference scores on the historical event temporal order test for the young, healthy old, and the MCI groups.

Analyses on groups divided by MTL-FL status

A separate analysis was conducted on four groups divided by their frontal lobe and medial temporal lobe function levels. An omnibus test was skipped and instead two planned contrast comparisons (i.e., high frontal lobe group vs. low frontal lobe group; high temporal lobe group vs. low temporal lobe group) were also conducted in order to examine the relative contributions of frontal lobe and medial temporal lobe function. The analyses revealed that the high and low frontal lobe groups did not differ significantly on this measure [$t(31)=1.13, p>.05$]; however,

the High MTL group demonstrated a significantly better performance on this task compared to the Low MTL group [$t(31) = 2.07$, $p < .05$]. Figure 6-14 shows the data for the four groups on the measure.

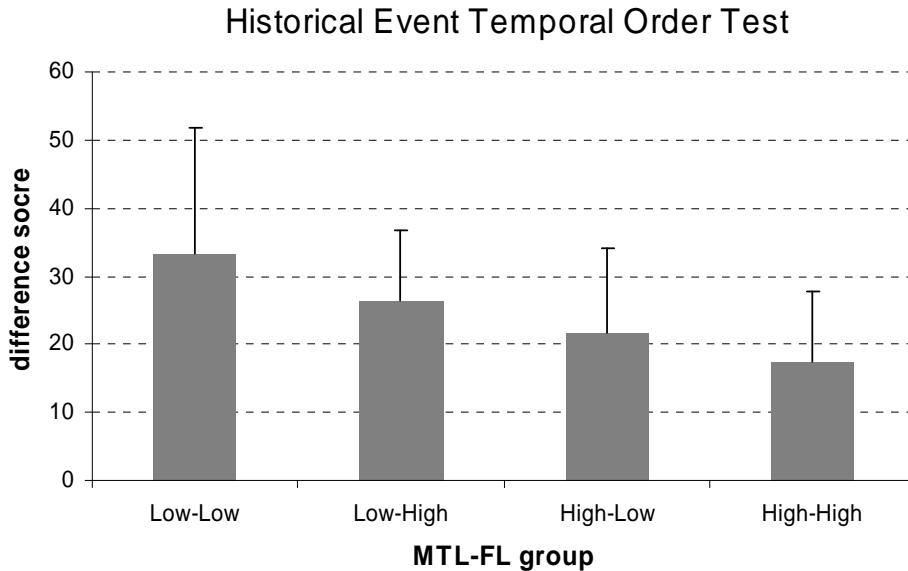


Figure 6-14. Data of the difference scores on the historical event temporal order test for the four groups divided by their medial temporal lobe and frontal lobe function levels.

Correlations between temporal order test and neuropsychological measures

The correlational relationship (Pearson correlations) between the event temporal order measure and frontal/ executive function measures was conducted through a one-tailed correlational analysis and the results revealed that the performance indicating by the absolute different scores (higher score = worse performance) on the event temporal order measure was negatively correlated with Similarities subtest (WASI) raw scores ($r = -.26$, $p < .05$), Matrix Reasoning subtest (WASI) raw scores ($r = -.25$, $p < .05$), Arithmetic subtest (WAIS) ($r = -.35$, $p < .01$), Letter-Number Sequencing subtest (WMS-III) ($r = -.23$, $p < .05$), COWA ($r = -.27$, $p < .05$), WCST total errors raw ($r = .23$, $p < .05$), and Frontal lobe composite scores ($r = -.30$, $p < .05$). The event temporal order measure was also positively correlated with Trails A time ($r = .24$, $p < .05$) and Trails B time ($r = .31$, $p < .05$).

Discussion

Several experimental tasks related to associations between different kinds of information were conducted. On the object-location association task, the results showed that the three groups demonstrated comparable item memory demonstrated through a recognition paradigm, although a clear pattern of group difference was shown in free recall. Memory for the object-location association followed the predicted pattern with the HY group having the best memory followed by the HO group and then the MCI group. Unexpectedly, the MCI group did not demonstrate significant forgetting for items or item-location associations over a 30-minute delay. On the parallel analyses conducting on the four groups divided by their FL-MTL function status, the results indicated that the four groups showed comparable item memory. However, the Low MTL-Low FL group, but not the Low MTL-High FL group, demonstrated significantly lower scores on the associative memory. The overall findings indicated that MCI individuals showed disproportionate difficulty in the associative memory, even though they demonstrated similar item memory compared to the healthy older adults. Furthermore, impairment on tasks associated with medial temporal lobe appeared to have the major contribution to this specific task. The frontal lobe appeared to play a “secondary” role on the associative memory in this specific measure. High vs. Low FL status came into play only on those comparisons involving the Low MTL groups.

The face-house relational association task in the present experiment was a very difficult task. Although the list was present at least three times for all participants, the healthy older participants’ scores on the face-house relational associative items were half these of the younger people. In fact, all of younger participants only needed 3 trials (minimal exposures) to reach an 80% accuracy criteria on the face recognition test, while the healthy old individuals needed an average number of 3.85 (SD =0.93, range: 3 to 7 trials) trials and the MCI individuals needed 4.9

trials ($SD = 1.14$, range: 4 to 7 trials) to reach similar performance on the item recognition test. Despite the difficulty of this memory task, the HO and the HY groups were able to demonstrate comparable item memory. In contrast to item memory, the healthy older group was able to get only half of the associative items correct as the younger people did during the immediate recall phase, although their memory for the associative items was as well-maintained over a 30-minute delay, as was that of the younger group. The HO and MCI groups demonstrated comparable item memory. The MCI group demonstrated a trend ($p=.05$) toward lower scores on the immediate associative memory compared to the HO group. After a 30-minute delay, the MCI group showed substantial forgetting on the associative memory, which actually fell below the chance level. In summary, with comparable item memory between groups, the younger individuals demonstrated the best memory for the relational association followed by the healthy old group and then the MCI individuals. The MCI group was further characterized by a faster forgetting rate on the relational associative task, while the other two groups remained stable memory for the same material.

On the parallel analyses conducted on the four groups divided by their FL-MTL function status, the four groups demonstrated comparable item memory. When further examining the relative involvements of medial temporal lobe and frontal lobe on the relational association memory, the Low MTL group, which combined the groups with high and low FL factor scores, demonstrated significantly poorer performance on the associative memory compared to the High MTL group, although the Low MTL group did not demonstrate further forgetting after a 30-minute delay. When comparing the two groups with either High or Low FL factor scores, regardless of their MTL function level, there was no significant difference found.

Overall, these findings indicated that medial temporal lobe rather than the frontal lobe function has more substantial involvement in relational associative memory. MCI individuals who were characterized by compromised MTL function demonstrated relatively lower performance compared to the healthy older control, and such memory dysfunction was further accentuated in a delayed recall condition. Indeed, previous studies in animals indicated a role for the hippocampus in the flexible expression of declarative memory (Bunsey and Eichenbaum, 1996). Studies conducted on patients or healthy adults also have suggested that hippocampus contributed to the process that conjoin novel relations between elements of learned associations (O'Reilly and Rudy, 2001; Preston et al., 2004).

Two experimental tasks were conducted, one with novel face materials and the other with historical events, in order to examine the temporal order of information in the episodic and semantic memory systems. The face recency task in the present experiment was also a very difficult task. Although each of the two lists was presented three times, the younger participants could identify only approximately 75 % of items correctly and the healthy older group could identify only approximately 60 % of items correctly. The performance of the MCI group was actually close to the chance level. Despite the difficulty of this task, the results still demonstrated a pattern as predicted, with the younger group showing the best performance, followed by the HO group and then the MCI group on the novel face recency task. This indicates that the MCI group was impaired in determining which of two stimuli had been seen more recently on a test using novel faces as stimuli and such impairment was disproportionately impaired compared to the item memory. In fact, the group effect was mainly derived from the difference on the between-list item discriminations rather than on the within-list item

discrimination, even after controlling the lags between two stimuli on the two discrimination conditions.

On the semantic temporal order test, an unexpected result was found in which the HY and HO groups showed a comparable performance that was better than the performance seen in MCI group. Overall, the results obtained from the two tests related to temporal order judgment indicated that the MCI individuals' ability in judging temporal information was impaired for both novel materials and materials that depended on the semantic system. Further, the disproportionately impaired temporal memory suggested that whatever process mediates judgment about when a stimulus occurred (i.e., recency judgment) was not identical to that which mediates judgments that a stimulus occurred (e.g., recognition judgment).

A parallel analysis was also conducted on groups classified by their FL and MTL function levels on the two temporal ordering tests. The findings indicated that on the novel face recency test, the Low FL group had a lower score on the within-list items in the immediate recall condition compared to the High FL group. The Low MTL group had a significantly lower score on the between-list discrimination during the delayed recall, and a tendency of a lower score on the within-list items during the immediate recall compared to the High MTL group. Another piece of evidence that supported both FL and MTL involvements came from the correlational analyses. Several neuropsychological measures that were assumed to tap frontal /executive functioning (e.g., Letter-Number Sequencing test, Animal Fluency, and Trails A & B tests) and medial temporal lobe memory functioning (e.g., Logical Memory, Verbal and Visual Paired Associates, and Visual Reproduction, and CVLT-II) were highly correlated with performance on the temporal order task using novel materials. Furthermore, the results found during the immediate recall, but not delayed recall, between High FL versus Low FL groups, and both

immediate (marginal, $p = .05$) and delayed recall effects between the High MTL versus Low MTL were interesting. Such findings were similar to the findings found in the Floresco et al. (1997) study, only their study was conducted with animals, and indicated the length of delay may be one of the critical factor to tease apart the role of hippocampus on the temporal memory (Floresco et al., 1997). On the historical event temporal order test, the group with higher MTL function demonstrated a better performance than did the group with lower MTL function. The high and Low FL groups did not demonstrate significant differences on this measure, although significant correlations were found between several frontal/executive function measures (e.g., Letter-Number Sequencing test, Trails B, and Arithmetic test) and performance on the temporal order test using public events. Overall, the evidence obtained from the group analysis and the correlational analysis indicated that both medial temporal and frontal lobe played a role in performance of a temporal order test that used semantic familiar materials as stimuli.

Collectively, these results indicated that MCI involves a loss of temporal order information beyond what is predictable from a general loss of item memory. Such information is fragile in MCI individuals, but it is fragile as well in normal old adults when compared to younger individuals. Additionally, these findings also support the view that association memory for temporal order and source depend additionally on frontal function (Milner et al., 1991; Schacter, 1987; Shimamura & Squire, 1987), as well as memory performance mediated by medial temporal lobe (Kopelman et al., 1997).

In sum, the findings obtained from the four associative memory tests indicated that the MCI group demonstrated disproportionate difficulties in different aspects of information associative memory as compared to the healthy older adults, who then demonstrated a poorer associative memory compared to healthy younger adults. Additionally, the evidence that medial

temporal lobe plays a primary role in the associative memory for different kinds of information emerged consistently from different experimental tasks mentioned above. However, the evidence regarding the role of frontal lobe system on associative memory for different kinds of information was less cohesive.

CHAPTER 7

CONCLUSIONS AND DISCUSSIONS

The present study aimed to overcome shortcomings of previous studies by systematically investigating multiple measures of associative memory in normal aging and MCI. The underlying question in this study was whether associative memory is disproportionately impaired in MCI, and whether impairment in associative memory could serve as a meaningful predictor of risk to develop dementia later in life. While the latter question awaits longitudinal confirmation, this study attempted to determine whether associative memory (memory for associated items) was disproportionately impaired compared to memory for single items in individuals with MCI on several associative memory tests. Previous work has shown that associative memory, particularly cross-modal associative learning, is a sensitive indicator of hippocampus involvement. In addition, structural imaging studies have demonstrated that MCI individuals have significant hippocampal volume reductions compared to normal healthy elderly and young adults. Therefore, we predicted that MCI individuals would demonstrate greatest and disproportional difficulty in associative memory tasks, particularly for the associations between different kinds of information (cross-modal) compared to healthy elderly. In addition, we expected that MCI individuals would show a greatest decline on the delayed recall condition compared to the immediate recall condition in both within- and between- subject analyses, given the well-established role of hippocampus in the long-term memory consolidation process (Frankland & Bontempi, 2005).

Additionally, the current study also attempted to determine the degree to which associative memory depends on medial temporal lobe functioning and frontal lobe functioning, given possible heterogeneity among older individuals. First, we examined heterogeneity in frontal

functioning using methods described by Glisky and her colleagues (1995) among healthy elderly and MCI individuals. We then examined its relationship with associative memory performance.

We predicted that older individuals with higher frontal-executive skills would demonstrate better performance on associative memory tasks than would elders with lower but still normal frontal-executive skills. Past studies have shown that giving explicit instruction during the encoding phase can improve memory performance only for people who have good frontal/executive functioning. In this present study, we also manipulated the instruction types during the encoding phase to explore the phenomena in normal aging and MCI individuals using an associative memory paradigm. We further expected to see an interaction effect of group by instruction, in which the High FL older adults would demonstrate a greater benefit from intentional than incidental instructions (a within-subject comparison) compared to Low FL elders (a between-subject comparison) on associative memory tasks in both conditions.

Disproportionate Impairment on the Associative Memory Compared to Item Memory

Across experimental tasks, our results clearly show that the MCI group demonstrated a disproportionate impairment in associative memory. Furthermore, the pattern of greater impairment of associative than item recognition shown on the MCI individuals is consistent with the pattern of performance displayed by patients with hippocampal pathology reported by Holdstock et al. (2005), Mayes et al. (2004), Turrizian et al. (2004) and Vargha-Khadem et al. (1997). It is a well-established finding that the hippocampus is critically important in associational processing (Eichenbaum, 1997; Moscovitch and Winocur, 1995). Numerous investigations have demonstrated that one of the primary functions of the hippocampus in memory is to bind elements together to form a memory that can later be retrieved. In addition, the MCIs' performance on several of the delayed recall tests (e.g., face-house association) dropped by a significantly larger amount than that of the healthy controls from the initial test to

the retest. It has been argued that the retest (delayed recall) relies more on recollection of the association of the item to its study context than does the initial test (Aggleton et al., 2000).

The pattern of disproportionate impairment on the associative memory shown in the MCI group was also seen in the healthy older control group when compared to the younger group, which was consistent with previous literature (Kirasic, 2001). One possible reason for the group difference found between young and healthy old groups was that moderate age-related atrophy of hippocampus occurs in a continuous fashion. Second, younger control subjects may use more elaborative encoding strategies than older subjects in memory tasks (Naveh-Benjamin, 2000). Elaborative encoding has been reported to benefit recollection more than familiarity; consistent with this, aging has been found to have a greater detrimental effect on recollection than familiarity (Yonelinas, 2001).

In the present study, we conducted several types of association tests which included associations between information stored in the same cortical region (e.g., word-word association), association between information represented in distinct cortical regions (e.g., object-location association), and relational association which focused on the flexible expression of relational information (e.g., face-face association through a face-house connection). One question raised in the literature review was whether hippocampal damage impairs all kinds of associative to the same extent. Collectively, our findings showed that the MCI group, compared with healthy old adults, demonstrated impaired performance on the word-word association, the associations that involved information represented in distinct cortical regions (including the object-location association and temporal order judgment tests), and the relational association.

Table 7-1. Effect sizes for all associative measures

Associative memory measures	Cohen's d	description of relative size
Intentional word pair recognition 1	1.09	Large effect
Intentional word pair recognition 2	1.15	Very large effect
Incidental word pair recognition 1	0.98	Large effect
Incidental word pair recognition 2	0.50	Medium effect
Semantic-novel pair free recall 1	1.34	Very large effect
Semantic-novel pair cued recall 1	1.14	Very large effect
Semantic-novel pair recognition 1	0.56	Medium effect
Semantic-novel pair free recall 2	1.43	Very large effect
Semantic-novel pair cued recall 2	1.07	Large effect
Semantic-novel pair recognition 2	1.14	Very large effect
Object-location recognition 1	0.94	Large effect
Object-location recognition 2	1.01	Large effect
Face house association1	0.62	Medium effect
Face house association2	1.40	Very large effect
Face recency judgment 1	1.28	Very large effect
Face recency judgment 2	1.14	Very large effect
Historical event temporal order	1.42	Very large effect

Note: The calculation of effect sizes were based on the comparison between healthy old and MCI groups. 1 indicates immediate recall; 2 indicates delayed recall

Table 7-1 displays the effect size calculated based on the group effect between healthy old and individuals with MCI for each associative memory measure. The effect sizes for the word-word association (intentional word pair) range from large effect (immediate recall) to very large effect (delayed recall). Similarly, the effect sizes for the tasks measure associations that involved cross-region information as well as the relational association memory were generally in the large to very large range, particularly for the delayed recall condition. From the effect size standpoint, the current data indicate that different associative memory measures used in the current study were sensitive to hippocampus dysfunction to a comparable level. The overall finding in the current study was consistent with findings reported by Turriziani et al. (2004) who found that patients with hippocampal lesions performed poorly on associations of same kind information as well as associations of different kinds of information.

Our findings based on experiment 2 and findings on the object-location association test also suggested that free recall was a more sensitive measure compared to recognition when investigating associative memory. This was consistent with the view that the hippocampus is critical for recollection whereas neocortical region are sufficient to support familiarity-based recognition memory decisions (Holdstock et al., 2002, Mayes et al., 2002). Interestingly, older participants continued to exhibit poorer associative memory on several associative memory tasks, even when tested using a recognition test which was supposed to reduce the retrieval demands involved in the free recall tests. Such finding indicated that providing greater amounts of contextual support (i.e., giving recognition tests) does not help the older adults, particularly individuals with MCI, to overcome their memory difficulties for associative information. This might suggest an encoding proficiency impairment among those older participants when performing the associative memory tests. We cannot rule out the possibility that retrieval difficulties are also accounting for the decline in associative memory observed in both normal aging and individuals with mild cognitive impairment. Moreover, healthy older adults benefited from the explicit encoding instruction and the effect has the tendency to last for a period of time while the MCI individuals only received a short-term benefit.

To summarize, the results of the study are in line with findings based on hippocampus lesion patients and lends additional support to the role of hippocampus in multiple aspects of associative memory. Specifically, the findings indicate a disproportionate impairment of associative memory relative to item memory in the MCI individuals (when compared to healthy aging) and normal aging (when compared to younger subjects), indicating that the associative memory measure may be a sensitive measure to differentiate individuals who may be at risk to

develop dementia later in life. Verifying this suggestion will, of course, await longitudinal confirmation.

Semantic Memory versus Episodic Memory

Numerous studies have suggested that the mild cognitive impairment is characterized by impairment in episodic memory, particularly delayed recall of newly learned materials, with relatively sparing of semantic memory. As a result, the findings based on the historical event temporal order test were interesting and unexpected. The healthy old adults demonstrate comparable performance as the younger adults; however, the MCI group demonstrated significantly impaired performance on this measure compared to the healthy older adults. The puzzling question was whether the impaired performance observed in the MCI group reflected an impaired ability in discriminating the temporal relationship between items, an early sign of breakdown of semantic system, or both.

From the temporal relationship standpoint, some studies have indicated that the aging process affects one's ability to discriminate the temporal sequence (Parkin et al., 1995; Schacter et al., 1991) and frontal lobe dysfunction has been proposed to account for the impairment observed in aging studies. Indeed, the results based on the recency test with novel faces as stimuli showed that the ability to discriminate the temporal sequence between items was decreased in both normal aging and the MCI group even after controlling for item memory. Furthermore, the time-tagging mechanism may be compromised in both healthy old adults and the MCI individuals based on above description; however, the healthy older adults, who have a relatively intact hippocampus compared to the MCI individuals, can still rely on trace strength information to make recency judgment while the MCI individuals appeared unable to do so. An alternative possibility is that the impairment in MCI somehow affects trace strength, thereby rendering it unreliable as a source of recency judgments.

One additional theoretical explanation for the poor performance of MCI patients on the public events ordering test is that the semantic system, which is affected dramatically in Alzheimer's disease, has begun to break down once the patient reaches the MCI stage. Indeed, several recent studies suggest that semantic knowledge breakdown might start appearing as early as in the stage of MCI. For example, a recent study conducted by Kraut et al. (2007) reported that 10 out of 35 Amnestic MCI individuals in their sample demonstrated impaired semantic memory measured by a semantic object retrieval test. They further indicated that a major distinction between the MCI individuals with semantic impairment, MCI individuals without semantic impairment, and healthy aging control is the relatively large number of false-positive memory errors. A relatively large false positive rate was seen in our MCI subjects in Experiment 1 of the present study. Similarly, Estévez-González et al. (2004) reported that MCI individuals who were diagnosed two years later with Alzheimer's Disease performed significantly worse in a task involving semantic knowledge of famous people than those MCI who did not convert to dementia later. The evidence obtained from the studies mentioned above seems to point out that there is a subgroup of Amnestic MCI who demonstrated semantic knowledge impairment and can be distinguished from the other Amnestic MCI who do not have semantic knowledge impairment and may have a better prognosis in the future. Although, with a small sample size, it is likely that some, if not all, individuals with MCI in the current study showed semantic knowledge impairment. In deed, in our MCI sample, we included both MCI amnestic single domain as well as MCI amnestic multiple domains in the analyses. It will be interesting to follow up those people with MCI in the present study and observe their prognosis in the future.

Overall, the evidence seems to suggest that impaired time –tagging mechanism and semantic knowledge could both account for the findings obtained in the historical event temporal

order task. As a result, it is somewhat difficult to tease apart the two different processes without including other semantic knowledge tests; doing so might be worthy of further study.

Frontal Lobe Involvement in Associative Memory and the Heterogeneity Among Older Adults

The primary goal of the current study was to examine associative memory in normal aging and individuals with mild cognitive impairment. The role of medial temporal lobe /hippocampus on associative memory is well established and can account for the impaired performance found in the MCI group. In addition to the role of medial temporal lobe in associative memory, we were also interested in investigating the additional contributions made by frontal-executive impairment that is prevalent in the aging population. In the present investigation, our interest in the heterogeneity among older adults and adults with MCI was mainly focused on the variation of the frontal /executive function and its effect on associative memory in these populations. In order to examine the relative involvements of frontal lobe and medial temporal lobe, we adapted Glisky's method and divided subjects based on their levels on the frontal lobe and media temporal lobe composite scores. Overall, the most significant differences were found between the High vs. Low MTL function groups instead of the High vs. Low FL function group, suggesting that the medial temporal lobe functioning plays a more critical role in associative memory function. However, we also found the frontal lobe may contribute to associative memory and that its importance usually does not become salient until the functional integrity of medial temporal lobe was compromised. For example, in the object-location association test, the two High MTL groups with either High or Low FL function did not differ significantly in their ability to recall the object-location association. However, in individuals with Low MTL functioning, an intact frontal lobe system may help mitigate impairment to some degree and may even allow performances comparable to that seen in patients with High MTL functioning. Such

findings are consistent with the view that the frontal lobe is important in initiation and execution of cognitive control processes or strategy usage during a memory process; however, the medial temporal lobe, particularly the hippocampus, is critical for the rapid formation of associative memory. An additional implication of these findings is that the Low MTL-Low FL group may be a specifically at-risk group that needs to be followed up from both diagnosis and intervention perspectives. Those individuals may have higher risk to convert to cognitive disorders, such as dementia, in the future. Moreover, some novel preventative memory intervention techniques may be found most helpful for people who are in the Low MTL-High FL or High MTL-Low FL group. Of note, the current findings were based on small sample sizes and the frontal lobe composite scores were not normally distributed in our sample. This might indicate an unrepresentative sample, suggesting caution in interpreting the current results. A larger sample size study is warranted in order to confirm the findings reported in the present study.

Study Limitations

One key limitation to this study is the sample size. Challenges in recruiting individuals with MCI, due to population prevalence in the local community and to the difficulty identifying them prior to the neuropsychological assessment and interview phase, resulted in a relatively small sample size for this group as well as a lack of ethnically diverse participants. In addition, the individuals who participated in the current study were healthy, highly educated older adults. In fact, the average education level of the older adults sample was higher than that of the younger control group. The high education level may serve as a protective factor, producing cognitive reserve that would mask the underlying pathological aging process in some individuals. Overall, the small sample size of the MCI group may result in reduced power, since in some analyses trends were observed that did not reach significance. The sample size issue also appeared in the four-group analyses using Glisky's factor approach.

Additionally, the MCI group had a significantly older mean age compared to the healthy old control group, which was consistent with previous literatures that suggested that the incidence of MCI increased significantly with age. To deal with the unmatched age issue, we choose to conduct analyses on healthy control that were older than 65 years.

Several studies have pointed out the issue of unreliable or unstable diagnosis of MCI, particularly for a cross-sectional study. We intended to minimize the possibility of misclassifying normal individuals as MCI or vice versa by including a large set of clinical neuropsychological battery data which included not only multiple cognitive domains (e.g., language, executive function, and visuospatial function) and mood measures, but also contained multiple memory measures in conjunction with strict exclusion criteria. Moreover, we adapted a consensus conference approach, consisting of a larger number of professionals, to classify individuals as normal or MCI. By doing this, we hoped to achieve a more stable and reliable group classification.

Another limitation of the study is the length of the study protocol. The study required at least two sessions to complete the Neuropsychological assessment and the experimental tasks. The time required to complete the two sessions ranged between six to nine hours. Some participants, particularly those with poor memory, tended to need longer time to finish the tests, which might have further introduced a confounding factor of cognitive fatigue. Additionally, those individuals with poorer memory often felt frustrated during the testing sessions. Some of the participants were not able to finish all required tasks due to the reasons mentioned above. Although we do not have any data to indicate whether the frustration they experience may have directly affected test results, the HO and the MCI group did not differ significantly on measures of depression or state anxiety collected during testing.

While attempting to provide tasks that were neither too difficult for the impaired participants, nor too easy for the cognitively intact individuals, including the younger participants, through several pilots during the task development stage, some of the tests still presented substantial difficulty for the participants, particularly the older ones. For example, even with the significant group effect, the face recency test seemed to be challenging for the two older groups, in which the MCI demonstrated almost a chance level of performance. The difficulty of the tasks also contributed to the fact that the HO and the MCI groups demonstrated different levels of item memory even with multiple exposures during the study phase

Future Direction

The findings of the current study have provided additional insight into the nature of associative memory in normal aging and individuals with mild cognitive impairment. In the short-term, a replication of the current study with a large sample size and different subtypes of mild cognitive impairment or groups based on their frontal lobe and medial temporal lobe function levels will help to examine the stability of the findings reported in the current study. A longitudinal follow-up of the HO and MCI participants might be able to provide a unique opportunity to investigate the diagnostic and predictive utility of the evaluation of associative memory on eventual conversion to dementia. A post-hoc analysis of MCI individuals who convert to dementia as well as to individuals who show no degenerative decline in cognitive functioning in the future would be valuable and may also result in increased opportunities for intervention. Data from both structural and functional imaging in addition to the behavioral data may provide insights regarding the involvement of frontal lobe and medial temporal lobe structures in the associative memory.

Conclusions

In summary, in the current study, older adults with Amnestic MCI demonstrated a pattern of disproportionate impairment on the associative relative to item memory. Similar but smaller effects were found in our normal elderly sample. The impaired associative memory found in the MCI group applied to association between items of the same kind, association between different kinds of information, inferred relationships, as well as to novel and pre-existing (semantic) associations. These findings suggest that associative memory impairment in MCI transcends the boundary between episodic and semantic memory. Furthermore, our data also indicate the frontal lobe involvement in the associative memory process, although its role is more likely to be secondary to the medial temporal lobe.

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BIOGRAPHICAL SKETCH

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