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Verbal Serial List Learning in Mild Cognitive Impairment: A Profile Analysis of Interference, Forgetting, and Errors

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Abstract

Using cluster analysis Libon et al. (2010) found three verbal serial list-learning profiles involving delay memory test performance in patients with mild cognitive impairment (MCI). Amnesic MCI (aMCI) patients presented with low scores on delay free recall and recognition tests; mixed MCI (mxMCI) patients scored higher on recognition compared to delay free recall tests; and dysexecutive MCI (dMCI) patients generated relatively intact scores on both delay test conditions. The aim of the current research was to further characterize memory impairment in MCI by examining forgetting/savings, interference from a competing word list, intrusion errors/perseverations, intrusion word frequency, and recognition foils in these three *statistically determined* MCI groups compared to normal control (NC) participants. The aMCI patients exhibited little savings, generated more highly prototypic intrusion errors, and displayed indiscriminate responding to delayed recognition foils. The mxMCI patients exhibited higher saving scores, fewer and less prototypic intrusion errors, and selectively endorsed recognition foils from the interference list. dMCI patients also selectively endorsed recognition foils from the interference list but performed similarly compared to NC participants. These data suggest the existence of distinct memory impairments in MCI and caution against the routine use of a single memory test score to operationally define MCI. (*JINS*, 2011, *17*, 905–914)

Keywords: Mild cognitive impairment, MCI, Declarative memory, Executive control, Philadelphia (repeatable) Verbal Learning Test, P(r)VLT, Cluster analysis, Boston Process Approach

INTRODUCTION

Clinical syndromes describing a decline in memory before the onset of dementia have a long history (see Reisberg et al., 2008, for review). Kral (1962) described two conditions – the syndrome of *benign senescent forgetfulness* or *senium naturale* where older adults may be unable to spontaneously recall some details of previously learned information but nonetheless have knowledge or access to this information; and a serious and malignant amnesia labeled *senile Korsakoff* or *senium ex morbo*, where older adults are unable to recall information even after a short interval. Kral viewed the first syndrome as consistent with normal aging and the second syndrome as consistent with dementia such as Alzheimer's disease (AD). Kral firmly believed that each syndrome was associated with different underlying cognitive and neurobiological mechanisms.

In the 1980s, two laboratories independently and simultaneously proposed psychometric rating scales designed to identify mild to clinically serious memory impairment. These scales continue to enjoy wide use (i.e., the Clinical Dementia Rating Scale [CDR]; Hughes, Berg, Danzinger, Coben, & Martin, 1982, & the Global Deterioration Scale [GDS]; Reisberg, Ferris, de Leon, & Crook, 1982) and consider other domains of cognitive functioning as well as patients' functional

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capacities to carry out important activities of daily living. During this same period, the syndrome of age associated memory impairment (AAMI; Crook, Bahar, & Sudilovsky, 1987; Crook & Larrabee, 1988) was proposed to describe mild, but nonetheless troublesome memory impairment in middle-aged and older adults who were otherwise healthy and living in the community. More recently, the term mild cognitive impairment (MCI; Petersen et al., 1999) has been put forth to describe clinically significant memory impairment, perhaps representing a prodromal or transitional state leading to dementia. During the early going, MCI tended to be viewed solely within the context of a transitional state leading to AD. It is now widely acknowledged that MCI is a heterogeneous condition with multiple presentations, different underlying etiologies, and variability with respect to prognosis and mortality (Bondi et al., 2008; Yaffe, Petersen, Lindquist, Kramer, & Miller, 2006).

Kaplan (1988) has emphasized the importance of the analysis of process and errors in understanding the brain–behavior relationships that underlie all aspects of cognitive functioning including memory. As such the verbal serial list-learning profile seen in AD can be characterized by a flat immediate free learning curve with rapid forgetting (i.e., poor savings) following the introduction of an interference test trial and after a delay, sensitivity to the effects of proactive interference (Loewenstein et al., 2004), the production of copious extra-list intrusion errors especially on cued recall trials (Davis, Price, Kaplan, & Libon, 2002; Delis et al., 1991; Massman, Delis, Butters, Levin, & Salmon, 1990; Price et al., 2009), and profligate responding to delay recognition foils such that overall performance is often at the level of chance. Further analysis of the errors produced by patients with AD suggests that their extra-list, cued-recall intrusion errors tend to be very prototypic or superordinate exemplars as related to their respective categories (e.g., *fruit* – "apples"; *tools* – "hammer"; Price et al., 2009). Cognizance of serial-list learning, extra-list intrusion errors is important since extra-list intrusion errors has been shown to predict progression to AD in non-demented elderly adults (Bondi, Salmon, Galasko, Thomas, & Thal, 1999).

The process analysis (Kaplan, 1988) of serial list-learning characteristics and errors in non-AD dementia syndromes suggests that patterns of impairment may be associated with source recall or frontal systems impairment (Baldo, Delis, Kramer, & Shimamura, 2002; Baldo & Shimamura, 2002; Libon et al., 2008; Price, Jefferson, Merino, Heilman, & Libon, 2005; Price et al., 2009). For example, in non-AD dementia syndromes such as Parkinson disease, Huntington disease, and primary degenerating dementia associated with moderate/severe MRI white matter disease there is less susceptibility to the effects of interference; higher saving scores; and the production of fewer extra-list intrusion errors (see Salmon & Bondi, 2009, for review). Price et al., (2009) pointed out that the extra-list intrusion errors produced in dementia patients presenting with moderate/severe MRI white matter disease tend to be more subordinate (i.e., constrained and concrete) as related to their respective categories. In some non-AD dementia syndromes patients present with relatively better scores on delayed recognition test conditions with false positive responses drawn from the preceding interference test condition and greater numbers of perseverations (Davis et al., 2002; Kramer et al., 1988; Massman et al., 1990; Price et al., 2009).

Using a multivariate cluster analysis technique Libon et al. (2010) analyzed memory, language, and executive test performance in patients with MCI and found three distinct neuropsychological syndromes: a memory disorder with low scores on delay free recall and recognition serial list-learning test conditions (labeled amnesic MCI [aMCI]), a dysexecutive disorder with low scores on tests of letter fluency and mental control (labeled dysexecutive MCI [dMCI]), and a mixed group where patients presented with difficulties in all three cognitive domains (labeled mixed MCI [mxMCI], (see Libon et al. (2010) for complete details). As compared to nomenclature used by Petersen et al. (2009) and Winblad et al. (2004) the aMCI group (Libon et al., 2010) is consistent with aMCI as characterized by other research groups. dMCI patients is similar to single domain, non-amnesic MCI as suggested by Petersen et al. and Winblad et al. The mxMCI group is similar to the multiple-domain MCI subtype described by Petersen et al.

The analyses reported by Libon et al. (2010) also revealed three distinct delayed free recall and delay recognition profiles as assessed with the Philadelphia (repeatable) Verbal Learning Test (P[r]VLT). Like patients with AD, individuals with aMCI demonstrated striking impairment on P[r]VLT indices measuring both delayed free recall and delayed recognition. Like healthy older adults, the dMCI exhibited generally intact performance on both the delayed free recall and delayed recognition test conditions. Multi-domain or mixed MCI patients (mxMCI) scored low on the delayed free recall trial, but improved on the delayed recognition test condition, a profile sometimes seen in non-AD dementia syndromes where the hippocampus and medial temporal are less affected.

Chang, Bondi, Fennema-Notestine, et al. (2010) have recently shown the importance of examining both learning and recall in characterizing MCI and predicting progression to AD (Grober & Kawas, 1997); however, to the best of our knowledge a detailed verbal serial list-learning error analysis has not been reported in MCI. Thus, the purpose of the present research was to assess whether the learning characteristics and errors that differentiate patients with AD from non-AD dementia syndromes can also differentiate patients with MCI presenting with different patterns of performance on delayed free recall and delayed recognition test conditions.

The primary questions addressed in the current study included (1) how verbal serial list-learning behavior in the *statistically derived* MCI subtypes differ from each other; and (2) to what extent these MCI groups produce patterns of impairment on a verbal serial list-learning test similar to known dementia syndromes. We expected the pattern of performance for aMCI patients presenting with low delayed free recall and low delayed recognition test scores to be

associated with rapid forgetting/low savings and susceptibility to interference from a competing word list; a proclivity for extra-list intrusion errors with high frequency within the English language; and indiscriminate responding to delay recognition foils. By contrast, the mxMCI group was hypothesized to present with less forgetting (i.e., relatively preserved savings) and less susceptibility to interference; fewer extra-list errors; but greater numbers of perseverations; and selective responding to recognition interference list foils. Finally, for the dMCI group, we expected their serial list-learning profile to be relatively intact and comparable to healthy controls.

METHOD

Participants

One hundred eight patients (Libon et al., 2010) were evaluated at an university-affiliated outpatient memory clinic (Center for Aging, University of Medicine and Dentistry of New Jersey) because of their self-perception of a memory disorder. Patients were evaluated by a neurologist, neuropsychologist, and a social worker for the presence of a dementia. Appropriate medical, neurological, laboratory, and imaging studies were obtained and a comprehensive neuropsychological evaluation was administered. Patients were recruited prospectively over a 5-year period (2002–2007), were ambulatory and medically well and stable, and were living independently in the community. Fourteen participants were excluded due to a prior history of stroke ($n = 1$), major medical illness such as cancer ($n = 2$), epilepsy ($n = 2$), thyroid disease ($n = 4$), closed head injury ($n = 1$), substance abuse ($n = 2$), and major depression or other serious psychiatric disorders ($n = 2$).

The diagnosis of MCI was determined using criteria established by Petersen et al. (2009) and Petersen and Morris (2005), that is, patients presented with the self-perception of a decline in memory; obtained a score of ≥ 24 on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) with no impairment in activities of daily living (ADLs; score 6/6) or instrumental activities of daily living (IADLs; score 15/17; Lawton & Brody, 1969). On the ADL/IADL questionnaire (Lawton & Brody, 1969), any problems identified by patients and/or their families were solely due to non-neurological reasons such as decreased visual acuity associated with limitations in driving or medical problems such as arthritis. In addition participants had to perform ≤ 1.5 standard deviation (*SD*) units below normative values on any one of the following six neuropsychological variables: the non-automatized index from the Wechsler Memory Scale-Mental Control subtest (Boston Revision; Lamar, Price, Davis, Kaplan, & Libon, 2002; Lamar, Swenson, Kaplan, & Libon, 2004); letter fluency (letters "FAS"; Spreen & Strauss, 2006); the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983); category fluency ("animals"; Carew, Cloud, Lamar, Grossman, & Libon, 1997; Monsch et al., 1992); and the long delay free recall or recognition trials from the P[r]VLT (Price et al., 2009). The rationale underlying the use of this neuropsychological protocol is discussed elsewhere (Libon et al., 2010).

Of the 94 remaining patients, 17 did not obtain a score of ≤ 1.5 *SD* units below normative values on any test. The remaining patients were subjected to a K-means cluster analysis which specified a three-cluster solution and classified patients into an amnesic group (aMCI) with deficits primarily in declarative memory; a dysexecutive group (dMCI) with low scores on executive tests; and a multiple-domain or mixed group (mxMCI) with difficulties in all three cognitive domains (i.e., memory, executive function, and language). The original cluster solution has been updated with 14 additional patients meeting MCI inclusion criteria recruited from the Drexel University, Department of Neurology Memory Disorder Clinic. The final MCI group ($n = 93$) consisted of 13 aMCI, 55 multiple-domain or mxMCI, and 25 dMCI patients.

A group of 24 healthy older adult normal control (NC) participants were prospectively recruited. All NC participants were living independently in the community, and they obtained a score of ≥ 27 on the MMSE (Folstein et al., 1975) and a score of < 9 on the Geriatric Depression Scale (GDS; Yesavage et al., 1983). Since the original cluster analysis, an additional 32 NC participants were recruited from the community using the same criteria as described above (Cosentino, Metcalfe, Holmes, Steffener, & Stern, in press). For all participants, consent was obtained consistent with standard Institutional Review Board regulations and the Declaration of Helsinki.

Philadelphia (Repeatable) Verbal Learning Test (P[r]VLT)

The P[r]VLT is a 9-word serial list-learning test with three versions designed specifically for use with dementia patients. The administration and construction of the P[r]VLT is identical to the original 16-word CVLT and the 9-word experimental version of the CVLT (Delis, Kramer, Kaplan, & Ober, 1987; Libon et al., 1996), except that the exemplars were generated from a corpus of cognitively normal older adults and includes equal numbers of recognition foil-types (semantic, interference, unrelated; see Price et al., 2009, for full details). The recognition test performance was assessed using the Recognition Discriminability Index [1 − (false positive + omissions / # possible correct)] × 100)] described by Delis et al. (1987).

To confirm that the additional MCI patients did not alter the original pattern of performance described by Libon et al. (2010), delayed free recall/recognition comparisons were re-assessed using NC standardized *Z*-scores. The aMCI patients' recognition test score was lower compared to their delayed free recall score (M delay free recall = -2.52 ± 1.00; M delay recognition = -4.22 ± 1.77; $t[12] = 3.19$; $p < .008$). Conversely, mxMCI patients' delayed recognition score was better than their delayed free recall scores (M delay free recall = -1.29 ± 1.19; M delay recognition = -0.67 ± 0.84; $t[54] = 4.11$; $p < .001$). The dMCI patients showed no

difference between these two measures (M delay free recall = −0.92 ± 1.35; M delay recognition = −0.53 ± 0.86; ns).

Variable Construction and Statistical Analyses

Savings indices

Two indices were constructed to assess savings and forgetting: (1) Long Delay Percent Savings = (Long Delay Free Recall/List A, Trial 5) × 100 (range, 0–100%). A higher score indicates greater savings and less forgetting; (2) Recognition Savings = Delay Recognition – List A – immediate free recall, trial 5 (see Massman, Delis, Butters, Dupont, & Gillin, 1992). For this analysis, *Z*-scores from the NC group were calculated and a lower score reflects greater forgetting and lower savings. The effect of group for both saving indices was assessed using one-way analysis of variance (ANOVA).

Proactive/retroactive interference

Proactive interference was assessed with a list A, trial 1; list B, interference condition repeated-measures ANOVA. Retroactive interference was assessed with a similar repeated-measures ANOVA for list A, trial 5 and list A, short delay free recall. Raw scores were used for both analyses. Proactive and retroactive interference were also assessed by summing the number of list A intrusion errors generated on the subsequent list B, interference recall trial (proactive interference); and list B intrusion errors generated on all subsequent list A (free/cued) recall test conditions (retroactive interference). This was analyzed with raw scores using separate one-way ANOVAs.

Extra-list intrusion errors and perseverations

Total free recall intrusion errors (FRI), cued recall intrusion errors (CRI), and perseverations were tallied and separate one-way ANOVAs assessed for between-group differences.

Extra-list intrusion word frequency

Using procedures described by Price et al. (2009), an average word frequency score was determined by aggregating total FRI and short and long delay CRI using the Francis and Kucera (1982) corpus. This measure was used as a proxy to assess the prototypicality of extra-list intrusion errors as related to their respective categories. We acknowledge that the purpose of the Francis and Kucera corpus is to provide a measure of word frequency, and, as such, frequency may not necessarily be equated to word prototypicality. The decision to use the Francis and Kucera corpus instead of other lists (e.g., Battig & Montague, 1969), was based on the fact that the 11 semantic categories used in the construction of the P[r]VLT were only represented in Francis and Kucera. A higher score indicates greater frequency in the English language. For MCI participants, a single score was created by summing all free and cued recall Francis and Kucera values. This resulted in a metric where distributions were significantly skewed with several groups presenting with extremely low and/or high values. Between-group differences were, therefore, assessed using the Mann-Whitney *U* statistic and the Moses Test of Extreme Reactions (Moses, 1952; Siegel, 1956).

For all parametric tests, the Bonferroni correction was used. Significance was set at $p < .050$. None of the analyses described above appeared in the cluster analysis of Libon et al. (2010).

RESULTS

Demographic Characteristics

No between-group differences were found for age, education, or depression (Geriatric Depression Scale; Yesavage et al., 1983). For the MMSE ($F[3,145] = 16.28$; $p < .001$) the NC group scored higher than all MCI groups ($p < .001$, all analyses), with no differences between the three MCI groups (Table 1).

Savings Indices

The ANOVA for the Long Delay Percent Saving Index yielded a significant effect for group ($F[3,146] = 14.69$; $p < .001$). *Post hoc* analyses found greater forgetting/less saving for aMCI participants compared to all other groups ($p < .002$, all analyses; Table 1) and less savings for mxMCI compared to NC groups ($p < .001$); however, dMCI and NC participants did not differ on this measure. The ANOVA for the Recognition Saving Index also produced a significant group effect ($F[3,145] = 23.86$; $p < .001$). *Post hoc* analyses found less savings and greater forgetting for aMCI participants compared all other groups ($p < .001$, all analyses, see Table 1). There were no differences among mxMCI, dMCI, and NC groups.

Proactive/Retroactive Interference

The repeated-measures ANOVA for proactive interference yielded neither a main effect for test condition (list A, trial 1; list B, interference condition), nor a significant the group × test condition interaction. The repeated-measures ANOVA for retroactive interference did produce a main effect for test condition (list A, trial 5; list A short delay free recall, $F[1,145] = 271.47$; $p < .001$) and a significant test condition by group interaction ($F[3,145] = 22.16$; $p < .001$). Subsequent one-way ANOVAs were significant both list A, trial 5 ($F[3,145] = 11.15$; $p < .001$) and list A, short delay free recall (($F[3,145] = 31.66$; $p < .001$). For list A, trial 5 *post hoc* analyses found that less recall for all MCI groups compared to the NC group ($p < .001$, all analyses) with no differences between the three MCI groups. For the short delay, free recall test condition aMCI patients recalled fewer words than all other groups ($p < .001$) and all MCI groups recalled fewer words compared to the NC group ($p < .001$; Table 1).

The one-way ANOVA for penetration of list A words onto list B (i.e., proactive interference) was significant ($F[3,122] = 5.51$; $p < .001$). *Post hoc* analyses found greater

Table 1. Group demographics and performance on the Philadelphia (repeatable) Verbal Learning Test (mean & standard deviation)

	aMCI ($n = 13$)	mxMCI ($n = 55$)	dMCI ($n = 25$)	NC ($n = 56$)
Demographics				
Age (years)	71.00 (9.14)	71.47 (9.34)	74.60 (9.73)	73.04 (7.67)
Education (years)	14.46 (2.75)	13.68 (2.30)	12.52 (2.45)	13.85 (2.32)
MMSE	26.46 (1.98)	27.25 (1.72)	26.96 (1.76)	28.88 (1.19)
GDS	4.17 (4.13)	5.67 (6.82)	5.09 (5.15)	3.02 (3.89)
Savings Indices				
Long Delay Savings Index (percent) (List A, Trial 5 vs. Long Delay Free Recall)	36.77 (27.79)	65.75 (28.44)	75.04 (30.63)	84.90 (17.56)
Recognition Savings Index (z-score) (List A, trial 5 vs. Delayed Recognition)	−2.87 (1.77)	0.34 (1.41)	0.57 (1.07)	0.10 (1.15)
Proactive Interference Effects				
List A, trial 1 (raw score)	4.46 (1.05)	4.07 (1.56)	4.28 (1.51)	5.56 (1.50)
List B (raw score)	4.38 (1.44)	4.18 (1.47)	3.72 (1.20)	5.15 (1.25)
List A words recalled on list B (raw score)	0.61 (0.96)	0.16 (0.50)	0.40 (0.20)	0.30 (0.17)
Retroactive Interference				
List A, trial 5 (raw score)	6.38 (1.04)	6.75 (1.54)	6.68 (1.31)	7.96 (1.16)
List A, trial 7 (raw score)	2.07 (1.89)	4.42 (1.96)	5.04 (1.98)	7.00 (1.79)
List B words recall on subsequent List A test trials (raw score)	2.53 (2.50)	0.98 (1.58)	0.48 (0.91)	0.53 (1.50)
Free, Cued Recall Intrusions/Perseverations (raw score)				
Free recall intrusion	5.30 (5.26)	2.30 (2.78)	1.96 (3.18)	1.03 (1.46)
Cued recall intrusion	6.07 (5.64)	1.76 (2.02)	1.12 (1.69)	0.82 (1.58)
Perseverations	1.30 (1.93)	1.09 (1.25)	1.60 (2.04)	1.85 (2.09)
Recognition Foils (raw scores)				
Semantic foils	3.30 (2.65)	0.76 (1.13)	0.48 (0.58)	0.44 (0.85)
Interference list B foils	4.15 (2.15)	1.30 (1.48)	0.92 (1.07)	0.42 (1.14)
Unrelated foils	1.00 (1.73)	0.05 (0.22)	0.04 (0.20)	0.05 (0.22)

Note. MMSE = Mini Mental State Examination; GDS = Geriatric Depression Scale; aMCI = amnesic mild cognitive impairment; mxMCI = mixed mild cognitive impairment; dMCI = dysexecutive mild cognitive impairment; NC = normal control.

proactive interference of list A words for aMCI patients compared to all other groups ($p < .001$). mxMCI, dMCI, and NC participants did not differ on this measure. Penetration of list B intrusion errors onto subsequent list A delay and cued recall was also significant ($F[3,120] = 5.84$; $p < .001$). *Post hoc* analysis found that aMCI patients produced more list B intrusion errors compared all other groups ($p < .001$); mxMCI, dMCI, and NC groups did not differ on this measure (Table 1).

Extra-List Intrusion Errors and Perseverations

ANOVAs for free recall ($F[3,146] = 8.76$; $p < .001$) and cued recall intrusion errors ($F[3,145] = 17.91$; $p < .001$) were significant. aMCI participants produced more free and cued recall intrusion errors than all other MCI and the NC groups ($p < .003$, all analyses). The mxMCI, dMCI, and NC groups did differ on either measure. Contrary to expectation there was no between-group difference for perseverations (see Table 1).

Extra-List Intrusion, Francis and Kucera Word Frequency

There was significant disparity in the numbers of MCI patients who made any extra-list intrusion errors (aMCI: 12/13 = 92%; mxMCI: 39/56 = 69%; dMCI: 11/25 = 44%). Because only 9 of 56 NC participants (16%) made extra-list intrusion errors this group was excluded from these analyses. The median Francis and Kucera (1982) value was highest for the aMCI group suggesting greater extra-list intrusion prototypicality (see Table 2). Mann-Whitney tests found greater prototypicality when aMCI were compared to mxMCI patients ($Z = -3.99$; $p < .001$). There was no difference for intrusion prototypicality when aMCI were compared to dMCI patients or when mxMCI were compared to dMCI patients (see Table 2). On the Moses Test for Extreme Reaction greater intrusion prototypicality was found when aMCI patients where compared to mxMCI ($p < .001$) and dMCI patients ($p < .030$). mxMCI and dMCI patients did not differ.

Recognition Foil Production

The multivariate effect for foil production was significant (Hotelling $F[9,425 = 12.36$; $p < .001$) as were all three subsequent univariate ANOVAs ($p < .001$, all analyses). Bonferroni between-group comparisons indicated greater semantic, list B, and unrelated foils production for aMCI patients compared to all other groups ($p < .001$, all analyses). Between-group analyses found that mxMCI, dMCI, and NC participants did not differ in their production of semantic and unrelated foils; however, mxMCI patients endorsed more list B, interference foils compared to NC participants ($p < .006$).

Table 2. Francis and Kucera Combined Free and Cued Recall Intrusion Prototypicality measures

	aMCI ($n = 12$)	mxMCI ($n = 39$)	dMCI ($n = 11$)
Mean	44.30	14.64	45.39
(*SD*)	(30.84)	(18.49)	(66.03)
Median	35.75	7.00	15.50
Mode	19.00	6.00	4.00
Range	12.50–105	1–89	4–208
Mann-Whitney Statistic (rank)	$U = 40.96$	$U = 21.40$	$U = 9.92$

Note. aMCI = amnesic mild cognitive impairment; mxMCI = mixed mild cognitive impairment; dMCI = dysexecutive mild cognitive impairment; NC = normal control.

Within-group NC participants endorsed equal numbers of semantic and list b interference foils, but more semantic ($t[55] = 3.56$; $p < .001$) and list B interference ($t[55] = 2.61$; $p < .011$) than unrelated foils. The aMCI patients also endorsed equal numbers of semantic and list b interference foils, but more semantic ($t[12] = 4.40$; $p < .001$) and list b interference ($[t12] = 7.77$; $p < .001$) than unrelated foils. By contrast, dMCI patients endorsed more list B, interference than semantic foils ($t[24] = 2.19$; $p < .038$). The dMCI participants also endorsed more semantic ($t[24] = 3.38$; $p < .002$) and list B, interference ($t[24] = 4.02$; $p < .001$ foils than unrelated foils. A similar profile was obtained for mxMCI patients where more list B, interference than semantic foils were endorsed ($t[55] = 2.17$; $p < .034$); and more semantic ($t[54] = 4.39$; $p < .001$) and list B, interference foils $t[54] = 6.23$; $p < .001$) were endorsed than unrelated foils (see Table 1).

DISCUSSION

The current nomenclature for MCI generally revolves around MCI subtypes presenting with clear evidence of an anterograde amnesia (aMCI in the current research); MCI patients who present with single domain, non-amnesic cognitive impairment (dMCI in the current research), or evidence for multiple domains of cognitive impairment (mxMCI in the current research). In our work, the terms aMCI, dMCI, and mxMCI were used to reflect the specific neuropsychological tests and accompanying cognitive constructs used to define our patients. We fully acknowledge that in the wider scope of MCI research our dMCI and mxMCI groups could be viewed as presenting with either a single domain, non-amnesic or multiple-domain, MCI syndrome.

Setting aside the issue of nomenclature, a prime motivation for the current research was to examine hypothesized patterns of serial list-learning impairment in three *statistically determined* MCI subgroups. The analysis of savings/forgetting, frequency and type of extra-list intrusion errors, and recognition foils described above provides greater breadth regarding memory deficits in MCI compared to prior research where performance is restricted to a single paragraph delay free recall measure (i.e., Logical Memory subtest), or findings based only on delay free recall/recognition test performance.

Consistent with our predictions, the data described above, in conjunction with our prior research (Libon et al., 2010), suggest that some MCI patients produce patterns of impairment on a verbal serial list-learning test similar to AD and non-AD dementia. Perhaps not unexpectedly, the deficits observed in the aMCI group is similar to serial list-learning deficits associated with AD, i.e., little saving and rapid forgetting, the production of many and prototypic extra-list intrusion errors, and profligate responding to recognition foils. Unlike prior studies (Loewenstein et al., 2004; Lowestein, Acevedo, Agron, & Duara, 2007), there was less evidence for proactive interference. However, analyses for retroactive interference found that, as compared to other groups, aMCI patients appeared to be very susceptible to the deleterious effect of the interference test condition along with greater penetration of list B words into subsequent list A recall. However, these conclusions must be tempered in that direct comparisons between MCI and AD patients were not conducted.

The dMCI exhibited relatively little impairment on the P[r]VLT when compared to all other MCI and NC participants. However, the dMCI group differed from NCs in foils endorsed on the delayed recognition test trial where more list b, interference foils were endorsed than semantic foils. This suggests the presence of a possible dysexecutive syndrome, a pattern linked to impaired frontal lobe functioning (Baldo et al., 2002; Baldo & Shimamura, 2002).

For the mxMCI group their savings was relatively intact; fewer extra-list intrusion errors were produced; and intrusion errors were more subordinate or constrained as related to their respective categories. However, between-group analyses indicated that mxMCI patients endorsed more list B, recognition foils than NC participates. Within-group analyses also showed that mxMCI patients endorsed more list B, interference than semantic foils. Thus, as compared to the dMCI group where there were no recognition differences compared to NC participants, and in conjunction with original cluster analysis (Libon et al., 2010), mxMCI patients present with more solid evidence of a retrieval-based difficulty, a profile sometimes associated with non-AD, subcortical dementia syndromes (see Salmon & Bondi, 2009, for review). The mxMCI patients described by Libon et al. (2010), presented with mildly reduced performance on tests measuring naming and category (“animal”) fluency with relatively intact P[r]VLT delayed recognition test performance. Collectively, the findings from the current study, combined with original cluster analysis (Libon et al., 2010) suggest that, in part,

lexical retrieval difficulties may underlie the verbal serial list-learning deficits mxMCI. Whether this is true and/or how possible lexical retrieval difficulty relate to possible progression to dementia should be the subject of future research.

The question now turns to whether the three MCI groups described above represent separate phenotypic/genotypic syndromes or a continuum of a single behavior/pathological process. Jak, Bangen, et al. (2009) have pointed out that multiple-domain or mixed patients may go on to develop AD. Nonetheless, our findings suggest that when multiple-domain or mixed MCI patients are operationally defined using the methodology of Libon et al. (2010), verbal serial list-learning deficits are best understood within the context of a frontal systems syndrome. The relationship(s) between dysexecutive and memory impairment in MCI have not been thoroughly researched and may yield new insights regarding the neurobiology of MCI. The current research suggests that labeling MCI individuals with impaired delay recall but intact recognition memory as 'amnesic' (whether single- or multi-domain) may not be the best characterization of this profile of memory dysfunction. Chang, Bondi, McEvoy, et al. (2010) has also urged caution against using a single measure of memory to diagnose MCI. The work of Anastasi and Urbina (1997) suggests that multiple measures of a cognitive domain provide a more reliable estimate of concomitant underlying cognitive constructs than a single measure. Diagnostic or nosological algorithms for MCI incorporating a variety of learning and memory-related constructs could result in greater knowledge of the etiology of MCI syndromes and progression to dementia.

The current research also speaks directly to the controversy regarding the appropriate algorithms used to operationally define MCI. In our prior research (Libon et al., 2010) distinct *statistically determined* serial list-learning profiles were obtained using cut scores that were −1.5 *SD* below normative values. Currently, the optimal cut score for memory and other neuropsychological tests to diagnose MCI is unknown and little attention has been paid to this important issue. Many MCI studies used a cut point of −1.5 *SD*; however, the normative neuropsychological studies of Heaton, Grant, and Matthews (1991) and Heaton, Miller, and Taylor (2004) have shown optimal separation of normal from neurologic populations to be at cutoff scores of −1.0 *SD*. Ganguli, Dodge, Shen, and DeKosky (2004) have shown that increasing the threshold for memory impairment from −1.0 to −1.5 *SD* reduces the diagnosis of MCI by half. Busse, Hensel, Guhne, Angermeyer, and Riedel-Heller (2006) have found that a cutoff of −1.0 *SD*, rather than −1.5 *SD*, had the highest predictive power for development of AD. Based on these findings, Jak, Bondi, et al. (2009) and Jak, Urban, et al. (2009) have suggested using cut scores where test performance is at least −1.0 *SD* below normative values, but with the added requirement that at least two indices within a cognitive domain fall below this cutoff in order for that domain to be defined as impaired. Thus, the lower cutoff for impairment (i.e., −1.0 *SD vs.* −1.5 *SD*) combined with the higher requirement of two impaired indices or measures within a cognitive domain may strike a balance between sensitivity and reliability to detect mild impairment (Anastasi & Urbina, 1997). Such neuropsychologically based definitions for the diagnosis of MCI have shown improvements in both stability of MCI diagnosis and prediction of progression to dementia (Jak, Bondi, et al., 2009; Loewenstein et al., 2009). Thus, results from the current research expand upon the diagnostic algorithm suggested by Bondi and colleagues (2008) in that maximum specificity for the eventual progression of a MCI syndrome to dementia may be realized when, say, low delay free recall is seen along with either a low saving score, prototypic extra-list intrusion errors, and/or indiscriminate responding to delay recognition foils.

New diagnostic criteria for *MCI due to Alzheimer's disease* have been proposed (Albert et al., 2011) with a keen interest in how both vascular risk factors and biomarkers (e.g., serum/cerebrospinal fluid Aβ and tau levels, amyloid imaging, MRI volumes, etc.) are useful for both predicting and diagnosing AD. Vascular risk factors have been associated with multiple-domain or mixed and non-amnesic MCI subtypes (Delano-Wood et al., 2008; Delano-Wood, Bondi, Jak, et al., 2010; Di Carlo et al., 2007; Solfrizzi et al., 2004; Verghese et al., 2008; Zanetti et al., 2006). Furthermore, there is some evidence that MCI patients with MRI periventricular white matter damage is associated with memory/language deficits, whereas deep white matter damage is associated with executive function/processing speed deficits (see Delano-Wood, Bondi, Sacco, et al., 2010; Price et al., 2011). Amyloid imaging studies (Clark et al., 2011), biomarkers such as the APOE ε4 allele (Saunders et al., 1993), and serum and spinal fluid Aβ/tau ratios (Cosentino et al., 2010) have been linked with aMCI and AD. It would be interesting to know how and/or if an analysis of serial list-learning process and errors (Kaplan, 1988) are related to amyloid, spinal, and/or serum biomarkers in *statistically defined* MCI groups. Such data could provide key information regarding the nature of prodromal states and help predict progression to AD and non-AD dementias.

The current research is not without limitations. First, our data are entirely cross-sectional. Without longitudinal follow-up to determine disease progression, we can only speculate as to the type of dementia which may result. This is why we relied heavily on previous reports drawn from the dementia literature for comparison purposes and acknowledge that direct comparisons with dementia groups and longitudinal follow-up is critical. Second, all participants in the current study were drawn exclusively from memory clinics. This could have biased our results. A population-based study would greatly increase the generalizibility of the data reported above.

With these limitations in mind, the current research is significant for two key findings. First, known profiles of memory impairment in patients with various dementia syndromes are present in at least some MCI patients; and second, the current research adds to a growing literature (Chang, Bondi, Fennema-Notestine, et al., 2010; Jak, Bangen, et al., 2009; Jak, Bondi, et al., 2009; Loewenstein et al., 2009) that

cautions against using a single memory test score to diagnosis MCI syndromes. Future studies combining a process analysis of neuropsychological test data (Kaplan, 1988) with dementia-related MRI and neuropathology biomarkers could advance our understanding of the phenotypic expression of amnesic and non-amnesic MCI syndromes. Taken as a whole, such work could have a significant impact on identifying and treating factors that impact upon the progression of preclinical states, to MCI, to dementia.

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