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ASSESSING WORKING MEMORY OF MILD COGNITIVE IMPAIRMENT WITH SERIAL ORDER RECALL

by
Sheina Emrani

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
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Thesis Chair: Dr. David Libon, Ph.D.

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Dedication

This thesis is dedicated to my friend Raffi (Ralph). Thanks for helping me put this together.

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Acknowledgment

I would like to show my appreciation to my advisor, Dr. David Libon for his guidance, patience, and mentorship. His ability to teach so eloquently and clearly and his abundance of knowledge is admirable. I look forward to learning more in the future.

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Abstract

Sheina Emrani
ASSESSING WORKING MEMORY OF MILD COGNITIVE IMPAIRMENT WITH SERIAL ORDER RECALL
2017-2018
David Libon, Ph.D.
Master of Arts in Clinical Psychology

Background: Working memory (WM) is often assessed with serial order tests such as repeating digits backward. In prior dementia research using the Backward Digit Span subtest (BDT) only aggregate test performance was examined. The current research tallied primacy/ recency effects; out-of-sequence transposition errors; perseverations and omissions to assess WM deficits in patients with mild cognitive impairment (MCI). Methods: Memory clinic patients (n= 66) were classified into three groups – single domain amnestic MCI (aMCI), combined mixed domain/ dysexecutive MCI (mixed/dys MCI), and non-MCI where patients did not meet criteria for MCI. Serial order/ WM ability was assessed by asking participants to repeat 7 trials of five digits backwards. Serial order position accuracy, transposition errors, perseverations, and omission errors were tallied. Results: A 3 (group) x 5 (serial position) repeated measures ANOVA yielded a significant group x trial interaction. Follow-up analyses found an absence of a recency effect for mixed/dys MCI patients. Mixed/dys MCI patients produced more transposition errors than both groups ($p < 0.010$); and more omissions ($p < 0.020$), and perseverations errors ($p < 0.018$) than non-MCI patients. Conclusions: The striking absence and/ or attenuation of a recency effect using serial order parameters obtained from the BDT may constitute a neurocognitive biomarker for WM deficits in MCI and provide additional diagnostic information regarding working memory deficits in MCI.

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Chapter 1

Introduction

Background

Mild cognitive impairment (MCI) is generally believed to be a prodrome that often results in the emergence of dementia syndromes such as Alzheimer's disease (AD) and is considered to be a useful construct to identify patients who are potentially at risk for developing a dementing illness. Diagnostic criteria for MCI include the subjective complaint of memory and/ or other neurocognitive problems, along with relative preservation of instrumental activities of daily living, in conjunction with objective evidence documenting a decline in memory and/ or other neurocognitive abilities (Albert et al., 2011; Peterson et al., 2005; Wimblad et al., 2004). Patients diagnosed with MCI can be classified as presenting with single versus multiple domain subtypes (Delano-Wood et al., 2009; Libon et al, 2010).

Significance of Study

The importance of investigating MCI subtypes revolves around several clinical as well as theoretical issues including a greater understanding of conversion to dementia and a clearer appreciation of the brain-behavior relationships that underlie MCI syndromes. For example, past empirical findings suggest greater reliability for the eventual emergence of dementia for amnestic and multi-domain MCI as compared to single domain dysexecutive MCI (Huey et al., 2013; Hessen et al., 2014; Johnson et al., 2010; Zhang et al., 2015; Hu et al., 2014). Recent research has also shown that when mixed/dysexecutive MCI patients are defined using neuropsychological criteria there tends to be faster progression to dementia than other groups (Bondi et al., 2014; Thomas

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et al., 2017). Second, the investigation of MCI subtypes pro- vides an opportunity to investigate the neurocognitive constructs underlying brain-behavior relationships associated with MCI. For example, Libon et al. (2011) have shown that patients with amnestic MCI differ from other MCI subtypes on a variety of linguistic as well as memory parameters obtained from a serial list learning test. Eppig et al. (2012) found that impairment on executive tests produced by mixed and dysexecutive MCI patients were similar and remarkable in that performance deteriorated as a function of time to completion and/or test epoch. The emergence of this striking negative slope, or steep temporal gradient as described by Fuster (2008), suggests difficulty maintaining mental set. Eppig et al. (2012) suggested that steeper temporal gradients may provide a useful heuristic for understanding brain-behavior relationships that underlie impairment on executive tests in patients with MCI. In addition to unique pat- terns of behavior obtained from neuropsychological measures, patients with dysexecutive MCI have also been distinguished from other MCI subtypes using and neuroimaging parameters (Delano-Wood et al., 2009; Chao et al., 2009; Delano-Wood et al., 2008; Pa et al., 2009).

Assessing Working Memory

Tests that examine serial order recall, such as the Backward Digit Span Test (BDT) (Lamar et al., 2007; Lamar et al., 2008) as described by Lamar et al. have been used to assess working memory deficits in both dementia and MCI. The BDT has previously been analyzed to generate two gross aggregate measures including *total any recall* – tallied as the total percent recall of digits regardless of their correct serial order and believed to provide a measure of auditory span; and *total serial order recall* – tallied as the total percent recall of digits in the exact serial order and believed to pro- vide a

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measure of working memory and the capacity for mental manipulation. Lamar et al. (2007, 2008) found that total serial order recall was able to differentiate patients with AD versus vascular dementia who presented with MRI evidence of subcortical white matter alterations. Moreover, reduced aggregate serial order recall was associated with greater MRI evidence of left-sided frontal and posterior parietal white matter alterations.

Karl Lashley (1951) was among the first researchers to address what he termed *The Problem of Serial Order*[1]. Subsequent experimental research assessing serial order, such as asking participants to repeat digits backward, have been used to operationally-define a number of specific parameters related to working memory including primacy and recency effects and the generation of specific pattern of errors (see Hurlstone, Hitch & Baddeley, 2014; ref 22, for a complete review). First, prior research has consistently shown that when young, healthy participants are asked to repeat numbers backward recency effects are enhanced and primacy effects are diminished (Hurlstone et al., ref 22, figure 1, page 6; 23, 2)]. Second, errors commonly seen in serial order research in younger adults most often include out-of-sequence, transposition errors, i.e., a response that is recalled in the wrong serial position. Third, transposition errors can be expressed in terms of a transposition gradient that measures the degree of displacement between its correct position and incorrect response position [Hurlstone el., ref 22; figure 2a; page 7]. Fourth, serial ordering research has also identified non-transposition errors, termed items

[1] Karl Lashley (1951) viewed the mechanism(s) that link individual or discrete behavior into complex cognitive operations to be poorly understood and dubbed this conundrum *'The Problem of Serial Order'.* Lashley's seminal paper on this topic was part of the famous Hixon Symposium. The Hixon Symposium was convened at the California Institute of Technology in September, 1948 by Lloyd Jeffress of the University of Texas and subsequently published in 1951. This symposium focused on a wide number of cerebral mechanisms that underlie brain and cognition. The symposium was composed of a distinguished group of neuroscientists such as Ward Halstead, Heinrich Kluver, Wolfgang Kohler, as well as Karl Lashley. The topics discussed were diverse and far reaching. Howard Gardner (1985) traces the origins of what has been termed "The Cognitive Revolution" to the papers delivered at this meeting.

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errors such as omissions and perseverations. Fifth, prior serial order research has suggested that item errors are far less frequent than transposition errors.

Purpose of Study

In the current research the BDT (Lamar et al., 2007; Lamar et al., 2008) was used to assess serial order recall in patients with suspected MCI. As noted above, prior research using the BDT tallied only aggregate serial order test performance. In the current study, detailed analyses of the five components of serial order recall described above were undertaken including the calculation of primacy/ recency effects; an analysis of transposition errors; the calculation of transposition displacement; and the occurrence of item errors. The primary goal of the current research is to assess how and/ if these five benchmark parameters measuring serial order recall that have been well-researched in younger research participants can differentiate between MCI subgroups. On the basis of prior research (Bondi et al., 2014; Thomas et al., 2017; Eppig et al., 2012) where both dysexecutive and mixed MCI patients presented with greater difficulty in sustaining mental set on executive tests, i.e., a steeper temporal gradient (Fuster, 2008), our primary prediction is that mixed/ dysexecutive MCI patients will present with attenuated recency effects, more total transposition errors along with greater transposition displacement, and greater numbers of item errors compared to other MCI groups.

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Chapter 2

Methods

Participants

Participants studied in the current research (n= 66) were recruited from the 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 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. Participants diagnosed with MCI presented with subjective cognitive complaints and/ or 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, and major psychiatric disorders including major depression, epilepsy, B12, folate, or thyroid deficiency. For all participants a knowledgeable family member was available to provide information regarding functional status. This study was approved by the Rowan University institutional review board with consent obtained consistent with the Declaration of Helsinki.

Neuropsychological Assessment

The neuropsychological protocol used to classify MCI subtype assessed three domains of cognition: executive control, naming/ lexical access, and declarative memory. From this protocol, nine parameters, three from each neurocognitive domain, were used to classify MCI subtype as described below. All tests were expressed as z- scores derived

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from normative data. We acknowledge that other neuropsychological tests/domains of cognitive functioning could have been used. The rationale for using the protocol described above was based on prior research showing that these tests are able to illustrate key neurocognitive constructs and differentiate between MCI subtypes (see Bondi et al., 2014; Thomas et al., 2017; Libon et al., 2011).

Executive control. This cognitive domain was assessed with three tests (see Table 1) including The Boston Revision of the Wechsler Memory Scale-Mental Control subtest (Lamar et al., 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; Reitan & Wolfson, 1985 for full detail). The dependent variables obtained from the letter fluency test and Trail Making Test-Part B was the demographically corrected score provide 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 et al., 1983); a test of semantic ('animals') fluency were participants were asked to produce as many names of animals in 60s excluding perseverations and extra-category intrusion responses (Carew et al., 1997); and the Wechsler Adult Intelligence Scale-III Similarities subtest (Wechsler, 1997). The dependent variables for the Boston Naming Test and 'animal' fluency tests were 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-Mental Status test (Delis et al., 2000). This test was

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scored and administered using standard instructions. Three CVLT-MS variables were used in the current research including total immediate free recall; delay free recall, and the delayed recognition measure.

Table 1

Neuropsychological Domains

Executive Function Domain	Language/Lexical Access Domain	Declarative Memory Domain
WMS – Mental Control Subtest	Boston Naming test	Immediate Free Recall
Letter Fluency – 'FAS'	'Animal' Fluency	Delayed Free Recall
Trail Making Test – Part B	WAIS-III Similarities Subtest	Delayed Recognition

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 of 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 of two of the three measures within a two or more cognitive domains. On the basis of these procedures 15 patients were diagnosed with single domain amnestic mild cognitive impairment (aMCI), 3 patients were diagnosed with single domain dysexecutive mild cognitive impairment, and 15 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

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subgroup (n= 18) was constructed. This decision was made on the basis of prior research (Bondi et al., 2014; Thomas et al., 2017; Eppig et al., 2012) where mixed and dysexecutive patients presented with similar patterns of impairment on executive tests.

Non-MCI group. Among the patients who presented for clinical evaluation 33 did not meet Jak, Bondi et al. (2009) criteria for MCI. A portion of patients (n= 17) performed such that all nine neuropsychological parameters were above 1sd. A second portion patients (n= 16) not meeting criteria for MCI presented with 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 3 patients produced neuropsychological test scores where only two neuropsychological parameters across different domains of cognitive functioning were below 1 SD. When these groups who did not meet criteria for MCI were compared on the serial order outcome variables described below no differences were found. For this reason, these patients were combined into a single group and labeled as presenting with non-MCI.

Three neuropsychological indices were created by averaging test performance within each neurocognitive domain. When the memory test index was assessed between-group aMCI patients scored lower compared to other groups (aMCI versus non-MCI; $p< 0.001$, aMCI versus mixed/dys MCI; $p< 0.005$); and mixed/dys MCI patients scored lower than non-MCI patients ($p< 0.003$).

Between-group analyses for executive test index found that mixed/dys MCI patients scored lowered than other groups (mixed/dysMCI versus non-MCI; $p< 0.001$, mixed/dysMCI versus aMCI; $p< 0.003$; respectively). Similarly, on the language test index mixed/dys MCI patients score lower than other groups (mixed/dysMCI vs. non-

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MCI; p< 0.001, mixed/dys MCI versus aMCI; p< 0.021; respectively; Table 2). Thus, patients with aMCI presented with circumscribed impairment on memory tests. The predominant neuropsychological impairment among mixed/dys MCI patients revolved around lower scores on executive and language tests as compared to other groups.

Table 2

Demographic and Clinical Information: Means and Standard Deviations

	non-MCI (n= 33) (F=19)	aMCI (n= 15) (F=11)	mixed/dys MCI (n= 18) (F=10)	Significance
Age	77.27 (6.26)	76.20 (6.48)	77.88 (5.46)	ns
Education	14.63 (3.00)	154.20 (2.67)	13.50 (2.95)	ns
MMSE	27.69 (1.75)	26.73 (2.21)	26.44 (1.58)	ns
WRAT-IV Reading subtest	116.30 (18.60)	116.46 (13.37)	110.61 (16.39)	ns
IADL abilities	14.90 (2.44)	13.38 (3.52)	14.23 (2.70)	ns
Geriatric Depression Scale	3.63 (2.52)	3.06 (2.71)	4.11 (3.12)	ns
Executive Index (z-scores)	-0.12 (0.36)	-0.37 (0.49)	-1.02 (0.77)	mixed/dys MCI < non-MCI; p< 0.001 mixed/dys MCI < aMCI; p< 0.003
Naming/ Lexical access Index (z-scores)	-0.10 (0.50)	-0.27 (0.60)	-0.91 (0.91)	mixed/dys MCI < non-MCI; p< 0.001 mixed/dys MCI < aMCI; p< 0.021

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Table 2 (Continued)

Memory Index (z-scores)	-0.04 (0.67)	-1.48 (0.49)	-0.71 (0.78)	aMCI < non-MCI; p< 0.001 aMCI < mixed/dys MCI; p< 0.005 mixed/dys MCI < non-MCI; p< 0.003
aMCI= amnestic mild cognitive impairment; mixed/dys MCI= multi-domain/ dysexecutive mild cognitive impairment; IADL= instrumental activities of daily living; WRAT-IV= Wide Range Achievement Test-IV; ns= not significant				

The Backward Digit Span Test (BDT)

The BDT is comprised of seven trials of 3-, 4- and 5-digit span lengths for a total of 21 trials. As described by Lamar et al. (2007, 2008) 4- and 5-span trials were constructed so that contiguous numbers were placed in strategic positions. Thus, in 4-span trials contiguous numbers were placed in either the first and third or second and fourth digit positions, e.g., 5269 or 1493. For 5- span trials contiguous numbers were placed in the middle three digits positions, e.g., 16579. This procedure cannot be used for 3-span test trials because of primacy and recency effects. The BDT was administered using Wechsler Adult Intelligence Scale administration procedures except that all 21 test trials were administered regardless of errors that were made. To maximize the assessment of serial order position effects only the seven 5-span trials were used in the current research.

Serial Order Recall/ Backward Digit Span Outcome Variables

Correct responses and primacy and recency effects. The number of correct responses for the seven 5-span trials was tallied (range 0–35, correct). The total percent

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correct for each of the five serial order positions was also tallied. Recency *recall* was defined as the first number heard and participants' subsequent last response. *Primacy recall* was determined as the last number heard and participants' subsequent first response. This terminology regarding primacy and recency effects is standard in serial order position research (Hurlstone, Hitch, & Baddeley, 2014 p. 5; 23-24).

Transposition errors and transposition gradient. Total instances of out-of-sequence or transposition errors were tallied. Transposition gradients were also expressed vis-à-vis the degree of displacement in relation to their correct serial position. *Anticipation transposition* errors were scored using a negative displacement value because they occurred *in advance* or ahead of their correct serial position. *Postponement transpositions* errors were scored using a positive displacement value because they occurred *after* their correct serial position. Correctly recalled test items were assigned a value of zero to reflect the absence of any displacement. For each group transposition gradients were plotted in terms of their displacement (Hurlstone el al., 2014; figure 2a; page 7).

Item errors. A variety of non-out-of-sequence or item errors were tallied as described below. Between-trial perseverations were tallied when a number from the preceding two trials was pulled into the current response; within-trial perseverations were tallied when a number within a trial is repeated. Between-trial capture errors were scored when a number from either of the preceding two trials is pulled into the current response creating a contiguous, automatized string of digits; within-trial capture errors were scored when number(s) within the same trial were incorrectly repeated also creating a contiguous string. Omissions were tallied when the patient responded with less than the

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number of digits administered. Because of the low frequency of some of these errors all perseveration and capture errors were summed and labeled dysexecutive errors. Omissions and total dysexecutive errors were summed to create a total item error score.

Statistical Analyses

The number of correct responses was analyzed using 1-way analysis of variance (ANOVA). Primacy and recency effects were examined using a 3 (group) x 5 (serial position) repeated measures ANOVA. Recency effects were also assessed within-group by comparing recency recall (5^{th} digit recalled, i.e., first number administered, last number recall) versus primacy recall (1^{st} digit recalled, i.e., last number administered, first number recalled). The effect of group for total transposition errors, total anticipation and postponement transposition errors was assessed with multivariate analysis of variance (MANOVA). Because of restriction of range transposition gradient/ displacement was expressed by averaging all anticipation and postponement transposition errors to create two separate indices and was assessed with a single MANOVA. Omission, dysexecutive, and total item errors were assessed with a single MANOVA. Finally, the relationship between BDT test performance, Mini-Mental State Examination (MMSE), and overall neuropsychological functioning was assessed with a regression analysis where 5-span serial order recall was the dependent variable. MMSE test performance was entered along with the three neuropsychological domain index scores calculated as described above. Significance was set at $p < .050$. The Bonferroni correction was used for all post-hoc analyses.

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Chapter 3

Results

Demographic Characteristics and ANY/ SERIAL Recall Information

Table 2 lists demographic and clinical information. No between-group differences were found for age, education, the Mini-Mental State Examination (MMSE; Folstein et al., 1975), depression assessed with the Geriatric Depression Scale, projected premorbid general intellectual abilities as assessed with the Wide Range Achievement Test Reading subtest-IV (WRAT-IV), or Instrumental Activities of Daily Living (Lawton, & Brody, 1969). For descriptive purposes Table 3 lists total aggregate any order and serial order recall for the three groups. A multivariate analysis of variance (MANOVA) found a significant effect for group (Hotelling's Trace F[4, 122.00]= 4.01, $p< 0.004$, $h_p^2= .116$). No differences were found for any order recall; however, differences were found for serial order recall (F[2, 63]= 7.68; $p< 0.001$, $h_p^2= .196$) where post-hoc (Bonferroni) analyses found that mixed/dys MCI patients scored lower compared to non-MCI patients ($p< 0.001$) and aMCI patients ($p< 0.043$).

Correct Responses and Primacy/ Recency Effects

One way ANOVA for the number of correct responses (range 0–35) was significant (F[2, 63] = 9.08, $p < 0.001$) and found that mixed/dys MCI patients recalled fewer correct responses only compared to non-MCI patients ($p<0.001$). The 3 group × 5 serial order position repeated measured ANOVA yielded a significant serial order position by group interaction (F[8, 118] = 4.57, $p < 0.001$; $h_p^2 = 0.237$). Follow-up ANOVAs found differences for middle serial position 3 (F[2, 63]=6.03; $p<0.004$), serial order position 4 (F[2, 63] = 6.43; $p < 0.003$), and recency serial position 5; F[2, 63] =

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18.57; $p < 0.001$) positions. *Post-hoc* (Bonferroni) comparisons found that mixed/dys MCI patients recalled less information than non-MCI patients for serial order position 3 ($p < 0.003$) and serial order position 4 ($p < 0.002$); and that mixed/dys MCI patients recalled less information compared to both groups for serial position 5 (recency; mixed/dys MCI versus non-MCI; $p < 0.001$; mixed/dys MCI versus aMCI; $p < 0.002$; Table 3; Fig. 1).

Table 3

Serial Order Recall: Means and Standard Deviations

	non-MCI (n= 33)	aMCI (n= 15)	mixed/dys MCI (n= 18)	significance
any order recall	94.37 (5.82)	92.00 (4.73)	89.68 (9.20)	ns
serial order recall	81.81 (17.28)	77.52 (10.46)	62.85 (19.32)	mixed/dys MCI< non-MCI; p< 0.001 mixed/dys MCI< aMCI; p< 0.043
correct responses (0 – 35)	29.03 (4.99)	26.13 (4.94)	22.22 (6.60)	mixed/dys MCI< non-MCI; p< 0.001
backward serial position 1 (primacy)	97.83 (6.30)	99.04 (3.68)	95.23 (8.48)	ns
backward serial position 2	91.34 (13.33)	93.33 (10.61)	84.12 (13.76)	ns
backward serial position 3	79.22 (19.26)	70.47 (21.91)	56.34 (27.92)	mixed/dys MCI < non-MCI; p< 0.003
backward serial position 4	67.27 (22.32)	55.23 (20.81)	40.47 (33.68)	mixed/dys MCI < non-MCI; p< 0.002

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Table 3 (Continued)

backward serial position 5 (recency)	83.11 (19.70)	69.52 (16.96)	38.09 (37.31)	mixed/dys MCI < non-MCI; p< 0.001 mixed/dys MCI < aMCI; p< 0.002
aMCI= amnestic mild cognitive impairment; mixed/dys MCI= multi-domain/ dysexecutive mild cognitive impairment; ns= not significant.				

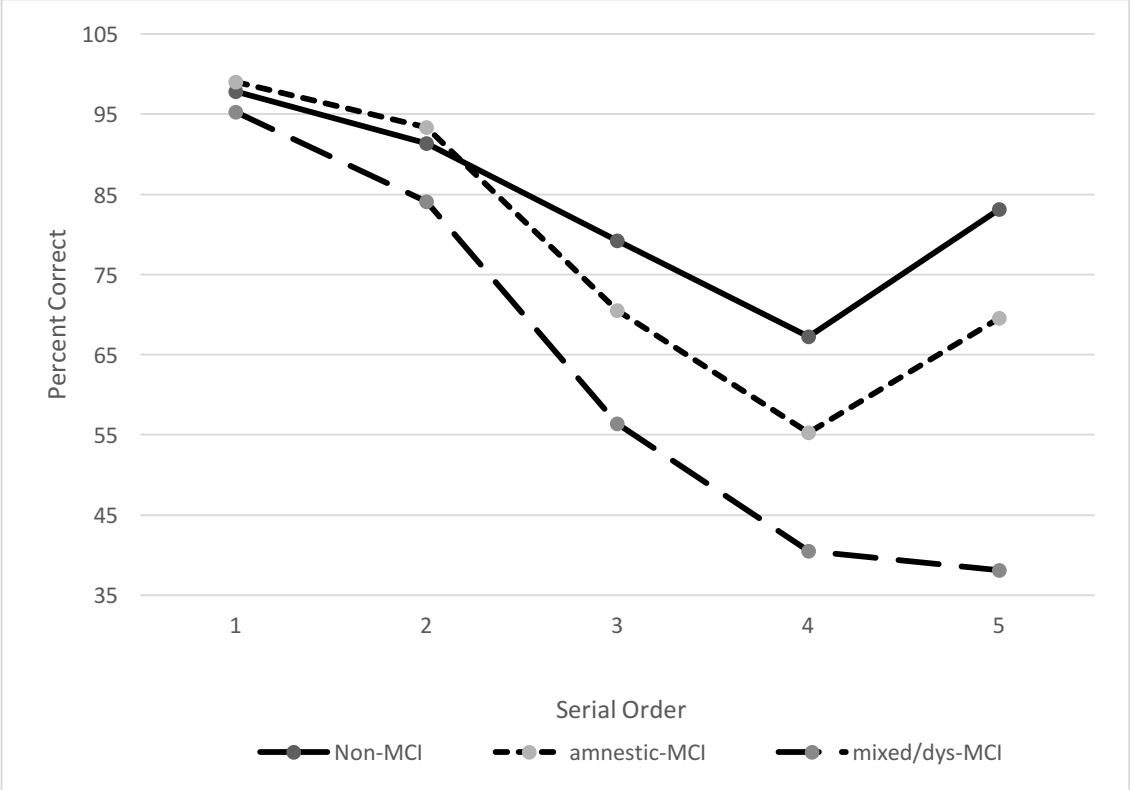

Figure 1. Percent Backward Serial Order Recall

Total Transpositions and Transposition Gradient

A multivariate analysis of variance (MANOVA) found a significant effect for group (Hotelling's Trace F[4, 122]= 5.38; p< 0.001, h_p^2= .150). Univariate group effects were found for total transposition errors, (F[2, 63]= 10.53; p< 0.001, h_p^2= .251), total

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anticipation transposition errors (F[2, 63]= 8.20; p< 0.001, h_p^2= .207), and total postponement transposition errors (F[2, 63]= 10.41; p< 0.001, h_p^2= .248). Post-hoc (Bonferroni) comparisons found that mixed/dys MCI patients made more total transposition errors compared to non-MCI (p< 0.001) and aMCI (p< 0.010) patients; more anticipation transposition errors than non-MCI patients (p< 0.001) and aMCI (p< 0.039) patients; and more postponement transposition errors than non-MCI (p< 0.001) and aMCI (p< 0.006) patients.

Transposition gradients are displayed in Figure 2. The MANOVA measuring the effect of group for averaged anticipation and postponement transposition displacement was significant (Hotelling's Trace F[4, 122]= 5.30; p< 0.001, h_p^2= .148). Group effects were obtained for both anticipation (F[2, 63]= 8.32, p< 0.001, h_p^2= .209) and postponement (F[2, 63]= 10.41, p< 0.001, h_p^2= .248) displacement. Post-hoc (Bonferroni) analyses found that mixed/dys MCI patients generated greater anticipation (mixed/dys MCI versus non-MCI, p< 0.001; mixed/dys MCI versus aMCI, p < .021) and postponement (mixed/dys MCI versus non-MCI, p< 0.001; mixed/dys MCI versus aMCI, p < .006; Figure 2) displacement than other groups.

Table 4

Backward Digit Span Errors: Means and Standard Deviations

Transposition Errors	non-MCI (n= 33)	aMCI (n= 15)	mixed/dys MCI (n= 18)	significance
total transposition errors	3.75 (3.48)	4.80 (3.12)	9.05 (5.29)	mixed/dys MCI > non-MCI; p< 0.001 mixed/dys MCI > aMCI; p< 0.01
total anticipation		2.93 (1.75)	5.11 (3.30)	mixed/dys MCI > non-MCI; p< 0.001

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Table 4 (Continued)

transposition errors	2.24 (2.12)			mixed/dys MCI > aMCI; p< 0.039
total postponement transposition errors	1.51 (1.58)	1.86 (1.59)	3.94 (2.43)	mixed/dys MCI > non-MCI; p< 0.001 mixed/dys MCI > aMCI; p< 0.006
average anticipation displacement	0.56 (0.53)	0.68 (0.44)	1.27 (0.82)	mixed/dys MC I> non-MCI; p< 0.001 mixed/dys MCI > aMCI; p< 0.021
average postponement displacement	0.37 (0.39)	0.46 (0.39)	0.98 (0.60)	mixed/dys MCI > non-MCI; p< 0.001 mixed/dys MCI > aMCI; p< 0.006
Item Errors	non-MCI (n= 33)	aMCI (n= 15)	mixed/dys MCI (n= 18)	significance
total omissions	0.09 (0.39)	0.46 (0.63)	0.61 (0.91)	mixed/dys MCI > non-MCI; p< 0.022
total dysexecutive errors	2.78 (2.25)	3.73 (2.25)	4.94 (3.26)	mixed/dys MCI > non-MCI; p< 0.017
total errors	2.87 (2.45)	4.20 (2.36)	5.55 (3.51)	mixed/dys MCI > non-MCI; p< 0.005
aMCI= amnestic mild cognitive impairment; mixed/dys MCI= multi-domain/ dysexecutive mild cognitive impairment; ns= not significant.				

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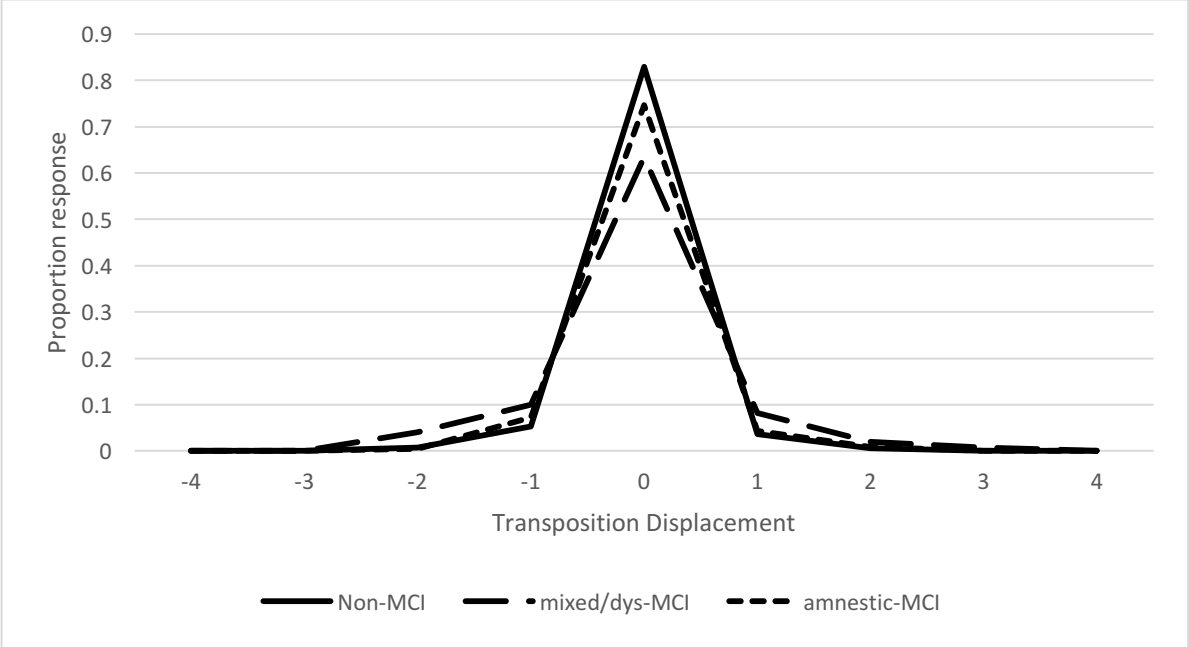

Figure 2. Transposition Gradient

Item Errors

The MANOVA that assessed for group differences for total omissions, total dysexecutive errors, and total errors was significant ($F[4, 120]= 3.40$, $p< 0.011$, $h_p^2= .102$). The effect for group was found for omissions ($F[2, 62]= 4.36$, $p< 0.017$ $h_p^2= .124$), dysexecutive errors ($F[2, 62]= 4.10$, $p< 0.021$ $h_p^2= .117$), and total errors ($F[2, 62]= 5.48$, $p< 0.006$ $h_p^2= .150$). Post-hoc (Bonferroni) analyses found great number of omissions, dysexecutive, and total errors for mixed/dys MCI patients compared to non-MCI patients (omissions – $p< 0.022$; dysexecutive errors – $p< 0.017$; total errors – $p< 0.005$; see Table 4). Three within-group tests were conducted to compare total transpositions versus total items errors. There was no difference between non-MCI and aMCI patients suggesting that these patient groups made equal numbers of transposition and item errors. However,

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mixed/dys MCI patient generate almost twice as many total transposition errors compared to item errors ($t[17]= 3.18$, $p< 0.005$).

Regression Analysis

The relationship between Backward Digit Span test performance, MMSE, and overall neuropsychological functioning was assessed with a regression analysis where 5-span serial order recall was the dependent variable. MMSE test performance was entered along with the three neuropsychological domain index scores. This analysis was significant with only the executive control index entering the model ([$r= 0.593$, $R^2= 0.351$, $df= 4, 61$, $p< 0.001$, $beta= 0.519$, $p< 0.001$).

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Chapter 4

Discussion

In prior research Eppig et al. (2012) found that both mixed and dysexecutive MCI patients exhibited derailed or worse performance as a function of time or test epoch compared to normal controls and amnestic MCI patients. These findings were interpreted to reflect greater impairment in sustaining mental set, behavior that is consistent with Fuster's (2008) model of temporal gradients. The current research sought additional information regarding working memory difficulty in MCI with the analysis of five well-researched parameters measuring serial order recall using the BDT. Serial order recall using both for- ward and backward digit span and related tasks has been thoroughly researched in young, healthy participants. However, to our knowledge there are no studies that have examined how and/or if impairment in serial order recall may provide important information regarding working memory deficits in MCI.

Overview of Results

Consistent with the goal and primary prediction of the current research the overall pattern of behavior described above found that parameters measuring serial order recall were able to differentiate mixed/dys MCI patients from non-MCI and aMCI patients; however, there were no differences when aMCI and non-MCI patients were compared. This finding is interesting to the extent that derailed serial order recall as described above might provide a means to characterize and operationally-define working memory deficits in MCI. As described above, mixed/dys MCI patients recalled fewer correct responses than other groups. More interesting were the striking between- and within- group serial order position effects. As shown in Fig. 1, both non-MCI and aMCI patients produced the

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expected recency effect. By contrast, and consistent with our prediction, there was an attenuated recency effect in the mixed/dys MCI group. Indeed, similar to the data described by Eppig et al. (2012) a relentless negative slope characterized performance in this group suggesting striking working memory deficits.

With respect to the analysis of transposition errors, non-MCI and aMCI patients did not differ; however, mixed/dys MCI patients generated more total, anticipation, and postponement transposition errors compared to other groups. Mixed/dys MCI patients also produced greater numbers of item errors including more omissions, dysexecutive errors, and total non-transposition errors.

In sum, the results of prior serial order research conducted with young, healthy participants seen in the laboratory (Hurlstone, Hitch, & Baddeley, 2014) comports well with the patterns of performance obtained from MCI patients seen in the clinic as described above. A notable exception revolves around the generation of item errors. Past serial order research conducted with younger participants has generally reported greater numbers of transposition compared to item errors. However, in the current research, non-MCI and aMCI patients produced equal numbers of transposition errors and item errors; and, mixed/dys MCI patients made almost twice as many transposition errors than item errors. Despite this exception, the data obtained in the current research suggests that serial order recall as measured with the BDT appears to provide an excellent means to operationally-define severity of working memory deficits in patients with suspected MCI. A limitation of the current research is the lack of imaging data that might be used to gain further insight into serial order recall.

Mixed/dys MCI patients scored lower on executive as well as other tests. This

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raises the question of whether the attenuated recency effect as described above and other indications of impaired serial order recall observed in the mixed/dys group are, in fact, specifically related to executive impairment. The regression analysis described above found that 5-span serial order recall was, in fact, associated only with executive test performance. Nonetheless, more research is required to address these issues.

Past Research

The current study is consistent with prior research demonstrating reduced serial order recall in other patient groups well-known to present with executive impairment. Zokaei et al. (2015) studied patients with Parkinson's disease (PD) and found that reduced digit span backward was correlated with impaired serial order recall for spatial orientation. Warden et al. (2016) examined PD patients with dementia, MCI, and no MCI and found that digit span back- ward test performance was able to differentiate PD-no MCI patients from other groups. Klekociuk and Summers (2014) found lower digit backward test performance in their sample of mixed MCI compared to aMCI patients. Hampstead et al. (2010) assessed serial order using a letter span task and found that vascular dementia patients associated with subcortical white matter alterations (i.e., leukoaraiosis) produced more dysexecutive errors compared to patients with AD suggesting greater working memory deficits in vascular dementia as compared to AD.

Competitive Queuing Model

Performance on serial order recall tasks, such as backward digit span, has been used to support constructs consistent with Competitive Queuing (CQ) models of working memory (Hurlstone, Hitch, & Baddeley, 2014; Grossberg, 1978a; Grossberg, 1978b; Houghton, 1990). CQ models of working memory generally posit the existence of two

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interconnected layers (1) an excitatory *parallel planning* mechanism; and (2) an inhibitory *competitive choice/response suppression* mechanism. *Parallel planning* is the mechanism that is believed to be responsible for the initial excitatory activation of all elements in the sequence to be recalled. In parallel planning neural nodes corresponding to each memoranda to be recalled are activated; however, the strength of activation for each node varies depending on task parameters. After initial activation, *competitive choice/response suppression* governs the actual output and order of recall. The item with the greatest activation is selected for recall. Following competitive choice, an inhibitory feedback system, known as response suppression, is believed to remove items from the planning layer so the next strongest activated item can be recalled. This process continues iteratively until all items are recalled (Hurlstone, Hitch, & Baddeley, 2014; Davelaar et al., 2005; Farrell., 2004). Recent electrophysiological research provides some evidence for CQ-related constructs. For example, when single cell activity from frontal regions were obtained from macaque monkeys, behavior similar to transposition errors were found in relation to diminished neural activity prior to a successfully executed movement (Averbeck et al., 2002; Averbeck et al., 2003a; Averbeck et al., 2003b). In humans, Agam and colleagues (2007, 2010) found decreased event related potentials associated with behavior similar to transposition errors.

Review of Neuroradiology

There is now substantial research demonstrating greater and more widespread gray and white matter compromise in mixed MCI compared to single domain MCI subtypes (Haller et. al., 2012; He et al., 2009; Li et al., 2014; Raamana et al., 2014; Li & Zhang, 2015). These neuroradiological findings are related to the current research in that

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both white matter and anterior and posterior gray matter integrity have been linked to performance on tests that assess working memory and executive control in normal controls and MCI. For example, in a sample of normal control participants Sasson et al. (2013) found that executive test performance was correlated with diffusion tensor imaging parameters involving both the superior longitudinal fasciculus and uncinate fasciculus. Bettcher et al. (2016) also studied a large sample of normal control participants with a wide array of executive tests including digit span backward. MRI parameters including both global gray matter and white matter structures such as the cingulum and corpus callosum contributed to intact performance on executive tests. Libon et al. (2016) showed that greater whole brain leukoaraiosis was associated with reduced aggregate BDT serial order recall in a sample of MCI participants. These observations are consistent with data reported by Lamar et al. (2008) showing that greater anterior and posterior left-hemisphere leukoaraiosis was related to impaired aggregate BDT serial order recall in patients with dementia thought to correspond to arcuate and longitudinal fasciculi. Interestingly, Lamar et al. (2008) have pointed out that visuospatial processing has been linked with successful number sequencing and that this cognitive operation is associated with a bidirectional network involving the parietal cortex (Hubbard et al., 2005). Moreover, past research examining backward digit test performance suggests that visuospatial imagery may be a strategy used to facilitate performance (Hoshi et al., 2000). It is possible that the attenuated recency effect in our mixed/dys MCI group, as well as the production of greater numbers of omissions and dysexecutive errors may be associated with a neurocognitive network involving inferior parietal and occipito-temporal regions combined with a disruption between posterior and

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frontal regions (Hubbard et al., 2005). However, this notion is speculative and must be the subject of prospective research. Also, there is considerable documentation that white matter alterations result in slow information processing speed in patients with MCI (Ciulli et al., 2016). Impaired information processing speed could have negatively affected performance on the BDT among our mixed/dys MCI patients. This is another area for further research. Coupling patterns of performance regarding serial order recall as expressed with tests such as the BDT with neuroradiological parameters may provide a means for assessing both the presence and severity of WM deficits in MCI.

Strengths and Limitations

The current study has several strengths including the analysis of process and errors to better understand serial order neurocognitive constructs (Kaplan, 1988; Kaplan, 1990) and the use of objective criteria to classify MCI and non- MCI subtypes. However, several limitations must be acknowledged including a modest sample size. First, our definition of MCI was limited to three neurocognitive domains. Other areas of cognitive functioning should be investigated in conjunction with serial order recall. Second, as noted above, no neuroradiological information was available for correlation with cognitive performance. Despite these limitations, our findings provide evidence that an analysis of serial order recall can reliably differentiate between MCI subtypes. Future work should investigate whether parameters measuring serial order recall obtained with the BDT can be dissociated using neuroradiological parameters in order to provide additional information regarding working memory deficits in MCI.

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