LEARNING PROFILES IN HEALTHY AGING, LATE-LIFE DEPRESSION AND ALZHEIMER'S DISEASE: THE SERIAL POSITION EFFECT IN FREE RECALL.

by

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Abstract

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THE SERIAL POSITION EFFECT IN FREE RECALL.

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Differentiating between healthy older adults (HC), patients with late-life depression (LLD) and early Alzheimer's disease (AD) poses a significant clinical challenge. Learning characteristics of LLD have been previously demonstrated using *Regional* serial position scores using the California Verbal Learning Test. The current study explores whether the differential patterns of learning semantically unrelated words on the Rey Auditory Verbal Learning Test distinguishes these three groups. Measures of serial position reliably differentiated among the groups. As previously shown, the LLD group differed from the HC group in lower recall of items from the middle region. The AD group showed typical reliance on the recency region and, although this group was able to demonstrate learning within this region with rehearsal, over time they showed typical decay. Contribution of working memory, processing speed and executive functions to pattern of learning are discussed.

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Chapter I

Introduction

Memory consists of a number of related cognitive processes that allow for encoding, storage, and recall of information. Memory functions involve multiple neural structures and pathways that make a special contribution to memory processes. There are several components of memory. A principal division of memory into working and long-term memory is based on the duration for which information is retained. Working memory refers to a complex set of interacting processes that allow for the temporary storage and maintenance of information (Baddeley, 2001). Long-term memory involves the acquisition and retention of information over longer periods of time. Long-term memory is further divided into explicit, or declarative memory, and implicit, or non-declarative memory (Squire & Knowlton, 1995). Both long-term and working memory dysfunction may be linked to damage to different brain systems. For instance, there are important structures within the medial temporal lobe that are involved in the formation of explicit memory. They include the hippocampus, together with the dentate gyrus and subicular complex, as well as adjacent, structurally related areas such as entorhinal, perirhinal, and parahippocampal cortices (Squire & Zola-Morgan, 1991; Zola & Squire, 2000). Working memory, as well as attentional and organizational aspects of encoding and retrieval of memories, seems to be mediated by the prefrontal cortex (Delis & Lucas, 1996).

Memory disturbance is found in many neurologic diseases (Armstrong, Onishi, Robinson , D'Espositio, Thompson, Rostani, et al., 1996; Hodges, 2000; Tierney, Nores, Snow, Fisher, Zorzitto, & Reid, 1994), and investigation of clinical syndromes involving

memory loss gives an opportunity not only to examine different memory systems, but also to explain how memory-impaired patients learn. The purpose of this study is to examine memory functioning in normal aging, late-life depression and early Alzheimer's disease (AD). There are a number of reasons why these clinical groups are of interest. First, differentiation between healthy aging, late-life depression and early AD poses a significant clinical challenge. There are several areas that contribute to difficulty in distinguishing late-life depression from changes due to healthy aging or early AD. Patients with AD have difficulty making new memories (e.g., Hodges, 2000). However, memory problems in late-life depression are largely associated with deficits in working memory and overall processing speed (Butters, Whyte, Nebes, Begley, Dew, Mulsant, et al., 2004; Nebes, Butters, Mulsant, Pollock, Zmuda, Houck, et al., 2000.) Indeed, cognitive and behavioral deficits that accompany late-life depression may mimic deficits associated with dementia (e.g., Caine, 1986; Marcopulos, 1989). Further, memory deficits in late-life depression may be more subtle than those in younger depressed persons (e.g., Bieliauskas, 1993; Burt, Zembar & Niederehe (1995) making it difficult for depression to stand out as the predominant explanatory basis for the memory problems in the older population.

To investigate learning patterns, it is important to understand how encoding occurs. This can be examined in learning performance using a paradigm of free recall of word list (e.g., Mitrushina, Satz, Chervinsky, & D'Elia, 1991; Carlesimo, Sabbadini, Fadda, & Caltagirone, 1995; Tierney et al., 1994; Delis, Massman, Butters, Salomon, Cermak, & Kramer, 1991). Several free recall tests like the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958), California Verbal Learning Test (CVLT; Delis,

Kaplan, Kramer, & Ober, 2000), Hopkins Verbal Learning Test - Revised (Brandt & Benedict, 2000) and Buschke Selective Reminding Test (Buschke, 1973) are available. It has been observed from the beginning of the study of memory that the position of words presented in a list influences recall of the words; the words both at the beginning and the end have an advantage (primacy and recency effects). When recall is plotted as a function of serial position, better recall of words from the beginning (primacy) and end (recency) of the list leads to the emergence of the distinctive U shaped curve (e.g., Murdock, 1962), thus defining the serial position effect.

Ebbinghaus (1885) was the first to observe and describe the serial position phenomenon and explain it both in terms of a chaining hypothesis as well as backward and forward remote associations. Chaining assumes that multiple series of pair-wise associations are formed between consecutive items on the list (see also Madigan & O'Hara, 1992; Li & Lewandowsky, 1993). Also, according to Ebbinghaus (1885), items on the list form direct associations with adjacent items, while remote associations form between non-adjacent items; practice strengthens these associations. Ebbinghous (1885) proposed that the accumulation of backward and forward remote associations in the middle of a list produce interference effects accounting for greater difficulty in remembering items in that region.

Since the Ebbinghaus' account of the phenomenon, the serial position effect has been reliably observed in numerous studies in different experimental (explicit and implicit memory domains: e.g., Gershberg & Shimamura, 1994; serial learning: e.g., Crowder & Green 2000; cued recall: e.g., Gershberg & Shimamura, 1994; aging: Mitrushina, et al., 1991) and clinical situations (e.g. depression: Gainotti & Marra, 1994;

schizophrenia: Elvevag, Weinberger, & Goldberg, 2001; focal brain damage: Hermann, Seidenberg, Wyler, Davies, Christensen, Moran, et al., 1996; Eslinger & Grattan, 1994; Alzheimer's disease: e.g., Burkart, Heun, Benkert, 1998; Carlesimo et al., 1995; Grafman, Weingartner, Lawlor, Mellow, Thompsen-Putnam & Sunderland, 1990; Parkinson's disease: e.g., Breen, 1993; Tierney et al., 1994; Huntington's disease: e.g., Delis et al., 1991). One of the most frequently cited explanations of the serial position phenomenon is offered by dual-storage models. According to these models, the serial position effect is a result of information being recalled from two different memory systems; the primacy and middle regions reflect functioning of a long-term memory storage, while the recency region reflects the operation of immediate or working memory (Atkinson & Shiffrin, 1968; Glanzer, 1971; Raaijmakers & Shiffrin, 1981). Thus, recall of information as a function of serial position can provide insight into the operation of two different memory systems. Serial position data can then also be implemented as a clinical tool of memory assessment.

The current study examines the performance on the free recall of a word list test. It utilizes the serial position phenomenon as a tool to compare memory functioning in patients with AD, late-life depression, and healthy older adults. This study uses the dual-storage model as a premise and assumes that information from working memory transfers to long-term memory storage. Clinical populations such as depressed and AD individuals represent two instances of memory deficits where impairment may involve disruption of transfer of information from working to long-term storage. These clinical populations therefore provide insight into the dual-storage model. The self-controlled, list-learning task puts significant demand on numerous aspects of cognition (e.g., working memory,

speed of processing, ability to focus) that are significantly affected by the presence of disease in older adults (e.g., Butters et al., 2004; Nebes et al., 2000). As fatigue level and inability to tolerate the lengthy testing process (e.g., motivation) can increase with age or presence of disease, there is a need to employ a short, efficient and informative way to evaluate memory in older adults. Examination of recall as a function of serial position provides an efficient way to examine patterns of learning and recall allowing for investigation of working and long-term memory systems.

The first section of this introduction will briefly describe the characteristics of the test of free recall. The dual-storage theory will be presented next as a theoretical framework of the serial position effect, with special emphasis on the role of working memory. The third section will briefly present neurological and cognitive changes related to aging, late-life depression and AD that may significantly influence memory performance and the serial position effect. The following section will present the review of the specific findings on the serial position effect in healthy aging, late-life depression, and AD. A list of specific hypotheses will conclude the introduction.

Chapter II

Theoretical Background

The free recall paradigm

Early free recall paradigm used a one-trial task (Murdock, 1962). In this paradigm participants were presented with a list of items (words, pictures, actions, etc.) and asked to recall them in any order, unaided by any cues. Without instructing the subject to remember the order in which the words were presented (serial-recall), or providing the subjects with additional prompts to recall the words (cued recall), this paradigm has been found to show a recall advantage for items at the beginning and at the end of the list, hence yielding the characteristic U shaped serial position curve.

The prominent findings in Murdock's (1962) free recall study were the strong recency effect, slightly lesser primacy effect, and a lower recall of items between the two peaks. The slopes of the curve that represented the primacy and recency regions were quite different; the primacy effect was characterized by a steep slope while the recency effect formed an "S" curve. The order of items recalled in free recall also tends to follow a common pattern: items from the end of the list are usually reported first, followed by items from the beginning of the list, and lastly the middle items are recalled (Glanzer, 1971; Chapman, Pellegrino, & Battig, 1974; Wright, 1982).

Since Murdock (1962), the serial position effect has been investigated in numerous studies (e.g., Glanzer & Schwartz, 1971; Postman & Philips, 1965; Watkins & Peynircioglu, 1983; Tan &Ward, 2000). One of the factors that may influence the pattern of recall in a free recall test is the composition of the list. For instance, semantically related words lead to overall increased recall, especially from the primacy positions

(Glanzer & Schwartz, 1971). One possible explanation of this enhanced recall is that the common semantic category may provide efficient organizational strategy, thus leading to better overall recall. In addition, as material can be mapped into existing categories, long-term memory benefits most from the organization of information affecting the recall from the primacy region. The semantic categories were introduced in the development of some tests of free recall, such as the California Verbal Learning Test (CVLT; Delis et al., 2000; Delis, Kramer, Kaplan, & Ober, 1987) containing 16 words from four different semantic categories. Some studies investigated serial position effect in CVLT (e.g., Delis et al. 1991; Foldi, Brickman, Schaefer, & Knutelska, 2003; Hill, Stoudemire, Morris, Martino-Saltzman, & Markwalter, 1993). These studies, however, leave open the possibility that semantic categorization confounds the true serial position effect. Therefore the current study uses the RAVLT (Rey, 1958), a list of 15 unrelated words that eliminates the possible influence of the semantic organization on the pattern of recall. It will allow for comparison of differences in recall patterns of the organized and unorganized lists of words.

Theoretical explanation of serial position effect

Dual-storage model – Search of Associative Memory model

As stated, the dual-storage model is accepted as a theoretical framework in the current study. Dual-storage models (Atkinson & Shiffrin, 1968; Baddeley, 2003; Glanzer, 1971; Raaijmakers & Shiffrin, 1981) assume that the serial position effect is produced by the output from two separate memory stores, a short-term storage or working memory and a more permanent long-term memory storage. These models associate the primacy effect with long-term storage operations and the recency effect with the short or working

memory operations. Working memory, which is limited and smaller, serves to hold and manipulate information that is being used at a given moment. The long-term memory store refers to a larger, organized storage, where information can be held for longer periods and, given that it had been adequately encoded, material can be retrieved for future use (Atkinson & Shiffrin, 1968; Glanzer, 1971; Raaijmakers & Shiffrin, 1981).

One example of a dual-storage model is the Search of Associative Memory model (SAM: Gillund & Shiffrin, 1984; Raaijmakers & Shiffrin, 1981), which explains the phenomenon of serial position effect in the following way. Initially, each item is placed into working memory (referred to as short-term storage in SAM) where it undergoes a process of rehearsal in the rehearsal buffer. As new items are placed into the working memory storage, some preceding items can continue to be rehearsed. If rehearsal time is sufficient, the items are transferred to long-term storage. Long-term storage enables an item to be associated with its context at the time of rehearsal and recall (e.g., environmental characteristics, physical sensations, thoughts, and emotional feelings), as well as any pre-existing semantic associations. However, as more items are added to the rehearsal buffer, they receive less rehearsal time, and therefore are less likely to be transferred to long-term storage. When asked to recall as many words as possible in any order, participants tend to give last items first, as these items are residing in the limited capacity, brief working memory and are readily available, although quickly forgotten. The items from the beginning of the list that benefited from the rehearsal and were transferred to a more permanent, long-term storage, are likely to be recalled next. The items from the middle region of the list, which have less chance to be stored in long-term memory and are no longer present in the working memory as the recency items have

replaced them, are less likely to be recalled than the items at either extreme end of the list (Raaijmakers & Shiffrin, 1981). The amount of rehearsal that a given item receives in the free recall paradigm is strongly related to the probability of recalling that item (Raymond, 1969). This rule does not apply to the items at the end of the list since, regardless of receiving minimal rehearsal time (or none at all), they are still very likely to be recalled (Gorfein, Arbak, Philips & Squillace, 1976). According to the model, items in the primacy region should benefit the most from multiple list presentations. In the current study, a list composed of the same words was repeated over five trials. Thus, if the assumptions of the SAM are correct, the predictions should be as follows. First, the number of items recalled on the fifth trial should show improvement as compared to the first trial. Second, items from the primacy, and subsequently from the middle region are the most likely to improve.

Concepts from the SAM model of short-term memory buffer and storage correspond to the phonological loop of the working memory model proposed by Baddeley and Hitch (1974), and later expanded by Baddeley (2001). SAM's rehearsal buffer mimics the articulatory rehearsal of the phonological loop where the rehearsal process of newly presented material takes place. In Baddeley's (2001) model, after being rehearsed the material is moved to the phonological storage where it can be stored for few seconds. Repeated rehearsal refreshes the memory trace and allows the material to be held in storage for a longer period of time. Items receiving adequate rehearsal eventually get transferred to the more permanent, long-term memory storage.

In summary, dual-storage models assume that end items (recency) are recalled directly from working memory while initial (primacy) and, possibly middle items, are

recalled for long-term memory storage. Deficits that are present in late-life depression and AD, such as reduced speed of processing (e.g., Nathan, Wilkinson, Stammers, & Low, 2001; Nebes et al., 2000), accelerated rate of forgetting (e.g., Carlesimo et al., 1995; Gainotti & Marra, 1996; Kopelman, 1985), and executive functions deficits (e.g., Baddeley, Bressi, Della Salla, Logie, & Spinnler, 1991; Channon & Green, 1999; Hashimoto et al., 2004), can potentially interfere with the amount of information learned as well as the pattern of recall. The following section will describe the relevant working memory components in more detail.

Working memory – Baddeley's model

The efficiency of working memory plays an essential role in the ability to hold and use information for a short period of time, as well as in the ability to form longer-lasting memories. In 1974, Baddeley and Hitch proposed a working memory model that divided short-term memory into three components to account for a wide range of complex cognitive activities (see also Baddeley, 2001, 2003). The three components include the verbal-acoustic storage system, or the phonological loop,, which processes auditory and verbal material, the visuospatial sketchpad responsible for processing of visual material, and the limited capacity attention system, or the central executive, that controls behavior of other two subsystems. The later model (Baddeley, 2001) also included a fourth component, the episodic buffer, which allows for integration, maintenance, and manipulation of information from working memory subsystems and from the long-term memory. The three components of the working memory model, the phonological loop, the central executive and the episodic buffer, play an essential role in the word-list learning, and are reviewed in more detail in the following sections.

The phonological loop that handles the initial processing of auditory and verbal material is further subdivided into two subcomponents: the phonological storage and articulatory rehearsal systems. The phonological storage system is thought to be responsible for holding memory traces a few seconds. The articulatory rehearsal system, in turn, serves the function of subvocal rehearsal of material that is being held in the phonological storage system. The articulatory rehearsal component of the phonological loop is responsible for the process of rehearsing information in order to keep it in the phonological storage and/or eventually transferring it to long-term storage. The material held in the phonological storage, unless refreshed by the rehearsal process, decays from memory after about two seconds. This storage system is assumed to be using phonological coding (Baddeley, 1966; Baddeley & Hitch, 1974, Baddeley & Wilson, 1985; Colle & Welsh, 1976; Kitsch & Buschke, 1969).

The operation of the phonological loop is likely to be influenced by processing speed and rate of forgetting, factors significantly affected by Alzheimer disease or depression in older adults. Speed plays an essential role in the rehearsal process. The speed of rehearsal partly determines the amount of information that can be held in working memory (Baddeley, 1996). In turn, the rate of forgetting is likely to affect the efficiency of the articulatory rehearsal and phonological storage systems.

The central executive subsystem is assumed to be responsible for attentional control of processes of working memory and to play an essential role in focusing, dividing attention and switching attention (Allport, Styles, & Hsieh, 1994; Baddeley, 1996). The central executive oversees and directs simultaneous operations of other systems of working memory. Spinnler, Della Sala, Bandera, & Baddeley (1988), suggest

that the learning of words in the middle region of the list depends on an activity of the central executive system. They hypothesize that over consecutive learning trials, participants selectively rehearse words that have not been encoded on the previous trials while inhibiting the words already learned. This selective attention is controlled by the central executive. Efficient functioning of the central executive would ensure learning of all the words during repeated presentation of the same word list. Spinnler et al. (1988) hypothesized that the deficient central executive would have the most detrimental effect on the words in the middle region of the list. Foldi et al. (2003) demonstrated that items from the middle region were most vulnerable in populations with impaired attentional functioning, namely depression. Middle region items in the depressed older participants correlated with measures of attention, which were impaired in this group. In controls whose attention was unimpaired however, similar correlations were not found. Hashimoto et al. (2004) attributed the recall deficiency of words in the middle region in mild AD to a functional disconnection in the network supporting the central executive, namely a temporo-parietal association. Deficits in functioning of the central executive were found in AD (e.g., Baddeley et al., 1991) and late-life depression (e.g., Nebes et al., 2001).

The link between the other working memory subsystems and long-term memory that was initially thought to be handled by the central executive (Baddeley, 1996) was eventually attributed to a new subsystem, the episodic buffer (Baddeley, 2001). This system is assumed to be able to link the phonological loop and the visuospatial sketchpad with the visual and verbal long-term memory. The episodic buffer allows for access of preexisting semantic and episodic information to aid the processing of information at

hand. This system is thought to have limited capacity and to depend heavily on the central executive, but unlike the central executive that is responsible for attentional control, the episodic buffer is concerned with storage of information. Baddeley (2001) proposed that retrieval from the episodic buffer requires conscious awareness.

Baddeley (1966a) also proposed that, when unrelated words are initially placed in the phonological loop, the meaning of the word is unimportant; however with multiple presentations the meaning becomes crucial to form a memory trace (Baddeley, 1966b). Baddeley also stated that, in contrast to the single presentation of short lists that is handled by short-term memory, multiple presentations of longer lists reflect the operation of long-term memory (Baddeley, 2003). Since long-term memory depends on semantic coding (e.g., Glanzer and Schwartz, 1971), meaning of the words can aid the learning process.

Chapter III

Neurological and neurocognitive changes associated with age and disease that may influence serial position effect

All participants in the current study, including both patient groups and the healthy controls, were older adults. Thus, age related structural, functional, and cognitive changes needed to be accounted for. In particular, structural and functional changes exert an effect on cognitive functioning that could lead to reduced ability to acquire new information and, possibly, differential or altered pattern of learning and memory.

Aspects of cognitive functioning affected by age, late-life depression, and AD, such as processing resources including working memory and speed of processing, the ability to use efficient learning and recall strategies, and the rate of forgetting, affect recall performance and what happens to recall from different portions of the serial position curve. For instance, Crawford and Stankov (1983) suggested that cognitive speed may be related more to primacy than to recency effects in free recall. The speed of cognitive processing could affect the efficiency of the rehearsal process carried on by the phonological loop. This in turn would affect the overall rate of learning and particularly recall from the primacy portion of the list as predicted by the dual-storage model. In line with the above expectations, Murphy, Craik, Li, & Schneider (2000) found that the speed of processing was associated with poorer recall of the first three (primacy) but not the last two (recency) item positions. If the strategy of tackling a task changes with age or as a function of disease, the ability to contextually or semantically organize information has the potential to affect memory performance as well as affect the pattern of serial position recall, particularly items in the primacy region (e.g., Glanzer & Schwartz 1971;Watkins

& Peynircioglu, 1983). Lastly, the rate of forgetting can also affect the recall as a function of the serial position of items on a word list. With more rapid rates of forgetting, items early in the list are vulnerable. The longer the list, the greater the chance of forgetting items from the beginning of the list. Hence, there are differences in recall pattern as a function of list length (e.g., Murdock, 1962; Postman & Philips, 1965; Tan &Ward, 2000).

The following three sections will describe age, late-life depression, and AD related neurological and cognitive changes (efficiency of working memory, processing speed, ability to utilize organizational strategies, and rate of forgetting) that may have a significant effect on performance on controlled memory tasks like free recall of a list and that also could differentially affect the serial position curve.

Healthy older adults

The efficiency of long-term and working memory depends on proper functioning of brain structures that underlie their operations. For instance, age related changes of the frontal systems could influence the serial position effect. Similarly, changes of the "bottleneck structures" (Markowitsch, 1995), specifically the hippocampal complex and diencephalon, may also influence the serial position effect. There is evidence of significant brain atrophy and neuronal loss in the hippocampal area in older adults (Albert, 1993; Terry, DeTeresa, & Hansen, 1987; Hyman & Gómez-Isla, 1998; Stafford, Albert, Naeser, Sandor, & Garvey, 1988). A substantial neuronal loss was found in subcortical areas supplying neurotransmitters important for memory function (Albert, 1998). Age related functional alterations in older adult human brain are associated with the shifts in cerebral metabolism or rewiring of the brain circuitry (Cabeza, McIntosh,

Tulving, Nyberg, & Grady, 1997; DeLeon et al., 1987; Moeller et al, 1996). It appears that older adults may be relocating processing resources, possibly to compensate for functional decline in other areas (Cabeza et al., 1997;Grady et al., 1994; Hazlett et al. 1998).

Age-related neurological changes affect a number of areas of cognitive functioning of older adults. For instance, Huppert and Kopelman (1989) found increased rate of forgetting as a function of age. Also, performance on demanding tasks requiring extensive attentional resources, have been found to decline with age (Anderson, Bothell, Liebier, & Matessa, 1998). It was also found that the reduced working storage capacity significantly accounts for the overall reduced performance of the older adults (e.g., Anderson et al., 1998; Foos, 1989). Another area affected by aging is cognitive slowing. Salthouse, Toth, Hancock, & Woodard (1997) found that reduction in cognitive speed accounts for most of memory impairment in older adults. Further, Anderson and Craik (2000) proposed that reduced attentional resources and cognitive slowing lead to decrement in overall cognitive control. There also seems to be a decline in source or context memory with age (Janowsky, Shimamura, & Squire, 1989; McIntire & Craik, 1987). Kliegl and Lindenberger (1993) found that older adults were less likely than younger adults to generate memory traces with contextual information, and as a result formed shorter lasting memory trace than the younger subjects. Therefore, speed of processing, allocation of attention and altered neurological mechanisms used for learning may all be instrumental in the pattern of serial position effect in normal aging.

Late-life depression

Late-life depression is associated with a number of cognitive and brain abnormalities. In terms of brain changes, depressed persons tend to show increased size of ventricles (e.g., Beats, Sahakian, & Levy, 1996; Kumar, Miller, Ewbank, et al., 1997), decreased density of the brain tissue (e.g., Pearlson, Robins, & Burns, 1991), and white matter changes (Baldwin & O'Brien, 2002; Firbank, Lloyd, Ferrier, & O'Brien, 2004; Kramer-Ginsberg et al., 1999). There are also specific reductions in frontal lobe volume associated with depression (Coffey, Wilkinson, Weiner et al., 1993). Simpson, Baldwin, Burns, & Jackson (2001) showed that reduced frontal and parietal volumes were associated with impaired immediate working memory and reduced temporal lobe volume with overall working memory impairment.

These neurologic structural changes appear to influence cognitive functioning in depression. Depression is often characterized by slowed mental processing, attentional deficits, and memory problems (Caine, 1986; Kramer-Ginsberg et al., 1999; Nebes, et al., 2000; Nebes et al., 2001). Nebes et al. (2000) showed that reduced attentional resources in late-life depression significantly accounted for neuropsychological deficits exhibited by depressed subjects. The nature of memory deficits in a late-life depression was investigated by Burt, Zembar & Niederehe (1995) in large meta-analysis. They found that older depressed adults exhibited memory deficits, however the association between memory and depression was significantly stronger in the younger than the older population. In other words, in regard to memory deficits, the difference between the healthy and depressed older adults is less obvious than the difference between the younger healthy and depressed individuals. In fact, although memory complaint is one of

the most distinguishable features of late-life depression, testing often shows memory to be within the limits of the healthy older population (e.g., Kaszniak, 1987; Williams, Little, Scates, & Blockman, 1987).

Depression is also associated with deficits in ability to use efficient learning and recall strategies (e.g., Channon & Green, 1999). Such impairments may reflect either inability to sustain attention long enough to use such strategies, or lack of motivation to use strategies (Cohen, Weingartner, Smallberg, Pickar, & Murphy, 1982; Tariot & Weingartner, 1986). In addition, depressed older adults are generally not able to take advantage of the semantic organization of material (Channon, Baker, & Robertson, 1993a; Weingartner,1984). Deficits in efficient use of learning strategies can be associated with impairment of the central executive of the working memory system (e.g., Channon, 1996; Channon, Baker, & Robertson, 1993b).

While the above deficits differentiate healthy individuals from depressed individuals, the rate of forgetting in late-life depression appears to be comparable to that of healthy older adults. Burt, Zembar, and Niederehe (1995) performed a meta-analysis investigating the relation of depression to memory problems. Most studies showed that depressed persons, although encoding occurred at a reduced rate, tended to remember what they had encoded comparably to healthy older adults.

Depressive symptoms may exert noteworthy effects even in non-clinically depressed older individuals. Bäckman, Hill, and Forsell (1996) investigated the influence of depressive symptomatology on memory in nondepressed older adults. They showed that symptoms, such as difficulty concentrating and lack of interest that affect ability to focus and sustain attention, significantly influenced performance on memory tests.

Additionally, Elliott, Sahakian, McKay, Herrod, Robins, & Paykel (1996) showed that patients with depression have difficulty sustaining motivation or tend to perceive failure when unable to keep up with the task. These findings indicate that attentional and motivational factors may significantly contribute to deficits associated with late-life depression.

Alzheimer's disease

The structural differences between AD and healthy aging are many (e.g., Moulin, James, Freeman, Jones, 2004; Lekeu et al., 2003). They include the number of abnormal formations of neurofibrillary tangles and neuritic plaques and marked neuronal loss in the hippocampal formation (Arriagada, Marzloff & Hyman,1992; Braak & Braak, 1995; Fox, Warrington, Hartikainen, Kennedy, Stevens & Rossor, 1992; Gómez-Isla, Hollister, West, Mui, Growdon & Petersen, 1997; Gómez-Isla, Price, McKeel, Morris, Growdon, & Hyman, 1996; Hyman, Von Hoesen, Damasio, & Barnes, 1985; Hyman, Von Hoesen, Kromer & Damasio 1986). Hippocampal formation, involved in formation and retrieval of explicit memory (e.g, Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996; Schacter, Alpert, Savage, Rauch, & Albert, 1996; Schacter, Savage, Alpert, Rauch, & Albert, 1996), is inevitably responsible for some aspects of the serial position effect. The hippocampal changes account for early deficits in acquisition and retention of new information in patients with AD (e.g., Kramer et al., 2004; De Toledo-Morrell et al., 2000).

Impairment in the ability to learn new information is a consistent finding in AD with memory for recent events and experiences affected in the initial stages of the disease. In contrast, access to already learned material tends to be preserved (Green,

Hodges, & Baddeley, 1995; Kopelman, Wilson, & Baddeley, 1989). Several studies showed that impaired free recall is the most consistent deficit in individuals who later develop AD (Bäckman, Small, & Fratiglioni, 2001; Grober & Kawas, 1997; Tierney et al., 1996). Woodard, Dunlosky, & Salthouse (1999) found significantly impaired encoding and consolidation across multiple trials of list learning in patients with AD. Also, Grafman et al. (1990) showed that patients with AD, unlike the healthy controls, were not able to benefit from multiple presentations of the same words in a single list. Although the above findings indicate that patients with AD are not able to benefit from the multiple repetition of the same material, the intention of the current study was to determine whether any portion of the list is amenable to learning.

Patients with AD demonstrate accelerated decline from immediate to delayed recall (e.g., Kopelman, 1985). Hodges (2000) proposed that this finding could be explained by usually preserved working memory that mediates immediate but not delayed recall. In other words, whenever recall relies just on working memory, as does recall of items from the recency portion of a list on immediate recall, there is relative sparing in the early stages of the disease. In contrast, the material that needs to be transferred from working to long-term memory, primacy items on immediate recall and all items on delayed recall, would be forgotten. This is in line with findings that patients with AD typically tend to show normal performance on simple tests of working memory such as digit span (e.g., Baddeley et al., 1991; Gliko, Espe-Pfeifer, Selden, Escalona, & Golden, 2000). In contrast, functioning of the central executive component of working memory, although it is controversial whether it is spared at the very early stages or not

(Green, Hodges, & Baddeley, 1995, Perry & Hodges, 2003), declines as the disease progresses (Baddeley, Bressi, Della Sala, Logie, Spinnler, 1991).

Chapter IV

Serial position profiles

There are differences in the overall amount of information recalled, as well as the pattern of recall as a function of item position in a list, in healthy older adults and those suffering from depression or AD. Free recall put a substantial demand on attentional processes and requires speedy processing. Decline in the efficiency of attentional systems and storage capacity, reduced speed of processing, or damage to anatomical structures mediating memory, may affect one's ability to acquire new information (Anderson & Craik, 2000; Balota, Dolan, and Duchek, 2000) and, potentially, have differential influence on the serial position effect. The following sections present the serial position profiles of the three groups.

Healthy older adults

The serial position effect changes with age by shifting the whole curve downwards. This reflects reduced ability to acquire information with the preserved pattern of learning (e.g., Carlesimo et al., 1995; Carlesimo, Fadda, Sabbadini, & Caltagirone, 1996; Mitrushina et al., 1991; Petersen, Smith, Kokmen, Irving, & Tangalos, 1992; Wright, 1982). This indicates that healthy older adults tend to learn in similar fashion to their younger counterparts, but acquire less material at all serial positions (e.g., Carlesimo et al., 1995; Carlesimo et al., 1996; Mitrushina et al., 1991; Petersen et al. 1992; Wright, 1982). Mitrushina et al. (1991), comparing different age groups on RAVLT, found that although the older adults recalled overall fewer words, the shape of the serial position curve was similar in all age groups. Reduced recall from all serial positions points to both less efficient long-term (reflected in reduced recall from primacy

and middle portions), as well as working memory (reflected in reduced recall from recency portion) in older as compared to younger adults.

It appears that older adults tend to show different patterns of forgetting as a function of serial position than younger counterparts during the process of multiple trial learning. Carlesimo et al. (1995) showed that there is a comparable forgetting rate among young and old adults from the primacy and middle portions of a list, however, older adults forgot almost three times more from the recency portion than other portions of the serial position curve. The authors concluded that young and old adults employ different memory mechanisms to encode information during multi-trial list learning. While younger individuals progressively transfer information to long-term memory the elderly continue to rely on short-term memory to recall items from the recency positions.

Late-life depression

Generally, late-life depression is associated with a U shaped serial position curve. Gibson (1981) compared depressed older adults with healthy age-matched controls and patients with dementia on list-learning tasks. Participants recalled seven different 10-item word lists on a single trial and the recall performance was combined. Depressed patients showed a U-shaped serial position curve, with overall lower recall of items from all list regions than healthy age matched controls. Gainotti and Marra (1994) contrasted AD, depressed patients, and healthy controls on the RAVLT (Rey, 1958). On cumulative recall of the RAVLT, the depressed patients recalled significantly fewer items than age-matched controls, but showed parallel and lower U-shaped learning curves, corroborating Gibson's (1981) findings. Massman and colleagues (Massman, Delis, Butters, Dupont, & Gillin, 1992) also found that depressed older patients, although recalling overall less

information, did not differ from healthy controls on recall from any region of the serial position. These findings suggest a parallel profile in late-life depression and healthy aging in terms of serial position effect with the difference only in the amount of information learned.

There are findings however ,suggesting that older depressed adults may differ from healthy cohorts in the pattern of learning and recall as function of serial position. Bemelmans, Goekoop, & van Kempen (1996), using lists of different lengths (6, 9, or 15 words), observed that depressed patients recalled more items from particular positions of the list (i.e. positions 3 or 4), which were deemed as part of the 'primacy' region of each list. Also in line with above predictions, Foldi et al. (2003) using newly designed regional scores showed that, while depressed patients recalled comparable amounts of information as healthy controls in the beginning (primacy) and end (recency) of the list, they recalled less information from the middle portion.

The factors that may provide an explanation for above findings are reduced processing speed (e.g., Lockwood, Alexopoulos, & Gorp, 2003; Vinkers, Gussekloo, Stek, Westendorp, van der Mast, 2004) and motivation (e.g., Elliott, Sahakian, McKay, Herrod, Robbins, & Paykel, 1996), which are among the major deficits associated with depression. In addition to affecting overall recall, these factors might influence recall from the specific area of a list. Also, since depressed patients seem to focus their attention best at the beginning of the task and their motivation tends to decline as time progresses, the middle portion of the list would more likely be affected than the primacy portion. However as noted in the earlier section, processing speed may also affect the rate of rehearsal of items in articulatory rehearsal buffer that is required to maintain these

items in phonological storage and subsequently transfer them to long-term memory. On multiple trial learning tests, participants have a chance to acquire more information with every list exposure. If processing speed plays a significant role in the ability to maintain items in working memory and transfer them to long-term memory, one would expect learning to be adversely affected in a group that exhibits slower speed of processing. More specifically, one would expect the primacy and middle portions of the list to be especially affected, as they presumably reflect the operation of the more permanent memory storage (e.g., Raaijmakers & Shiffrin, 1981). In summary, late-life depression is associated with reduced overall learning, with some indications of better recall of initial (primacy) items, and lesser recall of middle items of the list than healthy older adults that may be in part due to reduced processing speed and/or motivation.

Alzheimer's disease

With specific findings on the serial position effect, AD is associated with significantly reduced primacy and preserved recency effects (e.g., Bäckman & Small, 1998; Bigler, Rosa, Schultz, Hall,& Harris,1989; Bayley, et. al., 2000; Carlesimo et al., 1995; Capitani, Della Sala, Logie & Spinnler, 1992; Gainotti, Marra, Villa, Parlato, & Chiarotti, 1998; Gainotti & Marra, 1994; Gibson, 1981; Pepin & Eslinger, 1989; Tierney et al., 1994). Carlesimo et al. (1995) found that the rate of forgetting from the last portion of the list differentiated healthy control participants from the memory disordered patients, with disordered subjects forgetting significantly faster. Further, they also showed that patients with AD rely on the short-term memory for the recall of the terminal items in multi-trial learning to a greater extent than healthy older adults.

The pattern of learning and forgetting in AD may be at least partially affected by the amount of information presented. Bemelmans and Goekoop (1991), using multiple trials recall, found that patients with AD were able to learn initial items (primacy) when asked to remember short lists (6-9 words). When presented with the longer list (15 items), however, they recalled only terminal items (recency). The authors suggested that the findings indicate that ADs have reduced capacity to handle increasing amounts of information. Also, Carlesimo et al. (1996) found that when a small number (2-3) of terminal items was used as a recency measure, there was no difference in performance between healthy controls and AD patients. In contrast, when more words were considered, healthy subjects performed significantly better. Carlesimo et al. (1996) proposed that accelerated decay of the memory trace for items presented earlier in the list in demented patients is the reason for this difference.

Difficulties with remembering primacy items seem to be already evident in the preclinical stage of AD. Bäckman and Small (1998) showed that preclinical patients with AD, similarly to healthy counterparts, showed an ability to benefit from cognitive support such as increased study time, organization of material, and cuing at retrieval. Patients with AD were not able to take advantage of any of the above aspects of cognitive support to aid their memory. Inability to benefit from the organizability of the material is in line with predictions of the dual-storage model of the deficits associated with AD. This view assumes that items that are presented first (primacy region) are encoded into the long-term storage using semantic cues that are linked to the item in the process of rehearsal. Consequently, this would predict decline in the recall from the primacy portion with

preserved recency recall, as the last items are recalled from the rehearsal buffer that requires only a phonemic coding (Baddeley & Hitch, 1974; Baddeley, 2001).

The current study aims to further delineate characteristics of recall patterns as a function of the serial position in later-life depression and in AD, as compared to healthy older adults. As memory is differentially affected by the presence of depression and AD in older adults, the prediction would be that the pattern of recall as a function of the serial position would vary in these clinical groups. This study allows for the investigation of functioning of two separate memory systems, working and long-term memory, as delineated by the dual-storage models. This study examines overall memory ability as measured by the total amount of learned material, but it also investigates patterns of learning as measured by the recall in primacy, middle, and recency regions of the list. The amount of information remembered in each region of the list after a short-term delay will also be investigated. The current study is particularly interested in the identification of cognitive components of the dual-storage model that determine the ability to transfer information from working to long-term memory. Also, the effect of semantic organizability of information on serial position effect is investigated; the results of the current study using RAVLT a list of semantically unrelated words are compared to the findings of Foldi et al. (2003), that used CVLT a list of words that can be semantically organized.

Chapter V

Hypotheses

1. Learning over five trials

To test how much of the information was transferred from the working to the long-term memory, the overall learning as well as relative performance in primacy, middle and recency regions on the RAVLT was investigated. Specific issues were addressed.

a) Overall learning – total recall over five trials:

It is predicted that the healthy control (HC) group will perform significantly better than the Late-Life Depression (LLD) and AD group. The LLD group is also expected to show better performance than the AD group.

b) Serial position effect measures:

It is hypothesized that the HC and LLD groups will show better recall in the primacy and recency regions than in the middle portion of the list. Also, the LLD group will show lower performance in the middle region than the HC group (Foldi et al, 2003). The AD group will show better recall in the recency region than any other portion of the list. Also, the LLD will show similar performance in the recency region to the AD (Foldi et al., 2003).

Groups are expected to show similar serial position patterns on the RAVLT as on CVLT (Foldi et al., 2003); both depression and AD are unlikely to take advantage of semantic organization of material (e.g., depression: Fossati, Guillaume, Ergis & Allilaire, 2003; Bäckman & Small, 1998, AD: Barr & Brandt, 1996; Herlitz & Viitanen, 1991).

2) Short-Delay recall

The aim is to test whether the groups vary in the information retained after a delay. More specifically, it is questioned whether the information will be transferred to the long-term memory and held over time, and whether the information in working memory is lost. The prediction on the Short Delay Free Recall is that the primacy and middle region items are more likely to receive repeated rehearsals over multiple trials and are more likely than the recency items to be transferred to the memory storage, and more readily available on the Short Delay Free Recall. Also, the items in the primacy region are likely to receive more rehearsal over the learning trials than the middle region items. Therefore, they are more likely to be remembered than the items in the middle region. In contrast, as recency items are thought to largely reside in the working memory buffer they are less likely to be transferred into the long-term memory storage. With multiple exposures, some items in the recency region may be transferred into the long-term storage to become available on Short Delay Free Recall. It is predicted that recall of recency items on delay will drop significantly as compared to Trial 5.

With regards to group differences, it is predicted that the AD group will lose more information from all regions of the list after a delay than the HC and LLD groups. Also, the HC and LLD groups will forget more from the recency than the primacy and the middle regions.

3. Exploratory hypothesis- neuropsychological measures

To test differences in various aspects of working memory and processing speed in the three groups the following neuropsychological measures were used:

a) Attentional capacity - Digit Span Forward

It is predicted that the groups will not differ on the measure reflecting basic working memory buffer capacity as measured by Digit Span Forward

b) Working memory - Digit Span Backwards

It is hypothesized that the groups will significantly differ on the measure of concentration and working memory as measured by Digit Span Backwards. More specifically, the LLD and AD groups will perform more poorly than the HC group.

c) Psychomotor speed and attention – Trails-A

It is predicted that the groups will differ significantly on processing speed and attention as measured by Trails-A; the HC group will perform better than the LLD and the AD groups.

Chapter VI

Methods

Participants

Twenty-two healthy controls (NC: 9 women, 13 men), 24 subjects with late-life depression (LLD: 15 women, 9 men), and 34 subjects with probable Alzheimer's disease (AD: 14 women, 20 men) were selected for this study. Participants referred for testing between the years of 1995 and 2003 to the Neuropsychology Service of the Department of Psychiatry at Mount Sinai Medical Center, New York were chosen for this study. The diagnosis for all participants was determined by licensed psychologists with extensive neuropsychological experience with the geriatric population.

The three groups were similar in age, $F(2,79) = 0.70$, $p = .50$, years of education, $F(2, 79) = 1.90$, $p = .16$, overall premorbid intellectual functioning, $F(2, 79) = 2.78$, $p = .07$, and gender distribution, $\chi^2 = 58.49$, $p = .53$ (Table 1).

Characteristics of healthy controls (HC)

Inclusion criteria: HC participants were referred for neuropsychological evaluation by the Geriatric Clinic at the Mount Sinai Medical Center in order to assess their cognitive functioning. Geriatric Clinic patients underwent neuropsychological evaluations, which served as either a baseline (for participants without subjective complaints) or a cognitive assessment (for participants who report cognitive changes). None of the HC participants selected for this study exhibited cognitive symptoms beyond normal age associated function. None of the healthy controls met criteria for dementia (Clinical Dementia Rating =0) or depression (Geriatric Depression Scale >9). Also, as

determined by the neuroimaging report none of the HC participants showed any structural brain abnormalities.

Exclusion criteria: Potential participants with current or past history of neurologic (e.g., head trauma, CVA) or psychotic disorders (e.g., schizophrenia, bipolar disorder), substance abuse and/or undergoing treatment for ongoing severe medical illness affecting cognitive function (e.g., cardiac disease, cancer, urinary incontinence) were excluded from the study.

Characteristics of patients with late –life depression (LLD)

Inclusion Criteria: Thirteen participants met Diagnostic and Statistical Manual - IV (American Psychiatric Association, 1994) criteria for Major Depressive Disorder, as determined by a comprehensive clinical interview administered or closely supervised by a geriatric nurse practitioner, a geriatric psychiatrist, or a licensed clinical psychologist. The remaining 11 participants met criteria for minor depression. There are number of reasons that the participants with minor depression were included in the LLD group. Older adults often report depressive symptoms at the level below what is considered sufficient for a diagnosis of DSM-IV major depression, but meet the criteria for DSM-IV minor depression (Beekman, Copeland, & Prince, 1999; Heun, Papassotiropoulos, & Ptok, 2000). More importantly, older individuals with either major or minor depression were found to show significant cognitive deficits (Elderkin-Thompson et al., 2003). These participants were included in the study.

All participants in the LLD group had Geriatric Depression Scale (GDS; Yesavage, Rose, Lum, Huang, Adey, & Leirer, 1982) scores ranging from 11/30 to 27/30 indicating at least mild severity of depression. The GDS scores were significantly

different between the Healthy Control (mean = 3.18, Standard Deviation = 2.44) and LLD (mean = 18.17, Standard Deviation = 4.57) groups, $t(44)=-13.70$, $p<001$. Twenty one of the LLD participants had CDR scores of zero indicating no impairment in any of the six categories (memory, orientation, judgment, community affairs, home and hobbies, and personal care) assessed by the CDR. Four participants had a CDR score of .5 with mild impairments in areas other than memory. The functioning areas affected in these patients included community affairs, home and hobbies, or personal care and reflected impairments associated with depression. Loss of interest in previously pleasurable activities or reduced energy level (some of the criteria for depression) are likely to affect patients' interests in social interactions, pursuing hobbies, or taking care of themselves and their homes.

Exclusion criteria: Exclusion criteria were past history of Axis I psychotic disorders (e.g., bipolar disorder, schizophrenia), current psychiatric disorder other than depression (e.g., anxiety disorder), current or past history of substance abuse or neurologic disorder (e.g., stroke, head trauma, Parkinson's disease), positive neuroradiological findings that might contribute to cognitive impairment, and past history or current treatment of significant medical illness that would precipitate depression or cognitive disturbance (e.g., coronary artery bypass graft, active treatment for cancer).

Pharmacological treatment for patients with depression.

Although there are reports of improved cognitive performance after antidepressant treatment (Abas, Sahakian, & Levy, 1990; Butters et al., 2000; Tarbuck & Paykel, 1995), there are numerous studies indicating that psychopharmacological treatment (Selective Serotonin Reuptake Inhibitors – SSRI or tricyclic antidepressants)

does not significantly affect performance on cognitive tests in depressed population (e.g., Lewis & Kopelman, 1998; Nebes et al., 2000, 2001, 2003). Considering that all LLD patients met criteria for current major or minor depression and none were in remission, patients free of medication as well as those taking antidepressant medications at the time of testing were included in the LLD group. Eleven of the depressed patients were receiving pharmacological treatment at the time of neuropsychological testing; ten with SSRIs, and one patient was receiving low dose neuroleptic medication (i.e., Triavil) together with choline in order to minimize potential anticholinergic cognitive side effects from the medications. Depressed patients with dementia were ruled out. Specifically, none of the LLD participants exhibited major memory deficits or other cognitive deficits to qualify for the CDR score >= 1.0, which would indicate dementia. None of the LLD patients showed any other behavioral deficits consistent with dementia.

Characteristics of participants with AD (AD)

Subjects with AD met National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann, Drachman, Folstein, Katzman, Price & Stadlan, 1984) criteria for probable AD, including extensive interview with the subjects and third parties, medical and neurological examinations, laboratory screening, and structural imaging (CT or MRI). Participants with history of hypertension or those exhibiting any signs of vascular accidents as indicated by the focal deficits or imaging records were excluded from the study. None of the AD participants demonstrated significant linguistic deficits (e.g., aphasia). Five participants were taking donepezil (Aricept) at the time of testing and no patients were taking any antidepressant medications. Due to the severity of their

cognitive impairments and/or fatigue, only nine AD participants were given Geriatric Depression Scale. One of the possible factors that contributed to the AD participants' inability to complete the GDS might be the order of test administration; GDS was typically administered at the end of the neuropsychological battery. In addition, the patients' charts did not contain enough information provided by the caregivers to reliably determine the remaining patients' CDR scores. Lack of a GDS score opens the possibility that at least some of the AD participants were also suffering from depression. The impact of depression on cognitive functioning of patients with AD is unclear with some studies reporting increase in impairments (Devanand, 1999; Haupt, Kurz & Greifenhagen, 1995; Wefel, Hoyt & Massma, 1999) while others show no evidence that depression significantly exacerbate the cognitive deficits associated with AD (Berger, Fahlander, Wahlin, & Backman, 2002; Cummings, Miller & Hill, 1987; Garre-Olmo et al., 2003). Therefore, even though the AD group might have included participants with a mixed diagnosis of AD and depression, the performance of the selected sample is likely to reflect that of typical AD population.

Measures

Severity of impairment measures

Dementia - Clinical Dementia Rating (CDR; Hughes, Berg, Danziger, Coben & Martin, 1982) is a clinical scale for the staging of dementia that was developed at the Washington University. The CDR is used to assess the severity of dementia impairment on a 5-point scale in six functional areas (memory, orientation, judgment, community affairs, home and hobbies, and personal care). CDR scores range form 0-5: 0 = no dementia, 0.5 = uncertain or deferred diagnosis, 1.0 = mild dementia, 2.0 = moderate

dementia, 3.0 = severe dementia; 4= profound dementia; 5=terminal dementia. Memory constitutes a primary category while all of the remaining areas are secondary functional categories. Thus, some degree of memory deficit is necessary in order to assume a CDR score >= 1.0 (See Appendix for CDR scoring procedure). The CDR has been shown to be highly reliable (e.g., Burke et al., 1988), and it is widely used in research and clinical settings (e.g., Hashimoto et al., 2004; Howieson, et al., 2003; Steinberg, Munro, Samus, Robins, Randt & Lyketsos, 2004)

Depression - Geriatric Depression Scale (GDS) (Yesavage et al., 1982). The GDS is a 30-item questionnaire designed in a yes/no format for self- or caregiver administration. It was specifically designed for older adults as it minimizes questions about somatic and vegetative symptoms, which can overlap with symptoms of concurrent medical illness. Scores falling between 0-9 are considered normal, while 10-19 denotes mild depression, and 20-30 is indicative of severe depression. The GDS has been validated repeatedly in psychiatric settings (e.g., Almeida & Almeida, 1999; Fountoulakis, Tsolaki & Kazis, 2000; Lam, Lim, Low, Ng, Chiam & Sahadevan, 2004; Yesavage, Rose, Lum, Huang, Adey, & Leirer ,1983). GDS scores were found to be negatively correlated with scores on measures putting significant demand on attention and concentration abilities and are now thought to be a useful measure of effects of severity of depression on attention demanding, controlled free recall tasks (Green et al. 2000). In the current study the GDS was used as a measure of severity of depression in the LLD group. The GDS was also used to exclude depressed individuals from the HC group. As indicated above, only nine of the 34 AD participants were given the GDS.

Intelligence measures

North American Adult Reading Test (referred to as NAART or NART-R, Blair & Spreen, 1989) is a 61-word version of the National Adult Reading Test (NART, Nelson, 1982) that uses phonetically irregular words that can be read correctly only by persons who have been exposed to these words previously. NART was developed with the purpose of assessing the premorbid mental ability. NART-R was found to reliably estimate overall intellectual level as measured by the WAIS-R (Berry, Carpenter, Campbell, Schmitt, Helton, & Lipke-Molby,1994; Ryan & Paolo, 1992). This test has been used to estimate premorbid intellectual functioning in older healthy, demented, and depressed population (e.g., Nathan et al., 2001; Sharpe & O'Caroll, 1991). The formula for estimating IQ based on NART-R scores is as follows: 118.2 - .89 (NART-R errors + .64 (years of education). Premorbid intelligence for the ten NC, the seven LLD, and the participants with AD was estimated using NART-R.

Wechsler Adult Intelligence Scale (WAIS-R, Wechsler, 1981; WAIS-III, Wechsler, 1997) is the most widely used standard measure of intelligence in adults. It is comprised of 11 (WAIS-R, Wechsler, 1981) or 14 subtests (WAIS-III, Wechsler, 1997) and yields a Full Scale, Verbal and Performance IQ scores. Administration and scoring are standardized and extensive normative data is available.

For five of the HC and three of the LLD subjects, the Full Scale IQ was obtained by administering a full WAIS-R. Thirteen participants with AD were missing one of the required subtests to obtain an IQ score. For these participants the missing scaled score was substituted according to WAIS-R manual guidelines. Two of the LLD participants were administered full WAIS-III. Thirteen LLD and seven HC subjects' IQs were

calculated by substituting one of the missing subtests according to the guidelines in WAIS-III manual (Wechsler, 1997).

For the twelve participants with AD who were not able to take the required number of subtests (e.g., fatigue, frustration, etc), the premorbid IQ was estimated using the Best-3 method (Vanderploeg &Schinka, 1995). The Best-3 method uses formulas that combine performance on Information, Vocabulary, or Picture Completion subtests of WAIS-R with demographic variables (sex, race, age, education, occupation, and socioeconomic status) to calculate three scores for Full Scale, Verbal, and Performance IQs. The highest scores for the Full Scale, Verbal, and Performance IQs, are used as the best estimate of individual's premorbid IQ. The Best-3 method was found to be highly correlated with the actual WAIS-R intelligent quotient (Vanderploeg, Schinka, & Axelrod, 1996) and is also highly compatible to other methods estimating premorbid IQ (Axelrod, Vanderploeg, & Schinka, 1999).

Neuropsychological measures

Digit Span (Wechsler, 1981 and 1997) is a part of both the WAIS-R and the WAIS-III batteries. Participants are asked to repeat increasing sequences of numbers in forward or backward order, read aloud by the examiner. Raw scores of Digit Span Forward and Backward were converted into age-corrected scaled and percentile scores (Wechsler, 1987). Digit Span Forward is a measure of span (e.g., Banken, 1985) and efficiency of attention or freedom from distractibility (e.g., Kaufman, McLean, & Reynolds, 1991) while Digit Span Backward reflects operation of working memory including mental tracking (Lezak, 1995) and concentration (Groth-Marnat, 1999).

Trials Making Test – Part A (Trails-A, Reitan & Wolfson, 1985) is considered to be a test of psychomotor speed, attention, and visual and mental tracking ability (Groth-Marnat, 1999; Shum, McFarland & Bain, 1990). Participants are asked to draw lines, without lifting the pen from the paper, to connect consecutively numbered circles scattered randomly on a worksheet. Participants are also urged to perform the task as fast as they can. Raw scores can be converted to the age-corrected percentile scores (Reitan & Wolfson, 1985). Trails-A showed to be sensitive to cognitive decline in dementia (e.g., Nathan et al., 2001; Storandt, Botwinick, Danziger, Berg, & Hughes, 1984).

Fluency measures. For analysis of verbal fluency, measures of letter fluency (Controlled Oral Word Association – COWA or FAS, Benton & Hamsher, 1976) and category fluency (Animals; Newcombe, 1969) were used. Standard administration for letter and category fluency was followed, allowing participants to generate words for 60 seconds (Lezak, 1995). This test requires participants to freely produce words while monitoring their responses which loads on abstract mental operations similar to mental calculations and digit span test (Snow, Tierney, Zorzitto, Fisher, & Reid 1988). Impaired verbal fluency was associated with frontal damage (e.g., Jasnowsky, Shimamura, Kritchevsky, & Squire, 1989; Milner, 1975). In addition to the frontal lobes, bilateral temporal areas were shown to be involved in verbal fluency tasks. In addition, there are suggestions that poorer performers require more effort to carry out the fluency task (Parks, Loewenstein, Dodrill, Barker, Yoshii, Chang, et al., 1988). Reduced capacity to produce words may be associated with various deficits such as mental flexibility (e.g., Bayley, Trosset, Tomoeda,, et al., 1993; Brown & Marsden, 1988), semantic processing (e.g., Bayley, Salmon, Tomoeda, et al., 1989; Appell, Kertesh, & Fishman, 1982), or

deficits associated with late-life depression (Hart, Kwentus, Taylor, & Hamer, 1988). The fluency task was found to differentiate AD from aging (e.g., Barr & Brandt, 1996; Monsch, Bondi, Butters, Salmon , Katzman , & Thal, 1992), amnesia (e.g., Butters, Granholm, Salmon, Grant, & Wolfe, 1987), and other neurologic disorders (e.g. Pasquier, Lebert, Grymonprez, Petit, 1995; Rosser & Hodges, 1994). While the category fluency task has been shown to differentiate between the dementia and late-life depression, the letter fluency task does not differentiate these two disorders (Hart et al., 1988).

List-learning measures

Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958) was administered according to standard procedures. The RAVLT is composed of 15 unrelated, common words which are read to the participants in the same order over the five consecutive trials (list A). Each presentation is followed by a free recall; participants are asked to recall as many words as they can in any order. After the five trials, participants are read a different list of 15 words (list B) and asked to recall these in any order. List B serves as an interference immediately preceding the Short Delay Free Recall of the list A. The RAVLT was found to be reliable (e.g., Snow et al., 1988; Estevez-Gonzalez, Kulisevsky, Boltes, Otermin, Garcia-Sanchez, 2003), and is widely used in research and clinical settings (e.g., Estevez-Gonzalez et al., 2003; Crockett, Hadjistavropoulos & Hurwitz, 1992; Mitrushina et al., 1991;Woodard, Dunlosky, & Salthouse, 1999)

Measures of serial position. The *Percentage* (CVLT, Delis et al., 1987 and 2000) and *Regional* scores (Foldi et al., 2003) were used as dependent variables. These measures have no existing age based norms for RAVLT.

- *Percentage score*: *Percentage* scores from each region are based on the ratio of words recalled in each region (primacy, middle, recency) divided by the total number of words correctly recalled by the participant. *Percentage* scores were calculated for each of the five trials, as well as collapsed over the five learning trials and for Short Delay Free Recall. For individual trials the number of items recalled in each region was divided by the total recall for each trial while the collapsed scores were divided by the sum of total recalls of the five learning trials.
- *Regional score:* The *Regional* score was calculated as number of items recalled from a region (primacy, middle, recency) divided by the total number of items that were presented in each region of the list (4, 8, and 4 respectively). The primacy region included items 1-4, the middle region included items 5-11, and the recency region included items 12-15. The ratio was converted to a percentage. *Regional* scores were calculated for each of the five trials and for Short Delay Free Recall, as well as collapsed over the five learning trials.

Procedures

This study was approved by the Mount Sinai Medical Center and Queens College - CUNY Institutional Review Boards for retrospective review of records. All participants were assessed by an interview and comprehensive neuropsychological test battery, usually during a single session. Additional interviews were also performed with subjects' family members or caretakers. Neuropsychological testing was performed by licensed psychologists or by master's level students trained and supervised in neuropsychological testing during their externships or internships. All data were extracted from each subject's neuropsychological chart. The charts also contained medical and neuroimaging

records supplied by the referring physician that were also carefully reviewed and used to aid diagnosis and exclusion process.

Experimental design and statistical procedures

Mixed repeated-measures ANOVAs were conducted to compare effects of Group (3: HC, LLD, AD), Region (3: primacy, middle and recency), and Trial (5). A repeated-measures ANOVA was also used to determine the within group differences. For repeated-measures ANOVAs in which the repeated measure had more than two levels, the Greenhouse–Geisser procedure was used to correct for inflated degrees of freedom. The least significant difference (LSD) procedure was used for all post hoc comparisons. Pearson correlation procedures were employed to determine the associations between the measures.

Chapter VII

Results

Pattern of learning - serial position effects using Percentage scores

A 3 x 3 x 5 mixed repeated-measures ANOVA was conducted to analyze the learning patterns with Group (3; NC, LLD, AD) as the between-subjects variable and with Region (3; Primacy, Middle, and Recency) and Trial (5; Trials 1-5) as within-subjects variables using *Percentage* scores as the dependent variable. Greenhouse–Geisser procedures were used to correct for inflated degrees of freedom for the repeated measures that had more than two levels. The results of this analysis are presented in Tables 3 and 4, and Figure 1.

No group differences were evident, $F(2,77)=2.14$, $p=.124$. When all regions are collapsed, *Percentage* scores based on the total items recalled will of necessity be equal for all groups (i.e., 100%). However, a significant Group x Region interaction (see Figure 1), $F(3.84,147.89)=7.34$, $p<.001$, was present. Post hoc analyses showed that the groups did not significantly differ in the Primacy region, $p=.180$. There was a difference in the Middle region, $p<.001$, with the HC and LLD groups not different, $p=.181$, but the AD group significantly poorer than either the NC, $p<.001$, or the LLD, $p=.004$, groups. The groups also differed in the Recency region, $p<.001$, and again the HC and LLD groups were similar, $p=.439$, but the AD group was significantly better in the Recency region, $p<.001$, than either the HC and LLD groups.

Post hoc analyses were also conducted in order to investigate the recall pattern within each group. The HC group showed differential performance among regions, $p=.015$, recalling significantly fewer items in the Primacy than either Recency, $p=.003$, or

Middle, p=.027, regions, which in turn did not differ from one another, p=.787. The LLD group differed across regions, p=.007. The Recency region was significantly better than either the Primacy, p=.003, and the Middle, p=.029, which in turn were not different from one another, p=.542. The AD group, p<.001, showed a similar but more extreme pattern than the LLD group with similar recall in the Primacy and Middle regions, p=.855, and marked by better recall in the Recency region than either Primacy, p<.001, or Middle, p<.001, regions, indicating that a large percent of the items recalled by AD patients emanated from the recency region.

The significant Region x Trial interaction, $F(4.75, 365.86)= 6.96$, p<.001, indicated that the recall in the three regions of the list varied as function of trial. However, these patterns did not differ in the three groups, Group x Region x Trial, $F(9.50,365.86) = 1.32$, p=.219.

Pattern of learning - serial position effect using Regional scores

The *Regional* scores were a second dependent measure of serial position performance. These scores provide an insight into how much of the information presented in the particular region of the list had been processed. More specifically, the *Regional* scores help to estimate how much of the information presented in each region had been recalled (Foldi et al., 2003).

A mixed repeated-measures ANOVA using *Regional* scores as the dependent variable was conducted using Group (3; HC, LLD, AD) as between-subjects variable, and using the Region (3: Primacy, Middle, and Recency) and Trial (5: Trials 1-5) as within-subjects variables. For repeated-measures ANOVAs in which the repeated measure had more than two levels, the Greenhouse–Geisser procedure was used to correct for inflated

degrees of freedom. The source table for this analysis and post hoc results are presented in Table 5 and 6, and Figure 2.

The main effect of subject Group, $F(2,77)=38.21$, $p<.001$, showed that groups were all significantly different from each other, with the HC group performing better than the LLD, $p=.001$, and AD, $p<.001$ groups, and the LLD group better than the AD group, $p<.001$. The significant main effect of Region, $F(1.79,137.72)=89.71$, $p<.001$, demonstrated that there was differential recall from each region of the list with all regions significantly different from one another, $p<.001$.

A significant Group x Region effect, $F(3.58,137.72)=2.60$, $p=.045$, indicated a differential performance in Primacy, Middle, and Recency regions among subject groups. Figure 2 illustrates the U-shaped pattern for both HC and LLD groups, although the AD group shows relatively a U-shaped pattern, it shows greater reliance on the Recency region than the other two groups. As described in Table 6, post hoc analyses of each region were compared across subject groups. In the Primacy region, the HC and LLD groups performed similarly, $p=.083$, and both groups were significantly better than the AD group, $p<.001$. In the Middle region, all groups differed from one another, $p<.001$, with the HC group better than the LLD group, $p=.007$, who in turn were better than the AD group. Lastly, in the Recency region, the HC group had higher scores than the LLD group, $p=.045$, and AD group, $p=.002$, but the scores for the LLD and AD groups were similar, $p=.336$.

The three regions were compared within each group (see Figure 2). For the HC group, the scores in Middle region were significantly lower than either Primacy, $p=.002$, or Recency, $p<.001$, regions. But, the Recency region was higher than the Primacy

region, p=.010. For the LLD group, recall from the Primacy region exceeded item recall from the Middle region, p<.001, but was worse than the Recency region, p=.010. The recall in the Recency region was significantly better than in the Middle region, p<.001. For the AD group, the Recency scores were significantly better than either the Primacy, p<.001, or Middle scores, p<.001, but performance in the Primacy region was still significantly better than the Middle region, p=.001. In summary, all groups showed a similar pattern of recall collapsed over the five learning trials with best performance in the Recency followed by Primacy and the lowest recall in the Middle region.

A significant main effect of Trial, F(3.41,262.44)=116.54, p<.001, indicated that there was a differential performance over the learning trials. Post hoc analysis showed that the participants recalled more items on each consecutive trial 1 to 4. However, there was no significant difference in the performance on trials 4 and 5.

The three-way Group x Region x Trial interaction, F(13.20,508.17)=2.33, p=.005, was also significant, indicating that the groups showed differential patterns of learning across trials within each region. To investigate the learning pattern across the five trials, one-way, post-hoc analyses were conducted to determine the between-group differences in each of the regions (means and standard deviations are presented in Table 6 and results of the post-hoc analyses are reported below).

Learning in Primacy region across five trials

As seen in Figure 3a, the HC and LLD groups were similar in their learning pattern in the Primacy region in three of the five trials: only on trial 2, p=.031, and Trial 5, p=. 045 was the HC group significantly better than the LLD group. The HC group was always better than the AD group in the Primacy region on each of the five trials. The

LLD group performed significantly better in the Primacy region than the AD group on all but the first learning trial.

To determine whether the recall on the first and the last learning trial significantly improved, paired t-tests between Trial 1-Trial 5 were conducted for each group. First, each group showed significant improvement over five trials indicating that significant amount of learning took place within each group (NC: t=-5.78, df=21, p<.001; LLD: t = -4.54, df=23, p<.001; AD: t=-3.45, df=33, p=.002). The amount of information acquired from the first to the last learning trial was also contrasted across the three groups. Here, the HC and LLD groups were similar, p=.596, as were the LLD and AD groups, p=.099. However, the HC group was significantly better than the AD group, p=.031.

Learning in Middle region across five trials

In the Middle region (Figure 3b), the HC group performed significantly better than the LLD group on the first four consecutive learning trials, but by trial 5 both groups performed similarly. The LLD group recalled more items than the AD group, except at Trial 2 when both groups showed statistically similar performance. The HC group was always significantly better than the AD group across all five learning trials. Post hoc paired t-tests for each group showed that the recall from the first to the last learning trial did significantly increase in all three groups, p<.001. Using the Trial 1–Trial 5 difference scores, the HC and LLD groups had learned more than the AD group (p=.016, p=.017, respectively) but were similar to each other, p=.936. This shows that the amount learned by the HC and LLD groups over five trials was greater than the amount of information acquired by the AD group.

Learning in Recency region across five trials

In the Recency region (Figure 3c), the HC group performed similarly to the LLD group on all trials, and was better than the AD group on three out of five learning trials (Trial 1, p=.003, Trial 2, p=.026, and Trial 4, p=.002). On the remaining two trials the HC was similar to the AD group. The LLD and AD groups were similar on three (Trials 2, 3, and 5) out of five learning trials while the LLD group was significantly better on the two remaining trials (Trials: 1, p=.021, and 4, p=.050). Paired-t tests conducted for each group indicated that recall from the first to the last learning trial in the Recency region did not significantly differ in either the HC, p=.069, or LLD, p=.417, but it should be noted that these groups were performing relatively high at Trial 1 (65.9% of the items presented, and 60.4% respectively). In contrast, the recall of the AD group started lower at Trial 1 (44.1%) and significantly increased by the last learning trial (76.47%), p<001. The AD group therefore showed a greater relative improvement in the Recency region compared to the HC or LLD groups, which did not significantly increase the number of items learned over repeated consecutive trials. Thus, even despite the significant memory impairment in AD, these patients demonstrated an ability to learn over the multiple exposures to the same material.

Comparing Trial 5 to Short Delay Free Recall

To determine how much of the information learned by the fifth trial was retained on the Short Delay Free Recall (e.g., saving score), a mixed repeated-measures ANOVA was conducted using *Regional* scores as the dependent variable, with Group (3; NC, LLD, AD) as between-subjects factor and Region (3; Primacy, Middle, Recency) and Trial (2; Trial 5 and Short Delay Free Recall) as within-subject factor. Main effects of

Group, $F(2,77)=30.01$, $p<.001$, Region, $F(1.95, 150.01)=12.04$, $p<001$, and Trial, $F(1,77)=205.89$, $p<.001$, were significant, as were all interactions: two-way, Group x Trial, $F(2,77)=6.30$, $p=.003$, Group x Region, $F(3.90, 150.01)=4.85$, $p=.001$, and Region x Trial, $F(1.96, 151.16)=34.97$, $p<.001$, and three-way Group x Region x Trial, $F(3.93, 151.16)=3.41$, $p=.011$. Means are presented in Table 7, and the source table for this analysis is presented in Table 8.

Additional analysis were performed to determined whether the pattern of change over time varied across regions for each group, given the significant three-way Group x Region x Trial interaction (see Figures 4 a-c). First, the three regions were compared in each group individually.

- HC: At Trial 5 the HC group showed the typical U-shaped pattern; lower Middle than either Primacy, $p=.002$, or Recency region, $p=.024$ (Primacy > Middle < Recency). By Short Delay Free Recall, the U-shape was lost. Primacy region recall was significantly better than Recency ($p=.003$), but Primacy did not significantly differ from the Middle ($p=.088$), which in turn was not different from the Recency recall ($p=.119$).
- For the LLD group, the U-shape pattern at Trial 5 (Primacy = [Middle < Recency]) changes by Short Delay Free Recall, with the Primacy region significantly better than the Middle, $p=.034$ and Recency, $p=.008$, regions, which were not different from each other, $p=.871$ (Primacy > [Middle = Recency]).
- The AD group's prominent recency effect at Trial 5 ([Primacy = Middle] < Recency) decays over time; at Short Delay Free Recall less than 20% of the presented information is retained and there are no differences among regions.

To focus on the decay of information over time, comparisons between the performance on Trial 5 and Short Delay Free Recall were conducted. First, paired t-test analyses showed that all groups demonstrated significant loss of information from each region (see Table 9). Second, to determine whether the relative loss of information differed between the HC versus LLD group, a Group (2) x Region (3) repeated measures ANOVA was conducted with the saving score as the dependent variable (difference scores between *Regional* scores on Trial 5 and Short Delay Free Recall were calculated separately for each region). Both groups showed similar patterns (Main effect of Group, $F[1,44]=.635, p=.430$). Overall, loss in the Recency region was more pronounced (Main Effect of Region, $F(1,44)=13.31, p = .001$. Post hoc: comparison of Recency to Primacy, $p=.001$; Recency to Middle, $p<.001$) than in the Primacy and Middle regions, which show similar loss over time ($p=.747$). There was no significant Group x Region interaction on these saving scores $F(1,44)=.063, p= .802$. Thus, the loss of information by the HC and the LLD groups was similar. The Recency region, where information is residing in working memory is most vulnerable. Information in the Primacy and Middle also deteriorates (Table 10).

Neuropsychological Measures

As overall capacity and efficiency of the working memory, processing speed, and executive functioning play important roles in mediating different aspects of the serial position phenomenon, the neuropsychological measures of these areas of functioning were compared among the groups. A multivariate analysis of variance (MANOVA) was conducted to examine the performance on the estimates of attentional capacity (Digit Span Forward, percentile scores; Wechsler, 1997)), working memory (Digit Span

Backward, percentile scores; Wechsler, 1997), psychomotor speed and attention (Trails-A, completion time; Reitan & Wolfson, 1985)), and verbal fluency (FAS and Animals, mean total words generated) were used as the dependent variables. The mean values of neuropsychological measures are reported in Table 11. A significant overall effect, F=6.64, p<.001, was followed with univariate analyses, with LSD, p<.05, indicating significance.

Capacity and working memory measures – digit spans (Figures 5a and 5b)

Digit Span Forward scores (Figure 5a) did not significantly differ among the three groups, $F(2,77)$=1.34, p=.268, suggesting that the groups were similar in respect to the basic attentional capacity. In contrast (Figure 5b), the groups differed on the Digit Span Backward test, $F(2,77)$= 6.36, p=.003, with the HC group performing significantly better than both LLD, p=.014, and the AD, p=.001, groups. The LLD and AD groups did not differ, p=.422. This pattern of performance on the two measures indicates that the two patient groups showed similar attentional capacity, but the HC group showed significantly better ability to maintain and manipulate information.

Psychomotor speed and attention – Trails A (Figure 5c)

The measure of psychomotor speed and attention also differentiated groups, $F(2,77)$= 8.56, p<.001, with the HC group performing significantly better than the LLD, p<.001, and AD, p=.001, groups. Again, the LLD group performed similarly to the AD group, p=.589. The results indicate that the HC group demonstrated overall better psychomotor speed, attention, and visual and mental tracking ability than either the LLD or AD group.

Verbal fluency measures – FAS and Animals (Figure 5d and 5e)

There was a significant difference among the groups in average number of items generated to letter cue, $F(2,77)=5.78$, $p=.005$, as well as category cue, $F(2,77)=30.84$, $p<.001$. The HC group generated significantly more items to the letter cue (FAS) than the LLD, $p=.008$, and AD, $p=.002$, groups, which did not significantly differ from one another, $p=.784$. Similarly, on the category fluency test, the HC group generated significantly more items than the AD and LLD groups, $p<.001$. However, the LLD group generated significantly more items to the category cue than the AD group, $p=.002$.

The results of neuropsychological measures indicate that the LLD group tended to perform similarly to the AD group on tests of working memory and psychomotor speed and attention. Consistent with the literature, the LLD group did not differ from the AD group on letter fluency task (e.g., Hart, Kwentus, Taylor & Hamer, 1988) and the LLD group showed slower psychomotor speed than the HC (e.g., Butters et al., 2004; Nebes et al., 2000). Also, as Figures 5d and 5e illustrate, the AD group demonstrated the typical pattern of advantage on letter over category cue (e.g., Monsch et al., 1994).

Contribution of the working memory and processing speed to the recall as function of serial position

Working memory and speed of processing might play a critical role in the serial position recall. Considering that patient groups showed differential performance on working memory (Digit Span Backwards) as compared to Healthy Controls, it was entered into analysis to determine whether it affects the pattern of recall as function of serial position. Digits Backward scores were entered as a covariate in the mixed repeated-measures ANOVA with *Regional* scores as the dependent variable, and Group (3; NC,

LLD, and AD) as between-subject variable and Region (3; Primacy, Middle, and Recency) and Trial (5; Trials 1-5) as within-subject variables. The main effects of Group, $F(2,75)=26.59$, $p<.001$, Region, $F(1.79, 134.29)=16.29$, $p<.001$, and Trial, $F(3.43,256.92)=13.33$, $p<.001$, remained significant. However, the Group x Region interaction was no longer significant, $F(3.58, 136.03)=2.22$, $p=.077$, indicating that when working memory is statistically removed, the groups did not differ in their recall as function of region of the list. On the contrary, the Group x Region x Trial remained significant, $F(13.04, 509.30)=2.02$, $p=.017$, showing that even when the influence of the working memory was statistically removed, groups performed differently in the various regions of the list over the learning trials.

Similarly, when speed of processing (Trails-A) was entered as a covariate in the mixed repeated-measures ANOVA with *Regional* scores as the dependent variable, and Group (3; NC, LLD, and AD) as between-subject variable and with Region (3; Primacy, Middle, and Recency) and Trial (5; Trials 1-5) as within-subject variables, the main effects of Group, $F(2,76)=30.77$, $p<.001$, Region, $F(1.79, 136.06)$, $p<.001$, and Trial, $F(3.42, 259.94)$, $p<.001$, and Group x Region x Trial, $F(13.48, 512.14)$, $p=.002$, interaction remained significant. The Group x Region interaction was no longer significant however, $F(3.58, 136.06$, $p=.056$, indicating that when speed of processing is statistically removed, the three groups did not differ in their recall as function of region of the list.

Depression severity correlation – LLD group

The association between the neuropsychological measures of working memory (Digit Span Backward) and psychomotor speed and attention (Trails-A) with the

depression severity was investigated within the LLD group. Pearson Product Moment Correlations were applied using Geriatric Depression Scale (GDS) as the measure of depression severity. Results indicated that depression severity was not associated with measures the working memory, psychomotor speed and attention, or fluency: Digit Span Forward, r=-.30, *P*=.160; Digit Span Backward, r=-.31, *P*=.141; Trails A, r=-.108, *P*=.064; FAS, r=-.012, *P*=.954; Animals, r=-.23, *P*=.289. This finding indicated that, although the presence of depression had adverse affects on working memory, as well as psychomotor speed and attention, the severity of depression did not affect to the degree of these deficits.

The relationship between the depression severity and overall recall, as measured by the total *Regional* scores collapsed across the five learning trials, was also measured. Results were not significant, r= -.016, *P*=.940, indicating that, although having depression affects overall ability to learn as compared to controls, the severity of depression did not affect the degree of this deficit.

Pearson correlations were also conducted to investigate the relationship between the depression severity (GDS) and scores in the Primacy, Middle, and the Recency regions using both the *Percentage* as well as *Regional* measures of serial position. There were no significant correlations between the depression severity and any of the *Regional* scores, however the Recency *Percentage* scores were negatively correlated with depression severity, *r*=-.487, *P*=.016, thus indicating that the more severe the depression, the lower the percentage of all items recalled were emanating from the Recency region. This may reflect a reduction in capacity or efficiency of the working memory buffer with increasing degree of depression.

Subgroups of depression

Major vs. minor depression

The LLD group included 13 participants with the diagnosis of major depression and 11 with minor depression. The patients with major depression had significantly higher scores of depression severity (GDS), $t(22)=4.70$, $p<.001$, but the two subgroups did not differ on demographic variables of age, $t(22)=-.768$, $p=.450$, education, $t(22)=-.86$, $p=.399$, or gender distribution, $\chi^2(1)=.011$, $p=.916$. There were also no differences on any of the neuropsychological measures between the two subgroups: Digit Span Forward, $t(22)=-.25$, $p=.806$; Digit Span Backward, $t(22)=-.27$, $p=.792$; Trails A, $t(22)=-1.17$, $p=.257$; FAS, $t(22)=.24$, $p=.814$; Animals, $t(22)=-2.01$, $p=.057$.

To investigate whether the pattern of serial position recall was affected by these diagnostic categories, a three-way mixed repeated-measures ANOVA was conducted using Subgroup (2; major depression and minor depression) as between-subjects variable and with Region (3; Primacy, Middle, and Recency) and Trial (5; Trials 1-5) as within-subjects variables with *Regional* scores as the dependent variable. All effects related to the differences among the subgroups failed to reach significance: Subgroup, $F(1,22)=.05$, $p=.480$, Subgroup x Region, $F(1.76, 38.66)=2.32$, $p=.110$, and Subgroup x Region x Trial, $F(5.86, 128.96)=1.83$, $p=.101$. This indicated that the LLD patients performed similarly in the serial position curves, regardless of whether they had been given a diagnosis of major versus minor depression.

Effect of medications

Eleven of the LLD participants were taking medications at the time of testing (10 patients were taking antidepressants and one patient was on a low dose psychotropic

medication) while 13 were free of any medications. Independent sample t-test showed these two subgroups did not differ on demographic variables of age, $t(22)=-1.844$, $p=.079$, education, $t(22)=1.04$, $p=.308$, or gender distribution, $X^2(1)=.011$, $P=.916$. There also was no difference among the subgroups on any of the neuropsychological measures: Digit Span Forward, $t(22)=-1.284$, $p=.212$; Digit Span Backward, $t(22)=-.31$, $p=.76$; FAS, $t(22)=.38$, $p=.602$; Animals, $t(22)= 1.00$, $p=.237$. The severity of depression as measured by the GDS was also equivalent, $t(22)=.64$, $p=.532$. However, there was a tendency for the depressed patients free of medication to perform better on measures of psychomotor speed and attention, Trails A, $t(22)=2.067$, $p=.051$, suggesting that antidepressant medications may have adverse effects on speed of mental and motor processing.

To investigate whether the medication affected the pattern of recall as function of serial position, a mixed repeated-measures ANOVA was conducted using these subgroups (2; presence vs. absence of medications) as between-subjects variable and the Region (3; Primacy, Middle, and Recency) and Trial (5; Trials 1-5) as within-subjects variables. All effects related to the differences among the subgroups failed to reach significance: Subgroup, $F(1,22)=.17$, $p=.682$, Subgroup x Region, $F(1.89, 41.52)=.25$, $p=.971$, and Subgroup x Region x Trial, $F(5.78, 127.22)=2.11$, $p=.059$.

These findings indicated that the presence or the absence of medication failed to influence serial position performance. Not surprisingly, nine out of the 11 participants taking medications at the time of testing were also diagnosed with major depression thus resulting in a large overlap and indicating that patients who had worse depression also took more medication. Considering this significant overlap of the two subgroups, one of

the possible explanations for similar findings among participants with either a major and a minor depression diagnosis may have been that medication treatment significantly improved the cognitive functioning of the participants with major depression, therefore equating them with the less severely depressed subjects.

Dementia severity - AD group

Pearson correlations were used to analyze the association between the severity of dementia (Clinical Dementia Rating scale, CDR) and overall recall as measured by the total *Regional* scores collapsed across the five learning trials. The results showed a negative relationship, r=-.444, P=.008. Again these findings recapitulate the known data, indicating that more severe dementia was associated with more impairment in ability to acquire information (e.g., Barzotti et al., 2004).

Correlations between the dementia severity (CDR) scores and the measures of attention (Digit Span Forward), working memory (Digit Span Backward), psychomotor speed and attention (Trails A), and fluency (FAS and Animals) were also investigated. There were significant negative associations between the dementia severity and Digit Span Backward percentile score, r=-41, P=.018, and the letter, r=-.45, P=.008, and category fluency, r=-.44, P=.010, indicating known findings that dementia severity adversely affected working memory and overall fluency in participants with AD.

Chapter VIII

Discussion

Differentiation among healthy older adults , patients with late-life depression and patients with early AD poses a significant clinical challenge. The purpose of the current study was to explore differential patterns of learning and recall as a means of distinguishing these three groups. Using the serial position concept, the learning characteristics of these three groups were investigated as a means to understand what information is transferred from working to long-term memory, and what requirements are necessary for this process to be successful. While the two patient groups are known to have difficulty learning or transferring information from temporary, working memory to longer-lasting, long-term memory storage (e.g., Caine, 1986; Gainotti & Marra, 1994; Massman et al., 1992), it was posited that the LLD and the AD patients would show different strategies thus distinguishing them from each other and from healthy controls.

Three hypotheses were posed. The first hypothesis consisted of two predictions that addressed the ability to transfer information from working to long-term memory. This was done by exploring the total recall, as well as the recall in different regions of the list. The first prediction was that the healthy older adults would, overall, learn more information over the five learning trials than either patient group, but that depressed patients would learn more than the patients with AD. This hypothesis was confirmed. The healthy older adults learned more material as measured by the overall recall on the RAVLT than patients with depression and AD. Also as expected, the patients with depression showed better overall learning than the patients with AD. These data confirm previous studies (e.g., Foldi et al., 2003).

The second prediction focused on the serial position effect of the depressed patients in relation to healthy controls and patients with AD. It was hypothesized that the healthy control and depressed groups will show more recall in the Primacy and Recency regions than in the middle portion of the list, however, the depressed group will show relatively lower performance in the middle region than the healthy control group (Foldi et al, 2003). It was also predicted that the AD group will show more recall in the Recency region than any other portion of the list. In addition, it was hypothesized that the depressed group will show similar performance in the Recency region to the AD group (e.g., Foldi et al., 2003).

A comparison of the three groups using the *Regional* scores confirmed the hypothesis. First, healthy older adults and patients with depression both exhibited the U-shaped learning pattern over the five trials, with primacy and recency recall greater than recall from the middle portion of the list. The two groups were different however, in the relative recall of the middle region items. The depressed recalled significantly fewer items than the healthy controls. This confirms findings of the previous study (Foldi et al., 2003) using the CVLT, in contrast to this study using the RAVLT.

Although the AD group also showed relative U-shaped learning curve, this patient group relied predominantly on items from the recency region rather than the primacy and middle regions items. The AD group consistently recalled significantly less information from the primacy and middle regions than healthy and depressed older adults. This recapitulates the reports in the literature showing a similar pattern of performance among the patients with AD that indicates that items from working memory do not get transferred into long-term storage (e.g., Bäckman & Small, 1998; Bigler et al., 1989;

Carlesimo et al., 1995; Gainotti et al., 1998). The use of working memory was equivalent in the patient groups, who had similar recall from the recency region, both less than healthy controls. The patients differed however, in how they were then able to manipulate this material.

The second hypothesis addresses recall from three regions of the list (primacy, middle, and recency) after a short delay. Remembering items on delay, after interference, provides support to the notion that information has transferred from short-lived working memory into long-term memory store. The amount learned from each region at trial five (the point at which maximum learning has occurred) was compared to Short-Delay Free Recall. For all groups, items from all regions decayed over time. But in healthy and depressed older adults, items from the primacy and middle regions were better retained than items from the recency region. That is, as some items in the recency region were transferred to long-term memory, some still resided in working memory, had not been consolidated and were more vulnerable to the decay. This also indicated that items in the primacy and middle regions are transferred into long-term memory. This finding is in line with predictions of the dual-storage model (Raaijmakers & Shiffrin, 1981; Baddeley, 2001). The theory posits that the recency items residing in the short-lived working memory or phonological loop have less chance than the primacy and middle region items to be transferred to more permanent storage. In the AD group, the recall from all regions was equally poor, implicating inability to transfer information to long-term memory after the learning trials. This reconfirms that the information learned by the AD group was residing only in working memory, and despite rehearsal over five trials, the items fail to transfer to longer term storage.

The third, exploratory hypothesis centered on available capacity and ability to manipulate information. It was predicted that a neuropsychological measure of capacity (e.g., Digit Span Forward) would not differentiate the groups, but the measure of working memory (Digit Span Backwards) and processing speed (Trails-A) would differentiate the groups. The results indicated that this prediction was confirmed. Patients with AD and depression did performed more poorly on working memory and speed measures than healthy controls, but the capacity measure was equal among all three groups. These results parallel previous research, showing that Digit Span Forward is remarkably preserved in AD and late-life depression (e.g., Logie, Cocchini, Della Sala, & Baddeley, 2004).

This study used the dual-storage model as a framework to investigate the transfer of information from working to long-term memory (e.g., Raaijmakers & Shiffrin, 1981; Baddeley, 2001). Using information from the serial position curve, one is able to capture the operation of two different memory systems. The role of the primacy region reflects successful operation of transfer to the long-term memory while the recall of items in the recency area reflects the operation of the working memory. However, the role of the items in the middle region in the dual-storage model has not been entirely clarified. Spinnler et al. (1988) suggested that the ability to learn the items from the middle region depends on the efficient operation of the central executive component of working memory. Similarly, Foldi et al. (2003) suggested that the middle region was particularly vulnerable in patient groups that had limited capacity and/or attentional deficits, such as depression.

According to Baddeley's model of working memory (Baddeley, 2001), words in the phonological loop are represented by items in the recency region. With the repeated exposures to the same list, these items, together with items from the primacy and middle regions, can be transferred to long-term storage (Baddeley, 2003). In this study, the ability to complete this transfer varied across groups, being preserved in healthy and depressed older adults, but not in the AD group. In healthy older adults transfer benefited from rehearsal as demonstrated by the continued increase in the primacy and middle regions over the five trials. Depression provides a model of learning that is less efficient, and as a result has to draw on the attentional/executive functions to complete the transfer. In the current study these concepts were supported in the depressed group. This further suggests that while patients with depression can learn, the inefficiency of their working memory affects their performance. Further, covarying measures of working memory (i.e., Digit Span Backward) eliminates differences in the middle region between the healthy and depressed older adults.

After delay, for both Healthy Controls and LLD groups, some items from the recency region also remained in the phonological loop, since the decay of these items over time was very dramatic. In fact, the change from Trial 5 to Short Delay showed more similarities than differences between Healthy Controls and LLD patients. While the LLD group started by recalling fewer items, the amount of information recalled from each region and the resulting profile on delay recall were equivalent. Thus, the percentage lost over time by the depressed group appears to be equal to that of the healthy older adults.

How does this study help us learn about cognitive processing in depression, a group known for their cognitive deficits (e.g., Butters, 2004; Caine, 1986; Nebes, et al., 2000; Nebes et al., 2001)? Older patients with depression are widely known to exhibit deficits in effortful tasks (Cohen et al., 1982; Hammer, Lund & Hugdahl, 2003; Weingartner & Silberman, 1982), and recent evidence indicates that decreased processing speed largely accounts for memory and executive function deficits (Butters et al., 2004). The finding of the current study, that the middle region was more vulnerable in patients with depression than in healthy older adults, can similarly be explained by this mechanism. Reduced processing speed limits the ability to rehearse items within the same time span, and healthy individuals therefore benefit more with more frequent rehearsal of the same number of items. Corroboration of the disproportionately slowed processing speed by LLD patients was found in this study as measured by Trails-A. Also, the covarying measure of processing speed (Trails-A) eliminated group differences in terms of learning pattern.

The deficit in the middle region in the LLD group was already evident at Trial 1, where performance of the middle region in the depressed group (15% of the items presented from the middle region were recalled) was significantly poorer then the controls (25% recalled). The depressed group approached the performance of the controls over the next four trials, by trial 5 middle region recall for the depressed group was lower (50%) than the controls (61%), but the difference was no longer significant. In other words, the slow processing speed in depression renders inefficient processing of the items that are in the middle portion of the list to a greater extent than the items in the primacy region. One possibility is that, while the items from the middle region are being

presented, due to slower processing speed the items from the primacy region are still being rehearsed. As a result, middle region items do not receive an adequate amount of rehearsal to be transferred to long-term storage.

A corollary interpretation of deficient processing of items from the middle region may be the disruption of function of the central executive (Spinnler et al., 1988). Executive deficits are common features of depressive symptomatology (e.g., Lesser, et. al., 1996; Lockwood, et al., 2000; Butters et al., 2004), and LLD participants in the current study also demonstrated impaired performance on the neuropsychological measure of letter fluency, a task that notably weights on executive abilities (e.g., Jasnowski et al., 1989; Milner, 1975). As suggested by Spinnler et al. (1988) deficient executive functions can provide a partial explanation of the deficits in recall from the middle region over multiple trials in the following way. Once items are in the phonological loop, decisions must be made whether these items are already learned and if so, less attention is devoted to these item. However, an item that appears 'new' and is not already learned has to command additional attentional resources. Naturally, while executive in nature, this mechanism also depends on the speed of processing, such that slower speed may preclude the ability to identify and redirect attention to that item.

The current study also sheds light on whether semantic organization can aid patients with depression. Weingartner (1984) had proposed that depressed patients, unlike patients with AD, were able to benefit from cues that provided information about existing semantic organization. In that study free recall of lists was initially similar in AD and depression. However, once the existing semantic categories were made evident to participants only the depressed group would benefit, thus showing better recall. One of

the questions of the current study was whether lists with embedded organization provide additional advantage. There is a possibility that free recall lists that contain semantic grouping (e.g., CVLT: Delis et al., 1987 and 2000), could be potentially beneficial to depressed patients, while performance on non-semantically related lists (e.g. RAVLT) could reveal a different learning pattern. This difference may be more noted after the semantic organization is revealed (e.g. cued recall). The study of Foldi et al. (2003) used the CVLT in comparable groups, as did the current study. The results from the two studies show the same serial position pattern over five learning trials, with depressed patients recalling significantly less of the middle region items. Since this pattern was found using semantically related (CVLT), as well as semantically unrelated (RAVLT) lists, the lower middle region recall seems to be independent of any intrinsic semantic information in a list. In fact, the CVLT study showed that the depressed and healthy older adults did not differ in their use of semantic clustering in their recall pattern. In the current study, only 'semantic' abilities on category fluency measures were compared among the groups, and the healthy and depressed older adults performed similarly on that task.

The analyses of depression type (major vs. minor depression) or depression treatment (treated vs. untreated) did not influence the results. Neither the degree of depression nor medication significantly influenced the outcome of any measures with serial position during the learning as well as after delay staying robust. Although subjects diagnosed with major depression and those taking medications at the time of testing largely overlap, this suggests that, at least in these general subgroups, severity of depression did not influence the ability to transfer information from working to long-term

memory. These results corroborate Foldi et al's (2003) findings with a different group of depressed patients.

Compared to the patients with AD, the patients with depression were able to acquire more material overall, largely due to better processing of the items in the primacy and the middle regions. In fact, these two patient groups performed similarly in the recency region, albeit worse than the elderly controls. This latter difference and difficulty in processing items from the recency region both indicate deficient working memory for both patient groups. This was corroborated by an other neuropsychological measure of working memory (Digit Span Backward).

This study also revealed learning characteristics within the AD group. The traditional *Percentage* scores have always set the AD group apart from both the healthy and depressed older adults in this study showing far better recall in recency than other regions of the list, and were consistent with the notion that patients with AD almost wholly rely on working memory to learn new information. That information does not hold over time, leading to the rapid decay on short delay recall. This supports the long established decay of information in AD (Carlesimo, Fadda, Bonci, & Caltagirone, 1993;Gainotti et al, 1998) as a consequences to the underlying structural hippocampal and entorhinal damage (Arriagada et al., 1992; Braak & Braak, 1995; Hyman et al., 1985). The current findings using *Regional* scores showed new evidence in AD that performance within the recency region does change overtime. That is with repeated exposure, recall of these items improves, however this information is not retained over time. This improvement in all regions (particularly in the recency region) during the learning phase, raises the possibility that certain learning mechanisms are still operative,

which could be tapped. Possibly in addition to procedural learning and priming, mechanisms that are partially spared in AD (Deweer, Ergis, Fossati, Pillon, Boller, Agid, et al., 1994; Eslinger & Damasio, 1986; Hirono, Mori, Ikejiri, Imamura, Shimomura, Ikeda, M., et al., 1997; Libon, Bogdanoff, Cloud, et, al., 1998; Zenetti, Binetti, Magni, Rozzini, Bianchetti & Trabucchi, 1997). These data offer possibilities of understanding how some rehearsal mechanisms taking full advantage of spared working memory could be harnessed in the service of limited resources, albeit promising treatment.

There are several limitations to the current study. First, all participants for the study were selected from the referrals for neuropsychological evaluation by the psychiatric or medical geriatric clinics. As it also applies to the participants who were healthy controls, they are not fully representative of healthy older population from the community. Second, this was a retrospective study using records collected over a number of years by the Neuropsychology Service of the Department of Psychiatry at Mount Sinai Medical Center, New York. During that time the neuropsychological battery which was administered by the neuropsychological services had changed. Therefore, the measures were limited to those administered to all subjects. More measures of speed, executive functions, attention, and working memory would have been very valuable to the study. Lastly, there were limited measures of severity available both for the AD and LLD groups. More objective cognitive rather than clinical measures (e.g., Dementia Rating Scale; Mattis, 1988) would have provided a broader picture of subjects' overall cognitive functioning. Also, such measures could have been used and entered into the analyses.

The current study supports that the theory of working memory and transfer in a dual-storage model effectively explains the patterns of serial position learning. With this

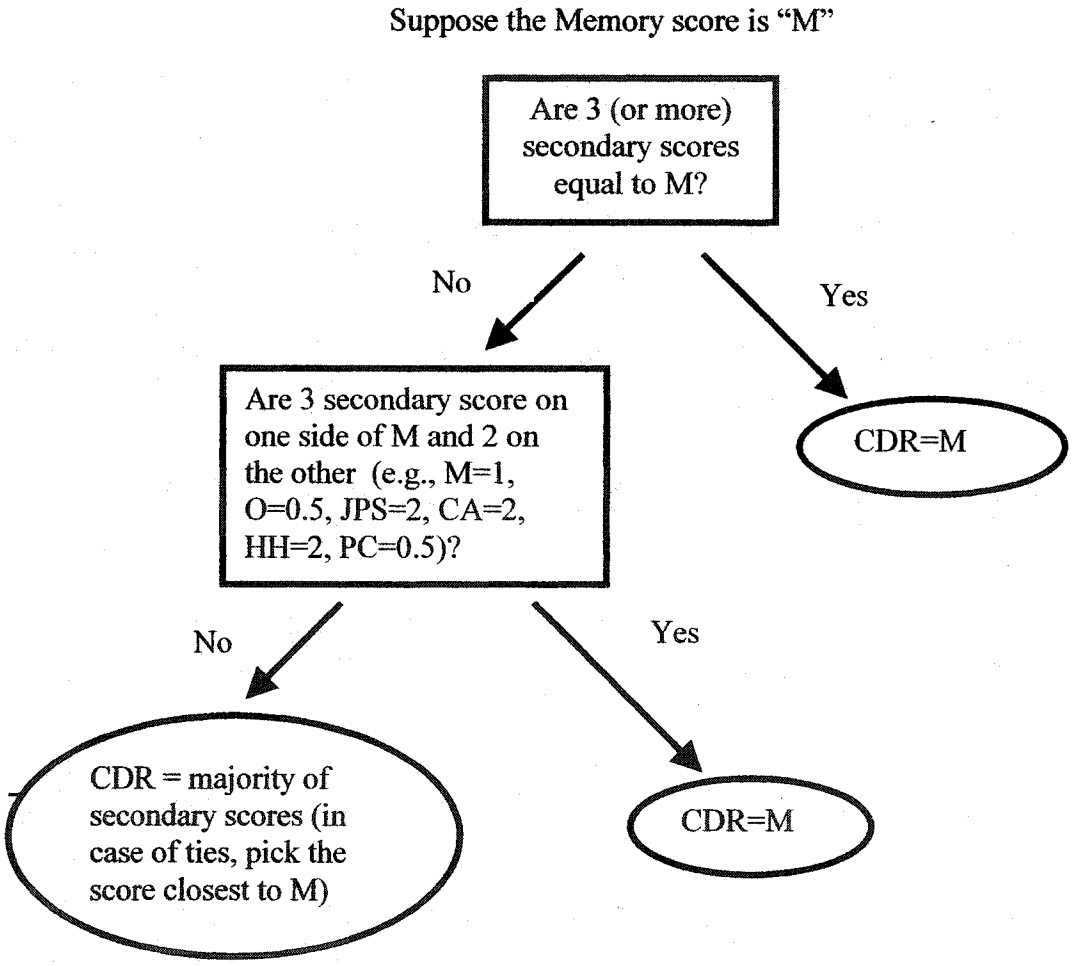
knowledge, we feel that these identifiable patterns can be used in clinical patient assessment. Analysis of the serial position recall using *Regional* scores confirmed that there are specific profile deficits in learning items that differentiate normal aging, from late-life depression, and from early AD. Impaired performance of the middle portion of the list is a new area of learning problems that may be associated with late-life depression, much like prominent recency recall is indicative of AD. In particular, lower recall from the middle region appears to differentiate depressed from healthy older adults. In the current study, it was also demonstrated that the patients with AD, when exposed to the same material repeatedly, are able to acquire some information and hold on to it for short period of time. The learning pattern revealed by the traditional *Percentage* scores reliably differentiated patients with AD from healthy and depressed older adults, however it did not set apart the depressed from healthy older adults. In turn, *Regional* scores, in addition to differentiating AD from healthy aging and depression, distinguished the depressed from healthy adults and AD. The validation of the *Regional* scores used in the current study emphasizes the usefulness of these measures and continued use of these techniques as clinical and experimental tools.

Appendix

Clinical Dementia Scale (CDR) = Manual scoring procedure

The global staging of dementia is based upon the Washington University Clinical Dementia Rating (CDR) instrument (Hughes et al., 1982). In this scale, the clinician uses all available information to rate the subject's performance in each of six cognitive categories: Memory (M), Orientation (O), Judgment and Problem Solving (JPS), Community Affairs (CA), Home and Hobbies (HH), and Personal Care (PC). However, Memory is the primary category; all others are secondary.

To assign a CDR score, use the following flowchart.



Special cases:

1. M = 0; 2 or more secondary scores greater than 0 → CDR = 0.5
2. M = 0.5; 3 or more secondary scores greater than or equal to 1 → CDR = 1
3. M > 0; majority of secondary scores equal 0 → CDR = M
4. Two secondary scores less than M; greater than M; one = M → CDR = M
5. M = 0; overall CDR must be >=0.5

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Tables and Figures

	Healthy Control N=22			Late-Life Depression N=24			Alzheimer's disease N=34		
Test	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Age	73.23	8.61	51 - 87	74.25	9.64	52 - 89	76.09	9.27	51 - 89
Education	15.73	3.18	9 - 20	13.42	4.46	6 - 20	14.15	4.37	4 - 22
Premorbid IQ	125.01	9.81	99 - 137	119.34	17.33	93 - 153	115.73	14.56	84 - 139

Table 1. Mean, range and standard deviation for age, education, and premorbid IQ.

CDR Score	HC N=22	LLD N=24	AD N=34
0.0	22	20	0
0.5	0	4	5
1.0	0	0	12
2.0	0	0	13
3.0	0	0	4

Table 2. Distribution of the Clinical Dementia Rating (CDR) scores in the Healthy Control (HC), Late-Life Depression (LLD) and Alzheimer's disease (AD) groups.

Source	Sum of Squares	Degrees of Freedom	Mean Square	F	p
GROUP	101.47	2	50.73	2.14	.124
Error	1823.52	77	23.68		
TRIAL	79.18	1.69	46.59	.79	.436
GROUP x TRIAL	180.39	3.39	53.07	.90	.451
Error	7686.27	130.85	58.74		
REGION	49362.94	1.92	25701.67	24.87	.000
GROUP x REGION	29138.89	3.84	7585.83	7.34	.000
Error	152831.52	147.88	1033.43		
REGION x TRIAL	18494.32	4.75	3892.32	6.96	.000
GROUP x REGION x TRIAL	7042.46	9.50	741.08	1.32	.219
Error	204760.82	365.86	559.66		

Table 3. RAVLT – *Percentage* scores
Source table: Group (3: HC, n=22; LLD, N=24; AD, N=34) x Region (3: Primacy, Middle, and Recency) x Trial (5: Trial 1-5).

	HC		LLD		AD		
	Mean	S.D.	Mean	S.D.	Mean	S.D	
Primacy	27.98	7.25	29.32	8.34	24.07	14.44	HC = LLD = AD
Middle	35.55	9.46	31.28	9.72	23.41	12.02	(HC = LLD) > AD
Recency	36.47	7.88	39.40	9.27	50.76	16.74	(HC = LLD) < AD

Table 4. RAVLT - mean *Percentage* scores for Primacy, Middle, and Recency; Healthy Control (HC; N=22), Late-Life Depression (LLD; N=24), and Alzheimer's disease (AD; N=34).

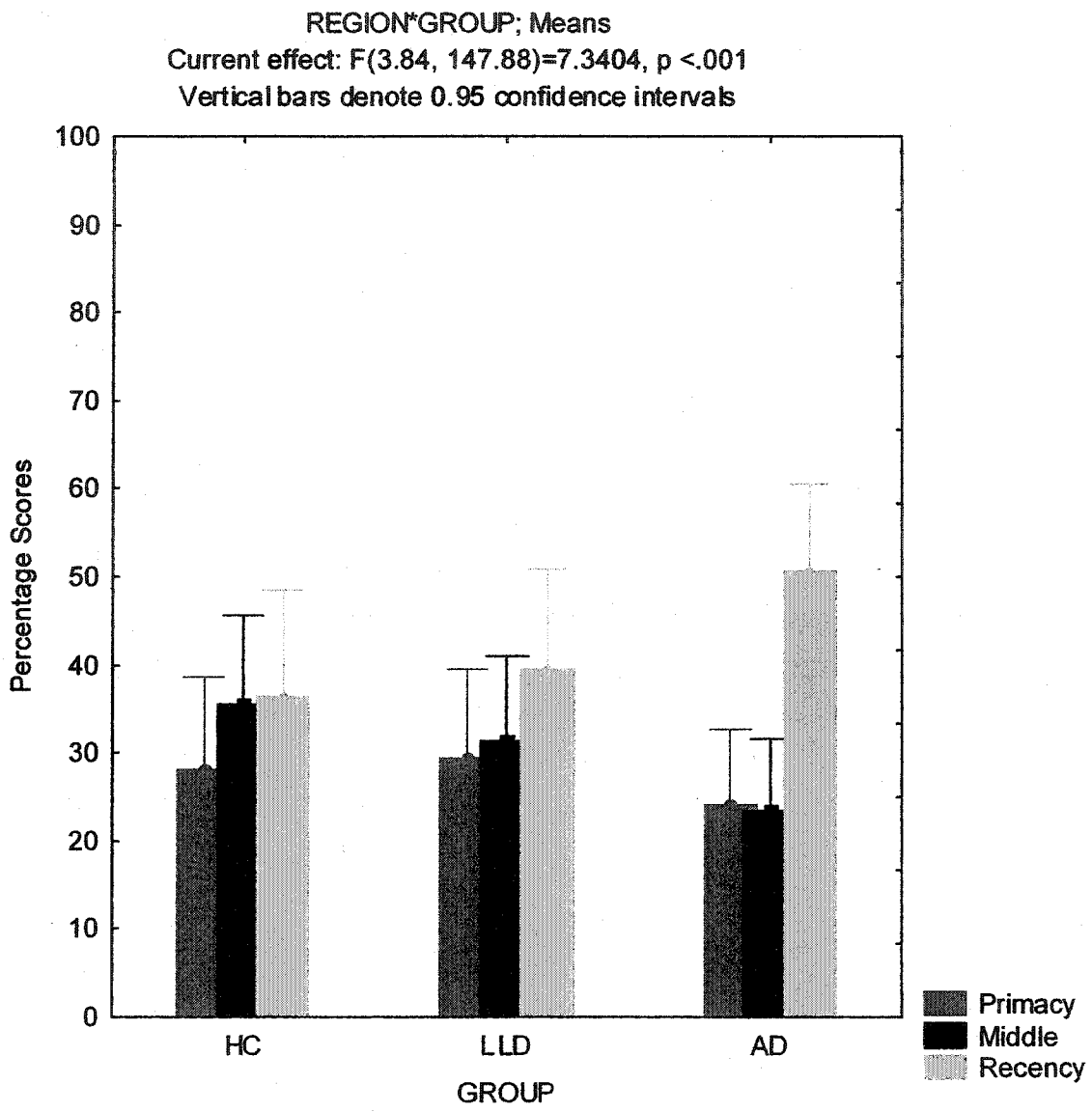

Figure 1. RAVLT – mean *Percentage scores* for Primacy, Middle, and Recency regions collapsed across five trials; Healthy Control (HC; N=22), Late-Life Depression (LLD; N=24), and Alzheimer's disease (AD; N=34).

Source	Sum of Squares	Degrees of Freedom	Mean Square	F	p
GROUP	115857.42	2	57928.71	38.21	.000
Error	116743.56	77	1516.15		
REGION	234299.90	1.79	130997.27	89.71	.000
GROUP x REGION	13585.51	3.58	3797.84	2.60	.045
Error	201098.14	137.72	1460.1		
TRIAL	109145.87	3.41	32023.62	116.54	.000
GROUP x TRIAL	3027.95	6.82	444.20	1.62	.133
Error	72117.03	262.44	274.80		
REGION x TRIAL	6941.40	6.60	1051.80	2.19	.037
GROUP x REGION x TRIAL	14752.37	13.20	1117.68	2.33	.005
Error	243730.00	508.16	479.63		

Table 5. RAVLT - *Regional* scores
Source table: Group (3: HC, N=22; LLD, N=24; AD, N=34) x Region (3: Primacy, Middle, and Recency) x Trial (5: Trial 1-5).

	HC		LLD		AD		
	Mean	SD	Mean	SD	Mean	SD	
Primacy	62.96	18.03	53.33	16.19	33.53	20.32	(HC = LLD) > AD
Middle	47.01	14.72	34.76	16.46	19.33	13.69	HC > LLD > AD
Recency	76.36	11.46	66.67	17.85	62.50	17.41	HC > (LLD = AD)

Table 6. RAVLT – mean *Regional scores* for Primacy, Middle, and Recency; Healthy Controls (HC; N=22), Late-Life Depression (LLD; N=24), and Alzheimer's disease (AD; N=34).

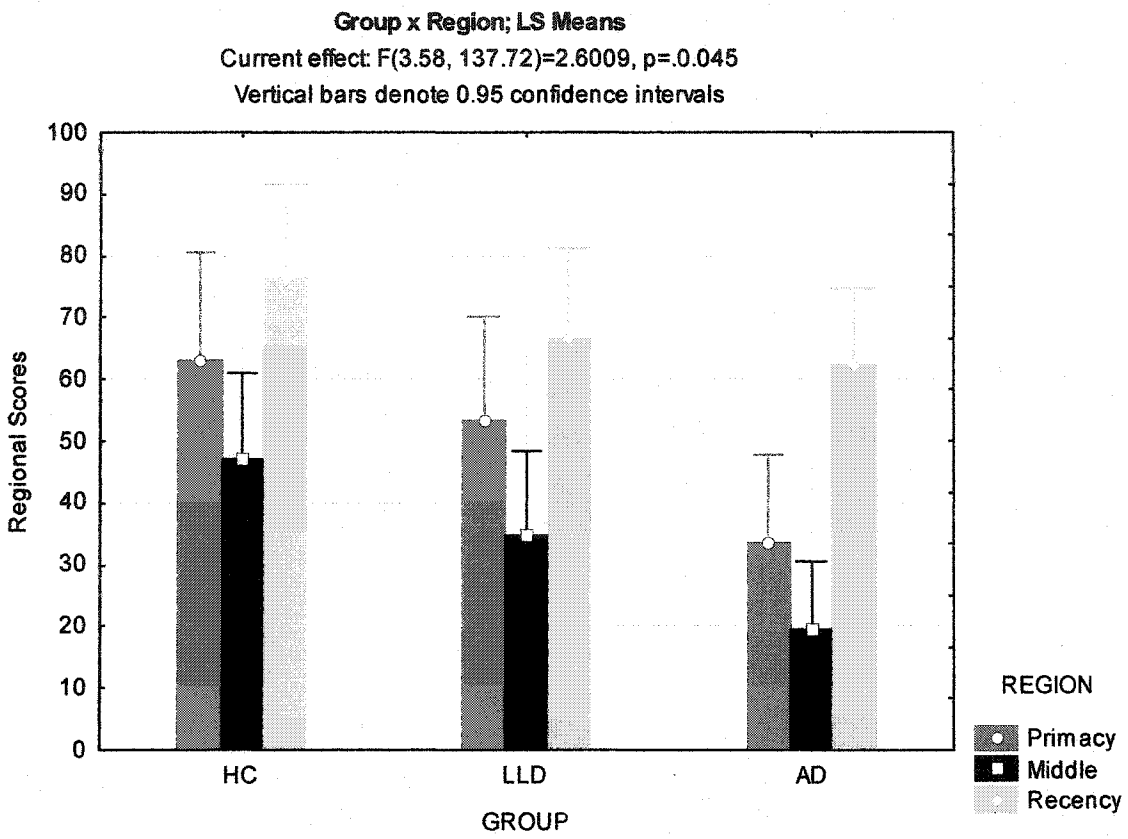

Figure 2. RAVLT - mean *Regional scores* for Primacy, Middle, and Recency regions collapsed across five trials; Healthy Controls (HC; N=22), Late-Life Depression (LLD;

		NC N = 22		LLD N = 24		AD N = 34		
Region	Trial	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Primacy	Trial 1	39.77	31.49	28.13	25.87	19.12	19.52	(NC = LLD) > AD
	Trial 2	61.36	24.06	45.83	19.03	30.88	26.87	NC > LLD > AD
	Trial 3	60.23	23.98	60.42	26.50	36.76	25.55	(NC = LLD) > AD
	Trial 4	72.73	24.29	68.75	25.80	41.91	31.21	(NC = LLD) > AD
	Trial 5	80.68	23.06	63.54	30.38	38.97	30.27	NC > LLD > AD
	Short-delay	63.64	25.27	52.08	31.20	19.12	24.66	(NC = LLD) > AD
Middle	Trial 1	25.32	15.85	15.48	10.25	7.98	10.07	NC > LLD > AD
	Trial 2	37.66	19.98	26.79	18.51	17.65	16.14	NC > LLD > AD
	Trial 3	53.25	21.68	38.10	20.49	20.17	16.91	NC > LLD > AD
	Trial 4	57.79	21.36	42.86	26.97	23.95	20.12	NC > LLD > AD
	Trial 5	61.04	21.23	50.10	25.62	26.89	23.53	(NC = LLD) > AD
	Short-delay	50.00	27.80	36.31	26.97	13.03	20.32	(NC = LLD) > AD
Recency	Trial 1	65.91	21.19	60.42	26.50	44.12	28.24	(NC = LLD) > AD
	Trial 2	73.86	21.10	64.58	22.01	58.82	27.44	NC=LLD; NC>AD; LLD=AD
	Trial 3	79.55	19.88	65.63	30.23	68.38	21.59	NC = LLD = AD
	Trial 4	82.95	16.16	76.04	21.47	64.71	23.93	(NC = LLD) > AD
	Trial 5	79.55	21.32	66.67	29.18	76.47	21.27	NC = LLD = AD
	Short-delay	39.77	21.35	35.42	29.41	12.50	19.70	(NC = LLD) > AD

Table 7. RAVLT – mean *Regional scores* for Primacy, Middle, and Recency for Trials 1-5 and Short Delay Free Recall ; Healthy Control (HC), Late-Life Depression (LLD), and Alzheimer's disease (AD).

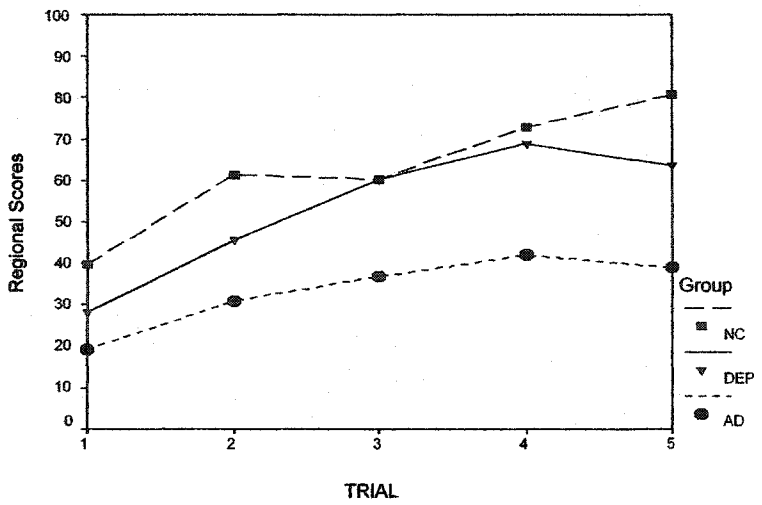

Figure 3a
Primacy

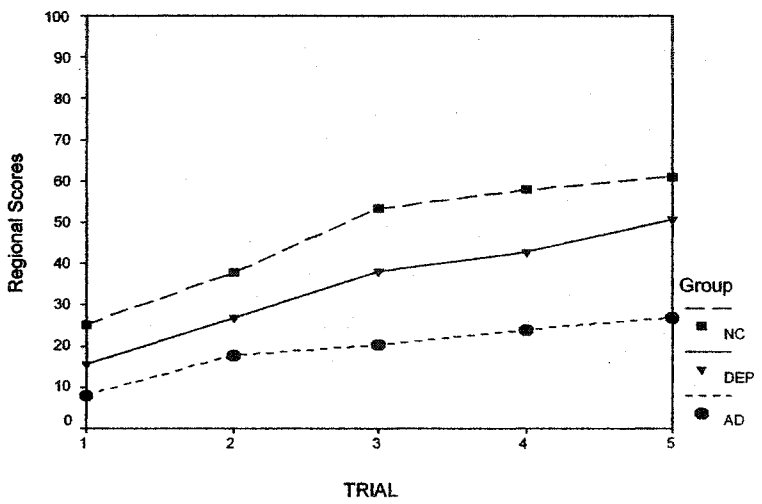

Figure 3b
Middle

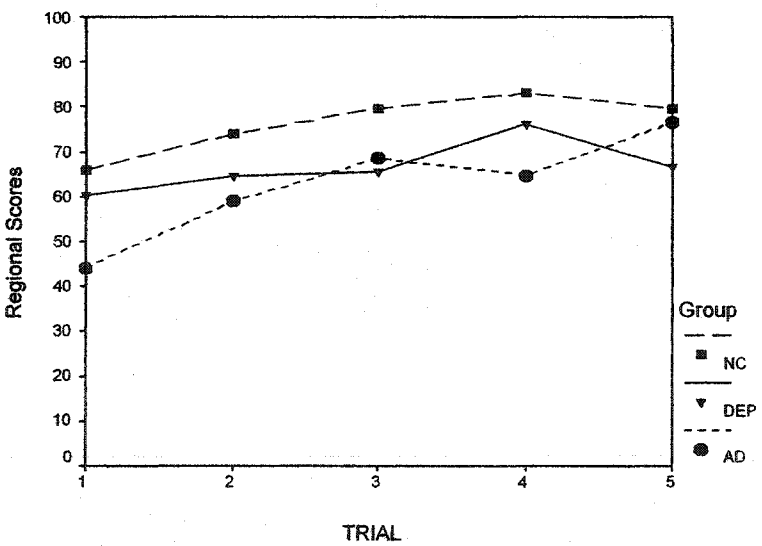

Figure 3c
Recency

Figure 3. RAVLT – mean *Regional scores*
a) Primacy, b) Middle, and c) Recency regions across five trials; Healthy Control (HC; N=22), Late-Life Depression (LLD; N=24), and Alzheimer's disease (AD; N=34).

Source	Sum of Squares	Degrees of Freedom	Mean Square	F	p
GROUP	83827.91	2	41913.95	30.01	.000
Error	107547.92	77	1396.72		
REGION	16796.71	1.95	8621.70	12.04	.000
GROUP x REGION	13527.63	3.90	3471.84	4.85	.001
Error	107398.13	150.01	715.93		
TRIAL	70829.98	1	70829.98	205.89	.000
GROUP x TRIAL	4331.98	2.00	2165.99	6.30	.003
Error	26489.63	77.00	344.02		
REGION x TRIAL	23981.99	1.96	12216.52	34.97	.000
GROUP x REGION x TRIAL	4677.64	3.93	1191.41	3.41	.011
Error	52804.87	154.00	342.88		

Table 8. RAVLT - *Regional* scores
Source table: Group (3: HC, N=22; LLD, N=24; AD, N=34) x Region (3; Primacy, Middle, and Recency) x Trial (2; Trial 5 and ort Delay Free Recall). Degrees of Freedom are reported with Greenhouse-Geisser corrections.

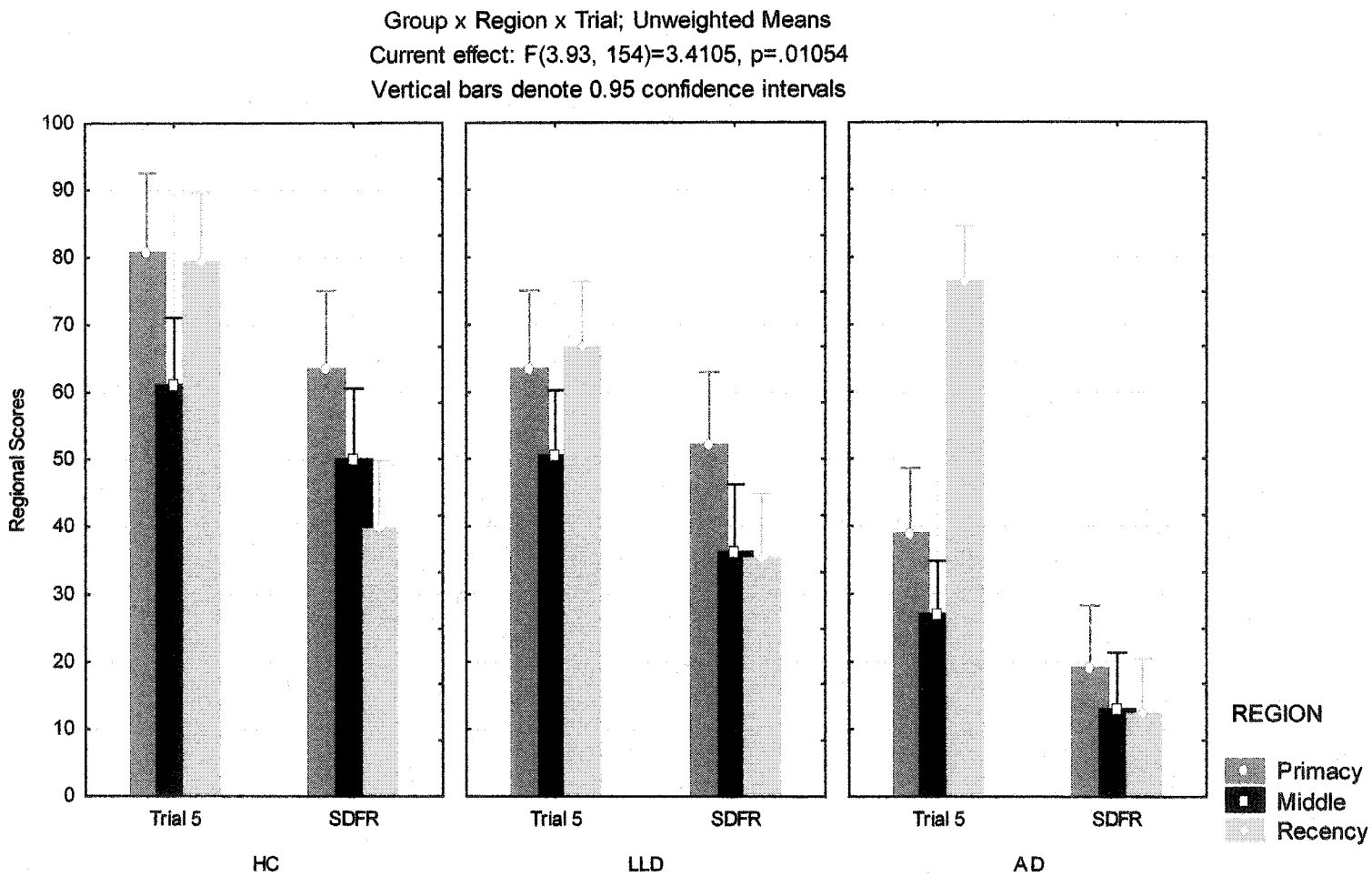

Figure 4. RAVLT – mean *Regional scores* for Primacy, Middle, and Recency regions on Trial 5 and Short Delay Free Recall ; a) Healthy Control (HC); N=22, b) Late-Life Depression, (LLD); N=24, and c) Alzheimer's disease, (AD); N=34.

Group	HC, N=22			LLD, N=24			AD, N=34		
	t	df	*p*	*t*	df	*p*	*t*	df	*p*
Primacy	2.45	21	.023	3.14	23	.005	4.65	33	<.001
Middle	3.58	21	.002	2.30	23	.031	3.78	33	.001
Recency	6.11	21	.001	4.51	23	<.001	13.17	33	<.001

Table 9. RAVLT – Primacy, Middle, and Recency regions
Paired t-test – loss of information from Trial 5 to Short Delay Free Recall in *Regional* scores

Source	Sum of Squares	df	Mean Square	F	p
GROUP	451.50	1	59640.35	.64	.430
Error	31279.59	44	710.90		
REGION	14945.76	2	7472.88	10.99	.000
GROUP X REGION	861.54	2	430.77	.633	.533
Error	59852.19	88	680.14		

Table 10. RAVLT – saving score (difference between *Regional scores* on Trial 5 and Short Delay Free Recall).
Source table: Group (2: HC; N=22, LLD; N=24) x Region (3: Primacy, Middle, and Recency).

	HC		LLD		AD		
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	
Digit Span Forward - percentile	71.14	29.89	67.54	29.12	57.88	34.22	NC = LLD = AD
Digit Span Backward - percentile	73.55	18.85	52.04	29.36	45.82	33.52	NC > (LLD = AD)
Trails A - percentile	64.82	27.72	32.29	30.76	36.53	29.13	NC > (LLD = AD)
Letter Fluency (FAS) - mean words per letter	14.41	4.42	10.43	4.37	10.07	5.5812	NC > (LLD = AD)
Category Fluency (Animals) - mean words	20.18	5.09	13.83	5.16	9.68	4.54	NC > LLD > AD

Table 11. Means of neuropsychological measures: Digit Span Forward, Digit Span Backward, Trails A, letter fluency (FAS), category fluency (Animals); Healthy Controls (HC; N=22), Late-Life Depression (LLD; N=24), and Alzheimer's disease (AD; N=34

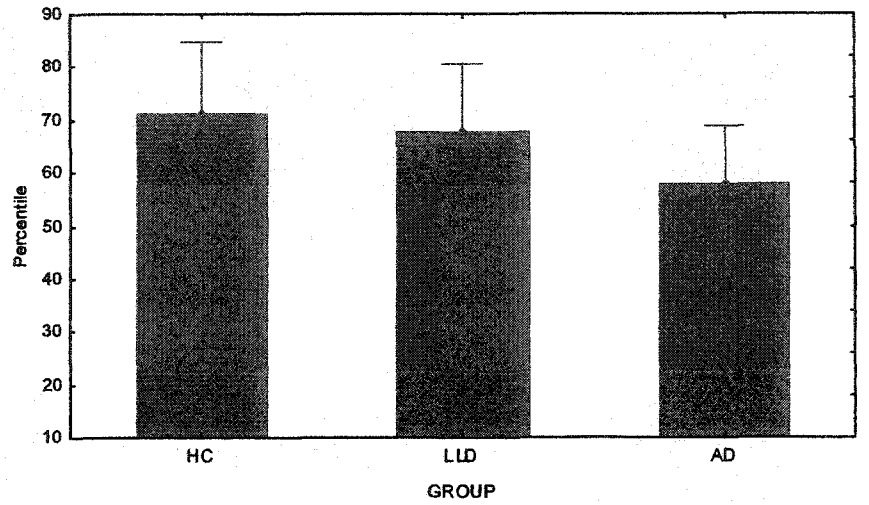

Figure 5a.

Digit Span Forward

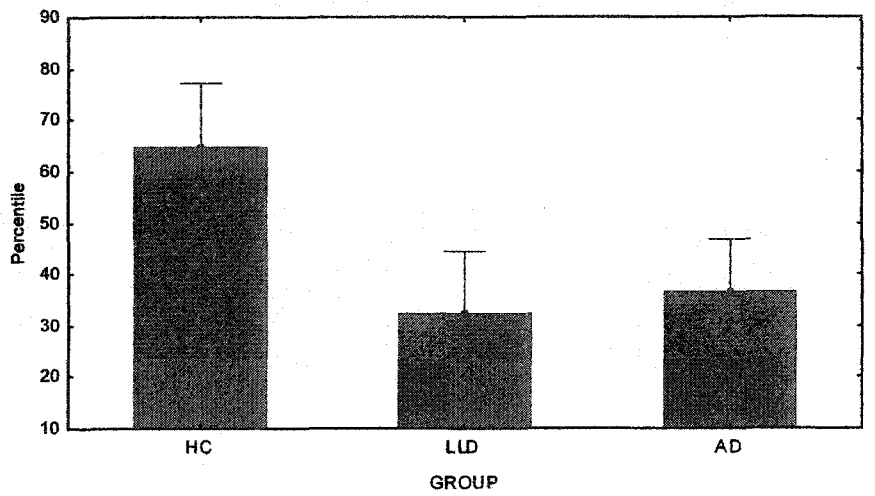

Figure 5b.

Digit Span Backward

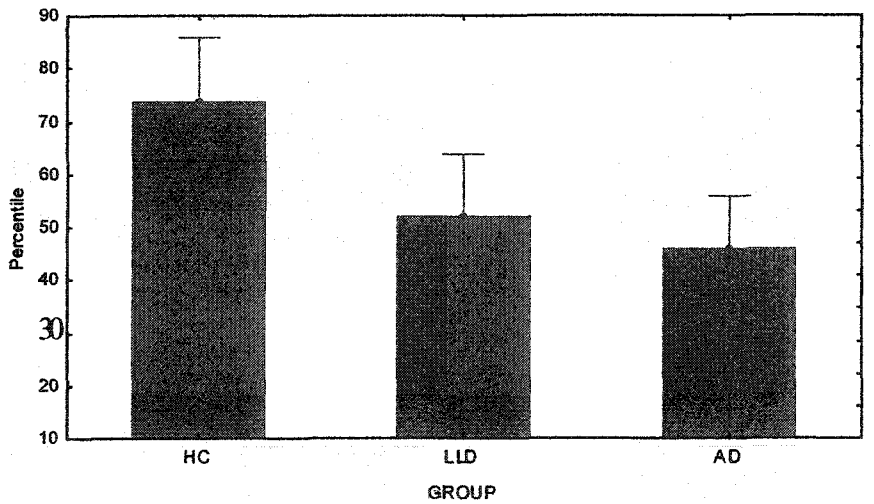

Figure 5c.

Trails-A

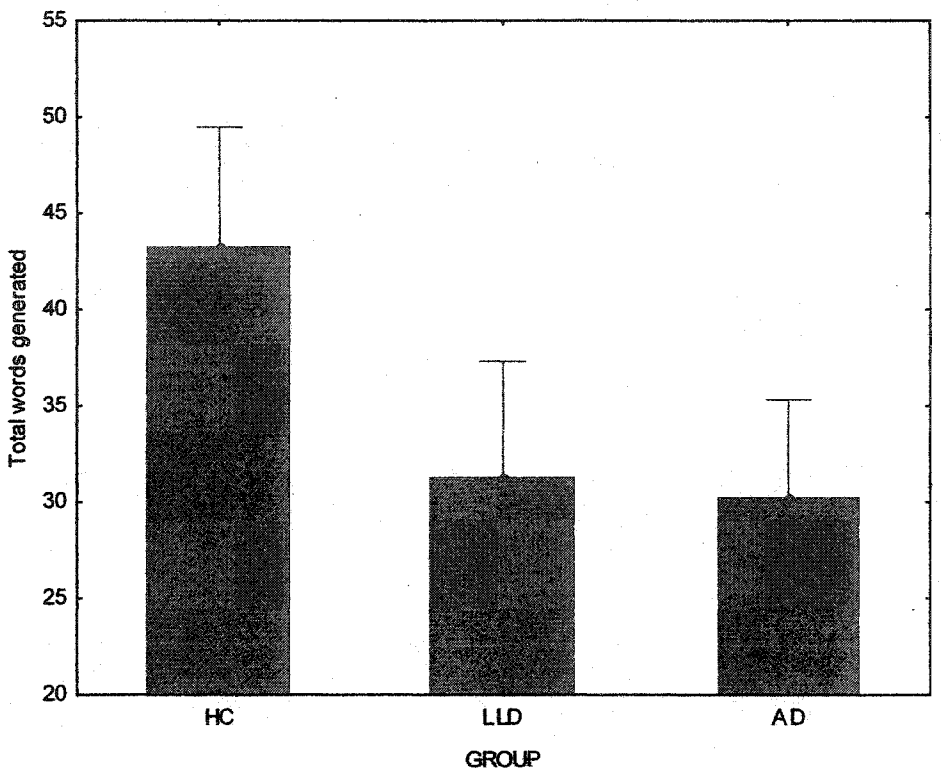

Figure 5d.

Letter Fluency: FAS

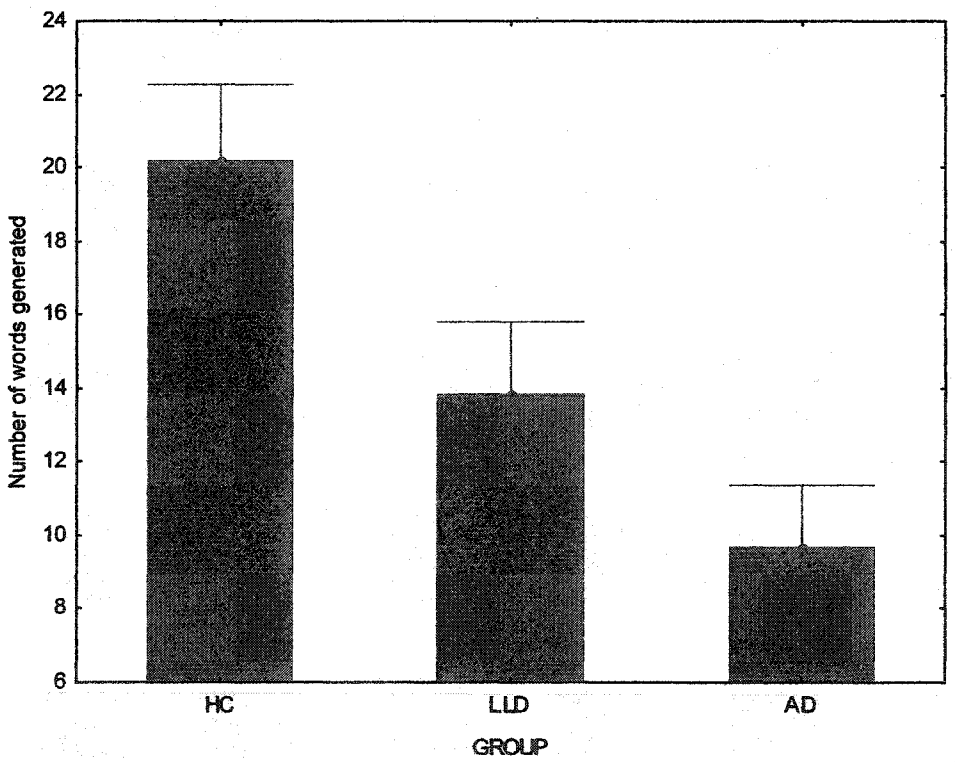

Figure 5e.

Category Fluency: Animals

Figure 5. Performance on neuropsychological measures: a) Digit Span Forward, b) Digit Span Backward, c) Trails-A, d) letter fluency (FAS) and e) category fluency (Animals); Healthy Controls (HC; N=22), Late-Life Depression (LLD; N=24), and Alzheimer's disease (AD; N=34).