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Longitudinal change in neuropsychological performance using latent growth models: a study of mild cognitive impairment

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Abstract The goal of the current study was to examine cognitive change in both healthy controls (n=229) and individuals with mild cognitive impairment (MCI) (n=397) from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We applied latent growth modeling to examine baseline and longitudinal change over 36 months in five cognitive factors derived from the ADNI neuropsychological test battery (memory, executive function/processing speed, language, attention and visuospatial). At baseline, MCI patients demonstrated lower performance on all of the five cognitive factors when compared to controls. Both controls and MCI patients declined on memory over 36 months; however, the MCI patients declined at a significantly faster rate than controls. The MCI patients also declined over 36 months on the remaining four cognitive factors. In contrast, the controls did not exhibit significant

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators with the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http:/adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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change over 36 months on the non-memory cognitive factors. Within the MCI group, executive function declined faster than memory, while the other factor scores changed slower than memory over time. These findings suggest different patterns of cognitive change in healthy older adults and MCI patients. The findings also suggest that, when compared with memory, executive function declines faster than other cognitive factors in patients with MCI. Thus, decline in non-memory domains may be an important feature for distinguishing healthy older adults and persons with MCI.

Keywords ADNI · Neuropsychology · Cognition · Mild cognitive impairment · Cognitive change · Executive function

Introduction

Neuropsychological assessment is an important component for the differential diagnosis of cognitive decline associated with neurodegenerative diseases, such as Alzheimer's disease and dementia with Lewy bodies. It can also be used to help identify subtle cognitive change associated with mild cognitive impairment (MCI), an intermediate stage between healthy aging and dementia (Petersen, Smith 1999; Winblad et al. 2004). However, a major challenge lies in distinguishing normal age-related cognitive decline from cognitive decline due to an underlying neurodegenerative disease, particularly because the neuropathology can begin decades before the onset of overt cognitive impairment (Albert et al. 2011; Morris et al. 2001). The administration of a comprehensive neuropsychological battery over time (e.g., annually) that assesses multiple cognitive domains is one strategy used to increase confidence in the diagnosis (Dowling et al. 2010). While approximately half of all MCI patients convert to dementia over 5 years, other MCI patients remain stable or revert to normal (Bennett et al. 2002; Manly et al. 2008; Petersen et al. 2001). Thus, it is important to better understand how cognition changes over time in both healthy older adults and those with MCI to help improve the early detection of neurodegenerative diseases.

There are a number of analytic methods to study cognitive change in longitudinal data, including application of repeated measures analysis of variance (ANOVA), mixed effects models (Laird and Ware 1982), and differences in means (Twisk 2003). Latent growth modeling is another method for analyzing longitudinal data to estimate growth, or trajectories of change (McArdle 1986; Muthén 1997; Muthén and Curran 1997). There are several advantages to using this method to study cognitive decline. First, latent growth models provide estimates of individual trajectories of change. In the context of structural equation modeling, they offer flexible extensions, such as the ability to model change in latent outcomes that represent common variation in multiple observed indicators (McArdle 1988; Stoel et al. 2003). Secondly, the models can help identify common constructs within neuropsychological test batteries, which often use multiple tests to measure several cognitive domains and generate a large number of test scores. For example, the Rey Auditory Verbal Learning Test, a common test of verbal list learning and memory, can yield multiple individual trial scores, a learning score, short- and long-delay recall scores, and recognition scores. As such, it can be challenging to select an optimal neuropsychological variable to represent a specific cognitive domain. Using multiple variables increases the Type I error rate, but controlling for multiple comparisons increases the risk of Type II errors. Thus, in addition to identifying common constructs, latent growth models help avoid these pitfalls through a principled data reduction method.

The goal of the current study was to apply latent growth models to examine cognitive change in both healthy controls and individuals with MCI. To accomplish this goal, we utilized data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Using five cognitive factors representing memory, executive function/processing speed, visuospatial ability, language, and attention (Park et al., this issue), we hypothesized that cognition (represented by factor scores) declines faster over time in individuals with MCI compared with healthy controls. Additionally, we hypothesized that there would be an interaction between change in cognitive factors and group, such that memory would decline faster than other cognitive domains in MCI patients. These hypotheses were assessed using latent growth models.

Methods

The Alzheimer's disease neuroimaging initiative

The ADNI is a private-public partnership launched in 2003 (Weiner et al. 2011) to develop optimized methods for acquiring longitudinal, multisite neuroimaging and chemical biomarkers, clinical, cognitive, and biomarker data in a large cohort of patients with AD, patients with MCI, and healthy controls to improve methods for evaluating progression in clinical trials. More than 800 participants, ages 55–90 years, have been recruited from 59 sites across the United States and Canada. The data used for the present study, which are freely available to subscribers and continuously updated, were downloaded on March 15, 2011.

Participants

The present study included data from ADNI participants who were diagnosed at baseline as healthy controls

(n=229) and MCI patients (n=397). The criteria for a diagnosis of MCI (Petersen et al. 2010) included: (i) age between 55 and 90 years; (ii) complaints of memory loss by the patient and confirmed by a family relative; (iii) Mini-Mental State Examination (MMSE; (Folstein et al. 1975) score greater than 23, (iv) Clinical Dementia Rating (CDR; (Morris 1993)) score of 0.5; and (v) evidence of memory impairment relative to age and education-matched peers on neuropsychological tests. Criteria for healthy controls included: (i) no memory complaints aside from those common to other normal subjects of that age range; (ii) normal memory function documented by scoring at specific cut offs on the Logical Memory II subscale from the Wechsler Memory Scale-Revised (Wechsler 1987b); (iii) MMSE score between 24 and 30 (inclusive); (iv) CDR score=0 and CDR memory box score=0; (v) clinical impression of cognitively normal, based on an absence of significant impairment in cognitive function or activities of daily living.

ADNI neuropsychological battery

For the present study, we included data from five ADNI study visits: baseline, 6 months, 12 months, 24 months, and 36 months. The ADNI neuropsychological battery includes tests that represent multiple cognitive domains (Petersen et al. 2010). Details about the administration and scoring are available at www.adni-info.org/Scientists/AboutADNI.aspx. Briefly, episodic memory is assessed using the Rey Auditory Verbal Learning test (AVLT) (Rey 1964), which includes 5 learning trials (of 15 words), immediate and 30-minute delayed recall, as well as an interference list and recognition test. Tests of executive function and attention include: Digit Span (Wechsler 1987a), the Trailmaking test A and B (Reitan 1958), and the Digit Symbol Substitution Test (Wechsler 1981). Verbal fluency is assessed using tests of category fluency (Morris et al. 1989), and object naming is assessed using the Boston Naming Test (Kaplan et al. 1982). In addition to these tests, the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog) (Rosen et al. 1984), MMSE, and the Clock Drawing Test (Goodglass and Kaplan 1983) are administered.

Factor structure of ADNI neuropsychological battery

As described in Park and colleagues (this issue), a factor analysis of the ADNI neuropsychological battery yielded five factors: memory, executive function/processing speed, visuospatial ability, language, and attention. The memory factor is represented by: AVLT, including learning (Trial 5 minus Trial 1), immediate recall, 30-minute delayed recall, and recognition scores, and the ADAS-Cog delayed recall and recognition. A factor representing executive function and processing speed is composed of: Trailmaking Test A (time to complete), Trailmaking Test (B minus A), number cancellation (number completed in 60 s), and the Digit Symbol Substitution Test (number completed in 90 s). Visuospatial ability is represented by: Clock Drawing Test (copy and drawing scores) and ADAS-Cog constructional praxis (number correct). Language is represented by: category fluency (animals and vegetables in 1 min), the Boston Naming Test (number of items spontaneously named), and ADAS-Cog Naming (number correct). Attention is represented by: the Digit Span (forward and backward span length).

To place parameters of interest on an interpretable scale and to compare relative change within and between cognitive domains, all neuropsychological test variables used in this study were standardized as T-scores [mean 50, standard deviation (SD) 10] at the baseline. Follow-up visits were similarly rescaled using the baseline mean and SD to preserve longitudinal change. Importantly, this scaling procedure facilitates comparisons within the present study sample, but absolute values of parameter scores are not generalizable to other studies.

Analysis

Longitudinal change in cognitive domains was assessed using a multiple indicator latent growth model with the latent variables derived from a previously validated factor analysis of the baseline ADNI neuropsychological battery (Park et al., this issue). Multiple indicator parallel process latent growth models were used to model domain-specific cognitive trajectories (see Fig. 1 for a model diagram). These are multiple indicator growth models because several observed indicators were used to define latent variables at each time point, which served as indicators for growth. The models are parallel process models because two growth processes (memory and another domain) were estimated together. A separate model was estimated for visuospatial, language, executive function/processing speed, and attention constructs. The memory growth process was part of each model to compare level and change in that domain with others. Parameters of interest are means of growth parameters, which included intercepts (initial status indicators) and slopes (linear trajectories). Observed indicator scores were all rescaled on a T-score metric. Therefore, a latent intercept is interpretable as the mean performance at baseline relative to the mean in the full MCI and healthy control sample. Slopes represent changes in T-score units per year. Two sample t-tests were conducted to test group differences in the intercepts and slopes of each model.

Constraints imposed are consistent with strict temporal invariance, which is consistent with a factor structure not changing over the course of disease (Park et al., this issue).

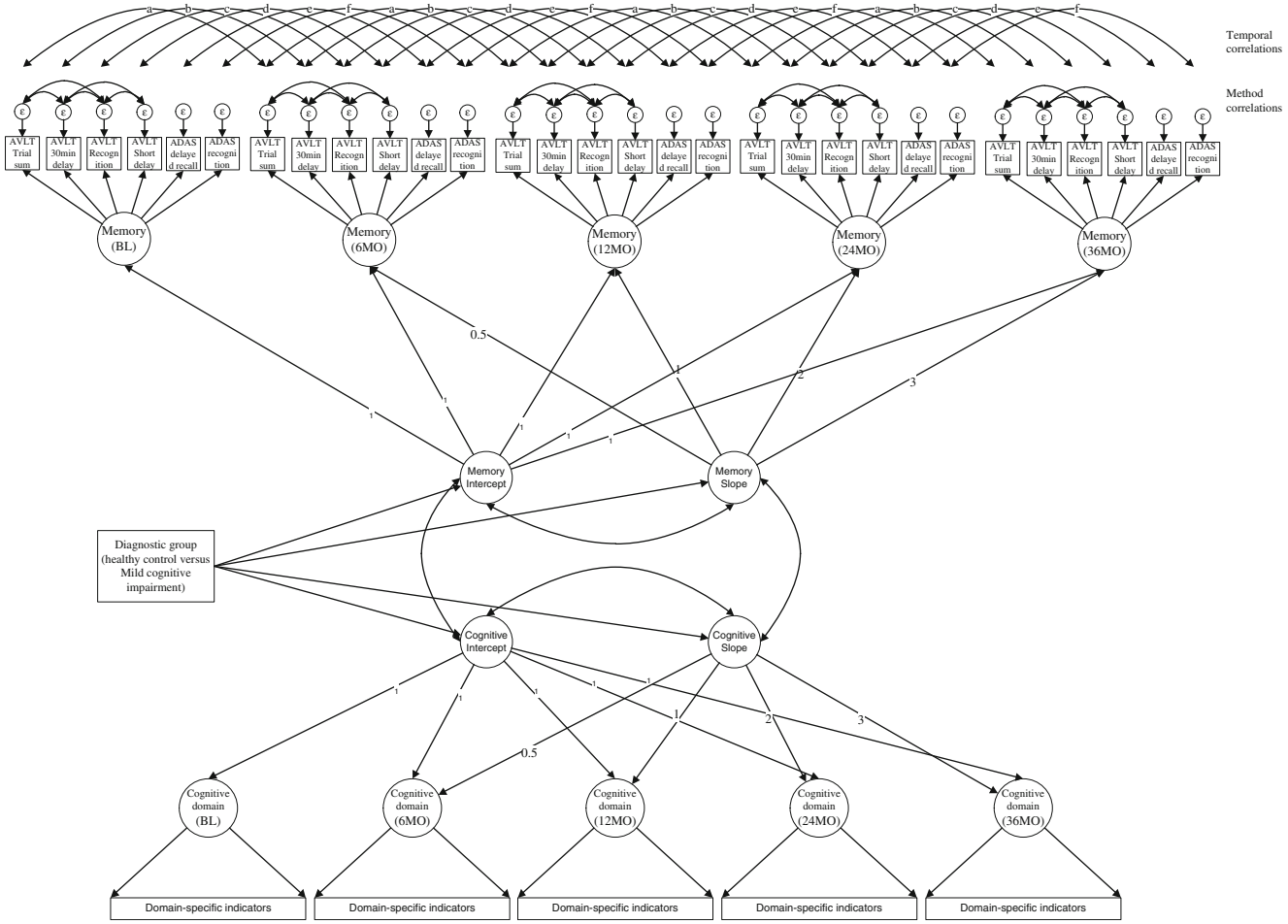

Fig. 1 Model Diagram of a Multiple Indicator Parallel Process Latent Growth Model for the ADNI Neuropsychological Test Battery. This figure shows the parameterization of the model of growth processes for memory and other cognitive domain (executive function, visuospatial ability, language, and attention) across five study visits in ADNI (baseline, 6, 12, 24 and 36 months). Latent variable outcomes (*in circles*) representing cognitive domains are measured by observed cognitive indicators (*in squares*) at each ADNI study wave. Latent variables capturing baseline or initial status (*intercept*) and annual trajectories (*slope*) were estimated using the latent variable outcomes at each visit. Numbers on arrows from growth parameters to latent variable outcomes are fixed factor loadings representing time steps from the baseline visit. The domain-specific indicators used at each study visit for executive function, visuospatial ability, language, and attention are shown in Table 1 and described in the Methods section

Specifically, factor loadings of indicators on constructs at each study visit were constrained to be equal across time points. Residual variances of the latent constructs are constrained to be equal. Temporal correlations were permitted between like indicators at one visit and the following visit (Fig. 1). Methods correlations are correlations among items from the same test that may not represent meaningful variance of a construct (Garner et al. 1956; Strauss et al. 2000). For our study, methods correlations were also included for items from similar tests within a visit to model residual correlations and better represent observed data (e.g., AVLT items; see Fig. 1).

Statistical analyses were conducted using Mplus statistical software, version 6.11 (Muthén and Muthén 1998–2010). Model fit was evaluated using the root mean square error of approximation (RMSEA; (Steiger 1989)) and comparative fit index (CFI; (Hu and Bentler 1999)). An RMSEA below 0.05 and CFI above 0.90 are generally considered indicators of good model fit (Hu and Bentler 1999).

Results

Baseline demographics and neuropsychological performance

Demographic information and group results on the neuropsychological tests are summarized in Table 1. The controls were slightly older than the MCI patients (76 versus 74 years) (p=0.04), and there was a higher percentage of males in the MCI group (p<0.01). There were no group differences in years of education. The ethnic composition of

Table 1 Baseline demographic characteristics and performance on individual tests

	Healthy control (n=229)	Mild cognitive impairment (n=397)	P-value for group differences
Age [M (SD)]	76.0 (5.0)	74.9 (7.5)	0.04
Years of education [M (SD)]	16.0 (2.9)	15.7 (3.0)	0.15
Sex, Male [n (%)]	119 (52.0)	256 (64.5)	<0.01
Race, White [n (%)]	210 (91.7)	371 (93.5)	0.30
Mini-Mental State Exam [M (SD)]	29.1 (1.0)	27.0 (1.8)	<0.001
Memory			
AVLT Learning (Trial 5 - Trial 1) [M (SD)]	5.9 (2.3)	3.3 (2.4)	<0.001
AVLT Short Delay [M (SD)]	8.1 (3.4)	3.8 (3.1)	<0.001
AVLT Long 30 min. Delay [M (SD)]	7.4 (3.7)	2.8 (3.3)	<0.001
AVLT Recognition [M (SD)]	12.9 (2.5)	9.7 (3.7)	<0.001
ADAS-Cog Delayed Recall [M (SD)]	2.9 (1.7)	6.2 (2.3)	<0.001
ADAS-Cog Recognition [M (SD)]	2.6 (2.3)	4.6 (2.7)	<0.001
Visuospatial ability			
Clock Score [M (SD)]	4.9 (0.4)	4.6 (0.7)	<0.001
Clock Copy Score [M (SD)]	4.7 (0.7)	4.2 (1.0)	<0.001
ADAS-Cog Constructional Praxis [M (SD)]	0.4 (0.5)	0.6 (0.6)	<0.001
Language			
Verbal Fluency - animals (1 min) [M (SD)]	19.9 (5.6)	15.9 (4.9)	<0.001
Verbal Fluency – vegetables (1 min) [M (SD)]	14.7 (3.9)	10.7 (3.5)	<0.001
Boston Naming Test, spontaneous recall [M (SD)]	27.3 (2.8)	25.1 (3.7)	<0.001
ADAS-Cog Naming, any incorrect [n (%)]	15 (6.6)	98 (24.7)	<0.001
Executive function/processing speed			
Trails B - Trails A (time) [M (SD)]	50.1 (31.6)	73.7 (47.6)	<0.001
Trails A (time) [M (SD)]	36.4 (13.2)	0.0 (0.9)	<0.001
Number Cancellation [M (SD)]	24.7 (5.1)	43.0 (18.1)	<0.001
Digit Symbol [M (SD)]	45.3 (9.6)	36.7 (11.1)	<0.001
Attention			
Digit Span Forward [M (SD)]	8.8 (2.0)	8.2 (2.0)	0.001
Digit Span Backward [M (SD)]	7.2 (2.0)	6.2 (1.9)	<0.001

M mean, *SD* standard deviation.

the sample was largely homogenous with a large percentage of subjects being white in both groups. As expected, participants with MCI scored worse than controls on all neuropsychological tests (all $p<0.001$).

Latent growth modeling Results of four multiple indicator parallel process models are shown in Table 2 and graphically in Fig. 2. The following results are described according to cognitive domain. Model fits were excellent (all RMSEA<= 0.06; all CFI>0.86; Table 2). For all cognitive domains, initial recall parameter variances were considerably larger than indicator residual variances, suggesting more between-person heterogeneity in cognitive performance than within-person variability.

Memory factor At baseline, the MCI patients performed approximately 1 SD below that of the healthy controls on memory, and this difference was statistically significant ($p<0.001$; Table 2 and Fig. 2). Both groups declined in memory performance over 36 months. However, the MCI patients declined in memory at approximately twice the rate of healthy control participants. Differences in the annual trajectories were statistically significant ($p<0.001$).

Executive function/processing speed factor Similar to the memory results, the MCI group's baseline performance on executive function/processing speed was significantly lower than healthy controls ($p<0.001$). The MCI patients declined by 1.6 SD per year in executive function/processing speed ($p<0.001$), while there was no decline in executive function/processing speed by healthy controls ($p=0.76$). The trajectory of decline in MCI patients was significantly different than healthy controls ($p<0.001$).

Visuospatial factor The results on the visuospatial factor are similar to executive function. MCI performance on the

Table 2 Model parameter estimates summarizing growth processes in five neuropsychological factors by diagnostic status: Results from ADNI (n=626)

	Memory		Executive function/ processing speed		Visuospatial		Language		Attention	
	Intercept (Mean)	Trajectory (Mean)	Intercept (Mean)	Trajectory (Mean)	Intercept (Mean)	Trajectory (Mean)	Intercept (Mean)	Trajectory (Mean)	Intercept (Mean)	Trajectory (Mean)
Means										
Healthy control	56.6*	−0.5*	53.8*	0.0	52.7*	−0.1	54.9*	0.1	52.8*	0.2
MCI	45.5*	−1.1*	47.4*	−1.6*	48.6*	−1.1*	47.6*	−1.1*	48.7*	−1.0*
Between-diagnostic status, within-domain differences										
	−11.1*	−0.6*	−6.4*	−1.7*	−4.1*	−0.9*	−7.3*	−1.2*	−4.1*	−1.1*
Within-diagnostic status, between-domain (memory) differences										
Healthy control	NA	NA	2.8*	−0.5*	3.9*	−0.3	1.7*	−0.6*	3.8*	−0.7*
MCI	NA	NA	−1.9*	0.5*	−3.0*	−0.1	−2.1*	−0.1	−3.2*	−0.2
Magnitude of Differences	NA	NA	4.6*	−1.0*	6.9*	−0.3	3.8*	−0.5*	7.0*	−0.5*
Residual variances, variance (SE)										
Growth parameters	34.8* (2.6)	1.5* (0.3)	59.1* (4.2)	2.6* (0.6)	31.4* (3.4)	2.4* (0.8)	37.4* (2.3)	0.0 (0.0)	57.3* (3.5)	0.0 (0.0)
Indicator residual variances	1.5* (0.4)		0.1 (0.4)		4.2* (1.3)		0.3 (0.4)		0.4 (1.1)	
Model fit statistics										
RMSEA			0.057	0.053	0.061	0.058				
CFI			0.891	0.905	0.884	0.914				

* p<0.05

Results from four multiple indicator parallel process latent growth models used to explore domain-specific growth in cognitive domains in ADNI healthy control and MCI participants. Means of latent intercept and trajectory parameters representing growth processes are shown in the first two rows for each cognitive domain. Between-diagnostic group, within-domain differences provide tests of differences in parameters between healthy control and MCI participants, which was accomplished by regressing growth parameters on an indicator for diagnostic group (see Fig. 1 and the Methods). Within-diagnostic group, between-domain differences provide tests of differences between parameters for a cognitive domain and memory. Because the memory growth process was part of all four models, fit statistics are not provided

visuospatial factor was significantly lower than controls at baseline (p<0.001). Again only the MCI patients declined significantly in visuospatial performance, and this trajectory was significantly different from healthy controls (p<0.001).

Language factor The MCI patients scored significantly lower than controls on the baseline language factor (p<0.001). Again, only the MCI patients declined on the language factor (p<0.001), while healthy controls did not decline (p=0.48). This difference was statistically significant (p<0.001).

Attention factor The MCI patients scored significantly lower than controls on the baseline attention factor (p<0.001). Only the MCI patients showed significant annual decline, and this decline was significantly different than in healthy controls (p<0.001).

Diagnostic group by cognitive domain interactions To better understand how domain-specific cognitive functions decline relative to each other, we compared the magnitudes of initial level and decline in each domain *contrasted with memory* within each diagnostic group. Differences in parameter intercepts and trajectories by diagnostic group are shown in Table 2 under *Within-diagnostic group, between-domain differences*. When considering the levels of baseline factor scores (i.e., parameter intercepts) in healthy controls, the baseline memory factor scores were significantly higher than the other non-memory cognitive factor scores (all p<0.001). In contrast, the baseline memory factor scores for the MCI patients were significantly lower than the other non-memory cognitive domains (all p<0.001). These baseline patterns were significantly different between groups, suggesting a diagnosis by cognitive domain interaction.

In terms of trajectory over time, among the MCI patients, executive function/processing speed declined 0.5 SD faster than memory (p<0.05). Other domains (visuospatial, language and attention) for MCI patients declined at a similar rate with memory (all p values>0.29). Thus, among MCI patients, decline in executive function/processing speed was faster than in memory and other cognitive factors. In contrast, executive function/processing speed, language, and attention factors declined significantly slower than the memory factor in controls. Table 2 shows significant differences in declines in executive function/processing speed,

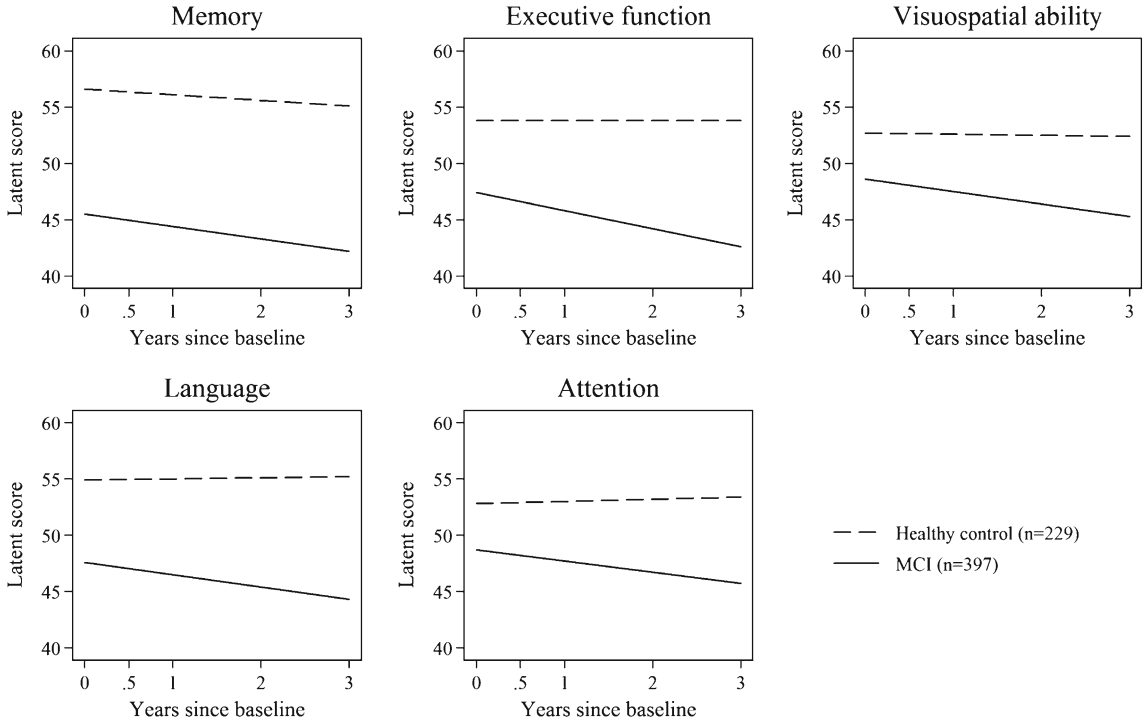

Fig. 2 Model-estimated trajectories of performance in cognitive factors by diagnostic status: Results from healthy control and MCI groups (n=626)

language, and attention factors relative to memory between controls and MCI. In summary, these results indicate at both baseline and over time that there are interactions between diagnostic group and cognitive domains, demonstrating interactions between diagnostic group and domain-specific cognitive decline.

Discussion

Overall, the present study used latent growth modeling to examine baseline and longitudinal change in five cognitive factor scores derived from the ADNI neuropsychological battery in healthy controls and MCI patients. At baseline, compared with controls, MCI patients demonstrated lower performance on all of the five cognitive factors (memory, executive function/processing speed, language, attention and visuospatial). Both controls and MCI patients declined on memory over 36 months; however, the MCI patients declined at a significantly faster rate than controls on memory. The MCI patients also declined over 36 months on the remaining four cognitive factors (i.e., executive function/processing speed, language, attention and visuospatial). In contrast, the controls did not exhibit change on any of these non-memory cognitive factors over 36 months, which differed significantly from the MCI patients. Within the MCI group, executive function declined faster than memory, while the other factor scores changed at the same rate as memory over time. The results also suggest that executive function/processing speed declines faster than other cognitive factors, including memory, in patients with MCI. Thus, these findings suggest different patterns of cognitive decline in healthy older adults and MCI patients both at baseline and over time (e.g. diagnostic group by cognitive domain interactions).

As expected, MCI patients had lower performance on tests of memory at baseline in the ADNI study. As discussed above, the inclusion criteria for the ADNI study require that MCI patients have impaired memory and controls have intact memory performance. It is also not surprising that the MCI patients had lower baseline factors scores than controls on the other cognitive domains, as several studies suggest that MCI patients have deficits in non-memory domains relative to healthy controls (Hodges et al. 2006; Kramer et al. 2006; Matsuda and Saito 2009). An international work group outlined criteria for both single- and multiple-domain amnestic MCI (Winblad et al. 2004), and it is likely that the MCI patients in the ADNI study are classified as multiple-domain amnestic MCI rather than single-domain MCI according to this classification. Indeed, the memory cut-off on the Logical Memory subtest used for inclusion in ADNI is conservative, which likely identified MCI patients who are more impaired than the average MCI patient and have deficits in multiple cognitive domains. Thus, the baseline results in the current study are consistent with other studies suggesting that MCI patients often have deficits in multiple cognitive domains.

When considering change in cognitive performance over 36 months, the results from the latent growth models

suggest that memory declined in both MCI patients and healthy controls. However, the rate of memory decline was different, with the MCI patients declining faster than controls. These results confirm other studies that document age-related memory decline in healthy older adults (Albert et al. 1995; Hayden et al. 2011; Wilson et al. 2002) and also other studies that document a steeper slope of memory decline in MCI patients compared with healthy controls (Bennett et al. 2002; Mungas et al. 2010). One recent study using random effects regression analysis reported that a majority (65 %) of healthy older adults declined at approximately 0.04 SD annually (equivalent to 0.4 factor units in the present study) on a global cognitive composite score (Hayden et al. 2011). Thus, the current findings about memory decline in both MCI and controls derived from the latent growth models are consistent with most studies using different methods and approaches.

The novel finding of the current study is that, while memory declined in both MCI and healthy controls, only MCI patients declined significantly on the other four non-memory cognitive factors (i.e., executive function/processing speed, language, visuospatial, and attention). This finding suggests that decline in non-memory domains may be an important feature for distinguishing healthy older adults and persons with MCI. That is, monitoring decline on non-memory domains may be more predictive of clinical progression than a decline in memory. A recent paper by Gomar and colleagues (Gomar et al. 2011), also using ADNI data, found that the change on the Trailmaking test B was a better indicator of conversion to Alzheimer's disease than change in memory. Although Carter and colleagues (Carter et al. 2011) argue that deficits in semantic cognition appear before executive dysfunction in MCI patients, several other authors have proposed that executive dysfunction is the second cognitive domain to be affected in MCI patients who progress clinically (for review see (Perry and Hodges 1999)). Other studies also suggest that the risk of converting to dementia is increased when multiple domains are impaired, including executive function (Albert et al. 2001; Nordlund et al. 2011). If only memory is assessed over time, it would be difficult to observe differences between healthy controls and MCI patients. Thus, examining non-memory domains may be a powerful tool for differentiating normal, age-related decline from cognitive decline due to underlying neuropathology.

Numerous studies suggest that healthy aging is associated with brain changes in both gray and white matter and also declines in several cognitive domains, including working memory and attention (Buckner 2004; Hedden and Gabrieli 2004; Raz et al. 1997). Although progress has been made in the understanding of the relationship between changes in the brain and patterns of cognitive aging, the neuroanatomical basis of these age-related changes in cognition continues to be a topic of debate (Raz and Kennedy 2009; Salthouse 2011). It is possible that the lack of decline on non-memory cognitive factors over 3 years by the controls in the current study reflects the profile of healthier "successful" agers compared with more "typical" agers (Hsu and Jones 2012; Negash et al. 2011). Additional longitudinal studies using comprehensive neuropsychological batteries are needed to help identify which cognitive features are the best predictors of conversion to dementia versus healthy aging.

In addition, when comparing the rates of change of different cognitive factors within the MCI group, the latent growth models suggest that executive function/processing speed changed at a faster rate than memory in MCI patients. In contrast, there was no decline in executive function/processing speed in the healthy controls. This diagnostic group by domain interaction shows a significant difference in the magnitude of change between memory and executive function between MCI and healthy controls. This suggests that executive function may be a potentially more sensitive measure of cognitive decline due to underlying neuropathology and may be a useful tool to distinguish healthy aging and MCI. Future studies are needed to further test this hypothesis. In contrast, the trajectory of decline in language, visuospatial, and attention in MCI was similar to the decline in memory, while there was no change over time on visuospatial and attention factors relative to memory in healthy controls. These domains appear less helpful for distinguishing MCI patients and healthy controls. Finally, because memory declined in both groups, it may also be useful to control for the rate of memory change when examining decline in executive function in future studies.

The second-order latent growth models used in the current study were robust and addressed the theoretical question at hand. Other multivariate alternatives are also available (McArdle 1988; Salthouse and Ferrer-Caja 2003). For example, to bolster causal inferences, it is possible to estimate two-stage piecewise longitudinal growth models in which earlier growth in one process predicts future change in another process or developmental stage (Chou et al. 2004). In the present study, we sought to compare trajectories among cognitive factors but do not make any causal attributions. It is also feasible to expect that mean levels and rates of decline in each cognitive domain do not describe trajectories of all participants equally well, and that there are subgroups of participants who decline faster or slower, depending on where they are in the pathological cascade of Alzheimer disease; such groups might be teased apart through growth mixture modeling (Leoutsakos et al. 2012). In yet another variation of longitudinal structural equation modeling, a bivariate dual change score model might be used to explicitly explore whether change in one cognitive domain is associated with change in another domain (McArdle and Prindle 2008); such models

require equally spaced visits, which we do not have in ADNI unless we exclude the 6-month visit. These and other research questions should be pursued in future research to extend our knowledge of domain-specific cognitive decline in older adults.

Several limitations of the present study are important to mention. First, because of the way the indicators in the current study are scaled, the factor scores are not generalizable to other samples. We strictly compared relative change in various domains between healthy controls and MCI patients in the ADNI sample. Second, the latent growth models in the present study accommodated linear change in cognitive factors, and the model fit statistics in this study suggested this assumption was adequate. However, it is possible that certain tests declined faster or slower than others within a domain, or even that change in some tests demonstrated quadratic change. We did not explore indicator-specific trajectories because our goal was to make inferences at the level of cognitive domains and not individual tests. It is also important to keep in mind that we did not exclude participants in either group that had a change in diagnosis (e.g., converted to dementia or reverted to normal). The ADNI study also focuses on prodromal stage of Alzheimer's disease, so the results do not generalize to the MCI stages of non-Alzheimer's disease dementias. In addition, the homogeneous racial composition, high educational level, and age composition of the participants in ADNI limit the generalizability to other community samples. As discussed above, the controls in the study may represent a group of healthier "successful" agers compared with more "typical" agers (Hsu and Jones 2012; Negash et al. 2011), which also limits the generalizability to other community samples.

In conclusion, latent growth modeling appears to be a useful tool for investigating longitudinal change in neuropsychological performance in both healthy older adults and persons with MCI. The results of the latent growth models suggest that cognitive decline differs between healthy aging and MCI. The latent growth models also suggest that executive function, in particular, declines at a faster rate than memory in MCI patients. The findings also underscore the importance of examining non-memory cognitive decline for potentially differentiating healthy aging and MCI. It is important to replicate these results in other large studies, particularly those with more ethnic diversity, and to determine how the latent factors might also help predict conversion to dementia or functional decline.

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