

Comparison of Education and Episodic Memory as Modifiers of Brain Atrophy Effects on Cognitive Decline: Implications for Measuring Cognitive Reserve

Dan Mungas^{1,*} , Evan Fletcher², Brandon E. Gavett³ , Keith Widaman⁴, Laura B. Zahodne⁵ , Timothy J. Hohman⁶, Elizabeth Rose Mayeda⁷, N. Maritza Dowling⁸, David K. Johnson⁹ and Sarah Tomaszewski Farias¹

¹Department of Neurology, University of California, Davis, 4860 Y Street, Sacramento, CA 95817, USA

²Department of Neurology, University of California, Davis, 1544 Newton Court, Davis, CA 95616, USA

³Department of Psychology, University of Western Australia, School of Psychological Science (M304), 35 Stirling Hwy, Perth, WA 6009, Australia

⁴Graduate School of Education, University of California, Riverside, 1207 Sproul Hall, 900 University Avenue, Riverside, CA 92521, USA

⁵Department of Psychology, University of Michigan, 530 Church Street, Ann Arbor, MI 48109, Australia

⁶Department of Neurology, Vanderbilt University, Vanderbilt Memory & Alzheimer's Center, 1207 17th Ave South, Suite 204F, Nashville, TN 37212, USA

⁷Department of Epidemiology, University of California, Los Angeles, UCLA Pub Hlth - Epidemiology, BOX 951772, 46-070B CHS, Los Angeles, CA 90095, USA

⁸Department of Acute & Chronic Care, The George Washington School of Nursing, 1919 Pennsylvania Street NW, Suite 500, Washington, DC 20006, USA

⁹ Department of Neurology, University of California, Davis, 100 N. Wiget Lane, Suite 150, Walnut Creek, CA 94598, USA

(RECEIVED April 2, 2020; FINAL REVISION September 4, 2020; ACCEPTED September 28, 2020; FIRST PUBLISHED ONLINE January 18, 2021)

Abstract

Objective: This study compared the level of education and tests from multiple cognitive domains as proxies for cognitive reserve. **Method:** The participants were educationally, ethnically, and cognitively diverse older adults enrolled in a longitudinal aging study. We examined independent and interactive effects of education, baseline cognitive scores, and MRI measures of cortical gray matter change on longitudinal cognitive change. **Results:** Baseline episodic memory was related to cognitive decline independent of brain and demographic variables and moderated (weakened) the impact of gray matter change. Education moderated (strengthened) the gray matter change effect. Non-memory cognitive measures did not incrementally explain cognitive decline or moderate gray matter change effects. **Conclusions:** Episodic memory showed strong construct validity as a measure of cognitive reserve. Education effects on cognitive decline were dependent upon the rate of atrophy, indicating education effectively measures cognitive reserve only when atrophy rate is low. Results indicate that episodic memory has clinical utility as a predictor of future cognitive decline and better represents the neural basis of cognitive reserve than other cognitive abilities or static proxies like education.

Keywords: Aging, cognitive change, Education, Cognitive reserve, MRI, Gray matter change, Cognitive decline, Brain atrophy

INTRODUCTION

Cognitive decline and dementia are major public health problems in older adults, but there is considerable heterogeneity of cognitive health outcomes in this population. Understanding why some lose cognitive function and become demented while others remain cognitively intact is critically important for promoting late life cognitive health. Cognitive reserve is a hypothetical construct used to explain why some individuals are able to maintain normal cognitive function in the face of late life brain changes (Jones et al., 2011; Stern, 2002, 2009).

It has relevance for both understanding late life cognitive decline and estimating risk for accelerated decline and dementia. A developing body of literature has contributed substantial advances in conceptualizing cognitive reserve, but measurement of cognitive reserve has not been well developed and this limits both scientific study and practical application (Jones et al., 2011; Stern et al., 2018).

Proxy variables are often used to operationalize cognitive reserve, and level of education has been the most commonly studied proxy variable. Studies of construct validity of education as a proxy for cognitive reserve have produced mixed results. Supporting evidence comes from studies showing that higher educational attainment is associated with delayed onset of clinical diagnosis of dementia, but faster rate of

*Correspondence and reprint requests to: Dan Mungas, Department of Neurology, UC Davis Medical Center, 4860 Y Street, Suite 3900, Sacramento, CA 95817, USA. E-mail: dmmungas@ucdavis.edu

cognitive decline after diagnosis (Amieva et al., 2014; Scarmeas et al., 2006; Stern, Albert, Tang, & Tsai, 1999; Ye et al., 2013). In contrast, studies that report no association between education and rate of cognitive change do not support the education as cognitive reserve hypothesis (Early et al., 2013; Gross et al., 2015; Masel & Peek, 2009; Mungas, Early, Glymour, Zeki Al Hazzouri, & Haan, 2018). A recent study from our group that used brain atrophy rate as a direct measure of the brain changes underlying cognitive decline and dementia helps to bridge these seemingly disparate patterns of results (Mungas, Gavett, et al., 2018). More education was associated with slower cognitive decline in those who had relatively low rates of brain atrophy, but faster cognitive decline in individuals with more rapid brain atrophy. Thus, education was protective against early cognitive decline but amplified cognitive decline in those with more advanced brain disease.

An alternate approach operationalizes cognitive reserve as a latent variable that captures the statistical residual in cognitive test performance that is not explained by measures of brain pathology and demographic variables that influence cognition in the absence of brain pathology (Reed et al., 2010, 2011; Zahodne et al., 2013). A related approach also uses regression models in which cognitive and clinical outcomes are regressed on purported reserve indicators, brain variables, and reserve indicator by brain interactions. Construct validity of the reserve indicator is supported if it is related to the outcome independent of brain effects and more strongly, if it modifies the brain effects on the outcome (Stern et al., 2018). Both approaches evaluate how a reserve indicator relates to an outcome independent of brain pathology and moderates the brain effect, but the latent variable approach explicitly models reserve as a latent variable whereas the regression approach infers reserve from the independent effects of the reserve indicator.

The Reed (2010) and Zahodne (2013) studies used latent variable modeling to capture variance in episodic memory that was not explained by demographic and brain variables and then examined the construct validity of this latent variable as an indicator of reserve. Non-episodic memory domains and episodic memory were examined as reserve indicators in a study involving a different sample, different cognitive tests, and neuropathology measures of brain integrity (Reed et al., 2011). Latent variables capturing residual variance in six cognitive domain summary scores that was not explained by neuropathology and demographic characteristics were highly correlated and well summarized by a single second-order factor. This suggests that non-memory cognitive domains might serve as effective indicators of reserve, but Reed et al. (2011) did not directly test the construct validity of non-episodic memory domains as reserve indicators.

The purpose of this study was to evaluate the construct validity of education and different cognitive domains as proxy measures for cognitive reserve. Several goals guided this study. First, we built upon Mungas, Gavett et al. (2018) and directly compared education and domain-specific measures of cognition as potential proxies for cognitive reserve

in a common sample. Second, we examined how these potential reserve indicators assessed at baseline relate to future cognitive decline and modify the association between longitudinal brain atrophy and cognitive decline. This is relevant because recent work from our group has shown longitudinal gray matter change is especially salient for explaining cognitive decline and demonstrates effects that are substantially stronger than cross-sectional brain measures (Fletcher et al., 2018; Mungas, Gavett, et al., 2018). Most previous studies examining moderation of brain effects have utilized cross-sectional brain measures (Reed et al., 2010; Steffener et al., 2014; Zahodne et al., 2013). Third, in previous latent variable studies, measures of episodic memory were used to operationalize reserve (McKenzie et al., 2020; Reed et al., 2010; Zahodne et al., 2013). In this study we also examined cognitive reserve effects of non-memory cognitive domains. We used a regression-based approach to construct validation of these purported reserve indices. Specifically, we evaluated (a) the extent to which these different measures predicted future cognitive decline independent of rate of concurrent brain atrophy and (b) whether these measures moderated the effects of brain atrophy on cognitive decline. These results are important for understanding how to measure cognitive reserve most effectively. Based on our previous work, we hypothesized that episodic memory would show cognitive reserve effects defined as predicting future cognitive decline independent of brain and demographic variables and moderating (diminishing) the effect of brain atrophy on cognitive decline. In contrast, we expected that education would moderate, but enhance, brain atrophy effects on cognitive decline as previously shown in this sample (Mungas, Gavett, et al., 2018). Finally, we hypothesized that non-episodic memory cognitive measures also would show cognitive reserve effects.

METHOD

Participants

The participants were from the UC Davis Diversity Cohort, a longitudinal study that includes substantial numbers of Latino, Black, and non-Latino White (White) older adults. This cohort is heterogeneous in race/ethnicity and educational attainment and spans a spectrum of cognitive function from normal to dementia. Cohort composition, recruitment methods, and inclusion and exclusion criteria are described in Hinton et al. (2010) (more detail in Supplementary Materials); the clinical evaluation and diagnosis protocol are described in Mungas et al. (2010) (more detail in Supplementary Materials). All participants signed informed consent, and all human subject involvement was overseen by institutional review boards at University of California at Davis, the Veterans Administration Northern California Health Care System and San Joaquin General Hospital in Stockton, California.

The participants were 315 persons who had received at least two cognitive evaluations and at least two MRI brain

scans. A rolling enrollment design led to variability in the number of evaluations completed by each individual. There were 150 Whites, 80 Latinos, 70 Blacks, and 15 other races/ethnicities; 39 Latinos were tested in Spanish, and all others were tested in English. A community screening program designed to identify and recruit individuals with cognitive functioning representative of the community-dwelling population in a six-county catchment area in the central Sacramento/San Joaquin valley and east San Francisco Bay area of Northern California identified 235 individuals (83 Whites, 75 Latinos, 64 Blacks, 13 Other). The remaining 80 (67 Whites, 5 Latinos, 6 Blacks, 2 Other) were initially seen for clinical evaluation at a university memory/dementia clinic and referred for research.

Clinical diagnosis was not a variable of primary interest in this study. We were specifically interested in examining how quantitative MRI measures relate to cognitive trajectories and how these brain effects are influenced by putative reserve indicators. However, inclusion of diagnoses across the impairment spectrum was by design and was intended to maximize heterogeneity of both brain measures and cognitive trajectories, thus enhancing ability to study cognitive reserve. Clinical diagnosis in this context is a manifestation of brain degeneration that results in cognitive decline and cognitive and functional impairment, and our approach was to directly study brain and cognition pathways that lead to the clinically relevant differences that are summarized by diagnostic labels.

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, Reed, Crane, Haan, & Gonzalez, 2004; Mungas, Reed, Marshall, & Gonzalez, 2000; Mungas, Widaman, Reed, & Tomaszewski Farias, 2011; Mungas et al., 2005a, 2005b) (more detail in Supplementary Materials). These measures have been used in many studies to characterize longitudinal cognitive trajectories and to identify brain, demographic, and life history variables that influence late life cognitive decline (Brewster et al., 2014; Carmichael et al., 2012; Early et al., 2013; Fletcher et al., 2018; Gavett et al., 2018; Melrose et al., 2015; Mungas et al., 2010; Mungas, Gavett, et al., 2018).

MRI Measures

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., 2010) (more detail in Supplementary Materials). White matter hyperintensities (WMH) were computed by an in-house method combining native Fluid-attenuated inversion recovery (FLAIR) with structural MRI as described previously (DeCarli, Fletcher, Ramey, Harvey, & Jagust, 2005).

Gray matter volume change

We computed longitudinal structural brain change between the two most widely separated MRI measurements. We used a tensor-based morphometry (TBM) method designed to enhance sensitivity and specificity for biological change by incorporating estimates of likely tissue boundaries (Fletcher, 2014; Fletcher et al., 2013). TBM generates deformation fields by nonlinearly registering brain scans at differing time points and using these to generate log-Jacobian estimates of local volume change between the scans (Ashburner & Friston, 2000). The log-Jacobians roughly represent percent change and were annualized by dividing by the number of years between scans. This processing was done via an in-house processing pipeline that has been previously described (Fletcher et al., 2016) (more detail in Supplementary Materials). Gray matter volume atrophy was computed as average volume change over frontal, parietal, temporal, and occipital lobar gray matter regions of interest (ROIs). Log-Jacobians from these ROIs from both hemispheres were averaged to constitute a global cortical gray matter change measure.

APOE genotyping

Apolipoprotein E (APOE) genotyping was carried out using the LightCycler ApoE mutation detection kit (Roche Diagnostics, Indianapolis, IN).

Data Analysis

Measures and data processing

SENAS measures of episodic memory, semantic memory, executive function, and spatial ability were longitudinal cognitive outcomes. Baseline values of each measure were used as independent variables to predict future change across all cognitive measures. Demographic variables (education, gender, race/ethnicity) and baseline MRI variables (volumetric measures of total brain, hippocampus, and WMH) that were used in a previous study of the residual reserve index (Reed et al., 2010) were included as independent variables in addition to gray matter volume change. Cognitive and MRI variables were transformed using the Blom inverse normal rank order transformation (Blom, 1958) to normalize these variables and establish a common scale (mean = 0, SD = 1). Additional covariates included age at baseline evaluation, language of test administration, recruitment source, APOE status, loss to follow-up due to death, and lost to follow-up for other reasons.

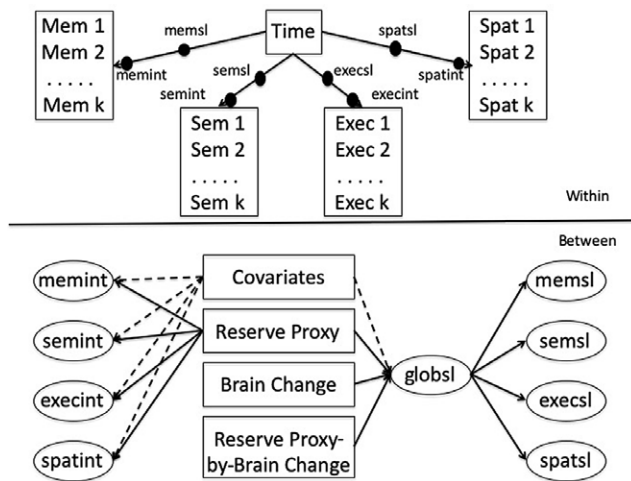


Fig. 1. Longitudinal analytic model. [The four cognitive domain scores are regressed on time in study in the Within level of the multi-level model and person-specific intercept and slope random effects from the Within model serve as primary outcomes in the Between level of the model. A global slope factor effectively summarizes covariance of the four slope random effects but individual intercepts provide optimal fit. The global slope random effect is regressed on the reserve proxy of interest (education or one of the four baseline cognitive domain scores), brain change, the interaction of the reserve proxy with brain change, and covariates. Intercept random effects are also regressed on covariates and the reserve proxy but effects on global slope are of primary interests and effects on intercepts are not reported. All effects in the Between and Within models are simultaneously estimated.]

Longitudinal modeling of cognitive trajectories

The mixed effects, parallel process longitudinal analyses were performed using Mplus version 8.2 multilevel modeling (Muthén & Muthén, 1998). Figure 1 shows a schematic of the basic modeling approach. The approach to modeling longitudinal change in this study has been described in detail in previous publications (Fletcher et al., 2018; Gavett et al., 2018) and is presented in Supplementary Materials. Briefly, in the Within part of this model, each of the four cognitive outcomes was regressed on time (years) in study, centered at the time of the baseline MRI scan. The initial MRI scan occurred at the time of the initial cognitive assessment for 92% of the sample and was within a ± 6 -month window of the cognitive assessment. The Within model generated person-specific intercept and linear slope random effects for each outcome. These random effects then served as dependent variables in the Between part of the model. The Within model included a term 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). We compared a series of models to determine whether intercepts and slopes could be summarized by second-order factors (more detail in Supplementary Materials). The best fit was obtained with the model that had a global slope second-order factor but individual intercept random effects.

Global cognitive slope was the primary outcome of interest and was regressed in the Between model on the demographic (including education) and MRI variables that were used to define the residual reserve index in Reed et al. (2010) and on the other covariates. The four cognitive intercepts also were regressed on these variables in analytical models, but the results are not shown. The baseline cognitive score of interest (episodic memory, semantic memory, executive function, or spatial ability) and global gray matter change were additional independent variables used to explain global cognitive change, as were interactions of gray matter change with education and baseline cognition. This basic model was estimated separately for each cognitive measure. A secondary analysis added interactions of baseline MRI measures with gray matter change to the basic model for episodic memory to evaluate whether reserve effects of education and cognitive variables were independent of potential reserve effects of baseline brain variables. An additional secondary analysis added baseline clinical diagnosis as a main effect predictor of cognitive trajectories and evaluated whether reserve effects were present after accounting for diagnosis.

RESULTS

Sample Characteristics

Sample characteristics are presented in Table 1, stratified by baseline clinical diagnosis to clarify the range of clinical expression of cognitive impairment covered in this study. Detailed information about the diagnostic composition of the sample is available in Supplementary Materials. About 59% were women and gender did not differ across diagnosis groups ($\chi^2[2] = 5.449$, $p = .066$). Race/ethnicity differed by diagnosis ($\chi^2[6] = 34.859$, $p = .001$) with Whites more likely to have a diagnosis of mild cognitive impairment (MCI). In total, 75% of the sample was recruited from the community. Recruitment source differed by diagnosis ($\chi^2[2] = 26.475$, $p = .001$), with individuals with MCI more likely to be clinic referrals. Average age was about 75 years and this differed across groups ($F[2,312] = 6.317$, $p = .002$) with Dementia older than MCI who were older than Normals. Average education was 13.4 years and differed across diagnosis groups ($F[2,312] = 5.520$, $p = .004$), with highest education in MCI, lowest in Dementia, and Normals in between. APOE $\epsilon 4$ differed by diagnosis ($\chi^2[2] = 11.700$, $p = .003$) with highest $\epsilon 4$ prevalence in individuals with dementia (62%) and lowest in those who were cognitively normal (32%). Average follow-up time was 7.2 years and differed by baseline diagnosis ($F[2,312] = 29.855$, $p = .001$); there were 6.8 assessments on average in the overall sample and this differed by diagnosis ($F[2,312] = 23.415$, $p = .001$). The number of assessments and follow-up time increased across Dementia, MCI, and Normal diagnoses, but even in the Dementia group, there was nearly 5 years of follow-up and 5 assessments on average. MRI follow-up time significantly differed across groups ($F[2,312] = 13.799$, $p = .001$).

Table 1. Sample characteristics. [Results are stratified by baseline clinical diagnosis: normal cognition ($N = 187$), mild cognitive impairment (MCI) ($N = 107$), dementia ($N = 21$)]

	Dementia	MCI	Normal	Total
Gender – Female	11 (52.4%)	55 (51.4%)	121 (64.7%)	187 (59.4%)
Age (baseline) – Mean (SD)	80.1 (± 4.2)	75.4 (± 7.1)	74.5 (± 7.0)	75.2 (± 7.0)
Education – Mean (SD)	11.9 (± 5.3)	14.5 (± 3.9)	12.9 (± 4.6)	13.4 (± 4.5)
Recruitment source – Clinic	8 (38.1%)	44 (41.1%)	28 (15.0%)	80 (25.4%)
Recruitment source – Community	13 (61.9%)	63 (58.9%)	159 (85.0%)	235 (74.6%)
Race/ethnicity – Black	3 (14.3%)	21 (19.6%)	46 (24.6%)	70 (22.2%)
Race/ethnicity – Latino	6 (28.6%)	10 (9.3%)	64 (34.2%)	80 (25.4%)
Race/ethnicity – Other	0 (0%)	4 (3.7%)	11 (5.9%)	15 (4.8%)
Race/ethnicity – White	12 (57.1%)	72 (67.3%)	66 (35.3%)	150 (47.6%)
APOE $\epsilon 4$ – $\epsilon 4$ Positive	13 (61.9%)	50 (46.7%)	59 (31.6%)	122 (38.7%)
Cognition follow-up time – Mean (SD)	4.8 (± 2.3)	5.7 (± 3.1)	8.4 (± 3.4)	7.2 (± 3.5)
Number of cognitive assessments – Mean (SD)	4.9 (± 2.2)	5.7 (± 2.6)	7.7 (± 2.9)	6.8 (± 3.0)
MRI follow-up time – Mean (SD)	3.5 (± 2.0)	3.6 (± 2.4)	5.1 (± 2.7)	4.5 (± 2.7)
Follow-up status – Active follow-up	5 (23.8%)	36 (33.6%)	97 (51.9%)	138 (43.8%)
Follow-up status – Deceased	12 (57.1%)	46 (43.0%)	46 (24.6%)	104 (33.0%)
Follow-up status – lost to follow-up	4 (19.0%)	25 (23.4%)	44 (23.5%)	73 (23.2%)
Global gray change (standardized ^a) – Mean (SD)	–.2 ($\pm .8$)	–.3 ($\pm .9$)	.2 ($\pm .7$)	0 ($\pm .8$)
Global gray change (percent ^b) – Mean (SD)	–.9 ($\pm .6$)	–.9 ($\pm .7$)	–.6 ($\pm .5$)	–.7 ($\pm .6$)
Episodic memory (baseline ^a) – Mean (SD)	–.9 ($\pm .5$)	–.3 ($\pm .6$)	.5 ($\pm .8$)	.1 ($\pm .8$)
Semantic memory (baseline ^a) – Mean (SD)	–.5 ($\pm .9$)	0 ($\pm .7$)	.1 ($\pm .9$)	0 ($\pm .8$)
Executive function (baseline ^a) – Mean (SD)	–.5 ($\pm .9$)	0 ($\pm .7$)	.4 ($\pm .9$)	.2 ($\pm .8$)
Spatial (baseline ^a) – Mean (SD)	–.4 (± 1.1)	.1 ($\pm .9$)	.2 (± 1.0)	.1 (± 1.0)

^aBlom transformed to have $M = 0$ and $SD = 1$ in this sample.

^bLog Jacobian $\times 100$.

Average follow-up time was longer for those who were cognitively normal compared with those with MCI or dementia. Lost to follow-up due to death or other reasons also differed across groups ($\chi^2[4] = 18.321, p = .001$). Cognitively normal individuals were more likely to be actively followed at the time of this study. Loss to follow-up due to death was highest in the Dementia group, lowest in Normals, and intermediate in MCI. Loss to follow-up for other reasons was similarly distributed across diagnosis groups.

Baseline gray matter volume and baseline cognitive test scores all differed across diagnostic groups ($ps < .001$), with a consistent pattern of Normal > MCI > Dementia. Gray matter volume change rate also differed across groups ($p < .001$); gray matter volume declined more slowly in individuals who were cognitively normal and at similar, faster rates in those with MCI and dementia. Education level was correlated with all baseline cognitive scores but varied in degree: education with episodic memory = .23, semantic memory = .50, executive function = .41, and spatial = .30.

Modeling of Longitudinal Cognitive Outcomes

In an unconditional parallel process model of cognitive trajectories, correlations among the four intercept random effects ranged from .476 to .763, while in contrast, correlations among slope random effects ranged from .952 to .987 (see Table 1 in Supplementary Materials for a complete

correlation matrix of intercept and slope random effects). Episodic memory intercept showed substantial correlation with slopes of all four cognitive domains (ranging from .491 to .597). Executive function intercept was significant but less correlated with slopes (ranging from .192 to .289). The best fitting unconditional model for intercept and slope random effects included individual intercepts and a second-order latent variable indicated by the four slope random effects (more detail in Supplementary Materials). Loadings on the global slope factor were: episodic memory – 1, semantic memory – .837, executive function – 1.118, and spatial – .747. The four cognitive domains all contributed substantially to the global cognitive slope. In subsequent analyses, individual domain intercepts and global cognitive slope were the cognitive outcomes.

Cognitive Domain Comparisons

Table 2 shows how different cognitive baseline scores and their interactions with gray matter change related to global cognitive slope independent of other variables in the model. Baseline episodic memory was related to global cognitive slope independent of covariates, demographic variables, and brain variables, and significantly modified the gray matter change effect. The baseline measures of the other three cognitive domains were not related to future cognitive change above and beyond covariates, education, and brain variables.

Table 2. Comparison of effects of baseline cognitive measures from different cognitive domains on global cognitive slope

Cognitive domain	Cognition main effect	Cognition by gray matter change interaction
Episodic memory	.016 (.007) ⁺	-.028 (.010) ⁺⁺
Semantic memory	.012 (.008)	0 (.012)
Executive function	.007 (.008)	-.011 (.012)
Spatial ability	-.003 (.006)	-.009 (.010)

Note. Tabled values are unstandardized regression weights (β s) with standard errors in parentheses. Results show estimates of cognitive variable main effects and interactions with gray matter change and are from models that included all demographic and brain variables and covariates. Estimates indicate the effects of 1 SD differences in dependent and independent variables. ($+p < .05$, $++p < .01$).

Table 3. Effects of covariates, brain variables, education, and baseline episodic memory on global cognitive slope

Independent variables	β	SE	<i>p</i>
Intercept (reference)	-.080	.016	0
Male ^a	-.004	.010	.720
Age (baseline – centered at 70)	0	.001	.961
Black ^a	.068	.013	0
Latino ^a	.028	.015	.070
Other non-White race/ethnicity ^a	-.001	.022	.961
Spanish ^a	.003	.018	.885
Clinic recruitment ^a	-.063	.016	0
APOE e4 positive ^a	-.040	.011	0
Lost to follow-up ^a	-.012	.012	.348
Deceased ^a	-.038	.013	.003
Brain volume (baseline)	0	.006	.972
Hippocampus volume (baseline)	.018	.006	.006
White matter hyperintensity volume (baseline)	-.008	.005	.111
Cortical gray matter (change)	.060	.011	0
Education (centered at 12 years)	0	.001	.978
Education by gray matter change	.004	.002	.027
Episodic memory (baseline)	.016	.007	.021
Episodic memory by gray matter change	-.028	.010	.003

Note. Tabled values are unstandardized regression weights (β s) with associated standard errors (SEs) and *p*-levels. 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. ^aDichotomous indicator variable.

Episodic Memory and Education Effects on Cognitive Change

Table 3 presents detailed results for the analysis with episodic memory as the indicator of cognitive reserve and shows how global cognitive slope was influenced by covariates, demographic variables, baseline brain variables, gray matter change, reserve indicators (education and episodic memory), and reserve indicator by gray matter change interactions. The reference for this analysis was an English-speaking,

non-Latino White woman recruited from the community who was 70 years of age with 12 years of education, was continuously followed, and APOE ϵ 4 negative. As in previous studies with this cohort (Fletcher et al., 2018; Mungas, Gavett, et al., 2018), gray matter change was strongly associated with cognitive decline, $\beta = .060$, $SE = .011$, $p = .001$. An individual whose gray matter declined 1 SD slower than average would be expected to decline cognitively at a rate of only $-.02$ SD/year, and in comparison, a person with average gray matter change in this sample would decline cognitively at a rate of $-.08$ SD/year, and an individual whose gray matter declined 1 SD faster than average would decline at a rate of $-.14$ SD/year. Better baseline episodic memory was incrementally associated with slower global cognitive decline, but education had no main effect on rate of decline. Interactions of both our putative measures for reserve – education and baseline episodic memory – with gray matter change were significant, but with opposite signs. Thus, higher baseline episodic memory resulted in a diminished effect of gray matter change on cognitive decline, but in contrast, more education was associated with an enhanced effect of gray matter change on cognitive decline.

These results are presented graphically in Figures 2 and 3. Figure 2 shows the interaction of gray matter change and episodic memory on expected trajectories for one specific cognitive outcome, executive function. Executive function was selected as the exemplar for these figures because it had the highest loading on the global cognitive change factor. Effects of episodic memory and gray matter change on executive function change were calculated as the effects of these variables on global cognitive change multiplied by the loading of executive function on global cognitive change in the primary, multivariable model (1.039). The three panels show model-predicted executive function trajectories for two levels of baseline episodic memory ($+1$ SD and -1 SD) and different amounts of gray matter change. To enhance clinical relevance of these figures, gray matter change values were chosen that represented average gray matter change in clinical diagnosis groups. The left panel represents gray matter change that is average for those who were Normal at baseline, the center corresponds to average gray matter change for individuals with a MCI diagnosis, and the right to average change for those with Dementia. There are several salient findings. First, baseline executive function differed substantially in relation to episodic memory, and in contrast, different gray matter change rates were not as strongly related to baseline executive function. Second, the difference in the rate of cognitive decline across individuals with different levels of gray matter change was minimal for those with above average episodic memory at baseline, but was more substantial when baseline episodic memory was below average. Stated differently, brain atrophy had a stronger negative relation to cognitive change for individuals with low baseline episodic memory, and of particular importance, better baseline episodic memory protected against the effects of more advanced atrophy.

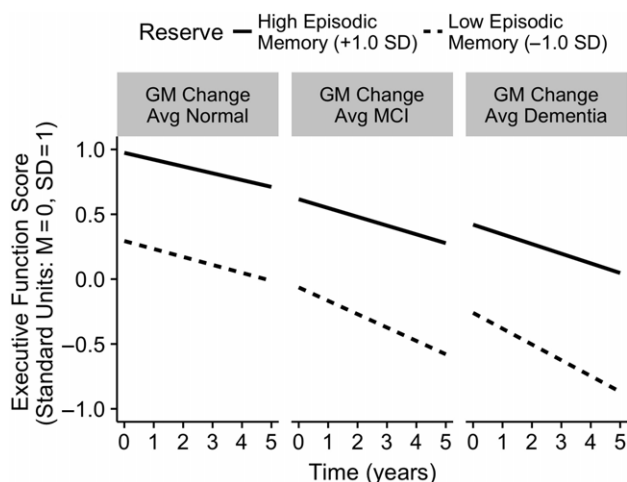


Fig. 2. Model-predicted trajectories of executive function decline by rate of gray matter change and baseline episodic memory. [Expected executive function trajectories are presented for three atrophy rates corresponding to average rates for Normal, MCI, and Dementia baseline diagnosis groups and two levels of episodic memory (+1.0 SD and -1.0 SD). Executive function slope is calculated as global cognitive slope \times 1.039 (executive function slope loading in primary, multivariable analysis). The interaction of baseline episodic memory with gray matter atrophy is significant ($p = .003$).]

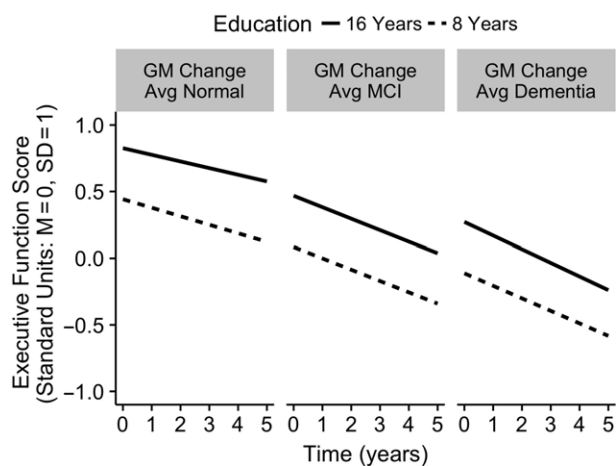


Fig. 3. Model-predicted trajectories of executive function decline by rate of gray matter change and education level. [Expected executive function trajectories are presented for three atrophy rates corresponding to average rates for Normal, MCI, and Dementia baseline diagnosis groups and two levels of education (8 and 16 years). Executive function slope is calculated as global cognitive slope \times 1.039 (executive function slope loading in primary, multivariable analysis). The interaction of education with gray matter atrophy is significant ($p = .027$).]

Figure 3 shows the moderation effects for education. The two hypothetical education levels are roughly 2 SD apart, similar to the values for episodic memory depicted in Figure 2. The education effect on baseline executive function was smaller than that for baseline episodic memory. More education was associated with a more positive executive

function slope in the hypothetically normal individual, but a more negative slope in the hypothetical dementia case.

A secondary analysis included interaction effects on global cognitive slope of baseline brain variables with gray matter change. None of the baseline brain by gray matter change interactions were significant; the episodic memory main effect and the episodic memory by gray matter change interaction continued to be significant. This suggests that the episodic memory modification of the gray matter change effect on cognitive decline cannot be explained by measured baseline brain variables that could influence baseline episodic memory. The results for education as a reserve proxy did not change.

We added diagnosis as a main effect in the model in an additional secondary analysis. The episodic memory by gray matter change interaction effect was significant ($\beta = -.027$, $SE = .010$, $p = .005$) and was essentially the same as this effect in the primary analyses (Table 3). This suggests that episodic memory performance has cognitive reserve properties that go beyond what can be explained by associations with diagnosis.

DISCUSSION

This study examined the construct validity of educational attainment and cross-sectional measures of different cognitive domains as proxies for cognitive reserve in a sample of diverse older adults. A cognitive reserve effect was inferred if a measure explained longitudinal cognitive change beyond the effects of baseline brain variables and longitudinal gray matter change and more importantly, moderated the gray matter change effect on cognitive change (Stern et al., 2018). Baseline episodic memory satisfied both of these criteria. Education failed to satisfy these criteria, as education was not related to cognitive change independent of gray matter change, demographic variables, and baseline cognition, and gray matter change effects on cognitive decline were stronger and more negative in those with more education. Baseline measures of semantic memory, executive function, and spatial ability also failed to show significant reserve-like effects.

Baseline episodic memory was associated with longitudinal cognitive change in all four domains, so it would be expected that baseline episodic memory would be associated with global cognitive change. However, this effect was independent of all other effects, including brain volume change, and in addition, it moderated the brain change effect on cognitive decline. In contrast, none of the other cognitive domain intercepts were incrementally associated with cognitive decline or did they moderate the brain change effect. Baseline executive function also was associated with cognitive change in all four domains in an unconditional model, and had the strongest loading on the second-order global cognitive change factor, but did not meet the criteria for construct validity as an indicator of cognitive reserve. The overall

pattern of the results suggests that episodic memory has unique cognitive reserve properties.

The results of this study provide evidence that episodic memory is an effective measure of cognitive reserve. This replicates and extends results from an earlier study with this cohort (Reed et al., 2010) and other studies involving different cohorts that utilized different episodic memory measures (McKenzie et al., 2020; Zahodne et al., 2013), and expands on these earlier studies by showing episodic memory effects in relation to longitudinal brain atrophy. Education, in contrast, was not related to cognitive decline independent of brain atrophy, and the education by brain atrophy interaction went in the opposite direction of the episodic memory–brain atrophy interaction. The obtained results suggest that education provides no prognostic information about cognitive decline in the absence of information about brain status; brain status measures or proxies like clinical diagnosis are required for fully understanding the impact of education on future cognitive decline. Clinically, a high level of education is a positive prognostic indicator in the context of minimal brain atrophy, which corresponds to roughly the upper 50% of the distribution of brain atrophy rate in cognitively normal individuals (Mungas, Gavett, et al., 2018). But higher educational attainment indicates poorer prognosis when brain atrophy is more rapid (lower 50% of MCI distribution and most of dementia distribution (Mungas, Gavett, et al., 2018)). An alternate way of considering these results is that episodic memory has the same effect on future cognitive decline across the entire range of baseline cognitive function, whereas education is associated with slower decline in those with relatively normal cognition but faster decline in those with significant cognitive impairment. While both have value as reserve indicators, higher episodic memory unambiguously signals a higher level of reserve, but education level may signal higher or lower reserve depending on the current degree of brain degeneration and cognitive impairment.

This study showed that episodic memory was superior to other cognitive domains as an indicator of cognitive reserve. There are important caveats to concluding that episodic memory is the only or best indicator of reserve. This study examined a limited number of non-episodic memory measures, and different measures might be effective reserve indicators. This is a question that should be addressed with additional measures in different and larger samples.

A hypothesis to explain the results of this study is that episodic memory represents the neural basis of cognitive reserve better than other cognitive abilities. Episodic memory is more strongly associated with brain measures in previous studies involving this cohort (Mungas, Reed, Farias, & Decarli, 2009; Reed et al., 2010) and other cohorts (Dowling et al., 2011) and is less associated with life exposure variables like education (Early et al., 2013). In this study, education was weakly associated with baseline episodic memory (explaining 5.3% of the variance) but more strongly associated with executive function (16.8% of variance) and semantic memory (25% of variance). The overall pattern that emerges is that episodic memory is more strongly associated with brain

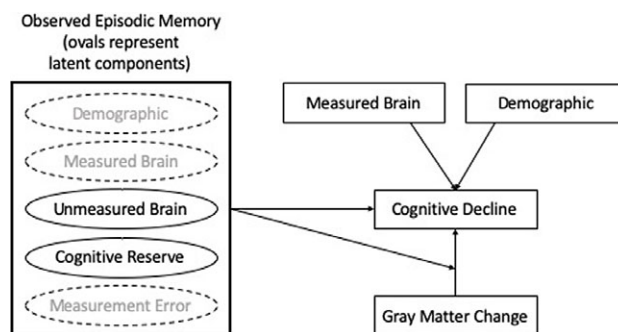


Fig. 4. Conceptual model of cognitive reserve effects of episodic memory on cognitive decline. [Rectangles represent observed variables and ovals represent latent/hypothetical variables. Observed episodic memory reflects latent variance components due to Demographics, Measured Brain, Unmeasured Brain, Measurement Error, and Cognitive Reserve. Observed cognitive decline is adjusted in the regression model for demographic and measured brain effects, so the regression effect estimate of observed episodic memory on cognitive decline represents the combined effects of unmeasured brain and cognitive reserve variance components.]

variables, independent of demographics including education, than are other cognitive domains and is less associated with education and other demographic variables including race/ethnicity. Thus, biological variables appear to have a stronger relative impact on episodic memory than on other cognitive domains. Brain function mechanisms that promote resilience to disease-related changes in brain structure are commonly regarded as the neural basis of cognitive reserve (Barulli & Stern, 2013; Park & Reuter-Lorenz, 2009; Stern, 2006). Future research could examine how measures of episodic memory and other cognitive domains are differentially related to functional imaging markers of cognitive reserve.

Collectively, the results of this study raise important questions about what cognitive reserve means and how it is best measured. Figure 4 presents a conceptual model of the episodic memory effect found in this study. The observed episodic memory score theoretically can be decomposed as in Reed et al. (2010) into uncorrelated components that represent variance explained by brain effects included in the model (Measured Brain), brain effects not included in the model (Unmeasured Brain), Demographic effects, Measurement Error, and Cognitive Reserve (everything else). The episodic memory effect is adjusted in the model for Measured Brain and Demographics, and Measurement Error by definition should not be systematically related to external variables like cognitive decline, so the independent episodic memory effect on cognitive decline is a result of Cognitive Reserve and Unmeasured Brain components. Unmeasured Brain variables may well account for additional episodic memory variance that influences cognitive decline. With better understanding of the brain mechanisms underlying episodic memory, Unmeasured Brain will diminish as it becomes Measured Brain, and the Cognitive Reserve

component will be more purely represented in the episodic memory effect on cognitive decline. The ultimate goal is to replace the Cognitive Reserve component entirely by known brain mechanisms.

The Cognitive Reserve and Unmeasured Brain components cannot be separated in the current study. Ultimately, labeling the episodic memory effect on cognitive decline as cognitive reserve is not entirely accurate because this does not account for unmeasured brain effects. Practically, however, these results show that measured episodic memory adds value for predicting cognitive decline above and beyond major brain effects, including longitudinal brain atrophy. Thus, episodic memory behaves as a cognitive reserve indicator should behave, and, pragmatically, provides unique information about future cognitive trajectories.

An important strength of this study is that the measures of the four cognitive domains were developed to have matched psychometric characteristics, specifically, similar levels of reliability across the ability continuum relevant to diverse older adults (Mungas et al., 2004). This minimizes the extent to which cross-domain differences in results are due to different basic psychometric properties. Additional strengths are the availability of comprehensive MRI measures of brain injury and brain degeneration, and a diverse sample with considerable longitudinal follow-up of both cognitive and brain measures. Limitations are other cognitive measures that might be relevant to cognitive decline were not included, notably measures of cognitive speed and single-word reading tests of life course acquisition of semantic knowledge. Despite attempts to recruit a sample that is representative of the communities from which it was drawn, this was not a population-based sample and unknown selection factors might bias results. Alzheimer's disease was the predominant etiologic diagnosis for those with dementia in this sample, and results could be influenced by the type and degree of pathology in a specific sample. Replication in different samples and in population-based samples is important.

CONCLUSIONS

The results of this study have direct clinical relevance. They suggest that assessment of episodic memory in an older adult will be important not only to characterize that person's clinical status, but also to predict their future cognitive trajectory and characterize their resilience to progressive brain disease. Measures from other cognitive domains are helpful for characterizing cognitive status and identifying clinically relevant patterns of cognitive impairment but will be less useful for measuring resilience to brain pathology. Education has limited prognostic value in the absence of information about brain or clinical status. With respect to cognitive reserve, more education is a positive indicator only when brain atrophy is minimal. Episodic memory, in contrast, is a positive indicator of reserve regardless of the degree of atrophy. Another advantage of episodic memory is that it can change over time and so can track dynamic changes in cognitive

reserve. This is important because understanding the implications of depleting reserve and its underlying neural basis are areas that have very limited research thus far. Future research is needed to better delineate brain mechanisms underlying episodic memory and other cognitive domains and to explain cross-domain differences in associations with brain degeneration and cognitive decline, with a goal of both predicting and understanding mechanisms of cognitive decline.

ACKNOWLEDGMENTS

We would like to acknowledge the devotion of the participants in this study who volunteered their time for comprehensive annual evaluations and repeated MRI scans. Many staff of the UC Davis Alzheimer's Disease Center made this study a reality. Esther Lara supervised all aspects of study implementation from participant recruitment through retention over time leading to successful longitudinal follow-up.

This work was supported by multiple grants from the National Institute on Aging (NIA) (P30 AG10129, R01 AG021028, and R01 AG047827, C DeCarli, PI; R01 AG10220, D Mungas, PI; R01/RF1 AG031563, B Reed/D Mungas, PI; R01 AG031252, S Tomaszewski Farias, PI; R01 AG051170, R Jones, PI; R01-AG059716 and K01-AG049164, T Hohman, PI; R00 AG053410, ER Mayeda, PI).

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit <https://doi.org/10.1017/S1355617720001095>

CONFLICTS OF INTEREST

The author(s) have nothing to disclose.

REFERENCES

- Amieva, H., Mokri, H., Le Goff, M., Meillon, C., Jacqmin-Gadda, H., Foubert-Samier, A., ... Dartigues, J.F. (2014). Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: A study of 20 years of cognitive decline. *Brain*, 137(Pt 4), 1167–1175. <https://doi.org/10.1093/brain/awu035>
- Ashburner, J. & Friston, K.J. (2000). Voxel-based morphometry – The methods. *Neuroimage*, 11(6 Pt 1), 805–821. <https://doi.org/10.1006/nimg.2000.0582>
- Barulli, D. & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. *Trends in Cognitive Sciences*, 17(10), 502–509. <https://doi.org/10.1016/j.tics.2013.08.012>
- Blom, G. (1958). *Statistical Estimates and Transformed Beta-Variables*. New York: Wiley.
- Brewster, P.W.H., Melrose, R.J., Marquine, M.J., Johnson, J.K., Naples, A., MacKay-Brandt, A., ... Mungas, D. (2014). Life experience and demographic influences on cognitive function in older adults. *Neuropsychology*, 28(6), 846–858. <https://doi.org/10.1037/neu0000098>

- Carmichael, O., Mungas, D., Beckett, L., Harvey, D., Tomaszewski Farias, S., Reed, B., ... Decarli, C. (2012). MRI predictors of cognitive change in a diverse and carefully characterized elderly population. *Neurobiology of Aging*, *33*(1), 83–95. <https://doi.org/10.1016/j.neurobiolaging.2010.01.021>
- DeCarli, C., Fletcher, E., Ramey, V., Harvey, D., & Jagust, W. (2005). Anatomical mapping of white matter hyperintensities (WMH) exploring the relationships between periventricular WMH, deep WMH, and total WMH burden. *Stroke*, *36*, 50–55.
- Dowling, N.M., Tomaszewski Farias, S., Reed, B.R., Sonnen, J.A., Strauss, M.E., Schneider, J.A., ... Mungas, D. (2011). Neuropathological associates of multiple cognitive functions in two community-based cohorts of older adults. *Journal of the International Neuropsychological Society: JINS*, *17*(4), 602–614. <https://doi.org/10.1017/S1355617710001426>
- Early, D.R., Widaman, K.F., Harvey, D., Beckett, L., Park, L.Q., Farias, S.T., ... Mungas, D. (2013). Demographic predictors of cognitive change in ethnically diverse older persons. *Psychology and Aging*, *28*(3), 633–645. <https://doi.org/10.1037/a0031645>
- Fletcher, E. (2014). Using prior information to enhance sensitivity of longitudinal brain change computation. In C.H. Chen (Ed.), *Frontiers of medical imaging* (pp. 63–81). Singapore; Hackensack, NJ: World Scientific.
- Fletcher, E., Carmichael, O., Pasternak, O., Maier-Hein, K.H., & DeCarli, C. (2014). Early brain loss in circuits affected by Alzheimer's disease is predicted by Fornix microstructure but may be independent of gray matter. *Frontiers in Aging Neuroscience*, *6*, 1–9. <https://doi.org/10.3389/fnagi.2014.00106>
- Fletcher, E., Gavett, B., Harvey, D., Farias, S.T., Olichney, J., Beckett, L., ... Mungas, D. (2018). Brain volume change and cognitive trajectories in aging. *Neuropsychology*, *32*(4), 436–449. <https://doi.org/10.1037/neu0000447>
- Fletcher, E., Knaack, A., Singh, B., Lloyd, E., Wu, E., Carmichael, O., & DeCarli, C. (2013). Combining boundary-based methods with tensor-based morphometry in the measurement of longitudinal brain change. *IEEE Transactions on Medical Imaging*, *32*(2), 223–236. <https://doi.org/10.1109/tmi.2012.2220153>
- Fletcher, E., Villeneuve, S., Maillard, P., Harvey, D., Reed, B., Jagust, W., & Decarli, C. (2016). Beta-amyloid, hippocampal atrophy and their relation to longitudinal brain change in cognitively normal individuals. *Neurobiology of Aging*, *40*, 173–180. <https://doi.org/10.1016/j.neurobiolaging.2016.01.133>
- Gavett, B.E., Fletcher, E., Harvey, D., Farias, S.T., Olichney, J., Beckett, L., ... Mungas, D. (2018). Ethnoracial differences in brain structure change and cognitive change. *Neuropsychology*, *32*(5), 529–540. <https://doi.org/10.1037/neu0000452>
- Gross, A.L., Mungas, D.M., Crane, P.K., Gibbons, L.E., MacKay-Brandt, A., Manly, J.J., ... Jones, R.N. (2015). Effects of education and race on cognitive decline: An integrative study of generalizability versus study-specific results. *Psychology and Aging*, *30*(4), 863–880. <https://doi.org/10.1037/pag0000032>
- Hinton, L., Carter, K., Reed, B.R., Beckett, L., Lara, E., DeCarli, C., & Mungas, D. (2010). Recruitment of a community-based cohort for research on diversity and risk of dementia. *Alzheimer's Disease and Associated Disorders*, *24*(3), 234–241. <https://doi.org/10.1097/WAD.0b013e318181ee01>
- Jones, R.N., Manly, J., Glymour, M.M., Rentz, D.M., Jefferson, A.L., & Stern, Y. (2011). Conceptual and measurement challenges in research on cognitive reserve. *Journal of the International Neuropsychological Society*, *17*(4), 593–601. <https://doi.org/10.1017/S1355617710001748>
- Lee, D.Y., Fletcher, E., Martinez, O., Zozulya, N., Kim, J., Tran, J., ... DeCarli, C. (2010). Vascular and degenerative processes differentially affect regional interhemispheric connections in normal aging, mild cognitive impairment, and Alzheimer disease. *Stroke*, *41*(8), 1791–1797. <https://doi.org/10.1161/STROKEAHA.110.582163>
- Masel, M.C., & Peek, M.K. (2009). Ethnic differences in cognitive function over time. *Annals of Epidemiology*, *19*(11), 778–783. <https://doi.org/10.1016/j.annepidem.2009.06.008>
- McKenzie, C., Bucks, R.S., Weinborn, M., Bourgeat, P., Salvado, O., & Gavett, B.E. (2020). Cognitive reserve predicts future executive function decline in older adults with Alzheimer's disease pathology but not age-associated pathology. *Neurobiology of Aging*, *88*, 119–127. <https://doi.org/10.1016/j.neurobiolaging.2019.12.022>
- Melrose, R.J., Brewster, P., Marquine, M.J., MacKay-Brandt, A., Reed, B., Farias, S.T., & Mungas, D. (2015). Early life development in a multiethnic sample and the relation to late life cognition. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *70*(4), 519–531. <https://doi.org/10.1093/geronb/gbt126>
- Mungas, D., Beckett, L., Harvey, D., Farias, S.T., Reed, B., Carmichael, O., ... DeCarli, C. (2010). Heterogeneity of cognitive trajectories in diverse older persons. *Psychology and Aging*, *25*(3), 606–619. <https://doi.org/10.1037/a0019502>
- Mungas, D., Early, D.R., Glymour, M.M., Zeki Al Hazzouri, A., & Haan, M.N. (2018). Education, bilingualism, and cognitive trajectories: Sacramento Area Latino Aging Study (SALSA). *Neuropsychology*, *32*(1), 77–88. <https://doi.org/10.1037/neu0000356>
- Mungas, D., Gavett, B., Fletcher, E., Farias, S.T., DeCarli, C., & Reed, B. (2018). Education amplifies brain atrophy effect on cognitive decline: Implications for cognitive reserve. *Neurobiology of Aging*, *68*, 142–150. <https://doi.org/10.1016/j.neurobiolaging.2018.04.002>
- Mungas, D., Reed, B.R., Crane, P.K., Haan, M.N., & Gonzalez, H. (2004). Spanish and English Neuropsychological Assessment Scales (SENAS): Further development and psychometric characteristics. *Psychological Assessment*, *16*(4), 347–359. <https://doi.org/10.1037/1040-3590.16.4.347>
- Mungas, D., Reed, B.R., Farias, S.T., & Decarli, C. (2009). Age and education effects on relationships of cognitive test scores with brain structure in demographically diverse older persons. *Psychology and Aging*, *24*(1), 116–128. <https://doi.org/10.1037/a0013421>
- Mungas, D., Reed, B.R., Haan, M.N., & Gonzalez, H. (2005a). Spanish and English Neuropsychological Assessment Scales: Relationship to demographics, language, cognition, and independent function. *Neuropsychology*, *19*(4), 466–475.
- Mungas, D., Reed, B.R., Marshall, S.C., & Gonzalez, H.M. (2000). Development of psychometrically matched English and Spanish language neuropsychological tests for older persons. *Neuropsychology*, *14*(2), 209–223.
- Mungas, D., Reed, B.R., Tomaszewski Farias, S., & DeCarli, C. (2005b). Criterion-referenced validity of a neuropsychological test battery: Equivalent performance in elderly Hispanics and Non-Hispanic Whites. *Journal of the International Neuropsychological Society*, *11*, 620–630.
- Mungas, D., Widaman, K.F., Reed, B.R., & Tomaszewski Farias, S. (2011). Measurement invariance of neuropsychological tests in diverse older persons. *Neuropsychology*, *25*(2), 260–269. <https://doi.org/10.1037/a0021090>
- Muthén, L.K., & Muthén, B.O. (1998). *Mplus User's Guide* (8th ed.). Los Angeles, CA: Muthén & Muthén.

- Park, D.C., & Reuter-Lorenz, P. (2009). The adaptive brain: Aging and neurocognitive scaffolding. *Annual Review of Psychology*, 60, 173–196. <https://doi.org/10.1146/annurev.psych.59.103006.093656>
- Reed, B.R., Dowling, M., Tomaszewski Farias, S., Sonnen, J., Strauss, M., Schneider, J.A., ... Mungas, D. (2011). Cognitive activities during adulthood are more important than education in building reserve. *Journal of the International Neuropsychological Society*, 17(4), 615–624. <https://doi.org/10.1017/S1355617711000014>
- Reed, B.R., Mungas, D., Farias, S.T., Harvey, D., Beckett, L., Widaman, K., ... DeCarli, C. (2010). Measuring cognitive reserve based on the decomposition of episodic memory variance. *Brain*, 133(Pt 8), 2196–2209. <https://doi.org/10.1093/brain/awq154>
- Scarmeas, N., Albert, S.M., Manly, J.J., & Stern, Y. (2006). Education and rates of cognitive decline in incident Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, 77(3), 308–316.
- Steffener, J., Barulli, D., Habeck, C., O'Shea, D., Razlighi, Q., & Stern, Y. (2014). The role of education and verbal abilities in altering the effect of age-related gray matter differences on cognition. *PLoS One*, 9(3), e91196. <https://doi.org/10.1371/journal.pone.0091196>
- Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, 8(3), 448–460.
- Stern, Y. (2006). Cognitive reserve and Alzheimer disease. *Alzheimer's Disease and Associated Disorders*, 20(2), 112–117.
- Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, 47(10), 2015–2028. <https://doi.org/10.1016/j.neuropsychologia.2009.03.004>
- Stern, Y., Albert, S., Tang, M.X., & Tsai, W.Y. (1999). Rate of memory decline in AD is related to education and occupation: Cognitive reserve? *Neurology*, 53(9), 1942–1947.
- Stern, Y., Arenaza-Urquijo, E.M., Bartres-Faz, D., Belleville, S., Cantillon, M., Chetelat, G., ... Conceptual Frameworks Workgroup (2018). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimers Dement.* <https://doi.org/10.1016/j.jalz.2018.07.219>
- Ye, B.S., Seo, S.W., Cho, H., Kim, S.Y., Lee, J.S., Kim, E.J., ... Na, D.L. (2013). Effects of education on the progression of early-versus late-stage mild cognitive impairment. *International Psychogeriatrics*, 25(4), 597–606. <https://doi.org/10.1017/S1041610212002001>
- Zahodne, L.B., Manly, J.J., Brickman, A.M., Siedlecki, K.L., Decarli, C., & Stern, Y. (2013). Quantifying cognitive reserve in older adults by decomposing episodic memory variance: Replication and extension. *Journal of the International Neuropsychological Society*, 19(8), 854–862. <https://doi.org/10.1017/S1355617713000738>