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Dysexecutive Functioning in Mild Cognitive Impairment: Derailment in Temporal Gradients

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Abstract

Libon et al. (2010) provided evidence for three statistically determined clusters of patients with mild cognitive impairment (MCI): amnesic (aMCI), dysexecutive (dMCI), and mixed (mxMCI). The current study further examined dysexecutive impairment in MCI using the framework of Fuster's (1997) derailed temporal gradients, that is, declining performance on executive tests over time or test epoch. Temporal gradients were operationally defined by calculating the slope of aggregate letter fluency output across 15-s epochs and accuracy indices for initial, middle, and latter triads from the Wechsler Memory Scale-Mental Control subtest (Boston Revision). For letter fluency, slope was steeper for dMCI compared to aMCI and NC groups. Between-group Mental Control analyses for triad 1 revealed worse dMCI performance than NC participants. On triad 2, dMCI scored lower than aMCI and NCs; on triad 3, mxMCI performed worse *versus* NCs. Within-group Mental Control analyses yielded equal performance across all triads for aMCI and NC participants. mxMCI scored lower on triad 1 compared to triads 2 and 3. dMCI participants also performed worse on triad 1 compared to triads 2 and 3, but scored higher on triad 3 *versus* triad 2. These data suggest impaired temporal gradients may provide a useful heuristic for understanding dysexecutive impairment in MCI. (*JINS*, 2011, *18*, 1–9)

Keywords: Mild cognitive impairment, Single domain mild cognitive impairment, Multiple domain mild cognitive impairment, Alzheimer's disease, The Titanic Effect, Executive control

INTRODUCTION

Mild cognitive impairment (MCI) was initially viewed rather narrowly in the sense that MCI was believed to be a prodrome more or less limited to Alzheimer's disease (AD). However, newer diagnostic criteria for MCI acknowledge amnesic MCI (aMCI) in addition to other single and multiple-cognitive domain MCI syndromes (Petersen et al., 2009; Winblad et al., 2004). This nosology is supported by empirically based population studies as well as clinical-based research obtained from patients referred to specialized memory clinics (Busse, Hensel, Gühne, Angermeyer, & Riedel-Heller, 2006; Chao et al., 2009; Fischer et al., 2007; Lopez et al., 2003; Pa et al., 2009; Solfrizzi et al., 2004; Yaffe, Petersen, Lindquist, Kramer, & Miller, 2006).

Delano-Wood et al. (2010) and Libon et al. (2010) subjected aggregate neuropsychological test scores from community referrals to a memory clinic to multivariate cluster analysis to better understand MCI subtypes. Despite differences in neuropsychological tests and clustering techniques, both studies reported three-group solutions. Delano-Wood et al. (2010) found evidence for an amnesic group, a combined amnesic/language group, and a group demonstrating impairment on tests measuring executive control and information processing speed. Libon et al. (2010) found evidence for distinct amnesic (aMCI) and dysexecutive (dMCI) groups. Similar to Delano-Wood et al. (2010), a mixed or multiple-domain group (mxMCI) was also identified. These participants presented with reduced scores on letter fluency, semantic fluency, visual confrontation naming,

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and delayed free recall, though delayed recognition performance was intact. Combined with other research findings (Lopez et al., 2003), such data suggest that neuropsychological tests selected on the basis of known brain-behavior relationships can make a substantial contribution in understanding brain-behavior relationships underlying MCI.

In the current research, we examined executive test performance as a function of the time necessary to complete tasks and/or test epochs (Lamar, Price Davis, Kaplan, & Libon, 2002). This approach is based on Fuster's (1997) model of the temporal organization of behavior which states that greater executive resources are necessary as a function of the time needed to complete demanding tests. Lamar et al. (2002) previously used Fuster's model of the temporal organization of behavior to explain dysexecutive impairment in patients with dementia and found differential decline across the four 15-s letter fluency epochs in patients clinically diagnosed with vascular dementia (VaD) with MRI evidence of significant white matter disease and dementia patients with Parkinson's disease (dPD) compared to patients clinically diagnosed with AD with little MRI evidence of white matter disease. Specifically, VaD and dPD patients generated their maximum output during the first 15-s interval after which there was a precipitous drop in output. By contrast, such a steep decline or negative slope was not observed with AD patients and a normal control (NC) group.

Using the same temporal gradient process approach, Lamar et al. (2002) also examined performance on the Boston Revision of the Wechsler Memory Scale Mental Control subtest (Leach, Kaplan, Rewilak, Richards, & Proulx, 2000), an expanded version of the original Mental Control subtest (Wechsler, 1945) in AD patients with little MRI evidence of white matter disease compared to VaD patients with MRI evidence of significant white matter disease. Consistent with their analysis of letter fluency test performance, VaD patients presented with a significant temporal gradient compared to AD patients. That is, when performance was divided into three test epochs or triads, patients with VaD exhibited a striking negative slope compared to AD patients. Specifically, patients with VaD demonstrated a consistent decline over the three Mental Control test epoch or triads whereas patients with AD suffered a decline from the first to middle test triad with no further decline on the latter or third test triad. Lamar et al. (2002) interpreted these data to suggest differential impairment in mental search and maintaining mental set, constructs consistent with Fuster's model of impaired temporal gradients (Lamar et al., 2002; Lamar, Price, Giovannetti, Swenson, & Libon, 2010). This negative slope or precipitous and continuous decline in test performance as a function of time and/or test epoch is termed the "Titanic Effect."[1]

In the current research, we sought to determine whether the findings of Lamar et al. (2002) demonstrating derailed temporal gradients in patients with VaD and dPD, but not AD dementia syndromes could also be found in different MCI subtypes. In the current research, the same sample of MCI patients as described by Libon et al. (2010) was studied. However, a normal control (NC) group and additional MCI patients were recruited to test whether Fuster's model of temporal gradients might provide a heuristic to better understand dysexecutive impairment in MCI. Using methods originally described by Lamar et al. (2002), performance on letter fluency and Mental Control data were examined as a function of time and/or test epoch. Acknowledging possible tautological issues in analyzing the same executive control tests used to originally classify MCI patients (Libon et al., 2010) a new cluster solution was calculated using different executive measures before the inspection of letter fluency and Mental Control test epochs.

Our first prediction was that there would be little to no difference between aMCI and NC participants such that these groups would show no decline as a function of time and/or test epoch (i.e., similar to AD patients described by Lamar et al., 2002). Our second prediction was that dMCI patients would produce a significant negative slope or impaired temporal gradient compared to other groups on both tests (i.e., similar to the VaD & dPD of Lamar et al., 2002). Our third prediction was that the mxMCI group might occupy a middle position between aMCI/NC participants compared to the dMCI group and present with some, albeit less evidence of a negative slope or impaired temporal gradient on both tests.

METHODS

MCI Diagnosis

The MCI patients and the overall methods used in the current research are similar as described by Libon et al. (2010). The diagnosis of MCI was determined, in part, using criteria established by Petersen and Morris (2005), that is, subjective complaints of a decline in cognitive functioning; a score of ≥ 24 on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975); and no impairment in activities of daily living (ADLs; score 6/6) and/or instrumental activities of daily living (IADLs; score 15/17; Lawton & Brody, 1968). Additionally, participants had to perform ≤ 1.5 standard deviation units below normative values on any single neuropsychological test as previously described by Libon et al. (2010).

MCI/Normal Control Participants

The MCI corpus described by Libon et al. (2010) consisted of 108 patients who were recruited prospectively over a 5-year period (2002–2007) and were self-referred to an outpatient, university-affiliated memory clinic. All participants were ambulatory, medically well and stable, and living independently in the community on the basis of self report and/or information provided by a family member. Fourteen participants

[1] The Titanic Effect is a reference to ill-fated voyage of 1912. While the ship began its journey with speed and efficiency, it struck a massive iceberg only 4 days into the trip. After this unfortunate incident, the vessel rapidly and tragically sunk, ultimately suffering a watery fate. Thus, the trajectory of the Titanic is analogous to the negative slope or precipitous decline in performance observed among patients with dysexecutive impairment.

were excluded because of major medical or psychiatric illness (see Libon et al., 2010, for details). Of the 94 remaining patients studied, 19 did not meet inclusion criteria for the current research because they did not obtain a score ≤ 1.5 *SD* units below normative values on any test. This initial sample of 75 MCI patients was subjected to a K-means cluster analysis specifying a three-cluster solution. This cluster analysis yielded an amnesic (aMCI) group, a dysexecutive (dMCI) group, and a mixed or multiple-domain group (mxMCI) with difficulty in all cognitive domains assessed (see Libon et al., 2010 for full details). Since the calculation of this initial cluster solution, additional patients meeting criteria for MCI were recruited and added to the database. As new patients were added the cluster analysis was updated. Thus, the final sample used in the current research consisted of 15 patients with aMCI, 18 patients with dMCI and 62 patients with mxMCI ($n = 95$). Twenty-four healthy elderly normal control (NC) participants were recruited prospectively along with MCI patients. All NC participants were living in the community and obtained scores on the MMSE ≥ 27 and a score on the Geriatric Depression Scale (Yesavage, 1986) of <9. For all participants, consent was obtained consistent with Institutional Review Board regulations and the Declaration of Helsinki.

New Cluster Solution

To avoid possible confounds related to circularity the original executive variables used by Libon et al. (2010); that is, total output on the letter fluency test and the total accuracy index from the Mental Control test, were removed, new executive measures were substituted, and a new cluster solution was calculated. Temporal gradients for letter fluency and Mental Control were then calculated on the basis of this new cluster analysis. The new cluster solution included the number of correct responses on the 60-item version of the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983); total number of responses in 60 s excluding perseverations and intrusion errors on a semantic (''animal'') fluency test (Carew, Cloud, Lamar, Grossman, & Libon, 1997; Monsch et al., 1992); and total delayed free recall and delayed recognition discriminability from the Philadelphia (repeatable) Verbal Leaning Test (P[r]VLT).

The executive measures included in the new cluster solution were drawn from the Backwards Digit Span Test of Lamar, Catani, Price, Heilman, and Libon (2008) and Lamar et al. (2007). The Backward Digit Span Test (BDT; Lamar et al., 2007, 2008) is a modification of the original Digit Span subtest (Wechsler, 1981) and consists of seven trials of three, four, and five digit span lengths for a total of 21 trials. All four and five span trials were constructed so that contiguous numbers were placed in strategic positions. For example, in four-span trials contiguous numbers were placed in either the first and third or second and fourth digit positions, for example, 5269 or 1493. In five-span trials, contiguous numbers were placed in the middle three digits positions, for example, 16579. Three-span test trials were not constructed in this manner because of primacy and recency effects. The BDT was administered using standardized WAIS-R Digit Span subtest procedures with the exception that the discontinuation rule was not applied as all patients received all 21 test trials of the BDT. The two BDT measures used in the new cluster analysis are described below.

Percent BDT Correct SERIAL-ORDER: This score reflects the total number of digits correctly recalled in accurate serial-position divided by the total possible correct and multiplied by 100, [(total # correct digits SERIAL-ORDER)/(total possible correct)] $\times$ 100. This variable is believed to measure executively demanding aspects of working memory associated with mental manipulation such as disengagement and temporal re-ordering (Lamar et al., 2007, 2008).

BDT Dysexecutive Errors: BDT errors were scored on the basis of digit span error scoring procedures previously suggested by Kaplan, Fein, Morris, and Delis (1991). Four types of dysexecutive errors were coded: (1) within-trial capture errors were coded only on 4 and 5 span trials if patients grouped contiguous numbers in serial order, that is, 1493 – *''3491''*; 16579 – *''95671''*; (2) between-trial capture errors were coded when participants incorporated a digit(s) from either of the two immediately preceding trials to form a group of contiguous numbers in serial order; (3) within-trial perseverations were coded when patients repeated a digit within a given trial, that is, 16579 – *''97569''*; (4) between-trial perseverations were coded if the participant included a digit(s) from either of the two immediately preceding trials but did not group them in contiguous serial order (to prevent double coding of between-trial capture errors). Errors were summed to obtain an aggregate BDT error score. These errors have been previously associated with dysexecutive impairment and reduced working memory (Lamar et al., 1997; Stuss, Shallice, Alexander, & Picton, 1995).

A new k-mean cluster analysis (SPSS v19) was conducted to identify relatively homogeneous MCI groups as described above. Three *a priori* clusters were specified. The new cluster solution produced similar results to the original analysis described by Libon et al. (2010; see Table 1a, b).

Group 1 (dysexecutive MCI; $n = 18$) presented with impaired performance on both BDT measures, that is, severely reduced serial-order recall and the production of many dysexecutive errors. Group 2 (amnesic MCI; $n = 15$) scored poorly on both P[r]VLT measures. Group 3 (mixed MCI; $n = 62$) scored low on the Boston Naming Test, ''animal'' fluency, and the P[r]VLT delayed recall test condition. The average Euclidean distance between clusters is also displayed in Table 1. The greatest distance was obtained between the two single domain MCI groups, that is, dMCI and aMCI patients. Cluster centers were approximately equal from the mxMCI to dMCI group and the mxMCI to aMCI group.

Dependent Variables and Statistical Analysis

To assess for the presence and severity of temporal gradients, we constructed and analyzed a series of new, process-based dependent variables (Kaplan, 1988) not included in the original Libon et al. (2010) corpus.

Table 1a. K-mean cluster analysis for patients meeting criteria for mild cognitive impairment ($n = 95$)

	dMCI ($n = 18$)	aMCI ($n = 15$)	mxMCI ($n = 62$)
Digits Backward: total serial order	61.09	86.05	84.08
Digits Backward: total dysexecutive errors	8.06	4.47	4.95
Boston Naming Test	51	51	46
"Animal" fluency	13.11	14.87	11.90
P(r)VLT – delayed free recall	5.00	2.00	4.76
P(r)VLT – delayed recognition	92.75	67.41	91.22

dMCI = dysexecutive MCI, aMCI = amnesic MCI, mxMCI = mixed, NC = normal control, P(r)VLT = Philadelphia (repeatable) Learning Test.

Letter Fluency Slope: The effect of time on letter fluency test performance was assessed by computing the slope as a function of test epoch. The principal slope analysis was calculated on the basis of all four 15-s test epochs. An additional slope calculation was computed on the basis of only the first and fourth 15-s epochs. For descriptive purposes, total output for letter fluency is included for all groups in Table 2. As this measure was part of the original cluster analysis no additional analyses were under taken.

Mental Control Triad Accuracy Indices: In addition to the original three tasks that comprise the standard Wechsler Memory Scale Mental Control (WMS-MC) subtest (i.e., counting backward from 20 to 1, reciting the alphabet, and adding serial 3's), the Boston Revision of the WMS-MC subtest includes four additional tasks, reciting the months of the year forward; reciting the months of the year backward; an alphabet rhyming task requiring patients to identify all letters that rhyme with the word "key"; and an alphabet visualization task requiring patients to provide all printed, capitalized letters with curved lines (Lamar et al., 2002; Leach et al., 2000). For all seven Mental Control subtests, separate accuracy indices were calculated using the following algorithm: Accuracy Index = [1- ((false positives+omissions)/# possible correct responses)] × 100. This algorithm yields a percentage score where a score of 100% indicates all targets were correctly identified with no omissions or false positive responses. Previous principal component analysis of these seven accuracy indices suggests that counting backward from 20–1, reciting the alphabet, months forward, and adding serial 3's load on an automatized mental control factor whereas months backward, alphabet rhyming, and alphabet visualization load on a separate, non-automatized mental control factor.

In the current research, only the three non-automatized subtests were examined. These non-automatized items were partitioned into three equal sections using procedures described by Lamar et al. (2002). For the two alphabet tasks triad 1 consisted of letters A through I; triad 2, letters J through Q; and triad 3, letters R through Z. For months backward, triad 1 included December through September; triad 2, August through May; and triad 3, April through January. A Mental Control accuracy index for each triad was subsequently determined by combining performance across the three subtasks and using the algorithm described above (i.e., triad accuracy index = [1- (false positives+omissions)/# possible correct responses)] × 100). Thus, the number of possible correct responses in the numerator for initial, middle, and latter Mental Control triads was 13, 9, and 10, respectively.

Mental Control Time to Completion: Individual time to completion for all three non-automatized WMS-MC subtests was summed to create a measure of total time to completion.

All variables were analyzed using a one-way analysis of variance with Bonferroni corrections and significance set at $p < .05$. Cohen's (1988) B omega statistic was used to calculate effect sizes (small, 0.10; medium, 0.25; large, 0.40).

Table 1b. Distances between final cluster centers

	Cluster 1 (dMCI)	Cluster 2 (aMCI)	Cluster 3 (mxMCI)
Cluster 1 (dMCI)		35.915	23.686
Cluster 2 (aMCI)	35.915		24.700
Cluster 3 (mxMCI)	23.686	24.700	

RESULTS

Demographic Characteristics/Global Cognitive Status

No significant differences were found for age or education. On the MMSE ($F[3,115] = 4.09$; $p < .008$), there were no differences between the three MCI groups. The NC group scored higher than dMCI ($p < .023$) and aMCI ($p < .026$) patients (Table 2). There was no difference on the MMSE between NC and mxMCI participants.

Letter fluency analyses

The one-way analysis of variance (ANOVA) for slope across all four 15-s letter fluency epochs was significant

Table 2. Demographic data (means & standard deviations)

	dMCI	aMCI	mxMCI	NC
Age	68.94 (10.00)	69.73 (9.02)	72.85 (9.27)	75.63 (9.39)
Education	12.78 (2.60)	13.93 (2.65)	13.59 (2.42)	13.73 (2.66)
MMSE	26.67 (1.74)	26.60 (2.09)	27.24 (1.68)	28.21 (1.25)

dMCI = dysexecutive MCI, aMCI = amnesic MCI, mxMCI = mixed, NC = normal control, MMSE = Mini-Mental State Examination.

($F[3,109] = 4.50$; $p < .005$) (Table 3). *Post hoc* analysis found a steeper slope for dMCI patients compared to aMCI patients ($p < .024$) and NC ($p < .008$) groups. There was no difference between mxMCI patients and other groups on this measure. The one-way ANOVA for slope of epoch 1 only to epoch 4 was also significant ($F[3,109] = 4.71$; $p < .004$). A more precipitous decline was, again, observed for dMCI patients compared to aMCI ($p < .022$) and NC participants ($p < .008$). mxMCI participants did not differ from other groups on this measure. The effect sizes for these analyses were somewhat modest perhaps due to unequal sample size.

Mental control triads

The effect of time/test epoch on MC Triad Accuracy Indices was assessed with a 4 (group) × 3 (test epoch) repeated measure ANOVA, with triad Accuracy Indices (TrAcI) as the dependent variable (Table 4). This analysis produced significant main effects for test epoch ($F[2,105] = 21.23$; $p < .001$), group ($F[3,106] = 33.36$; $p < .001$), and a significant test epoch × group interaction ($F[6,210] = 2.76$; $p < .013$). However, the assumption of sphericity was not met (Mauchly Test- $\chi^2 = 13.18$; $p < .001$; Huynh-Feldt = .973). Using the Huynh-Feldt correction, both the main effect for test epoch (Huynh-Feldt [1.86] = 18.26; $p < .001$) and epoch × group interaction (Huynh-Feldt [5.60] = 2.44; $p < .030$) were significant. The MANOVA conducted to assess for the multivariate effect of group for test epoch was significant ($F[9,308] = 11.75$; $p < .001$).

The effect of group on Mental Control test performance was assessed with one-way univariate ANOVAs for each triad. A significant effect for group was found for all triad accuracy indices (initial triad accuracy index: $F[3,104] = 3.81$; $p < .012$; middle triad accuracy index: $F[3,103] = 5.08$; $p < .003$; latter triad accuracy index: $F[3,103] = 3.59$; $p < .016$). *Post hoc* analysis for the initial Mental Control triad found lower test performance for dMCI *versus* NC participants ($p < .026$). For the middle Mental Control triad dMCI scored lower than aMCI ($p < .045$) and NC ($p < .001$) groups. On the third Mental Control triad mxMCI patients performed worse than NCs ($p < .036$).

Within-group Mental Control triad analyses found that aMCI and NC groups performed equally across all triads. mxMCI participants scored higher on triad 1 compared to triad 2 ($t[58] = 2.72$; $p < .008$) and higher on triad 1 compared to triad 3 ($t[58] = 4.68$; $p < .001$). There was no difference for mxMCI participants between triads 2 and 3. dMCI participants scored higher on triad 1 compared to triad 2 ($t[15] = 3.72$; $p < .002$) and triad 1 compared to triad 3 ($t[15] = 2.41$; $p < .030$). However, a better score was obtained on triad 3 compared to triad 2 ($t[15] = 2.20$; $p < .044$).

Mental control total time to completion

The one-way ANOVA for Mental Control time to completion was significant ($F[3,106] = 7.49$; $p < .001$). *Post hoc* analyses found slower time to completion for dMCI compared to

Table 3. Letter Fluency test performance (means & standard deviations)

	DMCI	aMCI	mxMCI	NC	Significance	Effect size (ω^2)
Letter Fluency: slope all four test epochs	−12.51 (8.18)	−6.71 (2.27)	−9.17 (5.88)	−6.37 (3.36)	dMCI > aMCI; $p < .024$ dMCI > NC; $p < .008$	0.09
Letter Fluency: slope epoch 1 and 4	−38.60 (24.92)	−20.16 (7.65)	−29.25 (18.53)	−19.41 (11.27)	dMCI > aMCI; $p < .022$ dMCI > NC; $p < .008$	0.09
total Letter Fluency (raw score)	27.72 (11.66)	42.11 (12.80)	26.03 (10.15)	45.36 (14.24)		

dMCI = dysexecutive MCI; aMCI = amnesic MCI; mxMCI = mixed; NC = normal control.

Table 4. Mental Control test performance (means & standard deviations)

	dMCI	aMCI	mxMCI	NC	Significance	Effect size (ω^2)
Mental Control – time to completion	124.94 (39.38)	83.73 (41.32)	97.80 (37.74)	66.55 (33.45)	dMCI > aMCI; $p < .016$ dMCI > NC; $p < .001$ dMCI > mxMCI; $p < .062$	0.15
Mental Control – 1st triad	82.21 (20.19)	93.84 (8.81)	87.61 (11.24)	94.87 (10.87)	dMCI < NC; $p < .026$	0.07
Mental Control – 2nd triad	63.70 (23.55)	84.44 (23.68)	79.28 (21.78)	91.35 (9.75)	dMCI < aMCI; $p < .045$ dMCI < NC; $p < .001$	0.10
Mental Control – 3rd triad	75.33 (14.57)	86.00 (17.23)	76.10 (19.56)	89.44 (12.58)	mxMCI < NC; $p < .036$	0.07

dMCI = dysexecutive MCI; aMCI = amnesic MCI; mxMCI = mixed; NC = normal control.

aMCI ($p < .016$) and NC ($p < .001$) groups. A borderline difference between dMCI and mxMCI participants ($p < .062$) was also noted. Based on Cohen's (1988) statistic the effect sizes for all analyses tended to be small, perhaps due to unequal sample size.

DISCUSSION

Our previous research (Libon et al., 2010) found that dMCI patients scored lower than some MCI subgroups and NC participants on total letter fluency output and the overall Wechsler Memory Scale – Mental Control accuracy index. However, aggregate test scores may not entirely reflect the neurocognitive constructs underlying this pattern of performance (Kaplan, 1988). Therefore, the current study focused on temporal gradients in MCI by examining letter fluency and Mental Control performance across time. To avoid issues related to circularity, before this analysis a new cluster solution was calculated using different executive measures than Libon et al. (2010).

Neuropsychological test data analyzed as a function of time is not a widely used methodology in dementia or MCI research. The methods and theoretical context used in the current research were based on previous research by Lamar et al. (2002) and Fuster (1997). Fuster's (1997) model of the temporal organization of behavior states that as demanding tasks require more time to completion, greater executive resources are necessary. On the basis of this construct, we hypothesized that dMCI patients would demonstrate a precipitous decline in test performance as previously reported with VaD/dPD patients or dementia syndromes with significant subcortical pathology (Lamar et al., 2002), suggesting some similarities regarding the underlying brain-behavior mechanisms responsible for this behavior.

Consistent with our expectation there were no differences between aMCI and NC participants on letter fluency performance. However, dMCI patients produced a steeper, negative slope compared aMCI and NC participants, a pattern analogous to VaD and dPD patients *versus* AD patients (Lamar et al., 2002). Moreover, these results were present regardless of the method applied to calculate slope (i.e., accounting for all letter fluency epochs or restricting analysis to the first and fourth epoch). Similar findings have been reported by Delano-Wood et al. (2011, July). There were no differences in letter fluency slope between mxMCI and other groups.

On the Mental Control test non-automatized time to completion was slower for dMCI than NC and aMCI participants. Additionally, a borderline effect was noted between dMCI and mxMCI patients, suggesting a modest bradyphrenia in dMCI patients. Greater time to completion among the dMCI group is also consistent with Fuster's model of temporal gradients. Further evidence for derailed temporal gradients as measured with the Mental Control test was obtained for dMCI and mxMCI participants. Between-group analyses found that dMCI produced lower accuracy indices on triad 1 *versus* NC participants. On triad 2, dMCI performed worse than aMCI and NC patients. Triad 3 revealed lower scores for the mxMCI group when compared to NC subjects. Within-group analyses demonstrated aMCI and NCs performed equally across all triads. mxMCI participants scored lower on triad 1 compared to triads 2 and 3. dMCI patients also scored lower on triad 1 *versus* triads 2 and 3, but performed better on triad 3 than triad 2. We acknowledge possible statistical difficulties caused by the uneven numbers of participants in our three MCI groups. Nonetheless, these data provide reasonable support of our predictions. aMCI and NC participants exhibited similar patterns with relatively steady performance across time or test epoch. mxMCI patients display some elements of impaired temporal gradients, particularly on the Mental Control test. dMCI patients provide strong evidence of derailed temporal gradients on both measures.

Fuster (1997) asserts that the time necessary to complete and sustain a complex mental set is a key function of the frontal lobes, that is, the capacity "to organize actions in the time domain is the most basic and essential of all prefrontal functions … and cannot be overstated" (pp. 3–4). As noted above, overall time to completion on the Mental Control test was generally slower for dMCI patients compared to other groups. Moreover, it is our contention that the declining test performance or the negative slope as a function of time/test epoch observed on both the letter fluency and Mental Control tests seen most predominantly in the dMCI patients involves a derailed temporal gradient associated with impaired frontal systems functioning. We acknowledge that tests of letter fluency and the Mental Control may not be optimal to explore these hypotheses. We also acknowledge that we were unable to recruit new research participants to replicate or generalize our findings. Clearly, further research is necessary to provide additional evidence for derailed temporal gradients in MCI.

Fuster (1997) has described three mechanisms that subserve frontally mediated temporal gradients: working memory, response inhibition, and preparatory set. Another limitation of our study is that the current tasks cannot readily isolate the relative contributions of each mechanism. A hypothesis for future research is that working memory and preparatory set may differentially involve the production of omissions, while response inhibition may be associated with commission errors (intrusions and perseverations).

If impaired temporal gradients are constructs that provide a framework for dysexecutive impairment in some MCI patients the question now turns to the exact neuroanatomic mechanism(s) driving this performance. Fuster (1997) has pointed out that the prefrontal cortex is defined, in part, by its reciprocal and intimate connections to the dorsal medial nucleus of the thalamus. Indeed, the presence of frontal-subcortical connecting pathways is well established (Alexander, Delong, & Strick, 1986). In dMCI it is possible the downwardly projecting pathways from the prefrontal cortex that run through the basal ganglia and ultimately connect to the dorsal medial nucleus are compromised. If this is the case, the reciprocal projections from the dorsal medial nucleus back to the frontal lobes could also be damaged, limiting the capacity of the frontal cortex to engage in its superordinate/executive functions. Presently this model, which assigns importance to a derailed thalamic gating mechanism (Pare, Curro-Dossi, & Steriade, 1991; Steriade, 2004), is speculative. However, this mechanism could provide the cognitive and neuroanatomic underpinning for the *"Titanic Effect"* or a precipitously declining slope that epitomized dMCI test performance.

Kaufman et al. (2008) studied MCI and NC participants, using fMRI to assess neural activity with a modified Stroop Test. MCI patients exhibited stronger pre-central and post-central thalamic activations, possibly reflecting more effortful response-selection processes; or alternatively, deficient inhibitory control, an account consistent with Fuster's model of response inhibition. Also, Price et al. (2011, February) has demonstrated a relationship between degraded deep white matter involvement, including white matter alterations near the caudate, and differentially worse performance on the total non-automatized Mental Control accuracy index, the measure originally used by Libon et al. (2010) to cluster MCI patients.

In addition to the theoretical implications of our findings these data speak to several important practical and diagnostic issues. First, Petersen et al. (2009) has suggested that there is a 2:1 ratio between aMCI and other MCI subtypes, suggesting that aMCI constitutes the vast majority of MCI cases. The data recently provided by Delano-Wood et al. (2010) and Libon et al. (2010) do not support this finding. The current research suggests that MCI patients presenting solely with circumscribed primary anterograde amnesia or a dysexecutive state, that is, single domain MCI, constitutes the minority of cases. mxMCI or multiple-domain MCI appears to be the most prevalent presentation of MCI.

Second, the data described above regarding possible temporal gradients associated with dMCI is best understood in conjunction with findings reported by Libon et al. (2011) where a detailed analysis of memory test behavior was presented. In this companion paper, where P[r[VLT test performance was obtained from the same participants used in the current research (Libon et al., 2011), aMCI patients produced evidence for a striking anterograde amnesia as has been described in patients with AD (Price et al., 2009), that is, rapid forgetting, many extra-list, cued recall intrusion errors, and indiscriminate responding to delay recognition foils. By contrast, P[r]VLT test performance among dMCI patients was intact and basically indistinguishable from NC participants. Finally, multiple-domain or mxMCI participants presented with evidence for a source recall, retrieval-based deficit, driven, in part, by their tendency to selectively respond to list B, interference foils on the delayed recognition test condition. Thus, aMCI patients appear to be closely aligned with cognitive deficits seen in AD, whereas dMCI patients appear to be closely aligned with cognitive deficits seen in dementia patients with subcortical pathology. Therefore, taken as a whole, when the current research regarding derailed temporal gradients is combined with a detailed analysis of verbal serial-list learning behavior (Libon et al., 2011), it is possible to operationally define, *in exquisite detail*, phenotype characteristics of single and multiple-domain MCI syndromes not generally appreciated. Such information underscores the value of the process approach (Kaplan, 1988). Moreover, this level of analysis can and should be incorporated into new diagnostic criteria for dementia and MCI (Albert et al., 2011) and offers a reasonable alternative to the diagnosis of MCI syndromes based solely on delayed free recall of a story (Albert et al., 2011). Using a single measure of memory, executive control, or any other cognitive domain may conflate MCI syndromes and prevent clinicians as well as researchers from fully appreciating the brain-behavior relationships that underlie test scores.

The current research is not without limitations, small Ns and unequal patient groups could have affected some of the findings described above. There is a need for the development of neuropsychological tests and procedures specifically designed to assess for the presence and severity of temporal gradients. We acknowledge that ≥ 24 cut point on the MMSE may have been too liberal and biased some test findings. This could place some limits on the external validity of our findings when data from the current study is compared to other research using a more conservative MMSE inclusion criterion.

With these limitations in mind, the approach used in the current research, that is, MCI groups statistically derived using neuropsychological measures chosen to test specific theoretical cognitive constructs, holds considerable promise in characterizing MCI and defining trajectories of progression to AD and non-AD dementia syndromes. This methodology could have significant implications for the appropriate use of biomarker data; providing feedback to patients and their families regarding care giving issues; and the development of targeted pharmacological treatments for MCI and dementia.

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