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Understanding heterogeneity in older adults: Latent growth curve modeling of cognitive functioning

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ABSTRACT

Background: Clarifying relationships between specific neurocognitive functions in cognitively intact older adults can improve our understanding of mechanisms involved in cognitive decline, which may allow identification of new opportunities for intervention and earlier detection of those at increased risk of dementia.

Method: The present study employed latent growth curve modeling to longitudinally examine the relationship between executive attention/processing speed, episodic memory, language, and working memory functioning utilizing the neuropsychological test battery from the National Alzheimer's Disease Coordinating Center. A total of 691 relatively healthy older adults (M_{age} = 69.07, SD = 6.49) were assessed at baseline, and 553 individuals completed three visits spanning a two-year period.

Results: Better cognitive performance was concomitantly associated with better functioning across domains. Subtle declines in executive attention/processing speed processes were found, while, on average, memory and language performance improved with repeated testing. Lower executive attention/processing speed performance at baseline predicted less incremental growth rate in memory. In turn, higher initial memory functioning was associated with incremental improvements in language performance.

Conclusions: These results are consistent with the notion that intact executive function and attention processes are important to preserving memory functioning with advanced age, but are also the functions most susceptible to decline with age. These findings also provide further insight into the critical role of practice effects in clinical assessment practice and have implications for pharmaceutical trials. Practice effects should be routinely considered as they may give the appearance of retention of function within the cognitive domains considered to be a hallmark of Alzheimer's disease pathology.

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Practice effects; sensitivity; cognitive aging; neuropsychological tests; preclinical Alzheimer's disease

Mechanisms of cognitive decline in early stages of neurodegenerative disorders, such as Alzheimer's disease (AD) are not fully understood. A continuum model of AD pathology (and other dementia disorders; Donohue et al., 2014; Sperling et al., 2011) provides a framework for investigating early cognitive change that might lead to improved insight of mechanisms involved in underlying disease processes. In this model, there is a preclinical stage, in which individuals display subtle signs of neurocognitive decline but do not yet meet criteria for mild cognitive impairment (MCI, defined as a transition stage prior to dementia along this continuum; R. C. Petersen, 2004). This preclinical stage (prior to substantial beta-amyloid accumulation and clinical symptoms of AD) can last for over a decade and may represent an opportunity for preventive measures and/or potentially more successful pharmacological and behavioral interventions within individuals who are defined as high risk for MCI/AD (Sperling et al., 2011). Notably, not all individuals with MCI convert to a dementia disorder, and although MCI was originally conceived as a prodromal stage for AD, there are MCI subtypes believed to confer risk for other dementia disorders. In this respect, better characterization of the interplay between specific cognitive domains over time may improve diagnostic capabilities in assessment of older adults at risk of cognitive decline.

Cognitive testing within these preclinical stages remains a critical tool in detecting those at risk of AD and other dementia disorders, as reliable biomarkers remain lacking. However, tests' ability to detect cognitive change is limited by several factors related to specificity and sensitivity. First, cognitive profiles show significant variability in early stages, and findings have been mixed as to the cognitive processes that are first affected in AD. In addition to the hallmark episodic memory impairments that characterize AD, subtle deficits in executive functioning, attention,

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processing speed, and language processing are present in the earlier clinical manifestations of MCI/AD (e.g., Bondi & Smith, 2014; Elias et al., 2000). Others have also noted declines in multiple cognitive domains prior to conversion to MCI (e.g., Howieson et al., 2008; Machulda et al., 2013). Johnson et al. (2012), when comparing domain-specific cognitive functions decline relative to each other using latent growth curve (LGC) analyses, specifically found that executive function/processing speed compared with memory declined faster in patients with MCI and that wider spread declines in cognitive processes rather than memory decline distinguished normally aging adults from MCI groups. However, there is also evidence that episodic memory declines are apparent years prior to executive function declines in those who develop AD (e.g., Grober et al., 2008). Notably, the neural correlates believed to underlie executive functioning and attention processes have been posited to help compensate for declines in other neural resources with advanced age in normally aging adults (e.g., age-related shifts in neural recruitment, such as increased bilateral activity in frontal and posterior parietal brain regions; Cabeza et al., 2004; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Grady, 2012). Thus, baseline functioning within these processes may at least initially influence the rate of decline on episodic memory tests.

Secondly, practice effects (defined as improvements as a result of repeated exposure to a test) are commonly found within longitudinal aging research (Calamia, Markon, & Tranel, 2012). Practice effects vary between individuals, frequency of and intervals between testing, test batteries used, and/or cognitive domain assessed (Bartels, Wegrzyn, Wiedl, Ackermann, & Ehrenreich, 2010). Practice effects on memory, language, visuospatial function, processing speed, and attention within normally aging adults is frequently found (e.g., Jonaitis et al., 2015; MacAulay, Brouillette, Foil, Bruce-Keller, & Keller, 2014; Machulda et al., 2013; Schaefer & Duff, 2017). While improvements in scores over time are common in cognitively intact older adults, they are often attenuated if not absent in MCI and AD (e.g., Gavett et al., 2016; Hassenstab et al., 2015; Machulda et al., 2013). This body of work indicates that practice effects may serve as a heuristic of cognitive decline (Duff et al., 2007); however, practice effects are not consistently found relative to risk (e.g., attenuated practice effect on memory and attention tests associated with neurodegeneration but not amyloidosis; Machulda et al., 2017), and differences in methodology across studies preclude any firm conclusions on its utility as a clinical measure (Duff et al., 2017).

While research has made progress in identifying cognitive trajectories in relationship to risk factors associated with MCI and progression to dementia (e.g., Brewster et al., 2014; Kryscio et al., 2016; Mungas et al., 2010; Runge, Small, McFall, & Dixon, 2014), our understanding of the interplay between specific neurocognitive domains is limited given significant heterogeneity of rates of change within and across diagnostic groups. In the context of dementia, AD is a heterogeneous brain disease with multiple interacting risk factors, suggesting equifinality. Although current research classification schemes have hypothesized distinct trajectories of progression from MCI to AD as compared to dementias of vascular origin, the external validity of these concepts remains to be established, given that the odds risk for dementia is significantly greater in individuals who demonstrate multiple risk factors than in those with a single pathology. Evidence points to factors commonly associated with vascular risk also increasing risk for AD (Gorelick et al., 2011). There is also work that suggests that baseline memory and executive function performance but not cerebrovascular disease predicts the likelihood to develop dementia in MCI (DeCarli et al., 2004). Relevantly, there is also research that suggests that intact executive function and attention processes are important to preserving memory and languages functioning in older adults (e.g., Raz, 2000; Salthouse, 2000, Salthouse, Atkinson, & Berish, 2003; Wingfield & Grossman, 2006). In this respect, investigating relationships between specific neurocognitive functions in relation to interdomain changes might improve our understanding of mechanisms involved in preclinical stages of cognitive decline and risk models for dementia disorders.

To clarify the relationship between factors posited to preserve cognitive function and the role of repeated test exposures, the present study employed multivariate LGC modeling to investigate domain-specific neurocognitive functioning relative to baseline and rates of change in older adults cognitively intact at baseline. Four latent variables—Memory, Executive Attention/Processing Speed, Language, and Working Memory—were formed based on prior work of the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) neuropsychological test battery that has found the posited factors to be consistent with strict factorial invariance (Hayden et al., 2011; Weintraub et al., 2009). Based on the literature, it was expected that: (a) Executive Attention/Processing Speed would decline over time and that baseline performance would predict rates of change in Memory and Language performance; (b) significant practice effects would be found in Memory (as indicated by a positive growth rate); (c) higher baseline Memory functioning would be associated with higher incremental increases in Memory over time and vice versa (those with initially lower memory functioning would demonstrate less growth); and (d) Memory, Language, Executive Attention/Processing Speed, and Working Memory performance at baseline would be

positively associated with one another, such that there would be lower scores on each of the other neurocognitive latent variables at baseline.

Method

Participants

Participants were part of an on-going longitudinal study (Louisiana Aging Brain Study: LABrainS) that investigates the effects of aging upon cognitive processes and daily living functioning in relatively healthy older adults. Study design and procedures have been previously described (MacAulay et al., 2014). Briefly, LABrainS is an open enrollment longitudinal study that has been following participants since 2009 (overall retention rate of 87%). It is a statewide study representing 37 different parishes within the state of Louisiana. Participants are recruited throughout Louisiana using traditional media sources (e.g., newspaper ads and television and newspaper press) as well as regular community outreach efforts of the Institute for Dementia Research and Prevention (IDRP). Telephone screening procedures are used. Eligibility criteria requires that participants are over the age of 60 with no existing diagnosis of dementia or cognitive impairment at the time of baseline screening. Exclusion criteria includes: a Geriatric Depression Scale score ≥6 (15-item version; Sheikh & Yesavage, 1986), and a history of untreated health conditions or neurological disorders (e.g., cerebrovascular disease, Parkinson's disease, and/or a traumatic brain injury, etc.) that might cause cognitive impairment. All participants have a Clinical Dementia Rating score of 0 and a Mini-Mental Status Exam (MMSE) score >25, consistent with the absence of dementia (Folstein, Folstein, & McHugh, 1975).

Participants included in study were generally college educated and on average 69 years old (see Table 1). There was a higher proportion of female and White participants. Given highly unbalanced race groups, racial differences are not investigated within this study. Information regarding apolipoprotein E (ApoE)-genotype and mental and medical history were collected but analyses of these predictor variables are reported elsewhere due to space constraints (MacAulay et al., 2017).

Research design

Data for this study were collected during annual cognitive assessments at the Pennington Biomedical Research Center's Institute for Dementia Research and Prevention (IDRP) between 2009 and 2013. Visits were approximately a year apart. A total of 694 participants were included in the study during this period (initial inclusion rate of 82.9%). A total of 72 participants formally withdrew from the study for a variety of reasons (e.g., transportation, not willing to participate, moving, caregiver status, etc.), 36 participants' inactivity is not accounted for due to either inability to respond or refusal to respond, 20 participants were not administered the full UDS battery (i.e., only Digit Symbol Coding was administered), seven died, and three converted to presumed AD. Three participants with physical impairments were missing data on neuropsychological tests that required intact visual or motor functioning (i.e., the Trail Making Test, TMT–A and B; Digit Symbol

Table 1. Group differences in neuropsychological raw test scores at baseline by enrollment status.

Neuropsychological test	Included total (N = 691) M (SD)	Dropout (n = 118) M (SD)	Completer (n = 576) M (SD)	χ^2/F
Age (years)	69.07 (6.49)	69.61 (6.40)	68.93 (6.51)	0.256
Sex (% female)	66.3	64.5	66.7	0.604
Education (years)	15.96 (2.49)	15.33 (2.56)	16.14 (2.44)	12.62**
Race				
White (%)	94.2	90.1	95.4	—
Black (%)	5.1	8.6	4.1	—
Other (%)	0.7	1.3	0.6	—
Cardiovascular risk factors	1.27 (1.18)	1.47 (1.30)	1.21 (1.14)	5.55*
National Adult Reading Test[a]	108.65 (7.91)	105.08 (9.06)	109.17 (7.64)	186.70**
Mini Mental State Exam[a]	28.98 (1.13)	28.42 (1.52)	29.01 (1.19)	16.05**
Logical Memory–I	13.00 (3.33)	12.36 (4.00)	13.04 (3.25)	2.98*
Logical Memory–II	11.83 (3.59)	10.97 (4.11)	11.89 (3.47)	5.12*
Digit Span Forward–Total Correct	9.03 (1.92)	8.42 (1.84)	9.17 (1.90)	15.00**
Digit Span Backward–Total Correct	6.96 (2.14)	6.15 (2.15)	7.11 (2.11)	20.16**
Category Fluency–Animals	20.98 (5.52)	18.65 (5.28)	21.29 (5.53)	22.59**
Category Fluency–Vegetables	15.18 (4.30)	13.96 (4.24)	15.40 (4.25)	11.37**
Trails Making Test–Trail A[a]	34.71 (12.61)	38.34 (14.04)	34.07 (11.98)	11.60**
Trails Making Test–Trail B[a]	86.19 (40.61)	107.75 (61.70)	83.99 (37.38)	16.14**
Digit Symbol Coding[a]	47.68 (10.58)	43.23 (9.96)	48.13 (10.60)	21.06**
Boston Naming Test[a]	27.45 (2.59)	26.54 (3.25)	27.57 (2.45)	10.52**

Note. Data presented are raw untransformed scores. Difference in the N total reflects that three extreme cases were removed from analyses.
[a]Measure contained significant skew and/or kurtosis.
*$p < .05$. **$p < .01$.

Coding (DSC)). All included participants have normal or corrected vision. The Pennington Biomedical Research Center Institutional Review Board approved all procedures included within this study.

Participants' demographic information was collected via clinical interview at baseline. The NACC UDS (Version 1) neuropsychological test battery was utilized for this study. The UDS test battery consists of a screener measure of global cognitive functioning (MMSE) and brief measures of attention, processing speed, executive function, episodic memory, and language that were selected due to their sensitivity to detect neurocognitive change in the elderly; specific subtests are listed below. The North American Adult Reading Test (NAART; Blair & Spreen, 1989) was administered as an estimate of intelligence. The NAART is a widely accepted measure for estimating premorbid intelligence levels; it has demonstrated acceptable convergence with a gold-star measure of intelligence (Wechsler Adult Intelligence Scale, WAIS, Fourth Edition) and has been validated for use in estimating intellectual functioning within patients with dementia (Uttl, 2002).

Analyses

Appropriate descriptive statistics were computed for all variables to determine that assumptions of normality were met. Potential confounds regarding attrition bias and demographic factors were assessed via one-way analyses of variance (ANOVAs) or chi-square tests prior to the structural equation modelling (SEM) analyses. Multivariate normality was measured through the use of Mardia's normalized estimate (Byrne, 2010). Mahalanobis distance (D^2) investigated for cases that significantly contributed to the multivariate non-normality as indicated by Mardia's coefficient (Gao, Mokhtarian, & Johnston, 2008). Skew and kurtosis indices were evaluated for each variable. Outliers (defined as greater than 2 *SD*s from mean) on the TMT and Boston Naming Test (BNT) were identified via box plots and were replaced with the less extreme values. The indicator variables (raw neuropsychological test scores) were converted to *T*-scores to allow comparison of the formed latent variables. As use of standardized scores is problematic in assessing systematic growth, to maintain longitudinal change Johnson et al.'s (2012) scaling method of utilizing the mean and standard deviation from the initial visit to compute *T*-scores for Visits 2 and 3 indicator variables was used. As well recognized, missing data are problematic, and there is not one inherently correct procedure to handling it. Given limitations to each missing data method, the present study utilized direct maximum likelihood estimate (MLE) to estimate means and intercepts givens its flexibility, efficiency, and stability in estimating model parameters. Statistical analyses were performed via SPSS (Version 23) and AMOS (Version 22).

A four-factor model based on previous confirmatory factor analyses (CFA) of the NACC's UDS neuropsychological test battery was utilized (Hayden et al., 2011; Weintraub et al., 2009). These studies have demonstrated a good fit for the proposed factor structure that is consistent with there being strict factorial invariance across a wide range of older adults with varying levels of cognitive functioning. Memory, Executive Attention/Processing Speed, Working Memory, and Language latent variables were formed based on obtained scores at each year. The Memory factor was composed of the Wechsler's Memory Scale–Revised (WMS–R) Logical Memory Story–A Immediate and Delayed Recall subtest scores. The Executive Attention/Processing Speed factor was formed from the WMS–R Digit Symbol Subtest and the TMT Parts A and B; this measure was posited to reflect aspects of executive function, attention, and processing speed. TMT raw scores were reverse scored so that better performance would reflect higher scores prior to any other score conversions. The Working Memory factor was composed of the Digit Span Forward and Backward tests. Lastly, the Language factor was formed from the BNT and Category Fluency (Animals and Vegetables) test scores.

Model specification was theory driven using a multivariate LGC curve-of-factor four-domain model. In the curve-of-factor model, the neuropsychological test scores at each visit were factor analyzed to compute the respective neurocognitive domain variables, which in turn were used for modeling the growth curves (Duncan, Duncan, & Strycker, 2013). Figure 1 presents a schematic of the parameters that were formed for each variable. For instance, Logical Memory I and II scores at each visit served as indicators that made up three Memory latent variables for each year (Memory Visits 1–3). These three variables were then used to form the overall Memory intercept and Memory slope variables. Parameters from a latent variable's intercept to its observed indicator test score values were held constant to allow for interpretation of the initial mean values, and parameters from the latent variable's slope were connected to their observed indicator measures and fixed at values (0, 1, and 2) reflecting each visit. The latent factors' covariances were allowed to covary over time. Residuals of each indicator were freely estimated at each time point, and correlations amongst the corresponding residuals' indicators were estimated. A scaling reference variable set to unity was used for each of

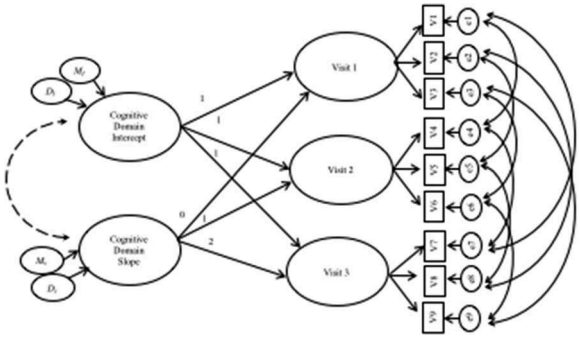

Figure 1. Schematic of the multivariate curve-of-factors latent growth curve (LGC) analyses illustrates the parameterization of the four-cognitive domain model of growth processes that were formed for Memory, Executive Attention/Processing Speed, Language, and Working Memory. For simplicity, not every parameterization is shown. Specific tests for variables are listed in the text, and each had unique error terms (e1–e9). Numbers on paths are fixed factor loadings from the second order to the higher order process for intercept and slope, respectively. Ovals represent latent variables (1) at each time point as measured by the observed indicators (cognitive test scores: V1–V9) in squares, and (2) the posited higher order cognitive domain's intercept and slope. Each intercept and slope has its associated mean (*M*) and variance (*D*).

the first common order factors, and consistent with strict temporal invariance, the remaining common factor loadings for the nonreferenced indicator measures to the respective latent constructs were constrained to be equal across time points.

Model analyses first examined the within-domain covariance estimates between the intercepts and slopes for the neurocognitive variables, followed by a second set of analyses that included the significant within-domain paths from the first set of analyses and added parameters to estimate the between-domain model. Effect sizes reported (Tables 2 and 3) are based on conventions for *r* (small *r* = .10; medium *r* = .30, and large *r* = .50; Duncan et al., 2013). Root mean square error of approximation (RMSEA) and comparative fit index (CFI) values based on Hu and Bentler (1999) criteria served as measures of model fit. Chi-square is reported with degrees of freedom (*df*) but is not used as measure of fitness, given its oversensitivity to large sample sizes (Kline, 2011).

Table 2. Between-neurocognitive-domain functioning at baseline.

Variables	Estimate	*SE*	CR	*r*	*p*
Memory int. ↔ Language int.	28.541	2.845	10.03	.58	<.001
Memory int. ↔ EA/PS int.	29.883	3.241	9.22	.45	<.001
Memory int. ↔ WM int.	19.426	2.936	6.62	.28	<.001
EA/PS int. ↔ Language int.	28.364	2.781	10.20	.68	<.001
EA/PS int. ↔ WM int.	25.438	2.894	8.79	.43	<.001
Language int. ↔ WM int.	17.220	2.330	7.39	.40	<.001

Note. Covariance estimates between intercepts (int.) represent the relationship between specific neurocognitive domains at baseline. CR = critical ratio; EA/PS = Executive Attention/Processing Speed; WM = Working Memory.

Table 3. Specific neurocognitive domain functioning at baseline and rate of change overtime.

Variables	Estimate	*SE*	CR	*r*	*p*
Memory int. ↔ EA/PS slope	0.835	0.686	1.22	.09	.224
Memory int. ↔ Language slope	1.490	0.760	1.96	.14	.050
EA/PS int. ↔ Memory slope	3.102	1.158	2.68	.11	.007
EA/PS int. ↔ Language slope	0.485	0.645	0.75	.03	.452
Memory slope ↔ EA/PS slope	1.049	0.358	2.93	.27	.003
Memory slope ↔ Language slope	1.589	0.376	4.22	.40	<.001
EA/PS slope ↔ Language slope	0.497	0.185	2.685	.46	.007
WM slope ↔ Language slope	0.648	0.274	2.364	.51	.018

Note. Covariance estimates between the intercept (int.) and slope represent the relationship between specific neurocognitive domains at baseline with rate of change over time; covariance estimates between specific neurocognitive domains slopes indicate that increases in one domain over time were associated with one another. Int = intercept; CR = critical ratio; EA/PS = Executive Attention/Processing Speed; WM = Working Memory.

Results

Participant characteristics and missing data

A total of 691 of 694 participants were included within the final analyses. Three participants identified as extreme outliers (D^2 distances greater than three standard deviations from the centroid) were removed due to their contribution to multivariate non-normality. Male participants (*M* = 70.10 years, *SD* = 6.68) were approximately 1.5 years older than female participants (*M* = 68.55 years, *SD* = 6.33), $F(1, 690) = 8.97$, $p = .003$. Males on average obtained a higher level of education (*M* = 16.79 years, *SD* = 2.33) than females (*M* = 15.54 years, *SD* = 2.46), $F(1, 690) = 41.11$, $p = .001$. Participants were generally of average estimated intelligence (NAART full-scale intelligence quotient, FSIQ: *M* = 108.65, *SD* = 7.91; IQ range = 85–124), and no sex differences were found on this variable.

Descriptive statistics are presented in Table 1 by enrollment status. Significant group differences between the "completers" and "dropouts" on the dependent variables and non-normality in the data were found. Completers were defined as those still enrolled in study with three consecutive visits. One-way ANOVAs and chi-square tests of independence examined for group differences in demographic factors (e.g., education and age), health-related risk factors, estimated intelligence, and neurocognitive test performance in those with three years of follow-up visits as compared to study dropouts. Completers had significantly higher estimated intelligence and baseline neurocognitive test scores than dropouts across each of the measures at baseline. Sex was not related to the likelihood of dropping out from the study, and completers did not significantly differ in age from dropouts. There was a greater likelihood of attrition in Black (*n* = 14; expected count = 7) than White participants (*n* = 120; expected count = 127), $\chi^2(2, N = 134) = 9.98$, $p = .019$. Completers as compared to

dropouts on average obtained greater years of education and had a significantly greater number of cardiovascular risk factors present.

MLE was employed to replace missing values (23.8% of cases). Although not reported here, comparison of parameter estimates and their respective fit indices using MLE as compared to listwise deletion methods were highly consistent with one another, thereby further increasing our confidence in the identified latent neurocognitive constructs and their relationships with one another (Byrne, 2010).

Examining within-domain cognitive function

The first model examined cognitive functioning relative to within-domain change and the specific cognitive domains at baseline. This model was adequately identified, $\chi^2(387) = 1089.95$, and the posited four-factor solution of Memory, Executive Attention/Processing Speed, Language, and Working Memory suggested that the model fit the data well (CFI = .948; RMSEA = .051; 90% confidence interval, CI [.048, .055]). Significant mean levels existed for all intercept parameters at baseline and almost all slope parameters. The intercepts represent the average score for each given domain at Visit 1, and the slopes reflect on average year-to-year linear change. Positive slope values indicated that Memory ($M_{slope} = 1.51$, $SE = 0.19$) and Language ($M_{slope} = 1.11$, $SE = 0.14$) scores increased over time, while a negative slope value indicated that Executive Attention/Processing Speed ($M_{slope} = -0.706$, $SE = 0.17$) declined, all $ps < .001$. No significant change over time was noted in Working Memory ($M_{slope} = -0.139$, $SE = 0.18$).

Contrary to the study's posited directionality, initially higher Memory functioning was associated with a slower annual growth rate in Memory (estimate = −9.54, $SE = 1.45$), $p < .001$. The negative value indicated that those with higher as compared to lower baseline memory functioning demonstrated less growth in scores over the three visits, and vice versa. The hypothesis that lower baseline Executive Attention/Processing Speed would predict greater decline in Executive Attention/Processing Speed was not supported. No significant relationships between the respective intercept and slopes of Language, Executive Attention/Processing Speed, and Working Memory were found. In accord with past research and the present study's hypotheses, individuals with initially lower Memory, Language, Executive Attention/Processing Speed, and Working Memory performance concomitantly had lower scores on each of the other neurocognitive latent variables at baseline, $ps < .001$.

Examining between-domain cognitive function

Next, between-cognitive-domain change relative to baseline Memory and Executive Attention/Processing Speed was examined. This set of analyses was specifically interested in: (a) whether rates of cognitive change differed over time in those with lower as compared to higher Memory and/or Executive Attention/Processing Speed at baseline, and (b) examining the interplay between specific cognitive domains with change relative to baseline functioning. The previous reported parameter estimates for baseline functioning remained statistically significant. Positive values indicate that those with higher baseline functioning had greater increases (or smaller decreases) in scores over time, whereas those with lower baseline scores demonstrated lower increases (or greater decreases) than those with higher scores for each of the given domains. The model provided an excellent fit for the data: $\chi^2(382) = 1010.86$; CFI = .952; RMSEA = .050; 90% CI [.046, .053]. Table 2 presents the significant covariance estimates between the neurocognitive domain intercepts.

Table 3 presents the significant covariance estimates between the specific neurocognitive domain intercepts and slopes. As hypothesized, older adults who demonstrated higher initial Executive Attention/Processing Speed functioning at baseline demonstrated greater incremental increases in Memory performance over time, while those with lower performance had less of an increase in scores. In turn, those with higher as compared to lower initial Memory functioning demonstrated greater incremental increases in their Language performance. The hypothesis that incremental changes in Language functioning would be predicted by baseline Executive Attention/Processing Speed performance was not supported. In analyzing the degree to which annual rates of neurocognitive change were associated with one another, results indicated that on average as Memory, Language, and Executive Attention/Processing Speed scores increased over time, there were respective increases in each of the other process scores with the exception of Working Memory, $ps < .001$. Notably, incremental increases in Language functioning from Year 1 to Year 3 was the only neurocognitive process to associate with gradual increases in Working Memory functioning. Figure 2 presents a schematic of the final model.

Discussion

The present study provides a conceptual model (based on compensation theories) that systematically investigated domain-specific neurocognitive functioning relative to baseline functioning and rate of change over

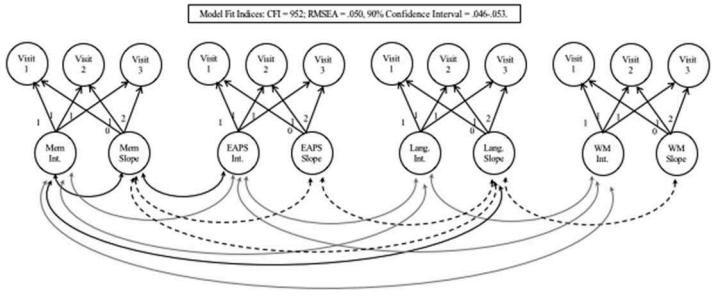

Figure 2. Multivariate latent growth curve models for the four-domain model of neurocognitive trajectories. Solid gray lines indicate the significant covariance estimates between baseline (intercepts) neurocognitive functioning, solid black lines indicate the relationship between baseline functioning and change (intercept–slope), and the black dashed lines indicate the covariance between the growth measures over time (slope–slope). Indicator variables and regression parameters not shown. Int. = intercept; Mem = Memory; Lang. = Language; EAPS = Executive Attention/Processing Speed; WM = Working Memory; CFI = comparative fit index; RMSEA = root mean square error of approximation.

time. In all, there was substantial heterogeneity and a significant amount of interplay between the specific cognitive functions in older adults. These results are consistent with the notion that intact executive function and attention processes are important to preserving memory functioning with advanced age, but are also the functions most susceptible to decline with age. No significant change over time in working memory performance was found. Notably, both memory and language performance on average improved over time, indicating that these processes benefited from practice effects within normally aging adults. As expected, lower executive attention/processing speed performance at baseline predicted lower incremental growth rates in memory, while lower baseline memory functioning was associated with less improvement in language functioning than in those with better baseline function. Executive attention/processing speed at baseline did not associate with within-domain or language growth rates as hypothesized; the latter may be partially due to the nature of the language tasks (category fluency and confrontation naming). These findings provide further insight into the critical role of practice effects in clinical assessment practice and have implications for pharmaceutical trials. Relevantly, within the context of MCI and dementia assessments, practice effects may give the appearance of retention of function within the cognitive domains considered to be a hallmark of AD.

There is a growing consensus that variability in normal age-related neurocognitive changes may be explained by shifts in neural resources and individual differences in potential compensatory mechanisms. Importantly, these neural changes are considered adaptive processes when they are connected to better neurocognitive performance as they are posited to counteract age-related cognitive decline (see Reuter-Lorenz & Park, 2014). In the context of our findings, it is possible that in order to optimally benefit from previous test exposures executive function and attention processes need to be intact, as those who started with higher executive attention/processing speed functioning at baseline demonstrated a steeper rate of growth in memory functioning over time. As practice effects are not entirely task-specific (S. E. Petersen, Van Mier, Fiez, & Raichle, 1998), novel verbal generation tasks may require greater effort and thus employ top-down cognitive control to effectively cope with increased cognitive demands. However, once learning processes have occurred (as suggested by greater proficiency at task), the task becomes more automatic and no longer requires higher cognitive control. This suggestion is somewhat consistent with scaffolding theories of aging that suggest that the neural networks believed to underlie executive function and attention processes play a vital role in learning processes that increase overall neurocognitive efficiency (Park & Reuter-Lorenz, 2009). Putting it all together, older adults who have preexisting vulnerabilities within any one of these regions (as evidenced by neurocognitive test performance and/or imaging studies) are at greater risk of MCI, which may become more evident as a function of age-related shifts in neural resources.

Mechanistically efficient semantic knowledge retrieval (particularly phonemic fluency) is believed to involve frontal lobe processes as well as language systems, while deficits in confrontational naming tasks (BNT) in older adults has been linked to damage in memory regions (left hippocampal damage, Lezak, Howieson, & Loring, 2004). There is evidence that the posterior parietal cortex plays an intermediary role in extending long-term memory processes through its interconnections with both the frontal lobe and the medial temporal lobe (Shannon & Buckner, 2004); these same regions are also implicated in early stages

of neuronal degeneration in MCI/AD (for review see, Jacobs, Van Boxtel, Jolles, Verhey, & Uylings, 2012). All considered, it might be that language tasks (which are believed to involve frontal and parietal cortices in addition to language systems) recruit similar compensatory processes, such as episodic memory, to preserve cognitive functioning with advanced age. We intend to follow up on these findings by examining the degree to which relevant demographic, genetic, medical, and psychiatric factors contribute to the heterogeneity within the specific cognitive domain trajectories (MacAulay et al., 2017). More longitudinal research integrating brain imaging with neuropsychological assessment is also needed to reconcile that the brain regions (frontal and superior parietal areas) posited to compensate for declines in other neural processes are also believed to be amongst the first to decline with age.

In contrast to expectations, lower as compared to higher initial memory scores were associated with greater memory gains from Year 1 to Year 3. While the intercept provides information on the average scores for the given domains at Visit 1, it is not informative as to whether individuals may have already started to decline prior to their baseline measure. Thus, it is important to consider whether those with higher memory functioning demonstrated a decline during this period or whether the negative relationship between baseline memory performance and less growth over time reflects the law of initial values (i.e., those who start with higher initial scores have less to gain; Byrne, 2010). In examining the overall findings, participants with higher memory functioning at baseline concomitantly demonstrated higher performance across each of the other neurocognitive domains. Additionally, higher memory functioning at baseline was associated with greater practice effects on language measures (as indicated by the positive covariance between memory's intercept and language's slope). Altogether, findings do not indicate declining memory capacity in those with higher memory functioning at baseline.

Significant between-group differences in demographic variables and in the neurocognitive test scores of study dropouts as compared to those with three consecutive visits from Year 1 to Year 3 were also found. Consistent with a previous cognitive aging study that investigated predictors of attrition over a three-year period (Van Beijsterveldt et al., 2002), individuals that dropped out obtained lower educational levels, had a greater number of cardiovascular risk factors, and demonstrated worse performance on neuropsychological tests at baseline. Black participants had a greater likelihood of attrition than White participants within the present sample. From a statistical standpoint, MLE methods tend to be fairly effective at recovering missing data (Little, 2013), and, although not reported here, comparison of the fit statistics and primary findings with other methods that handle missing data (listwise deletion) produced highly similar results, thus indicating a good fit for the data despite the missing values (Byrne, 2010). Other limitations include LABrainS participants are also predominantly White, which precluded our ability to investigate group differences by race, as well as generally being college educated with a higher proportion of females than male, which may limit the generalizability of these findings.

In sum, significant decrements over time in neuropsychological test measures of executive attention/processing speed were found in cognitively intact older adults, whereas episodic memory and language performance on average improved over time within the present sample—thus suggesting that practice effects are also occurring in the majority of participants. The relationship between better higher baseline functioning with incremental increases in memory and language scores provides further evidence that the ability to benefit from practice effects may serve as a useful heuristic of neurocognitive functioning. Overall, this work is consistent with that of others who have noted that practice effects appear to be enduring and are evident across multiple neuropsychological domains within the NACC UDS test battery (Gavett, Ashendorf, & Gurnani, 2015; Mathews et al., 2014). Practice effects not only mask cognitive change in assessment practice but can also increase Type 1 and 2 errors in pharmaceutical trials. There is increasing concern in how practice effects pertain to clinical trials for MCI and dementia disorders, given evidence that cognitive improvements in schizophrenia patients within several antipsychotic trials have been shown to be partially attributable to practice effects (see Goldberg, Harvey, Wesnes, Snyder, & Schneider, 2015). As such, methods that reduce task familiarity effects through massed trials, equivalent forms when available, and use of comparison groups to assess the retention of practice effects (e.g., Duff et al., 2011) may be useful to include in clinical trials' study design.

Additionally, integrating assessment measures that allow for analysis of learning effects in conjunction with relevant biomarkers and medical history to investigate whether disease pathology is present should be routinely implemented in longitudinal studies of cognitive change.

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