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Dynamic change of cognitive reserve: associations with changes in brain, cognition, and diagnosis

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ABSTRACT

Cognitive reserve is inherently a dynamic construct; however, traditional methods of estimating reserve have focused on static proxy variables. A recently proposed psychometric approach entails modeling reserve as residual cognition not explained by demographic and brain variables. In this study, we extended this approach to longitudinal measurement and examined how change in reserve relates to clinical outcomes in late life and influences the effect of brain atrophy on cognitive decline. Results indicated that cognitive reserve changes were associated with progression of clinical diagnosis. More rapid depletion of cognitive reserve was associated with faster decline in nonmemory cognitive functions, even after accounting for longitudinal brain atrophy. The effect of longitudinal brain atrophy on cognitive decline differed based on the extent to which an individual's reserve changed. Whereas depletion of reserve appeared to unmask the effects of brain atrophy on cognitive decline, maintenance of reserve buffered against the negative effects of brain atrophy. Study results highlight that changes in reserve may have important implications for individual differences in cognitive aging trajectories.

1. Introduction

A core feature of aging is the heterogeneity of cognitive trajectories. Clinically normal older adults and symptomatic older adults with memory impairment both show considerable variability in their cognitive courses, rendering it challenging to identify a single cause or etiology of individual differences in trajectories (Knopman et al., 2015; Nettiksimmons et al., 2014). The notion that cognition is influenced by multiple determinants originates from several lines of research, including recent evidence that canonical measures of brain disease (e.g., total gray matter [GM] volume, white matter hyperintensities [WMHs], and hippocampal volume) account for less than 50% of variance in memory performance (Boyle et al., 2013; Reed et al., 2010). In turn,

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accumulating evidence indicates that 20%–40% of nondemented older adults meet neuropathological criteria for Alzheimer's disease (AD) upon death (O'Brien et al., 2009; Price et al., 2009), suggesting that the presence of AD-related brain pathology alone does not fully account for individual differences in cognitive decline. The concept of "cognitive reserve" has been used to explain this well-documented mismatch between pathology and cognitive performance and has stirred considerable interest in the dynamic interplay between measurable brain pathology and cognitive outcomes over time (Stern, 2009).

Cognitive reserve is theorized to be an active process of cognitive adaptation to pathology. Within this framework, people display differential cognitive vulnerability to brain disease at a given time point as a function of their ability to adapt to neurological insults (Stern et al., 2018). Although cognitive reserve is inherently a dynamic construct, traditional methods of inferring reserve have focused on static proxy variables that represent a retrospective summation of early-life experiences (e.g., years of education). Numerous conceptual and methodological concerns accompany this approach, including the correlation between demographic proxies and other confounding historical variables (e.g., socioeconomic status), the oversimplification of individual differences in brain disease susceptibility, and the inability of these proxies to change during late life (Jones et al., 2011; Satz et al., 2011; Zahodne et al., 2015). More recently, a psychometric approach to the measurement of reserve has been proposed, wherein cognitive reserve is operationalized as the difference between observed and expected cognitive function as predicted by brain and demographic variables (Reed et al., 2010). Utilizing this psychometric approach results in a residualized reserve index for each individual, with a higher residual reserve index indicating that the individual's cognitive performance is better than expected when accounting for brain pathology and demographic characteristics.

The residual index approach circumvents many prior methodological concerns, as it provides a more direct estimate of cognitive reserve while minimizing the inherent confounds of historical proxy variables. Perhaps most importantly, the residual index methodology allows for the longitudinal estimation of cognitive reserve. To understand individual variability in aging trajectories and person-specific susceptibility to brain pathology, longitudinal appraisal of cognitive reserve in both asymptomatic and clinical populations is critically needed; however, to our knowledge, application of the residual index approach beyond a cross-sectional framework has been reported by only one study (Zahodne et al., 2015). In the context of their 2-time point study design, Zahodne et al. reported that dynamic changes in reserve might be a better predictor of future clinical status in initially nondemented older adults than reserve measured at a single time point; however, it remains unclear whether longitudinal change in cognitive reserve across more than 2 time points moderates or influences the association between brain atrophy and rate of change in cognitive test scores (i.e., slopes).

To extend this important, foundational work, the present study examined dynamic cognitive reserve in a fully longitudinal design using a residual reserve index approach. The overarching goal of the study was to develop longitudinal models of dynamic cognitive reserve in a diverse clinical aging cohort to examine how changes in reserve (1) relate to changes in clinical diagnostic status; (2) relate to cognitive decline; and (3) interact with changing brain status to influence cognitive decline. To minimize circularity in the definition of our reserve index, measures used to build the cognitive reserve index did not overlap with measures used to define clinical status. To accomplish our aims, we developed a latent variable model predicated on the assumption that changes in reserve, as defined by a memory residual index, influence the relation between changing brain structure and cognitive decline in late life.

2. Materials and methods

2.1. Participants

Study participants were from the UC Davis Diversity Cohort, a longitudinal study that includes high numbers of Hispanic (e.g., Latina/o and other Spanish origin), African American, and non-Hispanic white older adults. This cohort is also heterogenous in educational attainment, and their clinical severity levels span a spectrum of cognitive function from normal to mildly demented at baseline assessment. Cohort composition and recruitment methods are described in Hinton et al. (2010). In brief, participants were identified through a community screening program designed to recruit individuals with cognitive functioning representative of the community-dwelling population in a 6-county catchment area in the central Sacramento/San Joaquin Valley and East San Francisco Bay Area of Northern California or are referred for research following a clinical evaluation at a university memory/dementia clinic.

Participants in this study were evaluated and followed within the research program of the UC Davis Alzheimer's Disease Center. A rolling enrollment design, initiated in 2002, was used to build and maintain the cohort. Inclusion criteria for the larger cohort included age 60 or older at their first examination and ability to speak English or Spanish. Exclusion criteria included unstable major medical illness, major primary psychiatric disorder, or substance abuse or dependence in the last 5 years. All participants signed informed consent, and all human subject involvement was overseen by institutional review boards at UC Davis, the Veterans Administration Northern California Health Care System, and San Joaquin General Hospital in Stockton, California.

The present study included 338 participants who had received at least 2 cognitive evaluations (median = 6, range = 2–14) and at least 2 magnetic resonance imaging (MRI) brain scans (median = 2, range = 2–6). There were 160 non-Hispanic whites, 85 Hispanics, 76 African Americans, and 17 individuals from other racial and ethnic groups; 41 Hispanics were tested in Spanish, and all others were tested in English. The majority of the sample (91 whites, 80 Hispanics, 69 African Americans, and 15 other) was recruited through the community screening program. The remaining 82 (68 whites, 5 Hispanics, 7 African Americans, and 2 other) were recruited from the clinic.

2.2. Clinical diagnosis

All participants received multidisciplinary diagnostic evaluations at baseline and at approximately annual intervals following the baseline evaluation. Baseline and follow-up evaluations followed the same protocol with a detailed medical history, physical and neurological examination, and clinical neuropsychological assessment. A physician fluent in Spanish examined subjects who spoke only Spanish. A family member or other informant was interviewed to obtain information about cognitive and independent functioning. Clinical neuropsychological tests were different from the cognitive measures used in analyses in this study to estimate reserve and longitudinal cognitive trajectories. Routine dementia work-up laboratory tests were obtained at the baseline evaluation and when clinically indicated at the time of follow-up evaluations.

Diagnosis of cognitive syndrome (Normal, mild cognitive impairment [MCI], Dementia) and, for individuals with dementia, underlying etiology, was made in a multidisciplinary consensus conference following standardized criteria and methods. Dementia was diagnosed using Diagnostic and Statistical Manual of Mental Disorders-III-R (Association, 1987) criteria for dementia modified

such that dementia could be diagnosed in the absence of memory impairment if there was significant impairment of 2 or more other cognitive domains. MCI was diagnosed according to standard clinical criteria and was further subtyped according to current Alzheimer's Disease Centers Uniform Data Set guidelines (Morris et al., 2006). Normal cognitive function was diagnosed if there was no clinically significant cognitive impairment. All diagnoses were made blind to the neuropsychological tests that were analyzed in this study.

Change of diagnosis from the first to last evaluation was the independent variable in one of our primary analyses. This change variable included the following mutually exclusive groups: normal to normal (Stable Normal, N = 126), normal progressing to MCI (Normal to MCI, N = 46), normal progressing to dementia (Normal to Dementia, N = 31), MCI to MCI (Stable MCI, N = 29), MCI progressing to dementia (MCI to Dementia, N = 76), and dementia to dementia (Dementia, N = 22).

2.3. Cognitive assessment

The cognitive outcomes in this study were measures of episodic memory, semantic memory, executive function, and spatial ability derived from the Spanish and English Neuropsychological Assessment Scales (SENAS). The SENAS has undergone extensive development as a battery of cognitive tests relevant to cognitive aging that allow for valid comparisons across racial, ethnic, and linguistic groups (Mungas et al., 2000, 2004, 2005a,b, 2011). See Supplementary Materials for additional details.

2.4. MRI measures

2.4.1. MRI volume measurements

Brain image acquisition was performed under a standard protocol at the UC Davis Imaging Research Center or at the Veterans Administration Northern California Health System Medical Center in Martinez, CA. MRI baseline measurements were derived using an in-house processing pipeline described previously (Fletcher et al., 2014; Lee et al., 2012). WMHs were computed by an in-house method combining native fluid-attenuated inversion recovery with structural MRI as described previously (DeCarli et al., 2005).

2.4.2. Gray matter volume change

We computed longitudinal structural change between the 2 most widely separated time points. We used a tensor-based morphometry method designed to enhance sensitivity and specificity for biological change by incorporating estimates of likely tissue boundaries (Fletcher, 2014; Fletcher et al., 2013). Tensor-based morphometry generates deformation fields by registering brain scans at differing time points and using these to estimate local volume changes between the scans (Ashburner and Friston, 2000). This processing was done via an in-house processing pipeline that has been previously described (Fletcher et al., 2016). GM volume was computed over a cortical GM region of interest (ROI) that averaged volume change over frontal, parietal, temporal (excluding hippocampus), and occipital lobar regions. These were the same ROIs used for measuring baseline cortical GM. Log-Jacobian from these ROIs from both hemispheres were averaged to constitute a global cortical GM change measure. Longitudinal change over these regions was computed as the mean log-Jacobian over the ROI intersected with the segmented GM. Cortical GM change defined in this manner had the strongest effect on cognitive decline in a previous study based on this cohort (Fletcher et al., 2018). Change in a hippocampus ROI was separately measured using these same methods.

2.5. Data analysis

2.5.1. Measures and data processing

SENAS measures of episodic memory, semantic memory, executive function, and spatial ability were the primary dependent variables. Independent variables included: MRI GM volume change (average of frontal, temporal, parietal, and occipital ROIs); hippocampal volume change (average of left and right); MRI baseline cortical GM, hippocampus, WMH, and intracranial volumes; and the demographic variables race/ethnicity, education, gender, and language of test administration. We applied a rank-based inverse normal transformation (Blom, 1958) to normalize the variables and establish a common standardized scale (M = 0, standard deviation [SD] = 1). Education was centered at 12 years. Gender, race/ethnicity, and language of test administration were categorical covariates coded using indicator variables. Race/ethnicity was coded using 3 indicator variables: African American (1 = yes, 0 = no), Hispanic (1 = yes, 0 = no), and other minority (1 = yes, 0 = no); non-Hispanic white was the reference group. Gender (male = 1, female = 0) and language of test administration (Spanish = 1, English = 0) were represented by single indicator variables. This coding establishes a white female, with 12 years of education, tested in English, as a reference.

Change of diagnosis from the first to last evaluation was the independent variable in one of our primary analyses. The 6 groups of interest were represented by 5 indicator variables. The Stable Normal group was the reference group. There were a small number of individuals who reverted from MCI to normal (N = 8) who were not included in this analysis.

2.5.2. Longitudinal modeling of cognitive trajectories

Mixed-effects, parallel process longitudinal analyses were performed using the Mplus, version 8.1, multilevel modeling platform (Muthén and Muthén, 1998). Fig. 1 shows a schematic of the basic modeling approach. Within each person's longitudinal observations, each of the 4 cognitive outcomes was regressed on time in years since the first MRI scan. The within-subjects part of the model included terms to account for practice effects and a practice effect by Spanish test administration interaction that has been identified in previous studies with this sample (Brewster et al., 2014; Early et al., 2013; Melrose et al., 2015). Random intercepts and slopes estimated in the within-subjects part of the model served as dependent variables in the between-subjects part of the model. All parameters in the model, including within and between components, were estimated simultaneously. The multilevel modeling

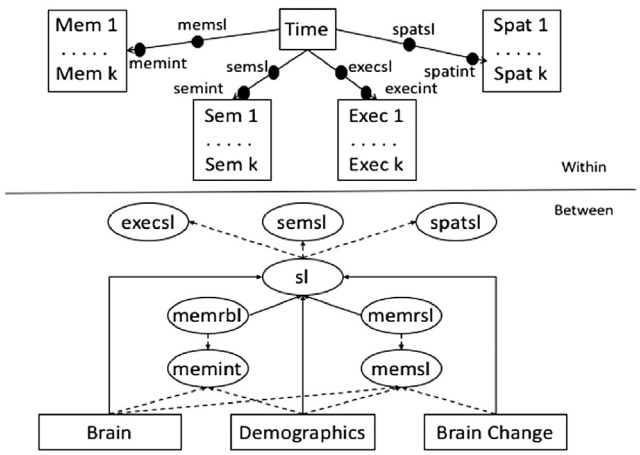

Fig. 1. Longitudinal reserve model.

platform allows for heterogeneity in the number of assessment time points and in the lags between assessments across persons.

Episodic memory intercept (memint) and slope (memsl) random effects were used to measure baseline cognitive reserve and longitudinal change in reserve. Baseline reserve (memrbl) was estimated as a latent variable that captured residual variance in memint that was not explained by demographic variables (race/ethnicity, education, gender, language) and baseline brain variables (cortical GM and hippocampus volumes, residualized in the model for intracranial volume, and WMH volume). Reserve change (memrsl) was a latent variable that captured residual variance in memsl that was not explained by demographic variables, baseline brain variables, and brain change variables (cortical GM and hippocampus volume change). Baseline reserve measured how each individual's observed memory intercept differed from what would be expected given that person's observed demographic and baseline brain characteristics. Reserve change measured how each individual's observed memory slope deviated from what would be expected given that person's observed demographic characteristics, baseline brain, and brain change measurements.

Our 3 primary analytic aims were (1) to examine how baseline reserve and reserve change differed across groups that were defined by clinical diagnosis at the first and last assessments, (2) to examine how baseline reserve and reserve change predicted change in nonmemory cognitive abilities, and specifically, the incremental effects of these reserve measures above and beyond effects of brain and demographic variables, and (3) to examine whether reserve measures interacted with and therefore modified effects of brain change variables on cognitive decline.

For aim 1, baseline reserve and reserve change were the primary dependent variables and diagnosis change indicator variables were the primary independent variables. The model depicted in Fig. 1 was modified by removing nonmemory cognitive variables from the within and between models and regressing baseline reserve and reserve change on diagnosis change indicator variables in the between part of the model. The Stable Normal group was the reference for group comparisons for both reserve variables. For aims 2 and 3, semantic memory (Semantic), executive function (Executive), and spatial ability (Spatial) slope random effects (semsl, execsl, and spatsl, respectively) were used as indicators for a second-order global cognitive slope factor. We used a model that had a global slope second-order factor but individual intercept random effects. Slopes were highly correlated, and this model provided optimal fit (see Supplementary Materials).

Aim 3 added interactions of baseline reserve and reserve change with brain variables. One model included all of the effects from the aim 2 model plus a Baseline Reserve by Cortical Gray Matter Change interaction effect, a second tested the Reserve Change interaction with Gray Matter Change, and 2 models tested the 2 reserve interactions with Hippocampus Change. Models for aims 1 and 2 simultaneously estimated all model parameters and effects. The aim 3 analyses involved interactions with latent variables. Although latent variable interactions are possible within Mplus, estimation is computationally intensive and we were not able to successfully estimate the latent variable interactions required for aim 3 within a single model estimation. We addressed this limitation by estimating a model in aim 2 that did not include interaction effects and saved the baseline reserve and reserve change factor scores from that analysis. These factor scores were entered as observed variables into analyses that included the brain by baseline reserve and brain by reserve change interactions. Because this approach problematically treats the reserve factor scores as observed variables without accounting for the error in their measurement (which could influence inferences by negatively biasing standard errors for effects involving the reserve factors), we further estimated the reliability of these reserve variables and their interactions with brain variables and modeled these empirical reliabilities in the models that included interaction effects. To estimate reliabilities, we used bootstrap resampling to estimate the reliability of the reserve factor scores and products of these factor scores with brain variables across 500 bootstrap samples. Each bootstrap draw could include duplicated records from the same participant, fewer records for a given participant than in the original data set, or no records for an individual. Cases that had only one unique record for a given participant were dropped from the draw. Reliability was estimated by calculating the intraclass correlation (ICC) of the relevant scores across the 500 bootstrap samples using the R ICC module (ICCest with THD confidence intervals). We then fixed error variances in the models with interaction effects to the estimated amount of error variance in these measures.

Table 1
Sample characteristics

	Demented	MCI	Normal	Total
Gender—Female	11 (50.0%)	60 (53.1%)	133 (65.5%)	204 (60.4%)
Gender—Male	11 (50.0%)	53 (46.9%)	70 (34.5%)	134 (39.6%)
Age_BL, Mean (SD)	78.5 (±7.7)	75.2 (±7.3)	74.2 (±7.0)	74.8 (±7.2)
Education, Mean (SD)	11.9 (±5.2)	14.5 (±3.9)	13.0 (±4.6)	13.4 (±4.4)
Recruitment source—Clinic	9 (40.9%)	45 (39.8%)	28 (13.8%)	82 (24.3%)
Recruitment source—Community	13 (59.1%)	68 (60.2%)	174 (85.7%)	255 (75.4%)
Recruitment source—Missing	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.3%)
Race/ethnicity—African American (N = 76)	3 (13.6%)	23 (20.4%)	50 (24.6%)	76 (22.5%)
Race/ethnicity—Hispanic (N = 85)	6 (27.3%)	10 (8.8%)	69 (34.0%)	85 (25.1%)
Race/ethnicity—Other (N = 17)	0 (0.0%)	5 (4.4%)	12 (5.9%)	17 (5.0%)
Race/ethnicity—White (N = 160)	13 (59.1%)	75 (66.4%)	72 (35.5%)	160 (47.3%)
Follow-up time (years), Mean (SD)	4.8 (±2.4)	5.5 (±3.1)	8.2 (±3.6)	7.1 (±3.6)
N Cognitive Assessments, Mean (SD)	4.8 (±2.3)	5.6 (±2.6)	7.6 (±3.0)	6.7 (±3.0)
N MRI, Mean (SD)	2.1 (±0.3)	2.4 (±0.7)	2.7 (±0.8)	2.5 (±0.8)
Global GM change (standardized), Mean (SD)	−0.0 (±0.0)	−0.0 (±0.0)	−0.0 (±0.0)	−0.0 (±0.0)
Global GM baseline (standardized), Mean (SD)	−0.1 (±1.0)	0.1 (±1.2)	−0.1 (±0.9)	−0.0 (±1.0)
Hippocampus change (standardized), Mean (SD)	−0.7 (±1.2)	−0.3 (±1.0)	0.3 (±0.9)	−0.0 (±1.0)
Hippocampus baseline (standardized), Mean (SD)	−0.8 (±0.8)	−0.1 (±1.0)	0.5 (±0.9)	0.2 (±1.0)
White matter hyperintensity baseline (standardized), Mean (SD)	0.2 (±0.7)	0.1 (±0.9)	−0.4 (±1.0)	−0.2 (±1.0)
Semantic memory BL, Mean (SD)	−0.5 (±0.9)	0.1 (±0.7)	0.1 (±0.9)	0.1 (±0.8)
Executive function BL, Mean (SD)	−0.5 (±0.8)	0.0 (±0.7)	0.4 (±0.8)	0.2 (±0.8)
Spatial BL, Mean (SD)	−0.4 (±1.1)	0.1 (±0.9)	0.2 (±1.0)	0.1 (±1.0)

Key: GM, gray matter; SD, standard deviation; MRI, magnetic resonance imaging; BL, baseline.

Table 2
Diagnosis change effects on residual reserve index

Reserve_type	Diagnosis_change	Estimate	SE	*p*
Baseline	Stable Normal (reference)	0.696	0.082	0.000
Baseline	Normal to MCI	−0.098	0.086	0.252
Baseline	Normal to Dementia	−0.356	0.125	0.004
Baseline	Stable MCI	−0.768	0.102	0.000
Baseline	MCI to Dementia	−0.915	0.099	0.000
Baseline	Dementia	−1.067	0.147	0.000
Change	Stable Normal (reference)	−0.053	0.012	0.000
Change	Normal to MCI	−0.066	0.013	0.000
Change	Normal to Dementia	−0.172	0.017	0.000
Change	Stable MCI	−0.015	0.021	0.472
Change	MCI to Dementia	−0.109	0.018	0.000
Change	Dementia	−0.096	0.026	0.000

The estimate represents the mean for the reference group; estimates for non-reference groups represent average differences from the reference group.
Key: MCI, mild cognitive impairment; Stable Normal, normal at first and last assessments (N = 126); Normal to MCI, normal at first assessment, MCI at last (N = 46); Normal to Dementia, normal at first assessment, dementia at last (N = 31); MCI to MCI, MCI at first and last assessments (N = 29); MCI to Dementia, MCI at first assessment, Dementia at last (N = 76); Dementia, Dementia at first and last assessments (N = 22).

2.6. Data availability

The raw data that support the findings of this study are available from the corresponding author upon request subject to establishing a data use agreement.

3. Results

3.1. Sample characteristics

Sample characteristics are presented in Table 1. Results are stratified by baseline clinical diagnosis to clarify the range of clinical expression of cognitive impairment covered in this study. Sixty percent of the sample was normal, 33% had a baseline diagnosis of MCI, and 7% were diagnosed with dementia. About 60% were females. Sex differed across diagnosis groups ($\chi^2[2] = 5.734$, $p = 0.057$); normals and dementia cases were more likely to be female, but MCI cases were evenly divided among males and females. About 22% were African Americans, 25% were Hispanics, 47% were non-Hispanic whites, and 5% were other races or ethnicities. Race/ethnicity differed by diagnosis ($\chi^2[6] = 36.532$, $p = 0.001$) with whites more likely to have a diagnosis of MCI. Approximately two-thirds of the sample were recruited from the community (76%). Recruitment source differed by diagnosis ($\chi^2[2] = 30.040$, $p = 0.001$), with MCI cases more likely to be clinic referrals. Average age was about 75 years, and this differed across groups ($F[2,335] = 3.902$, $p = 0.021$) with Dementia older than MCI who were older than Normal. Average education was 13.4 and differed across diagnosis groups ($F[2,335] = 5.968$, $p = 0.003$), with highest education in MCI and lowest in dementia. GM volume change, baseline GM volume, and baseline cognitive test scores all differed across diagnostic groups (p's < 0.001), with a consistent pattern of normal > MCI > dementia.

3.2. Reserve trajectories by diagnosis change

We first examined how the baseline reserve index and reserve change were related to change in diagnosis over the follow-up period. The average amount of follow-up time differed across the diagnosis change groups ($F[5,324] = 12.213$, $p = 0.001$; mean Stable Normal = 8.3 [SD = 3.6] years, Normal to MCI = 8.4 [3.8], Normal to Dementia = 7.7 [3], Stable MCI = 5.4 [3.1], MCI to Dementia = 5.4 [3], Dementia = 4.8 [3.6]). Length of follow-up was longer for those who started as Normal and was shortest for those who were demented at the baseline assessment.

Table 2 presents estimated diagnosis change group effects on Baseline Reserve and Reserve Change. Estimates in Table 2 are average values for the Stable Normal group and are average differences from Stable Normal for the other groups. As would be expected, Stable Normal had the highest Baseline Reserve and the Dementia group the lowest, with progressive gradations across the other Normal and MCI groups. Average Reserve Index Change was significantly negative in the Stable Normal group (−0.053 SD per year). Rate of decline in reserve in the Stable MCI group did not differ from that of Stable Normal, but all other groups showed more rapid decline. Clear group differences in average Baseline Reserve could be observed, as well as substantial group differences in rate of Reserve Change (see Fig. 2). It is noteworthy that the Normal to Dementia group had the fastest rate of decline (−0.225 SD per year). By contrast, Reserve Change in the MCI to Dementia and Stable Dementia groups were similar, (−0.162 and −0.149 SD per year, respectively), whereas Reserve Change in the Normal to MCI group was less dramatic (−0.119 SD per year) but still differed significantly from that of Stable Normal.

3.3. Incremental effects on nonmemory cognitive trajectories of reserve, demographic, and brain variables

To address aim 2, we estimated Baseline Reserve and Reserve Change using the latent variable model depicted in Fig. 1 and evaluated how these reserve indices, baseline brain variables,

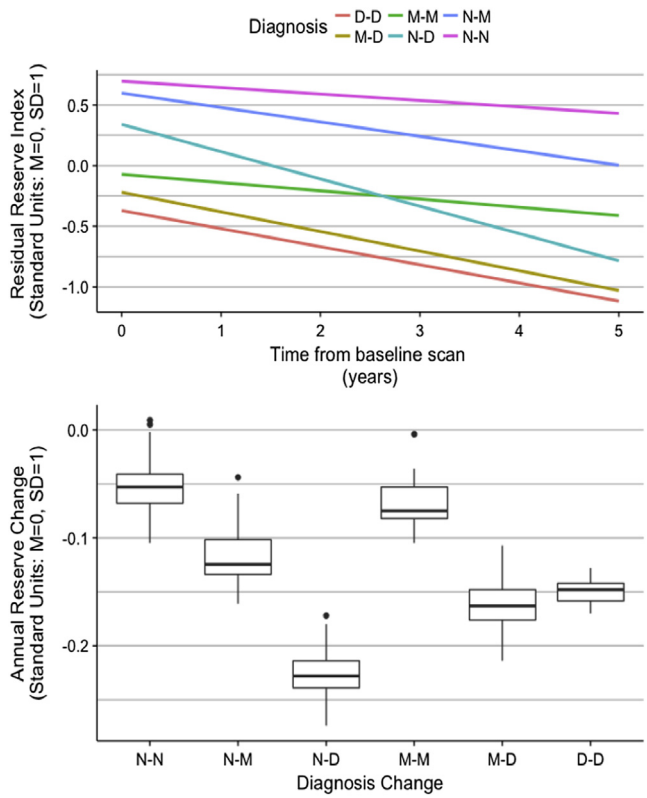

Fig. 2. Residual reserve index by diagnosis change. The upper panel shows average trajectories over time of reserve across groups defined by first and last clinical diagnosis. The lower panel shows distributions of reserve change by diagnosis change groups. Abbreviations: MCI, mild cognitive impairment; D-D, dementia at first and last assessments; M-D, MCI at first assessment, dementia at last; M-M, MCI at first and last assessments; N-N, normal at first and last assessments; N-M, normal at first and MCI at last; N-D, normal at first and dementia at last.

brain change variables, and demographic variables influenced cognitive decline. Results showing independent effects of the various classes of variables on global cognitive slope are presented in Table 3.

The average cognitive decline of a reference case (female, non-Hispanic white, 12 years of education, English speaking, average brain and brain change values in the sample) was −0.108 SD per year. African Americans (average decline rate = −0.037 SD/year) and Hispanics (−0.059 SD/year) declined at significantly slower rates on average. Of the brain variables, cortical GM change had the largest effect on cognitive decline (0.047 SD/year per SD of GM change), followed by baseline hippocampal volume (0.022 SD/Year/SD) and hippocampal change (0.017 SD/Year/SD). Reserve change was related to cognitive decline independent of all other predictors in the model (0.052 SD/Year/SD) and had an independent effect that was about equal to that of cortical GM change. Baseline reserve was not independently related to cognitive change ($p = 0.363$).

3.4. Interaction of reserve and brain change

Aim 3 examined whether the reserve indices modified the effects of brain change on cognitive decline. In terms of estimated reliabilities of the reserve indices and their cross-products with brain change variables, Baseline Reserve was more reliable (ICC = 0.845, 95% CI = 0.825–0.865) than Reserve Change (ICC = 0.727; 95% CI = 0.697–0.757), and the reliabilities of the cross-products were generally about the same as that of the involved reserve variables (Baseline Reserve by Cortical Gray Matter Change: ICC = 0.865; 95% CI = 0.847 to 0.882; Reserve Change by Cortical Gray Matter Change: ICC = 0.722; 95% CI = 0.692 to 0.752; Baseline Reserve by Hippocampus Change: ICC = 0.831; 95% CI = 0.801 to 0.861; Reserve Change by Hippocampus Change: ICC = 0.725; 95% CI = 0.682–0.767). Table 4 summarizes results from the 4 analyses that tested reserve by brain change interactions. Significant interaction effects were observed for Baseline Reserve by Gray Matter Change (estimate = −0.021, standard error (SE) = 0.005, $p = 0.001$), Reserve Change by Gray Matter Change (estimate = −0.015, SE = 0.006, $p = 0.008$), Reserve Change by Hippocampus Change (estimate = −0.013, SE = 0.004, $p = 0.004$), and Baseline Reserve by Hippocampus Change (estimate = −0.014, SE = 0.005, $p = 0.007$). These results can be interpreted to mean that the brain change effect is smaller in individuals with higher reserve indices. For example, the cortical GM change effect is 0.032 SD/year/SD GM change in those with Reserve Change 1 SD above average, 0.047 SD/year/SD in those with average Reserve Change, and 0.062 SD/year/SD in those with Reserve Change 1 SD below average.

The Reserve Change by Cortical Gray Matter Change interaction effect is presented graphically in Figs. 3 and 4. Fig. 3 shows annualized rate of nonmemory change on the y-axis and shows how this relates to Gray Matter Change rate (x-axis) for 2 levels of Reserve Change. Rate of cognitive decline was more strongly related to Gray Matter Change in those with more rapidly declining reserve (Reserve Change of −1 SD). Rate of cognitive decline was near 0 when there was little GM atrophy regardless of the Reserve Change level. In contrast, if an individual displayed rapidly declining reserve in the context of faster GM atrophy over time, then their annual rate of cognitive decline doubled (compared with those whose reserve decline less rapidly than average). Fig. 4 presents these results in terms of predicted cognitive trajectories for one outcome (semantic memory). The effect of Gray Matter Change on cognitive trajectories is stronger among participants with more rapidly declining reserve, but reserve that is declining less rapidly than average protects against the effects of declining GM.

Table 3
Brain, demographic, and reserve effects on global cognitive slope

Independent variable	Estimate	SE	*p*
Intercept (reference)	−0.108	0.011	0.000
Male	−0.013	0.009	0.129
Spanish	−0.009	0.013	0.487
Education (centered at 12 y)	0.001	0.001	0.379
African American	0.071	0.011	0.000
Hispanic	0.049	0.012	0.000
Other nonwhite Race/Ethnicity	0.024	0.019	0.209
Cortical gray (baseline)	−0.001	0.005	0.792
Hippocampus (baseline)	0.022	0.005	0.000
White matter hyperintensity (baseline)	−0.006	0.004	0.147
Cortical gray matter (change)	0.047	0.009	0.000
Hippocampus (change)	0.017	0.006	0.004
Residual reserve index (baseline)	0.003	0.004	0.363
Residual reserve index (change)	0.052	0.006	0.000

The intercept estimate represents the mean for the reference individual for group indicator variables and average values for continuous variables. Estimates for non-reference group indicator variables represent average difference from the reference value for that variable. Estimates for continuous values indicate the effect of a 1 SD difference in that variable.

4. Discussion

In a diverse cohort of aging adults with clinical severity levels ranging from normal to mildly demented, we developed longitudinal, latent variable models of cognitive reserve to examine how changes in reserve influence the effect of brain atrophy on cognitive decline. We measured the effects of reserve as residual memory performance not explained by brain and demographic variables. Results showed that this measure of cognitive reserve changed in tandem with progression of clinical diagnosis, with more rapid depletion of reserve observed in those who transitioned to a more impaired clinical state. Depletion of our indicator of cognitive reserve was related to faster decline in nonmemory cognitive domains, even after accounting for longitudinal brain atrophy. Finally, in a stringent test of the construct validity of the residual-defined dynamic measure of cognitive reserve, we found that maintaining reserve buffered the negative effect of brain atrophy on cognitive decline. Results from the study underscore the dynamic nature of

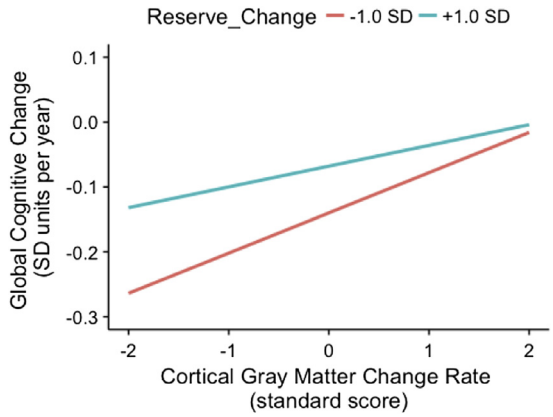

Fig. 3. Reserve Change by Cortical Gray Matter Change interaction effect on global cognitive slope. The graph shows the association between annual change in nonmemory cognitive function and annual change in cortical gray matter volume as a function of reserve status. Reserve status was based on model predicted trajectories that were faster than average (−1 SD, shown in red; rapidly declining reserve status over time) or slower than average (+1 SD, shown in teal; slowly declining reserve status over time). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 4
Reserve by cortical gray matter (GM) and hippocampus (HC) interaction effects (standard errors in parentheses)

Model	Reserve baseline	Reserve change	Brain change	Reserve by brain change
Reserve Baseline by GM Change	0.005 (0.004)	0.034 (0.004)[b]	0.048 (0.007)[b]	−0.021 (0.005)[b]
Reserve Change by GM Change	−0.001 (0.004)	0.036 (0.004)[b]	0.047 (0.007)[b]	−0.015 (0.006)[a]
Reserve Baseline by HC Change	0.002 (0.004)	0.036 (0.004)[b]	0.019 (0.005)[b]	−0.014 (0.005)[a]
Reserve Change by HC Change	−0.001 (0.004)	0.037 (0.004)[b]	0.020 (0.005)[b]	−0.013 (0.004)[a]

Separate models were used to test each of the 4 interactions. Main effects show average rate of global cognitive change for reference individuals with average values on other variables in the model. The interaction effects show how reserve variables modify the effects of brain change variables. ([a]$p < 0.01$, [b]$p < 0.001$).

reserve in late life and highlight that changes in reserve may have meaningful clinical implications for individual aging trajectories.

A primary aim of the study was to model changes in cognitive reserve and determine how these changes relate to longitudinal changes in clinical status (i.e., normal, MCI, dementia) adjudicated independently of the memory measure used to compute reserve. We extended cross-sectional (Hohman et al., 2016; Reed et al., 2010; Zahodne et al., 2013) and 2-time point (Zahodne et al., 2015) residual approaches through our use of an extended, longitudinal framework, and we used latent variable modeling to appraise change in cognitive reserve over an average of 7 assessments. In our study, all diagnosis groups experienced, on average, a decrement in this measure of reserve over time, although significant differences in rates of change in cognitive reserve were noted across most clinical status groups relative to individuals who remained in the Stable Normal category. Although change in reserve in the Stable MCI group did not significantly differ from that of the Stable Normal group, more robust declines in reserve were associated with worsening diagnostic classification over time (particularly Normal to Dementia status) and were also evident in individuals who entered the study with, and maintained, a dementia diagnosis.

The idea that cognitive reserve may be depleted over time is not a new concept and has been proffered as an explanation for the widely reported finding that older adults with higher reserve show a more precipitous decline in functioning after they cross a dementia severity threshold (Scarmeas et al., 2006; Stern et al., 1999) and/or as brain degeneration progresses (Mungas et al., 2018). These studies have utilized historical variables (e.g., education) as proxies for cognitive reserve, rendering it difficult to quantify the degree to which cognitive reserve changes over time and to measure how this change maps onto evolving clinical presentation. Change in cognitive reserve over time and its relation to clinical diagnostic status has previously been characterized by only one study (Zahodne et al., 2015), which reported that in nondemented, community-dwelling adults, change in reserve was a better predictor of a future dementia diagnosis than cognitive reserve measured at a single time point.

Our study further examined the association between dynamic cognitive reserve and longitudinal cognitive change and demonstrated that more rapid decline in our measure of reserve was associated with faster decline in nonmemory cognitive domains (i.e., global cognitive slopes, excluding memory function). These results were consistent with our hypotheses and intuitive in many respects. Our dynamic measure of reserve was defined by longitudinal memory performance, and it is reasonable to expect that declines in memory would be associated with nonmemory cognitive decline. Indeed, previous studies with this cohort have shown that rates of decline of the cognitive domains measured in this study are highly correlated (Fletcher et al., 2018; Mungas et al., 2018). However, widespread volumetric brain changes are often presumed to be the underlying cause of diffuse cognitive decline. Results from this study, however, indicated that declines in our measure of reserve (which, by definition, is memory performance not explained by brain atrophy) were associated with faster rates of global cognitive decline, independent of both baseline and longitudinal brain atrophy (i.e., cortical GM; hippocampal GM) and WMHs. To rephrase, dynamic change in our indicator of reserve was an independent predictor of cognitive decline, even after accounting for canonical measures of brain health. This is an important point regarding correlations between memory and other cognitive domains; if correlations between cognitive domains are *strictly* due to shared, underlying brain morphology, then we would not expect this outcome. Instead, our findings highlight a critical and independent role for reserve in global cognitive trajectories.

A primary tenet of the cognitive reserve construct is that it moderates the impact of brain insults on clinical presentation. Thus, a critical appraisal of the reserve change index is to assess how it influences the effect of brain change on cognitive decline. Consistent with our hypotheses, the present study demonstrated that maintenance of reserve reduces the impact of brain atrophy (both global cortical atrophy and hippocampal atrophy) on nonmemory cognitive decline. The effects sizes were notably strong, such that for a decline in reserve that was 1 SD faster than the average (i.e., depleting reserve), the effect of a 1 SD loss of hippocampal volume on nonmemory cognitive decline increased by 65% (from 0.020 to 0.033 SD/year). By contrast, if residual reserve change was 1 SD above average (i.e., maintaining reserve), the effect of longitudinal hippocampal atrophy on nonmemory cognitive decline was minimized (0.007 SD/year). Similar moderating effects of the residual reserve index were noted for the association between cortical GM change and nonmemory cognitive decline. Overall, these findings suggest that the effect of longitudinal brain atrophy on cognitive decline is markedly different based on the extent to which an individual's residual-defined measure of reserve changes. Thus, whereas depletion of reserve may reveal the effects of brain atrophy on cognitive decline, maintenance of reserve may exert a buffer

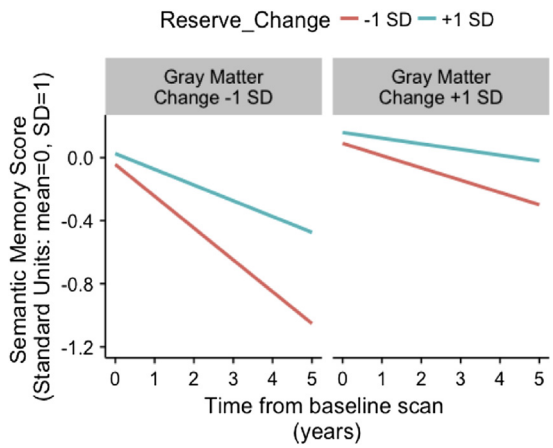

Fig. 4. Expected 5-y longitudinal cognitive trajectory of semantic memory for specific reserve change levels (−1 and +1 SD) and specific cortical gray matter atrophy rates (−1 and +1 SD).

against the effects of brain atrophy on cognitive decline. Our results also indicate that change in an individual's residual-defined measure of reserve is a much stronger predictor of cognitive change than is baseline cognitive reserve, which did not exert a meaningful effect on nonmemory cognitive slope independent of reserve change. This finding suggests that establishing a high level of cognitive reserve in and of itself may not confer protection against cognitive decline if that level of cognitive reserve cannot be maintained over time.

Our study design and hypotheses were rooted in the idea that heterogeneity in cognitive trajectories may be driven—in part—by individual differences in the ability to cognitively adapt to or stave off impending brain disease (Stern, 2009). The measurement of cognitive reserve has presented many methodological challenges and has raised questions regarding the utility of this construct in aging and AD research. Consistent with the consensus definitions and guidelines provided by the recent whitepaper on cognitive reserve (Stern, 2018), one of the advantages of the residual reserve approach is that it provides an objective estimate of reserve that is not reliant on retrospective proxy variables. Although our approach cannot be considered a *direct* measure of reserve, through the parameterization of residual variance in memory performance, we were nonetheless able to operationalize reserve and dynamically track its changes over time, which is critical for understanding how this construct relates to symptom onset and salient clinical features of AD and dementia more broadly.

Although our results suggest that applying a psychometric approach to the longitudinal measurement of cognitive reserve is not only feasible but also clinically meaningful, there are theoretical implications of this approach that warrant further consideration. A residual represents the variance in the outcome measure (in this case, memory performance) that is not explained by the predictors (in this case, demographics, baseline brain volumes and WMHs, longitudinal brain volumes). As such, within the residual reserve framework, cognitive reserve can be viewed as an index of what we do not know and what we may not currently be able to measure. This is also reflected in the broader literature, as cognitive reserve is frequently used to encapsulate the mismatch between pathology and measured cognition; however, it is more directly parameterized in the residual reserve index approach. With methodological advancements in the in vivo measurement of brain pathology, improved accuracy in the diagnosis of complex syndromes, and increased knowledge of functional brain mechanisms (e.g., neuroplasticity) that underlie cognitive reserve, the residual memory variance should become smaller. Taking this one step further, a long-term implication of this work is that residual memory variance should ultimately lose some of its utility as we gain empirical knowledge of the mechanisms of cognitive decline. This is not to undermine the importance of the construct, however, as delineating the mechanisms for cognitive reserve is pivotal to our understanding of how the brain compensates for or adapts to disease-related changes.

In terms of study limitations, the residual reserve index ultimately summarizes the effects of unknown variables that influence memory function, as noted previously. Although our latent variable modeling approach minimizes the influence of measurement error, the residual memory index may still capture error and unknown variables that do not truly reflect cognitive reserve (Reed et al., 2010). Our incorporation of measures of central nervous system integrity was also limited by (1) what was available in the study and (2) what is currently measurable in the field. Although we included common neuroimaging variables of brain structure into our models, measures of disease-specific pathology (e.g., amyloid, phosphorylated tau) were not available. Moreover, proteinopathies, vascular changes, and synaptic changes that are not measurable in vivo at this time may underlie the observed heterogeneity in memory performance; these unmeasured pathological factors are likely subsumed under the residual reserve component in this study, which remains an important conceptual issue to consider when interpreting the meaning of residual-defined reserve outcomes. An additional limitation of the study is that our residual-defined dynamic measure of cognitive reserve does not address underlying mechanisms of reserve. As noted previously, direct measures of reserve—and by extension, mechanisms of reserve—have historically been challenging to implement. Functional imaging methods have been proposed as a possible means of assessing cognitive reserve directly, although these approaches are still tied to specific methodologies, as noted in the recent whitepaper (Stern, 2018). Although the delineation of processes that explain why some individuals are able to adapt to pathology is critically important, these mechanisms are outside the scope of our study. Finally, given considerations related to sample size and number of MRI measurements, we were limited in our ability to appraise nonlinear trends in reserve trajectories; as such, our latent variable models assumed a linear change in both the residual reserve index and the cognitive outcomes, in the presence of modeled practice effects.

Of note, we elected to focus on episodic memory as the primary indicator of reserve. The decision to use episodic memory to define our reserve index was based on several factors, including prior literature on cognitive reserve (Reed et al., 2010; Stern et al., 1999; Zahodne et al., 2013, 2015), as well as its sensitivity to aging and AD (Bondi et al., 2014; Busse et al., 2006; Driscoll et al., 2003; Ewers et al., 2010). Prior studies suggest that the operationalization of reserve may be applied to nonmemory domains, with comparable findings (Reed et al., 2010, 2011). Nonetheless, an imperative for future research will be to further refine the generalizability and practicality of the measurement of reserve. Whether based on memory or nonmemory domains, the residual reserve index score is dependent on the characteristics of the study participant sample and the measures that are available, which limits its current applicability to clinical settings. For any given person, the same cognitive test and MRI results may yield a different residual index score in a different sample used to derive the regression model and if different methods are used to measure cognition and brain status. Consequently, there is a need for standardization of measures used to define reserve and for calibration of the measurement model for reserve in a suitably diverse sample that represents the diverse target population of older adults. Future work of this nature will be critical for establishing practical and clinically useful, dynamic measurement of cognitive reserve.

The present study has multiple strengths, including the use of latent variable modeling to measure residual reserve in a longitudinal design. By leveraging a residual reserve approach, we were able to operationally define, measure, and track changes in reserve over time. The application of the residual reserve approach to a longitudinal framework further allowed us to capitalize on multiple time points and thereby more precisely estimate cognitive slopes. Importantly, a long-term implication of this residual reserve approach is that we may ultimately be able to use this method to identify and better understand mechanisms for cognitive reserve in late life. An additional strength of the study was the minimization of circularity in our design. The measures used to define reserve (i.e., SENAS memory, MRI measures of central nervous system integrity) were not used to define clinical status or nonmemory cognitive change. Diagnostic status (i.e., normal aging, MCI, dementia) was based on a separate neuropsychological evaluation, with no overlapping cognitive measures. Moreover, in the context of correlated cognitive domains, circularity was further minimized by appraising the moderating effects of reserve on the relationship between brain atrophy and cognitive decline; given that reserve

was defined as residual memory performance *not explained* by brain atrophy and demographics, its modifying effects on the association between longitudinal brain changes and nonmemory decline are all the more striking. Finally, our sample was composed of ethnically diverse participants and included individuals with a range of cognitive impairment levels at baseline, both of which are critical to the generalization and applicability of study finding to a wider aging population.

In summary, our study suggests that cognitive reserve changes dynamically over time, is associated with change in clinical diagnostic status, and has modifying effects on the association between brain atrophy and cognitive decline. Importantly, the effects of GM atrophy on cognitive trajectories were unmasked by rapidly declining reserve, whereas maintenance of high reserve over time—or less rapidly declining reserve—exerted a protective buffer against the effects of changing brain status on cognitive decline. Our findings underscore the mutable nature of cognitive reserve and suggest that dynamic changes in reserve may have meaningful implications for the progression of clinical diagnostic status and individual cognitive trajectories.

Disclosure

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2019.08.016.

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