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Normal rates of cognitive change in successful aging: The Freedom House Study

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Abstract

We determined the rates of cognitive change associated with twenty individual measures. Participants included 547 noninstitutionalized septuagenarians and octogenarian residents of a comprehensive care retirement community who were studied over three years. Latent growth curves (LGC) of multiple cognitive measures were compared to a LGC model of the rates of change in Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL). All curves were standardized relative to each variable's baseline distribution. Baseline scores were within their expected normal age-specific ranges. Most measures showed significant rates of change over time. There was also significant variability about those rates, suggesting clinical heterogeneity. Many deteriorated over time, as did ADLs and IADLs. However, performance on some measures improved, consistent with learning effects. The rates of change in two measures, the Executive Interview and the Trail Making Test, were closely related to decline in IADLs. These results suggest that age-related cognitive decline is a dynamic longitudinal process affecting multiple cognitive domains. Heterogeneity in the rates of cognitive change may reflect the summed effects of age and comorbid conditions affecting cognition. Some measures may be ill-suited for measuring age-related changes in cognition, either because they are insensitive to change, or hindered by learning effects. Nonverbal measures appear to be particularly well suited for the prediction of age-related functional decline. These observations are relevant to the definition and diagnosis of "dementing" conditions. (*JINS*, 2005, *11*, 899–909.)

Keywords: Aging, Assessment, Disability, Dementia, Longitudinal, Executive function

INTRODUCTION

Age-related cognitive change is a dynamic process affecting multiple domains (Salthouse, 1999). However, the conclusions that can be validly drawn from cross-sectional aging studies may be severely limited (Kraemer et al., 2000). More recent studies have employed models of longitudinal change to describe normal aging. The Australian Longitudinal Study of Aging (Anstey et al., 2003), the Berlin Aging Study (Singer et al., 2003), and the Victoria Longitudinal Study of Aging (Hertzog et al., 2003) have published latent growth curve (LGC) models of latent constructs derived from multiple cognitive measures. This approach is meant to overcome, yet still obscures, the difficulties associated with the repeated administration of individual measures. Some may be ill-suited for detecting changes in cognition, either because they are insensitive to change, or because they are hindered by learning and practice effects.

Relatively few individual measures have been submitted to LGC analysis in normative aging populations. Suh et al. (2004) examined the association between change in the Mini-Mental State Exam (MMSE) and Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog) scores, over one year, among $N = 107$ elderly patients with Alzheimer's disease (AD). Ghisletta & Lindenberger (2004) have examined the rates of change in two cognitive measures (vocabulary and digit-letter substitution) in the Berlin Aging Study cohort. Sliwinski et al. (2003) examined LGC

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models of a single memory measure, the Selective Reminding Task, among $N = 391$ participants from the Bronx Aging Study.

In general, cognitive measures show significant variability with regard to both their baseline distributions and their interindividual rates of change. These may have different origins. Variability in the longitudinal rates of change on cognitive measures appears to be less heritable than that associated with cross-sectional baseline distributions (McGue & Christensen, 2002; Reynolds et al., 2002). This suggests that intraindividual rates of change may be environmentally determined, and thus more amenable to intervention or prevention. On the other hand, this heterogeneity may also reflect comorbid conditions affecting cognition.

Finally, few studies have examined the relative rates of change in both cognitive and functional measures in a normative aging cohort. Many epidemiological cohorts, including The Longitudinal Aging Study of Amsterdam (Comijs et al., 2004), or the Women's Health Initiative Memory Study (Rapp et al., 2003), contain only the MMSE, or similar bedside screening measures. Other more psychometrically sophisticated longitudinal studies either have not employed LGC (Ratcliff et al., 2003; Frerichs & Tuokko, 2005) or do not report functional outcome measures (Anstey et al., 2003; Hertzog et al., 2003).

However, we have been studying this issue among residents of Continuing-Care Retirement Communities (CCRCs) (Royall et al., 2003, 2004, 2005, in press). CCRCs provide longitudinal access to large, stable elderly populations receiving care across a wide range of services. The Freedom House Study (FHS) examines the incidence of Executive Control Function (ECF) impairment within a single CCRC, the Air Force Villages (AFV). In this FHS report, we present the longitudinal rates of change across a wide selection of cognitive and functional measures as a basis for future longitudinal studies.

List of Abbreviations

AD =	Alzheimer's disease
ADAS-cog =	Alzheimer's Disease Assessment Scale, cognitive subscale
ADL =	Activities of Daily Living
AFV =	Air Force Villages
AODM =	adult-onset diabetes mellitus
BNT =	Boston Naming Test
CAD =	coronary heart disease
CLOX 1–2 =	Parts 1 and 2 of CLOX, an executive clock-drawing task
CCRCs =	Continuing-care retirement communities
COWA =	Controlled Oral Word Association
CVA =	stroke
CVLT:1–5 =	total score from California Verbal Learning Test learning trials 1–5
CVLT–Short =	short-delay free recall from the CVLT
CVLT–Long =	long-delay free recall from the CVLT
DRS–MEM =	Mattis Dementia Rating Scale–Memory subscale
ECF =	executive control funtion
EXIT25 =	Executive Interview
FHS =	Freedom House Study
FSRP =	Framingham Stroke Risk Profile
GDS =	Geriatric Depression Scale, short version
HTN =	hypertension
IADL =	Instrumental Activities of Daily Living
ICVD =	ischemic cerebrovascular disease
LGC =	latent growth curve(s)
MCI =	mild cognitive impairment
MD =	physician
MMSE =	Mini-Mental State Examination
ns =	not significant
OARS =	Older Adults Resources Scale
RHMA =	right hemisphere model of aging
ROI =	regions of interest
SD =	standard deviation
Trails A =	Trail-Making Test, Part A
Trails B =	Trail-Making Test, Part B
WAIS–DSS =	WAIS–R Digit Symbol Substitution
WAIS–Block =	WAIS–R Block Design
WAIS–SIM =	WAIS–R Similarities
WAIS–Vocab =	Wechsler Adult Intelligence Scale–Revised, Vocabulary subscale
WCST–CAT =	Wisconsin Card Sort, categories achieved
WCST–CR =	Wisconsin Card Sort, conceptual responses

METHODS

Research Participants

Elderly retirees ($N = 547$) were recruited from a randomly ordered list of AFV residents over the age of 70, living at noninstitutionalized levels of care. These included garden apartments and congregate high-rises. Garden apartments were considered the lowest level of care. Each is a standard duplex apartment with a full kitchen/laundry, standard bath, and attached parking space. There is no special handicap access. In contrast, high-rise residents eat in common, there is handicap access, and handicap adapted bathroom facilities. Light housecleaning and laundry services are provided. Limited outpatient medical care including medication supervision is available on site. All AFV residents benefit from on-campus security and restricted public access. Informed consent was obtained prior to their evaluations. This protocol was approved by the University of Texas' Health Science Center at San Antonio's Institutional Review Board.

The FHS participants represented 57.3% of potentially eligible participants and did not differ significantly from nonrecruited residents with regard to age, gender, or baseline level of care. Participants were evaluated at three separate points over three years (mean interval = 18.2 ± 3.6 months). As functional status declined over time, frail participants were interviewed in their own residences. Collateral informants were used when available.

All FHS participants underwent detailed interviews to establish level of healthcare utilization, living arrange-

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ments, functional status, general cognition, and executive function. A random subset ($n = 193$) was selected at baseline to receive a much more detailed formal neuropsychological test battery. The attrition rate across the first two waves was 10.2% cases/year (4.0% to death, 5.5% to refusal, and 0.4% untestable at follow-up). However, unforeseen budget restrictions limited wave 3 data collection. We chose to examine only the surviving fraction of FHS participants who had been randomly selected at baseline to receive the detailed formal neuropsychological test battery. This subset ($n = 137$) represented 25.0% of potentially eligible FHS participants at wave 3, but 71.0% of those with baseline neuropsychological test data. Since this attrition was unrelated to clinical condition, and includes a high percentage of an initially representative subgroup, it satisfies the "missing at random" constraint on our analyses (discussed later).

Clinical Variables

Functional status and comorbid medical conditions were assessed using the Older Adults Resources Scale (OARS) (Fillenbaum, 1978). The OARS is a structured clinical interview that provides self-reported information on activities of daily living (ADL), instrumental activities of daily living (IADL), health history, healthcare utilization, and current medications. The OARS' IADL scale is scored inversely relative to disability such that lower scores indicate higher levels of disability.

Depressive symptoms were assessed using the short Geriatric Depression Scale (GDS) (Sheikh & Yesavage, 1986; Maixner et al., 1995). GDS scores range from zero to 15. Higher scores are worse. A cut-off point of 6–7 best discriminates clinically depressed from nondepressed elderly.

Psychometric Measures

The Mini-Mental State Examination (MMSE)

The MMSE (Folstein et al., 1975, 2001) is a well-known and widely used test for screening cognitive impairment. Scores range from 0–30. A score of 28/30 is the median for normal octogenarians of >12 years of education (Folstein et al., 2001). Scores below 24 reflect cognitive impairment. The MMSE has no items that are specifically addressed to executive control function (ECF), and may underestimate cognitive impairment in frontal system disorders (Royall & Polk, 1998).

Memory function

Memory was assessed with the Mattis Dementia Rating Scale–Memory subscale (DRS–MEM) (Mattis, 1988), and the California Verbal Learning Task (CVLT) (Delis et al., 1987). The CVLT assesses learning and memory processes. Several CVLT indices have been correlated with specific CNS activations. Saykin et al. (1999) have reported that novel word processing (similar to CVLT learning trial 1) and familiar word processing (similar to CVLT learning trials 2–5) cause left medial temporal activations seen by functional magnetic resonance imaging (fMRI). Similarly, Johnson et al. (2001) found a strong association between right hippocampal fMRI activations ($r = .76$) and novel word processing during CVLT trial 1. Thus, CVLT performance over the first five learning trials may offer a convenient proxy for the quality of hippocampal functions, that is, in assessing preclinical Alzheimer's disease.

Verbal measures

Verbal function was assessed by the Boston Naming Test (BNT) (Kaplan et al., 1983), the Wechsler Adult Intelligence Scale–Revised (WAIS–R) Similarities (SIM) and Vocabulary (Vocab) subtests (Wechsler, 1981).

Nonverbal measures

Visuo-spatial functions were assessed by part two of CLOX, an executive clock-drawing task (CLOX2) (Royall et al., 1998a, 1998b), Trail Making Test, Part A (Reitan, 1958), and WAIS–R Block Design (Block) (Wechsler, 1981).

Executive control function

Executive functions were assessed by CLOX, Part 1 (CLOX1) (Royall et al., 1998a, 1998b), the Executive Interview (EXIT25) (Royall et al., 1992), the Controlled Oral Word Association (COWA) (Benton & Hamsher, 1989), the Trail Making Test, Part B (Reitan, 1958), the WAIS–R Digit Symbol Coding (DSS) (Wechsler, 1981), and the abbreviated Wisconsin Card Sorting Task (WCST) (Haaland et al., 1987).

CLOX (Royall et al., 1998a, 1998b) is a brief ECF measure based on a clock-drawing task (CDT). It is divided into two parts. CLOX1 is an unprompted task that is sensitive to executive control. CLOX2 is a copied version that is less dependent on executive skills. CLOX1 is more "executive" than several other comparable CDTs (Royall et al., 1999). Each CLOX subtest is scored on a 15-point scale. Lower CLOX scores are impaired. Cut-off points of 10/15 (CLOX1) and 12/15 (CLOX2) represent the 5th percentiles for young-adult control subjects.

The EXIT25 (Royall et al., 1992) provides a standardized clinical ECF assessment. Items assess verbal fluency, design fluency, frontal release signs, motor/impulse control, imitation behavior, and other clinical signs associated with frontal system dysfunction. It requires 15 minutes and can be administered by nonmedical personnel. Interrater reliability is high ($r = .90$). EXIT25 scores can be specifically associated with left frontal system lesions by MRI (Royall et al., 2001). It correlates well with other ECF measures including the Wisconsin Card Sorting Task (WCST) ($r = -.54$), Trail Making Part B ($r = .64$), Lezak's Tinker Toy test ($r = -.57$), and the Test of Sustained Attention

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(Time, $r = .82$; Errors, $r = .83$). EXIT25 scores range from 0 to 50. High scores indicate impairment. A score of 10/50 reflects the 5th percentile for young adults. Scores $\geq 15/50$ suggest clinically significant ECF dysfunction.

The abbreviated WCST (Haaland et al., 1987) is an adaptation of the original two-deck (128 cards) WCST (Heaton et al., 1993; Kongs et al., 2000). The abbreviated WCST utilizes one deck of 64 cards. Brief, standardized instructions are presented to the patient who must determine the correct criteria (color, shape, and number) for sorting the cards into appropriate categories and must periodically shift sorting strategies in order to meet changing task requirements.

Analysis

Missing data

Data in the third wave was limited to approximately 30% of the eligible participants. Rather than discarding information from the first two waves by limiting our analysis to cases with complete data, we used Full Information Maximum Likelihood (FIML) methods to address this problem (Arbuckle, 1996; Wothke, 1999). FIML uses the entire observed data matrix to estimate parameters with missing data. In contrast to listwise or pairwise deletion, FIML yields unbiased parameter estimates and preserves the overall power of the analysis (Schafer, 1997; Wothke, 1999). This analysis was performed using AMOS software (Arbuckle, 1994).

FIML can accommodate significant data loss provided the data are "missing at random" (McArdle & Hamagami, 1992). Because the vast majority of missing data was suffered at wave 3, and because the participants observed at wave 3 represent the survivors from a random subset of the original sample, the missing data points should satisfy this constraint. As a test of this assumption, we examined six clinical variables available for all participants at baseline (i.e., cross-sectional age, education, gender, EXIT25, GDS, and MMSE scores) for those with complete data at wave 3 *versus* those lost to follow-up. Attrition had no significant effects on these variables [by ANOVA: $df\,(1, 546)$, all $p = \text{ns}$]. We also retrospectively tested the survival rates (mean observation time = 60.9 ± 15.3 months) to the outcomes of death, next transition in level of care, and nursing home placement, for those with complete data *versus* those lost to follow-up at wave 3. Survival to each of these outcomes was unaffected by attrition (by log rank test, all $p = \text{ns}$).

Latent growth curve analysis

Data were submitted to latent growth curve (LGC) modeling. In contrast to multiwave autoregressive models, which estimate interindividual rates of change across measurements, LGC models estimate the full trajectory of change across each individual's measurement points (Willet & Sayer, 1994). The first and second factor loadings on the latent growth parameter were fixed to 0 and 1, respectively. The last time point loading was freely estimated from the data. The covariance between intercept and slope was estimated and residual variances were constrained to be equal across time unless a better model fit was obtained by releasing the constraints.

The latent growth variables of interest [e.g., the rates of change in IADL (ΔIADL) and cognitive measures] reflect the mean rates of change in functional status and cognition, respectively. The variances about these means are also of interest because they indicate whether there is heterogeneity among the individual growth curves within the sample. Significant variation in the rate of change in a latent growth variable indicates that there are statistically significant interindividual differences in the rates of change. Nonsignificant variation would indicate that all participants were following the same change trajectory.

Goodness of fit

The fit of each individual growth model was compared to a competing model of "no growth." The validity of structural models was assessed using three common test statistics. A nonsignificant chi-square signifies that the data are consistent with the model (Bollen & Long, 1993). A root mean square error of approximation (RMSEA) of $\leq .05$ indicates a close fit to the data with models up to .10 viewed as acceptable fit (Browne & Cudeck, 1993). The comparative fit index (CFI) compares the specified model with a model of no change (Bentler, 1990). With values ranging between 0 and 1, values below .95 would suggest model misspecification. Values $> .95$ indicate adequate to excellent fit. All three fit statistics should be simultaneously considered to assess the adequacy of the models to the data.

RESULTS

Cross-sectional Analysis

Baseline clinical and demographic data are presented in Tables 1 and 2. The mean GDS score was well below its clinical threshold (Table 1). Only 12 individuals scored $>$ 6/15 on the GDS. 83.2% of participants estimated their health as either "good" or "excellent." Baseline test scores were within age-specific normal ranges (Table 2).

Longitudinal Analysis

Table 3 presents latent growth curve models of the rates of change in each cognitive measure. All models showed excel lent fit (all chi-squares $p > .05$; RMSEA = .01–.03; CFI = .980–.999). Most measures showed significant rates of change over time (all $p \leq .001$). However, BNT [mean slope: $m = .00$ *SD*/yr (standard deviation/year)] and CLOX1 ($m = -0.01$ *SD*/yr), showed no significant change (both $p > .05$). CVLT–Short ($m = 0.09$ *SD*/yr), DRS–MEM ($m = -0.07$ *SD*/yr), and MMSE ($m = -0.07$ *SD*/yr) showed modest rates of change that did not survive Bonferroni correction (Table 3).

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Table 1. Baseline clinical features of cases*

Variable	Mean (*SD*)
Age	77.9 (4.9)
Female (%)	58.3%
Education (years)	15.1 (2.4)
Those at lowest level of care (%)	46.3%
Those living alone (%)	27.8%
MD visits in previous 6 months	3.8 (4.1)
Those reporting (%):	
Glaucoma	18.3%
Arthritis	61.2%
HTN	41.9%
CAD	22.5%
AODM	5.6%
CVA	6.3%
Thyroid illness	17.7%
"Good" or "Excellent" self-rated health	82.3%
GDS	1.6 (1.9)
Those needing assistance with (%):	
Telephone use	3.4%
Transportation	12.7%
Shopping	10.6%
Cooking	7.7%
Housework	18.8%
Medications	4.8%
Finances	6.1%
Those using prostheses (%)	12.0%

Note. See abbreviations list. IADL = instrumental activities of daily living from the Older Adults Resources Scale.
*$N = 547$.

Table 2. Raw baseline variable means*

Variable ($N = 193$)	Mean (*SD*)
ADL	13.5 (1.4)
BNT	51.6 (8.1)
CLOX1	10.1 (3.3)
CLOX2	13.1 (2.1)
COWA	32.0 (12.6)
CVLT:1–5	32.8 (14.1)
CVLT–Short	15.0 (3.8)
CVLT–Long	16.0 (3.7)
DRS–MEM	21.5 (4.3)
EXIT25	14.6 (5.5)
IADL	13.3 (1.7)
MMSE	27.3 (2.7)
Trails A	63.4 (87.4)
Trails B	132.8 (80.8)
WAIS–Block	19.1 (8.8)
WAIS–DSS	33.2 (11.6)
WAIS–SIM	17.5 (5.2)
WAIS–Vocab	49.1 (10.4)
WCST–CAT	2.0 (2.0)
WCST–CR	36.9 (12.8)

Note. See abbreviations list.
*Baseline means for the entire sample ($N = 547$) are available for most measures in Royall et al., (2000).

There was also significant variability about the intercepts and rates of decline in most measures (Table 3), suggesting clinical heterogeneity at baseline or in the longitudinal processes affecting the sample, respectively. However, BNT, CVLT–Short, DRS–MEM; WAIS–Block, WAIS–Sim, WAIS–Vocab; WCST–CAT and WCST–CR; showed no significant variability in their rates of change, despite significant variability in their intercepts (all $p > .05$).

Most measures deteriorated over time, as did IADLs. However, the magnitude of this decline was generally less than 0.5 *SD*/3 years (Fig. 1). The greatest rates of decline were seen in Trails B (−0.17 *SD*/yr), the EXIT25 (−0.18 *SD*/yr), IADLs (−0.22 *SD*/yr), Trails A (−0.23 *SD*/yr), and CLOX2 (−0.27 *SD*/yr) (Table 3).

However, performance on a few measures improved, suggesting possible learning effects. These included COWA, CVLT:1–5; CVLT–Long; CVLT–Short, WAIS–Vocab, WAIS–SIM, WCST–CAT, and WCST–CR, each of which improved by at least a quarter of a standard deviation over this period of observation. WAIS–SIM improved by almost three quarters of a standard deviation (Fig. 1).

The rates of change in three measures, the XIT25, Trails A and B were most comparable to the rate of decline in IADLs. ADLs declined at a significant, but relatively slow rate (−0.11 *SD*/yr) (Table 3). This was most closely related to the significant rate of decline in WAIS–Block, and the marginally significant rates of decline in DRS–MEM and MMSE (Table 3).

Table 3 also presents the covariances between LGC intercepts and slopes. These could not be estimated in the absence of significant variability about both parameters. When available, they were used to estimate the correlations between a measure's intercept and slope. Significant associations were observed for IADLs and Trails A. Marginally significant associations were observed for the EXIT25 and MMSE. The rate of change in IADL was strongly associated with its intercept ($r = .89$), whereas the rates of change in EXIT25, MMSE, and Trails A were moderately associated with their intercepts ($r = .45$, .38, and .57, respectively). Most other measures did not display a significant association.

DISCUSSION

We have observed heterogeneity in the longitudinal rates of cognitive change in a "successfully" aging cohort. Heterogeneity is observed both within and across measures. The heterogeneity across measures may reflect age effects in specific cognitive domains, clinical heterogeneity within the FHS sample, differences in the sensitivity of individual measures to age-related cognitive change, and/or comorbid conditions affecting cognition.

Some measures may also be ill-suited for measuring longitudinal change, either because they are insensitive to it, or because they are hindered by learning effects. In this study, BNT and CLOX1 did not change significantly from their baseline values (CVLT–Short, DRS–MEM, and MMSE showed a trend), despite the observed declines in IADLs

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Table 3. Mean variance and correlations between LGC intercepts and slopes

Parameter[1]	Average Annualized Slope and Standard Error	Intercept Variance	Slope Variance	Covariance between Intercept and Slope	Correlation between Intercept and Slope
ADL	−0.11 (.03)***	0.62***	0.27***	.02[ns]	.06
BNT	0.00 (.03)[ns]	0.83***	0.03[ns]	—	—
CLOX1	−0.01 (.04)[ns]	0.43***	0.14*‡	−.10[ns]	−13.00
CLOX2	−0.27 (.03)***	0.02[ns]	0.00[ns]	—	—
COWA	0.12 (.03)***	0.82***	0.06**‡	.02[ns]	.08
CVLT:1–5	0.21 (.04)***	0.80***	0.13***	−.04[ns]	−.12
CVLT–Short:	0.09 (.03)**‡	0.78***	0.04[ns]	—	—
CVLT–Long	0.17 (.04)***	0.78***	0.10***	.01[ns]	.05
DRS–MEM	−0.07 (.03)*‡	0.90***	0.03[ns]	—	—
EXIT25†	−0.18 (.05)***	0.43***	0.06*‡	.07**‡	.45
IADL	−0.22 (.03)***	0.57***	0.14***	.25***	.89
MMSE[1]	−0.07 (.03)*‡	0.91***	0.42**‡	.23**‡	.38
Trails A†	−0.23 (.07)***	0.60***	0.33***	.26***	.57
Trails B†	−0.17 (.05)***	0.77***	0.16***	−.04[ns]	−.10
WAIS–Vocab	0.18 (.04)***	0.06	0.75***	0.01[ns]	—
WAIS2–SIM	0.34 (.04)***	0.72***	0.02[ns]	—	—
WAIS3–DSS	−0.15 (.03)***	0.82***	0.05*‡	−.05[ns]	−.19
WAIS4–Block	−0.12 (.03)***	0.87***	0.01[ns]	—	—
WCST–CAT	0.22 (.06)***	0.47**‡	0.02[ns]	—	—
WCST–CR	0.17 (.05)***	0.55***	0.07[ns]	—	—

See abbreviations list.
[1]Baseline mean standardized to zero for all variables. Units in standard deviations relative to each measure's baseline distribution.
†Inverted to reflect inverse scoring.
‡ Not significant with Bonferroni correction.
* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

and significant change on most other cognitive measures. The fact that the same measures also showed no significant variability in their rates of change (CLOX1 and MMSE showed marginally significant trends) suggests that their stability may reflect measurement issues (e.g., ceiling and floor effects), which could limit their utility in longitudinal, or repeated measure designs.

Evidence for learning effects was strongest for CVLT–Short, WAIS–Sim, WAIS–Vocab, WCST–CAT, and WCST–CR. Each improved over time, in contrast to the observed decline in IADLs. Moreover, there was no heterogeneity in the rates of their improvement, despite the fact that there was significant variability about their respective baseline distributions. This suggests that the apparent improvement in these test scores was a psychometric artifact. Similarly, Ferrer et al. (2004) reported that memory measures are associated with stronger learning effects than are measures of spatial abilities or processing speed. Learning effects have specifically been identified as a problem for the WCST and COWA (Basso et al., 1999, 2001; Lineweaver et al., 1999).

We have factor analyzed the baseline FHS data and shown that COWA, CLOX1, EXIT25, and WAIS–DSS colabel a "procedural control" factor that is uniquely associated with functional status (Royall et al., 2003). Unfortunately, the present data suggest that only the EXIT25 would be suitable for the longitudinal study of functional outcomes (at least in older persons). COWA and CLOX1 appear insensitive to change, whereas change in WAIS–DSS appears less well related to functional (IADL) decline (Fig. 1).

The Trail-Making test also appears to be well suited for the prediction of age-related functional decline. The EXIT25, Trails A, and Trails B showed slopes that closely matched the rates of change in IADLs. This is consistent with previous FHS findings. The EXIT25 is an independent correlate of IADL in an adjusted cross-sectional model (Royall et al., 2000). Similarly, *change* in EXIT25 is a strong independent correlate of *change* in IADL in fully multivariate LGC models, adjusted for age, level of care, medical comorbidity, baseline EXIT25, and IADL (Royall et al., 2004). In that study, we showed that changes in EXIT25 scores are causally associated with changes in IADL and mediate much of age's effects on the rate of change in IADL. Similarly, the rates of change in MMSE, CVLT, and WCST scores are not significantly associated with change in IADL, independently of the EXIT25 (Royall et al., 2004, 2005, in press).

The current data suggest that several cognitive measures are deteriorating, in addition to EXIT25 score. Like the EXIT25, they appear to have nonverbal qualities (Fig. 1). The fact that the FHS sample is demonstrably experiencing a decline in nonverbal and ECF measures that is strongly and selectively associated with a similar decline in IADL suggests a clinically significant longitudinal process (Royall et al., 2003). Left unaddressed, the cohort could eventually be disabled by it.

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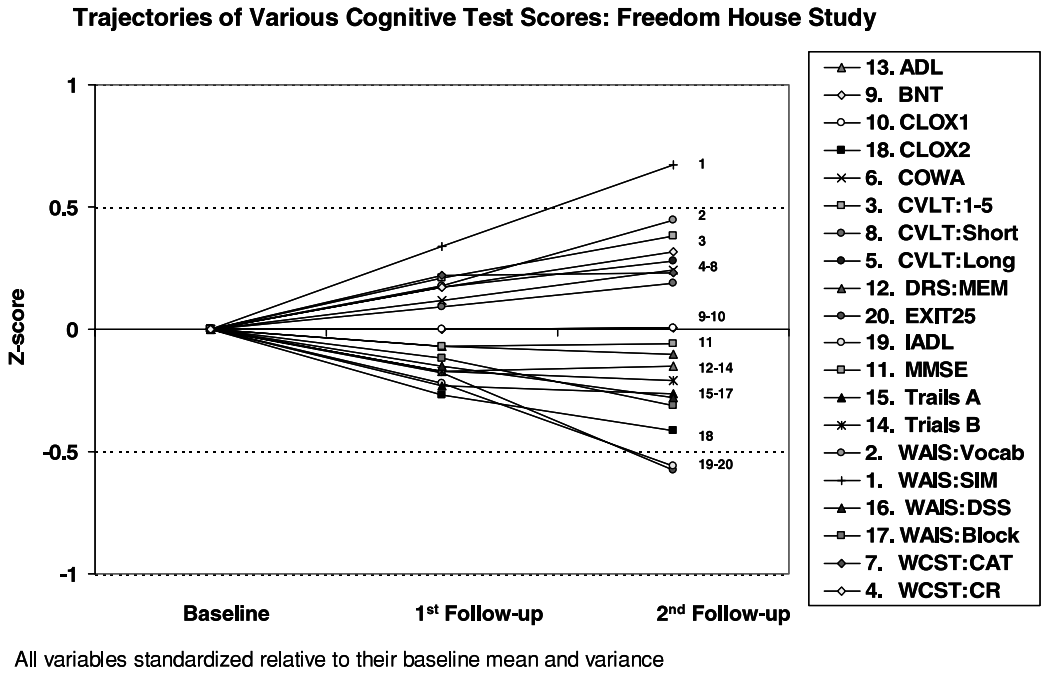

Fig. 1. Latent growth curve models of the rates of change in cognitive measures.

However, this process is likely to be a result of normal aging rather than the preclinical stages of a specific disease [i.e., preclinical AD or mild cognitive impairment (MCI)]. First, the slopes we are describing in this analysis are representative *of the entire sample*, and thus reflect a normative age-related functional (and its associated cognitive) decline. In contrast, only a small fraction of the FHS sample (estimated at 7.8%) would meet criteria for MCI at baseline (Petersen et al. 1999; Royall et al., 2004). This is partly an artifact of the convention by which MCI is defined by memory (or other cognitive impairments) ≤ 1.5 *SD* below *an age-specific norm*. Thus, by definition, the dementing processes described by MCI can affect only a minority of older persons.

Moreover, the rates of change in cognition we report in this study differ substantially from those associated with MCI. MCI is thought to precede conversion to dementia, presumably the dementia of AD (Petersen et al., 2001). The average rate of change in MMSE scores in MCI cases has been estimated to be about 1.0 point/yr (Petersen et al., 1999). None the less, in this sample, the MMSE has declined at a rate <0.15 points/yr, *for over three years*. Moreover, as of the third observation, the mean MMSE score was still well within its normal range (i.e., mean $= 27.16 \pm 2.79$; range 15–30) (Royall et al., 2004).

Jacqmin-Gadda et al. (1997) developed similar random effects models of change in MMSE scores by age in a large community sample of initially "nondemented" elders. Over four years of follow-up, MMSE scores declined 3.4 points/yr among the subset of cases who developed incident AD. In contrast, the mean change in MMSE scores among those who escaped incident dementias were 0.06 points/yr among those aged 75–79, and 0.09 points/yr among those aged 80–84. These latter figures are similar to those we have observed for the MMSE in the FHS*, and yet, multiple other measures are demonstrably evolving in time, at rates that are highly correlated with the change in IADL* (Royall et al., 2004, 2005, in press).

There is a small possibility that these trends reflect even earlier preclinical stages of AD, rather than normal aging *per se*. AD pathology, albeit insufficient to be detected as "dementia," is endemic in this age range (Braak & Braak, 1997), and neuropsychometric changes precede the onset of dementia by several years (Linn et al., 1995).

However, because AD pathology evolves hierarchically in both space and time (Thompson et al., 2003), AD pathology is unlikely to arrive in neocortical regions of interest (ROI) *unless and until* (1) the hippocampus has been affected (Braak & Braak, 1998) and (2) *clinical* dementia develops (Royall et al., 2002). Thus, the observed declines in executive and visuo-spatial function cannot be easily attributed to neocortical AD pathology in the absence of clinical dementia. Moreover, few FHS cases can meet clinical criteria for even amnestic "MCI" on the basis of *either* their CVLT or DRM–MEM performance (Royall et al., 2004).

The positive (improving) slope in CVLT scores is particularly inconsistent with preclinical AD, as performance on that measure can be specifically associated with hipppocampal function/structure (Johnson et al., 2001; Saykin et al. 1999). Although the DRS–MEM showed some decline, that measure's rate of change was only marginally significant. Moreover, although it might be argued that the observed improvement in CVLT scores reflects a learning effect, the observation of that effect would itself argue against an insid-

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ious decline in memory, specifically hippocampally mediated memory function.

The relative lack of decline in memory within the FHS cohort is inconsistent with preclinical AD. Sliwinski et al. (2003) decomposed the observed slope of change in memory scores among $N = 391$ initially nondemented older adults from the Bronx Aging Study. Of these, 98 (25%) were subsequently diagnosed with incident dementia. Disease progression, not age, accounted for almost all the intraparticipant memory declines in the emergent dementia group, and mediated age's apparent effect on memory test performance across the entire sample. Thus, our failure to detect significant rates of decline across several memory measures in the FHS argues strongly against preclinical AD as the cause of the observed declines in nonverbal and executive measures.

Nonetheless, these observations still do not rule out common non-AD processes, notably ischemic cerebrovascular disease (ICVD), as potential causes of our observed cognitive declines. For example, Elias and coworkers (2004) recently demonstrated significant cross-sectional associations between Trail-Making and the Framingham Stroke Risk Profile (FSRP), a previously validated estimate of 10-year longitudinal stroke risk, in a large community-based sample. However, this cross-sectional association may be explained by prevalent "silent" frontal system ICVD (Royall, 2005). It would be much harder to argue that ICVD could *selectively* affect the longitudinal slopes of nonverbal measures while verbal measures *simultaneously* improve.

In fact, the dissociation we observed between the rates of improvement in memory and verbal measures *versus* the rates of decline in functional status, nonverbal, and executive measures is one of the most striking features of this analysis. Our recent factor analysis of baseline FHS data suggests that the latter colabel a single cognitive dimension that is specifically associated with age-related functional changes (Royall et al., 2003). Latent variable analyses suggest that visual working memory and executive function are strongly associated longitudinally as well (Miyake et al., 2001).

Interestingly, Ratcliff et al. (2003) have reported the ten-year rates of change in multiple verbal and nonverbal measures in a large elderly community sample. They did not employ LGC analysis. However, they observed "significant" cognitive declines (i.e., > 1 *SD*/10 years) twice as frequently with nonverbal measures as with verbal measures. Although the Berlin Aging Study has reported memory composite scores to decline between ages 70 and 100 in an LGC analysis, those curves were constructed from relatively small subgroups, stratified by decade, and followed for roughly six years (Singer et al., 2003). Other studies have shown that the age gradient associated with the inter-participant heterogeneity in cognitive intercepts is much steeper and more negative than that associated with intra-participant slopes observed longitudinally (Ferrer et al., 2004; Jacqmin-Gadda et al., 1997). Thus, the decline in memory reported by Singer et al., may reflect the contribution of intercept variance more than longitudinal change.

Selective declines in nonverbal skills has been described as a feature of normal aging [i.e., the so-called "right hemisphere" model of aging (RHMA)] (Elias, 1979). However, the RHMA was developed before the advent of neuroimaging. It is now appreciated that it would be very difficult to localize "nonverbal" cognitive performance to a single hemisphere. Nevertheless, this does not rule-out the possibility of selective age-related changes in one or more (right hemisphere dominant) distributed circuit(s) related to "nonverbal" skills. Moreover, visual inspection of Figure 1 suggests that age-related decline in nonverbal measures appears to match the decline in functional status. This too has been previously described. Artero et al. (2001) studied the three-year longitudinal associations between a comprehensive battery of psychometric measures and activities of daily living in 368 community-dwelling seniors. After adjusting for adjusted for age, education, gender, medical comorbidity, and premorbid IQ, visuospatial skills were significantly associated with each of seven IADLs, *and were the only significant correlates of five of those*. Similarly, the FHS data suggest that disability seems uniquely associated with a nonverbal dimension of cognition (Royall et al., 2003), whereas the rate of change in IADL is most strongly associated with the rates of change in nonverbal and executive measures. (Royall et al., 2005, in press).

It is possible that our findings are an artifact of self-reported IADL. Loss of insight and the capacity to give valid self-report can be associated with right hemisphere lesions (Jehkonen et al., 2000). However, the EXIT25 and CLOX, for example, are independent correlates of level of care in the AFV (Royall et al., 2000), while the EXIT25 has also been reported to be indicative of capacities as diverse as the ability to make an advance directive (Royall et al., 1997), to give informed consent for medical care (Dymek et al., 2001), medication adherence (Mann et al., 1999), and learning to correctly manage an inhaler (Allen et al., 2003). Thus, it seems unlikely that these associations are merely the result of invalid self-report.

Finally, we note that Ghisletta & Lindenberger (2004) have reported a similar divergence in the LGC slopes associated with vocabulary (improving) and digit-letter substitution (deteriorating) in a large community elderly sample. However, their interpretation of this finding as support for a two-component ("fluid" *vs.* "crystalline") model of cognitive aging would not be consistent with our data. We find instead that "fluid" measures tended to either improve or decline as a function of their verbal or nonverbal content, respectively.

In summary, age-related cognitive decline is a dynamic longitudinal process affecting multiple cognitive domains. Some measures may be ill-suited for measuring age-related changes in condition, either because they are insensitive to change or hindered by learning effects. Our data confirm that nonverbal measures appear to change in parallel with functional declines. This is consistent with earlier descriptions of the "right hemisphere's" selective vulnerability to age-related declines. These changes are consistent with a clinically significant cognitive decline affecting the major-

ity of older persons. The use of age-specific norms to define MCI and cognitive "impairment" generally, may blind us to an important cause of normative functional decline among the elderly.

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