Rowan University

Rowan Digital Works

10-16-2018

Visual and verbal serial list learning in patients with statistically-determined mild cognitive impairment

Victor J. Wasserman
Rowan University

**VISUAL AND VERBAL SERIAL LIST LEARNING IN PATIENTS WITH
STATISTICALLY-DETERMINED MILD COGNITIVE IMPAIRMENT**

by

Victor J. Wasserman

A Thesis

Submitted to the
Department of Psychology
College of Science and Mathematics
In partial fulfillment of the requirement
For the degree of
Master of Arts in Clinical Psychology
at
Rowan University
October 5, 2018

Thesis Chair: David Libon, PhD

Dedications

To my sister, my parents, and my wife; for caring, caring too much, and feigning indifference about this project.

Acknowledgments

This study would simply not have taken place without the mentorship and
patience of David J. Libon and Sheina Emrani, from whom I have learned so much in so
short a time. Their manifest competence and dedication to neuropsychology set the goal
markers for what I seek from my own education.

Abstract

Victor J. Wasserman
VISUAL AND VERBAL SERIAL LIST LEARNING IN PATIENTS WITH
STATISTICALLY-DETERMINED MILD COGNITIVE IMPAIRMENT
2018-2019
David Libon, PhD
Master of Science in Clinical Psychology

Objective: To compare verbal versus visual serial list learning test performance in mild cognitive impairment (MCI) and assess relationships between serial list learning and hippocampal volume. Methods: Patients were diagnosed with non-MCI, amnestic MCI (aMCI), and combined mixed/dysexecutive MCI (mixed/dysMCI). Outcome measures included immediate/delay free recall, and delay recognition performance from the 12-word Philadelphia Verbal Learning Test (PrVLT) and the Brief Visuospatial Memory Test-Revised (BVMT-R). Lateral hippocampal volumes were obtained. Results: Non-MCI patients scored better than other groups on P(r)VLT immediate/delay free recall. aMCI patients scored lower than other groups on P(r)VLT delay recognition. Non-MCI patients were superior to MCI groups on all BVMT-R parameters. All groups scored lower on BVMT-R compared to analogous P(r)VLT parameters. Better P(r)VLT immediate/delay free recall was associated with greater left hippocampal volume. BVMT-R 2-point, full credit responses were associated with greater right hippocampal volume; memory for object location was associated with left hippocampal volume. Conclusions: Both serial list learning tests identify memory impairment. The association for the BVMT-R and bilateral hippocampal volume suggests a wider neurocognitive network may be recruited for visual serial list learning. These data suggest that visual serial list learning may be particularly sensitive to emergent cognitive impairment.

Table of Contents

Table of Contents (Continued)

List of Figures

List of Tables

Chapter 1

Introduction

The term "*episodic memory*," or the memory for specific autobiographical events, was initially coined by Tulving (1972) and is conceptualized as part of declarative memory. Episodic memory plays a crucial role in most theoretical models of memory. The Baddeley-Hitch multicomponent model (Baddeley, 2003), perhaps the most influential memory model, outlines that the construct involved for encoding visual information is a 'visuospatial sketchpad,' while verbal information is processed by a 'phonological loop.' Together, these constructs form the working memory system and enable the rehearsal and subsequent encoding of information into long term memory. The episodic buffer was later proposed as a multimodal space for integrating information across sensory modalities and binding object features such as shape and location, enabling more meaningful context. This "global workspace" provides an explanation regarding how constructs involving working memory are brought together and contribute to encoding information into long term memory.

Other models of memory have used similar multi-dimensional conceptualizations to explain the transitional differences of short and long term memory. Brown, Neath and Chater's Temporal Ratio Model of Memory (2007) argues that short and long term memory are not distinct, but that all retrieval is a multi-dimensional discrimination process in which each dimension, including time since original encoding, is a categorical feature and the target trace must be parsed from dimensionally-similar traces. This model suggests that forgetting is a consequence of high confusability among similar features. Within this model, time since original encoding is treated as temporal distance, a

1

logarithmically compressed timeline where more recent traces are more easily discerned from one another than distant ones. This is argued to explain the observation that errors and forgetting become more frequent as time elapses. In both of these models, the treatment of episodic memory as a multi-dimensional workspace for the integration of features underlines the importance of episodic memory for creating meaningful relationships and context to aid in accurate retrieval.

In healthy adults, visual and verbal memory are similarly affect by aging. Kumar and Priyadarshi (2013) observed visual and verbal working memory following similar patterns of age-related decline with no significant difference between modalities in terms of working memory span. Bender et al. (2017) studied face-name association recognition in healthy adults. These authors observed that recognition for associations experience greater age-related decline than recognition for items; however, age-related deficits are not apparent when employing stimuli with low contextualization, indicating that the binding cost of visually complex stimuli may influence associative memory deficits. Bender et al. (2017) found no differences for item recognition when considering visual vs. verbal stimuli type, supporting that visual and verbal memory do not differ in healthy adults.

The early detection of emergent dementia including Alzheimer's disease (AD) has become a major public health initiative. As such there is great interest in the diagnosis of mild cognitive impairment (MCI), a clinical syndrome believed to convey risk for the eventual emergence of dementia such as AD. A key neuropsychological feature for the diagnosis of MCI revolves around patterns of performance on episodic memory tests using serial-list learning test paradigms. Performance on verbal serial list learning tests

in MCI has been extensively researched (Libon et al., 2011; Lim et al., 2012). For example, research has consistently shown an intermittent level of free recall performance produced by MCI patients as compared to healthy older adults and AD patients (Albert et al., 2011; Lim et al., 2012; Snyder et al., 2011) and greater primacy versus recency recall among MCI and AD patients (Lim et al., 2012; Ribeiro, Guerreiro, & De Mendonça, 2007). Libon et al., (2011) assessed patterns of performance in statistically determined groups of patients with amnestic MCI (aMCI), dysexecutive MCI, and multi-domain/mixed MCI using the 9-word Philadelphia (repeatable) Verbal Learning Test (PrVLT). aMCI patients displayed greater decline in free recall test performance, no improvement with recognition testing, and produced more extra-list intrusion errors compared to other MCI groups, a pattern of performance qualitatively similar to patients with AD (Price et al., 2009). Other serial list learning tests, such as the Rey Auditory Verbal Learning Test (RAVLT) and the Free and Cued Selective Reminding Test (FCSRT), have also been shown to be effective in differentiating between normal controls and MCI patients, with normal control groups recalling more test items than MCI samples; and between MCI subtypes, for whom amnestic cases have worse recall than non-amnestic individuals (Bondi & Smith, 2014; Derby et al., 2013; Wagner M., 2012).

There has been less research regarding performance on visual episodic memory as related to differential performance between MCI subtypes. Gifford et al., (submitted for publication) examined a group of community dwelling participants using the Biber Figure Learning Test (BFLT), a visual serial list learning test that was modeled after the original California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987).

These researchers found that reduced BFLT total learning, delayed recall, recognition test scores were associated with smaller medial temporal lobe volume and higher cerebrospinal fluid (CSF) tau concentrations; indices thought to be closely related and indicative of the presence and severity of neurodegeneration. There was also no association with CSF amyloid β 42, a biomarker related to AD. Ye and colleagues (2014) studied a group of aMCI patients using a visual recognition test and grouped patients with respect to material-specific performance deficits, i.e., a visual-aMCI group, a verbal-aMCI group, and a combined dual-modality group. Patients in the visual-aMCI group were judged to be at greater risk to progress to dementia. De Anna et al. (2014) followed MCI patients longitudinally using a visual recognition memory test and found that visual recognition test performance may be able to identify subtle baseline alterations in cognition that may predict eventual conversion to AD. These findings are consistent with additional longitudinal research suggesting that visual recognition and visual serial list learning memory test performance may be particularly sensitive to AD conversion (Didic et al., 2013; Okonkwo et al., 2014).

An issue that has not been extensively addressed is the extent to which verbal versus visual serial list learning test yield convergent, as well as divergent, patterns of performance among patients with MCI. Bonner-Jackson and colleagues (Bonner-Jackson, Mahmoud, Miller, & Banks, 2015) studied groups of MCI patients with verbal (Hopkins Verbal Learning Test-Revised; HVLT-R) and visual (Brief Visuospatial Memory Test-Revised; BVMT-R) serial list learning tests and obtained measures of hippocampal volume. This research was primarily designed to investigate relations between hippocampal volume and memory test performance. Verbal and visual serial list

learning immediate and delay free recall were assessed. The analyses suggested that both

tests were able to identify memory impairment. Nonetheless, BVMT-R performance

demonstrated greater association with hippocampal volume than performance on the

HVLT-R.

Purpose of Study.

      Hypothesis 1. The current research aims to build on the findings reported by

Bonner-Jackson et al. (2015). A primary goal of the current research was to assess for

convergent as well as divergent patterns of impairment associated with both free recall

and recognition test performance in statistically-determined patients presenting with non-

MCI, amnestic MCI, and combined mixed/ dysexecutive MCI syndromes. Similar to

Bonner-Jackson et al., (2015) verbal and visual serial list learning tests were assessed

using the 12-word Philadelphia (repeatable) Verbal Learning Test P(r)VLT and the Brief

Visuospatial Memory Test-Revised (BVMT-R), respectively. For both tests, MANCOVA

analyses assessed immediate and delay free recall. To extend the findings reported by

Bonner-Jackson et al. (2015), MCI and non-MCI groups were diagnosed using the

comprehensive neuropsychological diagnostic criteria suggest by Jak, Bondi et al.,

(2009). Delay recognition test performance was also assessed and within group

comparisons were performed, because of the demonstrated contribution of delayed

recognition assessment in determining risk for disease progression. Based on previous

research by Jackson et al., (2015), we predicted that both MCI groups would demonstrate

impairment on the verbal test of episodic memory relative to the non-MCI group, while

only the aMCI group would show differential impairment on the visual episodic memory

test.

Hypothesis 2. This study is also intended to determine how lateralized measures of hippocampal volume may be uniquely associated with verbal versus visual serial list learning test performance. To determine if lateral or bilateral relationships exist between serial list learning test performance and left versus right hippocampal volume, stepwise forward entry regressions were performed. On the basis of prior research (Bonner-Jackson et al., 2015), we predicted that better verbal episodic memory test would be associated with greater left hippocampal volume, while better visual episodic memory performance would be related to both larger left and right hippocampal volume.

Hypothesis 3. Because visual serial list learning tests are not as widely studied as verbal tests of episodic memory, a secondary aim was to determine the relative contributions of item memory and associative memory to accurate discrimination between diagnoses for visual serial list learning. Previous work by Troyer et al. (2008) found that associative memory, including memory for a target object's location at the time of encoding, may be particularly sensitive to early changes in cognitive status for individuals with aMCI, with a target object's location at encoding demonstrating a high sensitivity and specificity for discriminating between aMCI and non-MCI with the BVMT-R. In the current research, we sought to determine if memory for object versus memory for object location may prove more sensitive to cognitive status. Receiver operating characteristic (ROC) curves were used to determine the sensitivity and specificity of memory for object location (MOL; a measure of associative memory) and memory for object (MFO; a measure of item memory) for the BVMT-R. We predicted that MOL would demonstrate better discriminability between non-MCI and other groups than MFO.

Chapter 2

Methods

Participants

Participants studied in the current research (n= 97) were recruited from Rowan University, New Jersey Institute for Successful Aging, Memory Assessment Program (MAP). All MAP patients underwent a comprehensive neuropsychological evaluation and were also examined by a social worker and a board certified geriatric psychiatrist. An MRI/CT study of the brain and appropriate serum blood tests were obtained to evaluate for reversible causes of dementia. A clinical diagnosis was determined for each patient at an interdisciplinary team conference. All participants presented with subjective cognitive complaints. Patients diagnosed with MCI produced evidence of cognitive impairment relative to age and education, preservation of general functional abilities, and the absence of dementia. Participants were excluded if there was any history of head injury, substance abuse, or major psychiatric disorders, including major depression, bipolar disorder, and epilepsy, as well as B12, folate, or thyroid deficiency. For all participants, a knowledgeable family member was available to provide information regarding functional status. The final study sample was primarily white (99%) and included one African American participant.

Demographic and gross clinical characteristics including age, education, Mini-Mental State Test performance (MMSE; Folstein, Folstein, & McHugh, 1975), depression assessed using the Geriatric Depression Scale (Yesavage, 1986), Wide Range Achievement Test-IV Reading subtest performance, and instrumental activities of daily

living (Lawton & Brody, 1969) are displayed in Table 1. This study was approved by the Rowan University institutional review board with consent obtained consistent with the Declaration of Helsinki.

Table 1

Demographic Information: Means and Standard Deviations

Group	age	education	IADLs	MMSE	GDS	WRAT-IV Reading
non-MCI (n=48)	75.27 (7.37)	15.14 (2.74)	15.16 (2.28)	28.13 (1.70)	3.27 (2.84)	114.04 (16.43)
mx/dys MCI (n=24)	73.75 (6.18)	14.58 (2.65)	14.18 (3.17)	26.75 (2.13)	3.17 (2.56)	112.54 (12.54)
aMCI (n=25)	76.19 (6.80)	14.00 (2.95)	14.48 (2.32)	26.92 (1.94)	3.58 (2.64)	107.03 (16.79)
Non-MCI = Non-Mild Cognitive Impairment; mx-MCI = Mixed Mild Cognitive Impairment; aMCI = Amnestic Mild Cognitive Impairment; MMSE= Mini-Mental State Examination; GDS= Geriatric Depression Scale; WRAT-IV= Wide Range Achievement Test						

Neuropsychological Assessment

The methods and neuropsychological protocol used to classify patients into non-MCI versus MCI subtype are the same as described by Emrani et al. (2018). Clinical classification was based on the assessment of three domains of neuropsychological functioning including executive control, naming/ lexical access, and verbal episodic memory. As described by Emrani et al. (2018), nine neuropsychological parameters, three from each neurocognitive domain, were used to classify patients as presenting with non-MCI versus MCI the subtype described below. All test scores were expressed as z-scores derived from normative data (Table 2). The rationale for using the protocol described above was based on prior research showing that these tests are able to illustrate

key neurocognitive constructs that differentiate between MCI subtypes (Bondi & Smith, 2014; Libon et al., 2011; Thomas et al., 2018).

Executive control. This cognitive domain was assessed with three tests including The Boston Revision of the Wechsler Memory Scale-Mental Control subtest (Lamar, Price, Cynthia, Kaplan, & Libon, 2002), the letter fluency test ('FAS'; Spreen & Strauss, 1990); and the Trail Making Test-Part B (Reitan & Wolfson, 1985). The dependent variable for the Mental Control subtest was the total non-automatized accuracy index (AcI; see Lamar, Price, Cynthia, Kaplan, & Libon, 2002 for full details). The dependent variables obtained from the letter fluency test and Trail Making Test-Part B were the demographically-corrected scores provided by Heaton et al. (2004).

Lexical access/ language. This domain was also assessed with three tests, including the 60-item version of the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983); a test of semantic ('animals') fluency where participants were asked to produce as many names of animals in 60s excluding perseverations and extra-category intrusion responses (Carew, Lamar, Cloud, & Libon, 1997); and the Wechsler Adult Intelligence Scale-III Similarities subtest (Wechsler, 2004). The dependent variables for the Boston Naming Test and 'animal' fluency tests were scaled scores based on norms obtained from Heaton et al., (2004). The dependent variable obtained from the WAIS-III Similarities subtest was the age-corrected scale score.

Memory and learning. This cognitive domain was assessed with the 9-word California Verbal Learning Test-short form (Delis, Kramer, Kaplan, & Ober, 2000). This test was scored and administered using standard instructions. The three CVLT-short form

variables used for classification included total immediate free recall, delayed free recall, and the delayed recognition discriminability measure.

Determination of Mild Cognitive Impairment Subtypes

   Single and multi-domain MCI. Jak, Bondi et al. (2009) criteria were used to determine MCI subtype. Single domain MCI syndromes were diagnosed when participants scored >1.0 standard deviation below normative expectations on any two of the three measures within a single cognitive domain. Mixed MCI syndromes were diagnosed when participants scored >1.0 standard deviation below normative expectations on any two of the three measures within two or more cognitive domains. On the basis of these procedures, 24 patients were diagnosed with single domain amnestic mild cognitive impairment (aMCI), 9 patients were diagnosed with single domain dysexecutive mild cognitive impairment, and 16 were diagnosed with mixed or multi-domain mild cognitive impairment (mxMCI). Because of the small number of dysexecutive MCI patients a combined mixed/dysexecutive (mixed/dys) MCI subgroup (n= 25) was constructed.

   Non-MCI group. Among the patients who presented for clinical evaluation, 48 patients did not meet Jak, Bondi et al. (2009) criteria for MCI. Some of these patients (n= 22) performed such that all nine neuropsychological parameters were above 1sd. A second group of patients (n= 26) not meeting criteria for MCI presented with some, but very little cognitive impairment, such that 13 patients produced tests scores where only 1 of the 9 neuropsychological parameters was below the 1sd cut-off; and 13 patients produced neuropsychological test scores where only two neuropsychological parameters across different domains of cognitive functioning were below 1sd. When patients not

meeting criteria for MCI were compared on the verbal and visual episodic outcome

measures described below, no differences were found. For this reason, these patients

were combined into a single group and labeled as presenting with non-MCI. Table 2 lists

neuropsychological parameters used for diagnosis and classification (Table 2).

Table 2

Neuropsychological Test Performance: Z-Scores, Means and Standard Deviations

Neuropsychological Test	non-MCI	aMCI	mx/dys MCI	significance
WMS Mental Control - Non-Automatized Index	-0.01 (0.65)	0.07 (0.75)	-1.13 (1.09)	mx/dys MCI < non-MCI, aMCI; p< .001
Letter ('FAS") Fluency	0.00 (0.93)	-0.64 (0.90)	-1.48 (0.92)	mx/dys MCI < aMCI < mx/dys MCI; p< .018
Trail Making – Part B	-0.14 (0.75)	-0.30 (0.88)	-0.79 (0.96)	mx/dys MCI < non-MCI; p< .012
Boston Naming Test	0.21 (0.94)	-0.20 (0.88)	-0.65 (1.13)	mx/dys MCI < non-MCI; p< .005
'animal' Fluency	-0.60 (0.94)	-0.95 (0.83)	-1.17 (1.14)	mx/dys MCI < non-MCI, aMCI; p< .014
WAIS-III Similarities subtest	0.01 (0.67)	-0.24 (1.03)	-0.43 (0.68)	ns
CVLT: short form, immediate free recall, Trails 1-4	0.08 (0.87)	-1.16 (1.01)	-0.90 (0.74)	aMCI < non-MCI; p< .001 mx/dys MCI < non-MCI; p< .001
CVLT: delay free recall	-0.15 (1.10)	-1.82 (0.55)	-0.88 (1.14)	aMCI < mx/dys MCI < non-MCI; p< .017
CVLT: delay recognition	0.19 (0.81)	-1.44 (0.71)	-0.47 (0.95)	aMCI < mx/dys MCI < non-MCI; p< .007
non-MCI = non-Mild Cognitive Impairment; aMCI= amnestic Mild Cognitive Impairment; mx-MCI= mixed Mild Cognitive Impairment; WMS= Wechsler Memory Scale-Mental Control; WAIS-III= Wechsler Adult Intelligence Scale-III; CVLT= California Verbal Learning Test-short form; ns= not significant.				

Verbal and Visual Episodic Memory Outcome Measures

Verbal and visual episodic memory was assessed with the 12-word Philadelphia (repeatable) Verbal Memory Test (Bezdicek et al., 2014; Gifford et al., submitted), a test that was constructed and administered consistent with the 9-word P(r)VLT and original 16-word CVLT (Delis et al., 1987); and the Brief Visuospatial Memory Test-Revised, respectively. Neither test was used to categorize patients into their respective groups.

P(r)VLT outcome measures of interest included total immediate free recall, list A trials 1-5, delay free recall, and the delayed recognition discriminability index as described by Price et al., (2009) and the original CVLT (Delis et al., 1987). BVMT-R outcome measures included total immediate recall trials 1-3, delay free recall, and a delay recognition discriminability index. BVMT-R outcome measures were expressed as z-scores based on available normative data. For the BVMT-R variables for patients age 80 and older, normative data provided by Kane et al. (2014) was used to calculate z-scores. P(r)VLT outcome measures were also expressed as z-scored using normative, age proband data provided by Jefferson et al., (2016).

Hippocampal Measures

NeuroQuant software (CorTechs Labs, Inc., San Diego, CA, USA) was used to obtain left, right and total hippocampal volume. NeuroQuant is a commercially available FDA-approved software program for measuring brain MRI regions of interest. Participant brain scans were obtained using three scanner models, all compatible with the analysis software. Acquisition protocol details are as follows: TR/TE= 2300/1.87/900, 192 × 192 matrix, 160 slices, voxel size = 1×1×1.2 mm. The scanners are detailed as follows: Siemens 3T Verio scanners with 16 and 32-channel head coils,

Siemens 3T Skyra scanners with a 32 channel head coil, and Siemens 1.5T Aera scanners

with a 16 channel head coil (Siemens Medical Systems, Erlangen, Germany). Images

were obtained from a sagittal 3D spoiled gradient recalled (SPGR) sequence, an

acquisition method that uses semi-random changes in the phasing of radio frequency

pulses to achieve a spatially independent phase shift. Following acquisition, sagittal

images of the brain were sent to the image analysis lab at South Jersey Radiology

Associates for volumetric analysis. Table 3 lists volumetric parameters and group means

for this study (Table 3).

Table 3

Hippocampal Volumes: Means and Standard Deviations

Hippocampal Volume	non-MCI	aMCI	mx/dys MCI	Significance
Total Hippocampal Volume	6.12 (0.99)	5.74 (0.80)	5.38 (0.87)	ns
Left-side Hippocampal Volume	3.10 (0.66)	2.78 (0.41)	2.53 (0.50)	ns
Right-side Hippocampal Volume	3.09 (0.56)	2.91 (0.51)	2.82 (0.42)	ns
non-MCI = non-Mild Cognitive Impairment; aMCI= amnestic Mild Cognitive Impairment; mx-MCI= mixed Mild Cognitive Impairment				

Statistical Analysis

   Norm-based analyses. Between-group differences for P(r)VLT and BVMT-R

total immediate free recall, delay free recall, and delay recognition discriminability were

analyzed with multivariate analysis of variance (MANCOVA) controlling for MMSE test

performance with Bonferroni post-hoc analyses. Within-group t-tests were used to assess

for material specific immediate, delay free recall, and delay recognition test performance.

Raw score BVMT-R full credit, memory for object (MFO), memory for

object location (MOL) responses. BVMT-R responses were tallied to reflect full credit,

2-point responses; partial credit, 1-point responses reflecting correct memory for

individual test stimuli or *memory for object* (MFO, 1-point); and partial credit, 1-point

memory for object location (MOL, 1-point). From this corpus, five additional variables

were analyzed, including total output or number of responses either correct or incorrect

summed across all free recall trials; 2-point, full credit responses; 1-point MFO

responses; 1-point MOL responses; and 0-point responses. These variables were

analyzed using 1-way ANCOVA or MANCOVA with Bonferroni correction as indicated.

Because no normative data is available for these variables, raw data was analyzed

controlling for age and MMSE. The relative contribution for MFO versus MOL as

related to MCI diagnosis was also assessed with three separate Receiver Operating

Characteristic (ROC) curves for 2-point; 1-point MFO, incorrect for MOL; and 1-point

MOL, incorrect for MFO responses (Table 4). The cutoff for maximizing sensitivity and

specify was determined using the Youden's index (Maximum = Sensitivity + Specificity

− 1).

Table 4

Memory Test Performance: Z-Scores, Means and Standard Deviations

	non-MCI	aMCI	mx/dys MCI	Significance
P(r)VLT Immediate Free recall: z score	0.52 (0.90)	-0.54 (0.80)	-0.49 (0.86)	mx/dys MCI, aMCI < non-MCI; p< .004
P(r)VLT Delay Free recall: z score	0.55 (0.82)	-0.73 (0.78)	-0.42 (0.89)	mx/dys MCI, aMCI < non-MCI; p< .004
P(r)VLT Delay Recognition discriminability: z score	0.55 (0.73)	-0.77 (1.00)	-0.23 (1.12)	aMCI < non-MCI; p< .001 mx/dys MCI < non-MCI; p< .018 aMCI < mx/dys MCI; p< .030
BVMT-R Immediate Free Recall: z score	-0.95 (0.99)	-1.98 (0.66)	-1.83 (0.97)	aMCI < non-MCI; p< .001 mx/dys MCI < non-MCI; p< .003
BVMT-R Delay Free Recall: z score	-0.91 (1.20)	-2.06 (0.76)	-1.97 (0.97)	aMCI < non-MCI; p< .001 mx/dys MCI < non-MCI; p< .002
BVMT-R Delay Recognition discriminability: z score	-0.24 (0.95)	-2.00 (1.96)	-1.37 (1.41)	aMCI < non-MCI; p< .001 mx/dys MCI < non-MCI; p< .012
BVMT-R Total Figures Drawn	17.9 (4.09)	12.24 (4.76)	14.17 (5.22)	mx/dys MCI, aMCI < non-MCI; p< .015
BVMT-R: 2- point Responses	8.59 (4.43)	3.86 (3.10)	4.78 (4.04)	mx/dys MCI, aMCI < non-MCI; p< .001
BVMT-R: 1- point MFO	1.95 (1.82)	0.90 (1.04)	1.56 (1.54)	ns
BVMT-R: 1- point MOL	0.82 (1.70)	0.67 (1.06)	0.89 (1.97)	ns
BVMT-R: 0- point responses	6.13 (3.56)	6.62 (4.21)	6.67 (3.31)	ns

non-MCI= non-Mild Cognitive Impairment; aMCI = amnestic Mild Cognitive Impairment; mx-MCI= Mixed Mild Cognitive Impairment; P(r)VLT= Philadelphia (repeatable) Verbal Learning Test; BVMT-R= Brief Visuospatial Memory Test- Revised

Hippocampal analysis. Measures of hippocampal volume were available for a portion of our sample (n= 40). Neuroanatomic specificity regarding memory test performance and hippocampal volume were assessed with a series of stepwise multiple regression analyses. For these analyses, age and MMSE score were entered in the first block followed by left and right-side hippocampal volume entered in the second block. Dependent variables were P(r)VLT delay free recall raw scores, P(r)VLT recognition discriminability; and BVMT-R free recall 2-point responses, 1-point BVMT-R MFO, and 1-point BVMT-R MOL responses.

Chapter 3

Results

Demographics

Groups (65% female) did not differ for age, education, Geriatric Depression Scale scores (Yesavage, 1986), estimated pre-morbid abilities assessed using the WRAT-IV Reading subtest performance, and IADL abilities (Lawton & Brody, 1969). On the MMSE, non-MCI patients scored higher than aMCI and mixed/dys MCI patients (p< .009). MMSE test performance was co-varied on all subsequent analyses.

Philadelphia (repeatable) Verbal Learning Test: Norm-Referenced Immediate/ Delay Free Recall and Delay Recognition

63 participants (non-MCI=32; aMCI= 15; mx/dys MCI= 16) completed the P(r)VLT. The three P(r)VLT free recall and recognition outcome variables were assessed using a multivariate analysis of variance (MANCOVA). Between group analysis found a multivariate effect for group [F= 3.56, df= 6, 112; p< .003; $\eta2$= .160); all univariate ANCOVAs were significant (p< .011); post-hoc comparisons found that, for immediate and delay free recall, non-MCI patients scored better than aMCI and mixed/dys MCI groups (p< .004, all analyses). aMCI patients obtained a lower P(r)VLT delayed recognition discriminability score than both non-MCI and mixed/dys MCI patients (p< .030).

Brief Visuospatial Memory Test- Revised: Norm-Referenced Immediate/ Delay Free Recall and Delay Recognition

74 participants (non-MCI= 37, aMCI= 18, mx/dys MCI= 19) completed the BVMT-R. The multivariate effect for group for the three recall and recognition outcome

variables was significant (F= 5.61, df= 6, 134, p< .001, $\eta2$= .201); all subsequent

univariate ANCOVAs were significant (p< .001); post-hoc analyses found that both MCI

groups scored lower compared to non-MCI patients on all BVMT-R outcome measures

compared to both MCI groups (p< .012, all analyses). aMCI and mixed/dys MCI groups

did not differ on any BVMT-R outcome variable.

Within-Group Comparisons

58 participants (non-MCI= 30, aMCI= 14, mx/dys MCI= 14) completed both the

P(r)VLT and the BVMT-R. Paired t-tests were used to assess for within-group

differences regarding immediate and delayed free recall and delay recognition test

performance. For all three groups, lower scores were obtained on BVMT-R as compared
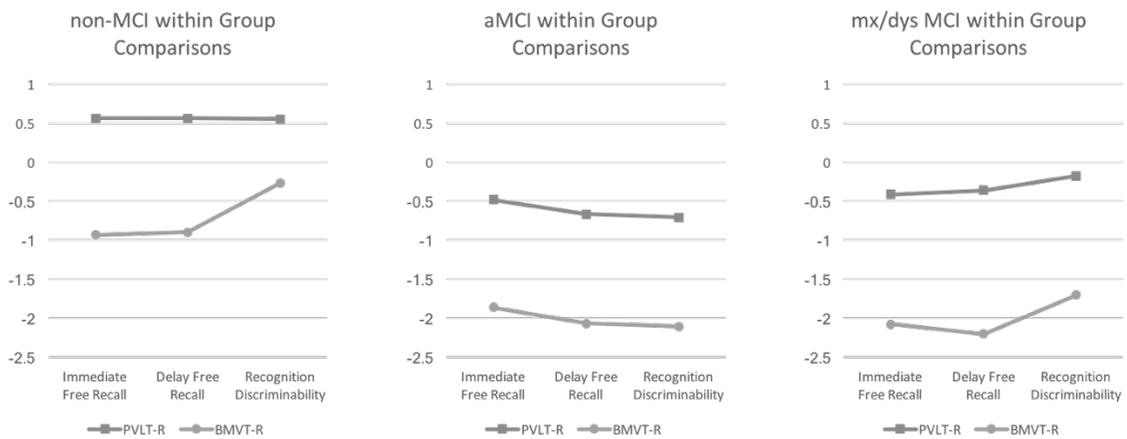
to the P(r)VLT parameters (p< .036, all analyses).

Figure 1. *Within-Group Comparisons of P(r)VLT and BVMT-R performance*

BVMT-R Total Output, Memory for Object (MFO), and Memory for Object

Location (MOL)

One-way ANCOVA controlling for age and MMSE for total number of responses was significant (F= 7.87, df= 4, 71, p< .001; $\eta2$= .181); Bonferroni post-hoc analyses found that non-MCI patients produced more total output than either MCI group (p< .015, both analyses); however, between-group analyses for 1-point MFO and 1-point MOL and 0-point responses were not significant. Complete ROC curve statistics are displayed in Table 5 and Figure 2; area under the curve for 2-point and MOL responses were .783 and .615, respectively. Area under the curve for MFO (.498) was below acceptable cut off.

Table 5

BVMT-R Receiver Operating Characteristic Curves

	Sensitivity	Specificity	AUC
2- point responses	.692	.744	.783
1- point MOL	.718	.436	.615
1- point MFO	.051	.974	.498
MFO= Memory For Object; MOL= Memory for Object Location; AUC= Area Under Curve			

BVMT-R: ROC 2-point response: Area under the curve= .783

BVMT-R: ROC 1- point Memory for Object Location: Area under the curve= .615

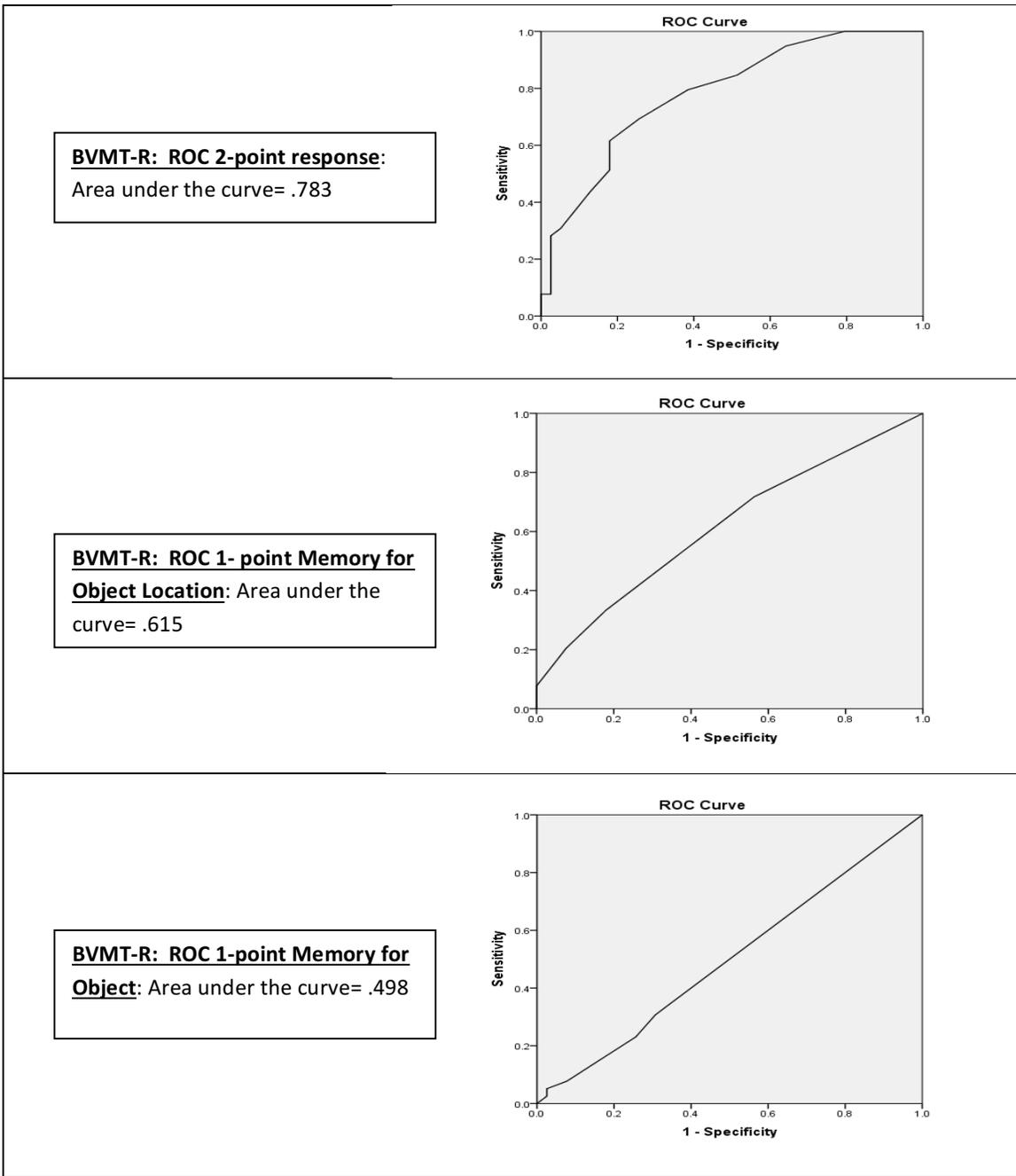**BVMT-R: ROC 1-point Memory for Object**: Area under the curve= .498

Figure 2. *BVMT-R Receiver Operating Characteristic Curves*

Memory Test Performance and Hippocampal Volume

No between-group differences were obtained for total, left, or right hippocampal volume (Table 2). Stepwise regression analyses looking for hippocampus/ material-specific relationships found that P(r)VLT delay free recall was associated with greater left hippocampal volume (r= .658, R^2= .433, df= 2, 27, p< .003, beta= .526). P(r)VLT delayed recognition test performance was also associated with greater left hippocampal volume (r= .600, R^2= .360, df= 2, 27, p< .042, beta= .367). BVMT-R full credit 2-point responses was associated with greater right-sided hippocampal volume (r=.549, R^2= .302, df= 1, 35, p< .001, beta= .549). BVMT-R 1-point MOL responses was associated with left-sided hippocampal volume (r= .378; R^2= .143; df= 1, 35, p< .021, beta= .378). The regression analysis examining BVMT-R 1-point MFO and left/ right hippocampal volume was not significant.

Chapter 4

Discussion

In the current research, the comprehensive neuropsychological diagnostic criteria as suggested by Jak, Bondi et al. (2009) was used to classify memory clinic patients into non-MCI, aMCI, and combined mixed/dys groups. Outcome measures were obtained from well-known verbal and visual serial list learning paradigms. Our goal was to extend previously findings described by Bonner-Jackson et al. (2015) and to assess for convergent as well as divergent verbal versus visual serial learning patterns of performance.

Overview of Results

Consistent with Hypothesis 1, performance on the P(r)VLT indicated that non-MCI patients scored substantially better as compared to MCI patients on all free recall and recognition test conditions. By contrast, aMCI and mixed/dys MCI patients did not differ on any free recall test condition. However, on the delay recognition discriminability index, aMCI patients scored lower compared to other groups. This profile is consistent with prior P(r)VLT research examining dementia patients diagnosed with AD versus vascular dementia (VaD) and statistically-determined MCI groups (Libon et al., 1998, 2011). Performance on the BVMT-R also found that non-MCI patients outperformed both MCI groups on all free recall and recognition test conditions, counter to Hypothesis 1, where we had hypothesized that performance on the BVMT would only differentiate amnestic MCI from non-MCI. Further, unlike the P(r)VLT as described above, MCI groups did not differ on the immediate/ delay free recall and the recognition discriminability index. Equally interesting were the within-group analyses demonstrating

lower BVMT-R compared to P(r)VLT test performance in all test conditions across all groups.

Overall, the patterns of performance obtained on both serial list learning tests are convergent in that both tests are able to identify memory disorder in MCI patients. However, some divergence regarding test performance was also found. For one, greater P(r)VLT delay recognition deficits were obtained for aMCI patient compared to other groups. Additionally, lower test scores for all groups were observed for the BVMT-R as compared to the P(r)VLT. Lower visual versus verbal serial list learning test performance may be explained on the basis of diversity of neurocognitive skills necessary for successful test performance. The ability to encode a verbally presented "shopping list," rich in semantic context, is likely circumscribed to ventral cortex involving left temporal regions of the brain. By contrast, successful performance on the BVMT-R required a wider array of neurocognitive operations including the ability to encode the attributes of the object (MFO), correct object location (MOL), as well as motor skills necessary to execute a response. The diversity of neurocognitive operations that are necessary for successful BVMT-R performance likely include ventral cortex for object identification, dorsal cortex for object location, and the necessary brain regions that govern the generation of an appropriate graphomotor response.

Supporting hypothesis 2, the wider array of neurocognitive operations for successful BVMT-R as compared to P(r)VLT test performance is consistent with the results of regression and ROC analyses. P(r)VLT immediate and delay free recall was uniquely associated with left hippocampal volume. By contrast, BVMT-R test performance was essentially associated with bilateral hippocampal volume in that full

credit 2-point responses were associated with greater right-sided hippocampal volume and 1-point MOL was associated with greater left-sided hippocampal volume. Consistent with hypothesis 3, the ROC curve analyses underscore the importance of MOL for successful BVMT-R test performance.

Past Research

The data described above is consistent with prior research described by Troyer et al. (2008). In this research, the BVMT-R was administered to aMCI patients and normal controls. These researchers found that accuracy for diagnostic classification were higher for BVMT-R object location than object identification. Prior research has also demonstrated that memory for object is associated with the right-sided hippocampal volume in patients with AD and healthy controls (de Toledo-Morrell et al., 2000; Piekema, Kessels, Mars, Petersson, & Fernández, 2006), while memory for object location has been linked to a wider neurocognitive network involving both the hippocampus and bilateral parietal cortical regions (Fujimori et al., 2000). Piekema et al. (2006) has suggested that the role of the hippocampus within this network may be to synthesize visual information that is not integrated by earlier higher order visual processing, such as an object and its spatial context. This conceptualization may explain the absence of an association between BVMT-R memory for object and hippocampal volume observed in this study.

Hampstead et al. (2011) studied patients with aMCI and heathy controls using a sophisticated object location protocol. As expected, heathy controls scored better than aMCI patients. fMRI was used to identify regions of the brain associated with object location. Heathy controls activated object identification ventral cortex in the occipital

and temporal regions; spatial location dorsal cortical regions; as well as activation involving the hippocampus and dorsolateral frontal lobes. aMCI patient presented with a similar, but less active pattern of brain activation indicating that individuals with amnestic impairment may be less effective in processing visual information. Alescio-Lautier et al. (2007) studied AD, MCI, and heathy controls and found greater deficits for object location than memory for object among their patient groups, as well as evidence to suggest that deficits involving object location may evolve before deficits involving memory for object. Additionally, there was a dissociation in the apparent origins of deficits for object location and memory for object such that impairment for object location appeared to be a consequence of memory deficits while impaired visual memory was connected to attentional deficits. In sum, a visual serial list learning test such as the BVMT-R that evaluates for both memory for object and memory for object location appears to draw on a wide neurocognitive network, requiring bilateral contributions to succeed at the task.

Strength and Limitations

The strengths of the current research include episodic memory assessment using well-known test paradigms and the classification of non-MCI and MCI patients using validated psychological methods. However, several limitations must be acknowledged including the modest number of patients where MRI-hippocampal volume were available and the need for an analysis of a wider array of MRI-defined areas of interest. Despite these limitations the data reported above suggests episodic memory assessment using the P(r)VLT and BVMT-R provide complimentary information related to the diagnosis of MCI and further classification of MCI subtypes.

References

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., … Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on. *Alzheimer's & Dementia*, *7*(3), 270–279. http://doi.org/10.1016/j.jalz.2011.03.008.The

Alescio-Lautier, B., Michel, B. F., Herrera, C., Elahmadi, A., Chambon, C., Touzet, C., & Paban, V. (2007). Visual and visuospatial short-term memory in mild cognitive impairment and Alzheimer disease: Role of attention. *Neuropsychologia*, *45*(8), 1948–1960. http://doi.org/10.1016/j.neuropsychologia.2006.04.033

Baddeley, A. (2003). Working memory: Looking back and looking forward. *Nature Reviews Neuroscience*, *4*(10), 829–839. http://doi.org/10.1038/nrn1201

Bender, A. R., Naveh-Benjamin, M., Amann, K., & Raz, N. (2017). The role of stimulus complexity and salience in memory for face-name associations in healthy adults: Friend or foe? *Psychology and Aging*, *32*(5), 489–505. http://doi.org/10.1037/pag0000185

Bezdicek, O., Libon, D. J., Stepankova, H., Panenkova, E., Lukavsky, J., Garrett, K. D., … Kopecek, M. (2014). Development, validity, and normative data study for the 12-word philadelphia verbal learning test [czP(r)VLT-12] among older and very old czech adults. *Clinical Neuropsychologist*, *28*(7), 1162–1181. http://doi.org/10.1080/13854046.2014.952666

Bondi, M. W., & Smith, G. E. (2014). MCI subjects Need of Input from Neuropsychology. *Journal of the International Neuropsychological Society : JINS*, *20*(2), 129–134. http://doi.org/10.1017/S1355617714000010.Mild

Bonner-Jackson, A., Mahmoud, S., Miller, J., & Banks, S. J. (2015). Verbal and non-verbal memory and hippocampal volumes in a memory clinic population. *Alzheimer's Research & Therapy*, 1–10. http://doi.org/10.1186/s13195-015-0147-9

Brown, G. D. A., Neath, I., & Chater, N. (2007). A Temporal Ratio Model of Memory. *Psychological Review*, *114*(3), 539–576. http://doi.org/10.1037/0033-295X.114.3.539

Carew, T. G., Lamar, M., Cloud, B. S., & Libon, D. J. (1997). Impairment in category fluency in ischaemic vascular dementia. *Neuropsychology*, *11*(3), 400–412.

De Anna, F., Felician, O., Barbeau, E., Mancini, J., Didic, M., & Ceccaldi, M. (2014). Cognitive Changes in Mild Cognitive Impairment Patients With Impaired Visual Recognition Memory. *Neuropsychology*, *28*(1), 98–105. http://doi.org/10.1037/neu0000032

de Toledo-Morrell, L., Dickerson, B., Sullivan, M. P., Spanovic, C., Wilson, R., & Bennett, D. a. (2000). Hemispheric differences in hippocampal volume predict verbal and spatial memory performance in patients with Alzheimer's disease. *Hippocampus*, *10*(2), 136–42. http://doi.org/10.1002/(SICI)1098-1063(2000)10:2<136::AID-HIPO2>3.0.CO;2-J

Delis, D., Kramer, J., Kaplan, E., & Ober, B. (1987). *The California Verbal Learning Test*. New York: Psychological Corporation.

Delis, D., Kramer, J., Kaplan, E., & Ober, B. (2000). *The California Verbal Learning Test-II*. New York: Psychology Corporation.

Derby, C. A., Burns, L. C., Wang, C., Katz, M. J., Zimmerman, M. E., L'italien, G., … Lipton, R. B. (2013). Screening for predementia AD: Time-dependent operating characteristics of episodic memory tests. *Neurology*, *80*(14), 1307–1314. http://doi.org/10.1212/WNL.0b013e31828ab2c9

Didic, M., Felician, O., Barbeau, E. J., Mancini, J., Latger-Florence, C., Tramoni, E., & Ceccaldi, M. (2013). Impaired visual recognition memory predicts Alzheimer's disease in amnestic mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders*, *35*(5–6), 291–299. http://doi.org/10.1159/000347203

Emrani, S., Libon, D. J., Lamar, M., Price, C. C., Jefferson, A. L., Gifford, K. A., … Au, R. (2018). Assessing Working Memory in Mild Cognitive Impairment with Serial Order Recall. *Journal of Alzheimer's Disease : JAD*, *61*(3), 917–928. http://doi.org/10.3233/JAD-170555

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. http://doi.org/10.1016/0022-3956(75)90026-6

Fujimori, M., Imamura, T., Hirono, N., Ishii, K., Sasaki, M., & Mori, E. (2000). Disturbances of spatial vision and object vision correlate differently with regional cerebral glucose metabolism in Alzheimer's disease. *Neuropsychologia*, *38*(10), 1356–1361. http://doi.org/10.1016/S0028-3932(00)00060-9

Gifford, K. A., Liu, D., Neal, J. E., Acosta, L. M. Y., Bell, S. P., Babicz, M. A., … Jefferson, A. L. (n.d.). Brain MRI and cerebrospinal fluid correlates of the Philadelphia Verbal Learning Test: The Vanderbilt Memory & Aging Project. *Dementia and Geriatric Cognitive Disorders EXTRA*.

Hampstead, B. M., Stringer, A. Y., Stilla, R. F., Amaraneni, A., & Sathian, K. (2011). Where did I put that? Patients with amnestic mild cognitive impairment demonstrate widespread reductions in activity during the encoding of ecologically relevant object-location associations. *Neuropsychologia*, *49*(9), 2349–2361. http://doi.org/10.1016/j.neuropsychologia.2011.04.008

Heaton, R. K., Miller, S., Taylor, M., & Grant, I. (2004). *Revised comprehensive norms for an expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults scoring programs. Psychological Assessment Resources*.

Jak, A. J., Bondi, M. W., Delano-Wood, L., Wierenga, C., Corey-Bloom, J., Salmon, D. P., & Delis, D. C. (2009). Quantification of five neuropsychological approaches to defining mild cognitive impairment. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry*, *17*(5), 368–75. http://doi.org/10.1097/JGP.0b013e31819431d5

Jefferson, A. L., Gifford, K. A., Acosta, L. M., Bell, S. P., Donahue, M. J., Davis, L. T., … Liu, D. (2016). The Vanderbilt Memory & Aging Project: Study design and baseline cohort overview. *Journal of Alzheimer's Disease*, *52*, 539–559.

Kane, K. D., & Yochim, B. P. (2014). Construct validity and extended normative data for older adults for the brief visuospatial memory test, revised. *American Journal of Alzheimer's Disease and Other Dementias*, *29*(7), 601–606. http://doi.org/10.1177/1533317514524812

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *The Boston Naming Test*. Philadelphia, PA: Lea and Febiger.

Kumar, N., & Priyadarshi, B. (2013). Differential effect of aging on verbal and visuo-spatial working memory. *Aging and Disease*, *4*(4), 170–7. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3733580&tool=pmcentrez&rendertype=abstract

Lamar, M., Price, C. C., Cynthia, D., Kaplan, E., & Libon, D. J. (2002). Capacity to maintain mental set in dementia. *Neuropsychologia*, *40*(4), 435–445.

Lawton, M., & Brody, E. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *The Gerontologist*, *9*(3), 179–186.

Libon, D. J., Bogdanoff, B., Cloud, B. S., Skalina, S., Carew, T. G., Gitlin, H. L., & Bonavita, J. (1998). Motor Learning and quantitative measures of the hippocampus and subcortical white alterations in Alzheimer's disease and Ischaemic Vascular Dementia. *Journal of Clinical and Experimental Neuropsychology*, *20*, 30–41.

Libon, D. J., Bondi, M. W., Price, C. C., Lamar, M., Eppig, J., Wambach, D. M., … Penney, D. L. (2011). Verbal serial list learning in mild cognitive impairment: A profile analysis of interference, forgetting, and errors. *Journal of the International Neuropsychological Society*, *17*(5), 905–914. http://doi.org/10.1017/S1355617711000944

Lim, Y. Y., Harrington, K., Ames, D., Ellis, K. A., Lachovitzki, R., Snyder, P. J., & Maruff, P. (2012). Short term stability of verbal memory impairment in mild cognitive impairment and Alzheimer's disease measured using the International Shopping List Test. *Journal of Clinical and Experimental Neuropsychology*, *34*(8), 853–863. http://doi.org/10.1080/13803395.2012.689815

Okonkwo, O. C., Oh, J. M., Koscik, R., Jonaitis, E., Cleary, C. A., Dowling, N. M., … Johnson, S. C. (2014). Amyloid burden, neuronal function, and cognitive decline in middle-aged adults at risk for alzheimer's disease. *Journal of the International Neuropsychological Society*, *20*(4), 422–433. http://doi.org/10.1017/S1355617714000113

Piekema, C., Kessels, R. P. C., Mars, R. B., Petersson, K. M., & Fernández, G. (2006). The right hippocampus participates in short-term memory maintenance of object-location associations. *NeuroImage*, *33*(1), 374–382. http://doi.org/10.1016/j.neuroimage.2006.06.035

Price, C. C., Garrett, K. D., Jefferson, A. L., Cosentino, S., Tanner, J. J., Penney, D. L., … Libon, D. J. (2009). Leukoaraiosis severity and list-learning in dementia. *Clinical Neuropsychologist*, *23*(6), 944–961. http://doi.org/10.1080/13854040802681664

Reitan, R. M., & Wolfson, D. (1985). (1985). *The Halstead-Reitan neuropsychological test battery: Theory and clinical interpretation (Vol. 4)*. Reitan Neuropsychology.

Ribeiro, F., Guerreiro, M., & De Mendonça, A. (2007). Verbal learning and memory deficits in mild cognitive impairment. *Journal of Clinical and Experimental Neuropsychology*, *29*(2), 187–197. http://doi.org/10.1080/13803390600629775

Snyder, P. J., Jackson, C. E., Petersen, R. C., Khachaturian, A. S., Kaye, J., Albert, M. S., & Weintraub, S. (2011). Assessment of cognition in mild cognitive impairment: A comparative study. *Alzheimer's and Dementia*, *7*(3), 338–355. http://doi.org/10.1016/j.jalz.2011.03.009

Spreen, O., & Strauss, E. A. (1990). *Compendium of Neuropsychological Tests*. New York: Oxford University Press.

Thomas, K. R., Eppig, J., Edmonds, E. C., Jacobs, D. M., Libon, D. J., Au, R., … Bondi, M. W. (2018). Word-list intrusion errors predict progression to mild cognitive impairment. *Neuropsychology*, *32*(2), 235–245. http://doi.org/10.1037/neu0000413

Troyer, A. K., Murphy, K. J., Anderson, N. D., Hayman-Abello, B. A., Craik, F. I. M., & Moscovitch, M. (2008). Item and Associative Memory in Amnestic Mild Cognitive Impairment: Performance on Standardized Memory Tests. *Neuropsychology*, *22*(1), 10–16. http://doi.org/10.1037/0894-4105.22.1.10

Tulving, E. (1972). Episodic and semantic memory. In E. Tulving & W. Donaldson (Eds.), *Organization of Memory* (pp. 381–403). New York: Academic Press.

Wagner M., W. S. (2012). Biomarker validation of a cued recall memory. *Neurology*, 379–386. http://doi.org/10.1212/WNL.0b013e318245f447

Wechsler, D. (2004). *WAIS-III: Administration and scoring manual: Wechsler adult intelligence scale*. Psychological Corporation200.

Ye, B. S., Chin, J., Kim, S. Y., Lee, J. S., Kim, E. J., Lee, Y., … Seo, S. W. (2014). The heterogeneity and natural history of mild cognitive impairment of visual memory predominant type. *Journal of Alzheimer's Disease*, *43*(1), 143–152. http://doi.org/10.3233/JAD-140318

Yesavage, J. A. (1986). The Use of Self-Rating Depression Scales in the, 213–217.