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# Cognitive reserve predicts future executive function decline in older adults with Alzheimer's disease pathology but not age-associated pathology

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ABSTRACT

Cognitive reserve has been described as offering protection against Alzheimer's disease (AD) and other neurodegenerative conditions, but also against age-associated brain changes. Using data from the Alzheimer's Disease Neuroimaging Initiative, we defined cognitive reserve using the residual reserve index: episodic memory performance residualized for 3T MRI-derived brain volumes and demographics. We examined whether cognitive reserve predicted executive function (EF) decline equally across 2 groups of older adults—AD biomarker−positive (n = 468) and −negative (n = 402)—defined by the tau-to-amyloid ratio in cerebrospinal fluid. A significant interaction between the residual reserve index and biomarker group revealed that the effect of cognitive reserve on EF decline was dependent on pathology status. In the biomarker-positive group, higher cognitive reserve predicted EF decline over five years. However, cognitive reserve did not predict EF decline in the biomarker-negative group. These results suggest a certain level of AD pathology may be needed before cognitive reserve exerts its protective effects on future cognition; however, further research that tracks cognitive reserve longitudinally is needed.



## 1. Introduction

The theory of cognitive reserve hypothesizes that individual differences in cognitive processing cause some individuals to cope better with pathological brain changes than others, resulting in delayed or reduced cognitive decline in the presence of neuropathology (Stern, 2002). Cognitive reserve, which is thought to be positively influenced by cognitively stimulating lifetime experiences such as education and occupational complexity (Stern, 2009, 2002), is theorized to protect against age- and disease-related changes in the brain (Stern et al., 2018). As such, it is expected that greater cognitive reserve would be associated with more positive outcomes during typical and pathological aging. For example, when neurodegenerative disease pathology is present in equal amounts, we would expect to see less severe cognitive impairment in individuals with higher reserve compared to those with lower reserve (Stern, 2009, 2002).

There is a large body of research supporting the protective effect of cognitive reserve, as estimated by proxies such as education level, literacy, and intellectual functioning, on incident dementia risk (e.g., Amieva et al., 2014; Brayne et al., 2010; Stern et al., 1994). However, findings on the protective effect of cognitive reserve on decline in cognition have been mixed, as the results differ depending on whether the participants are typically aging or cognitively impaired. In nonclinical older adults, cognitive reserve proxies are positively associated with baseline cognitive function, but not rate of change: that is, they do not predict rate of cognitive decline (Zahodne et al., 2011). Conversely, in individuals who are

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

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cognitively impaired and diagnosed with preclinical Alzheimer's dementia, higher standing on cognitive reserve proxies is associated with accelerated decline (Soldan et al., 2017). Similarly, of the studies that have used biomarkers of pathology, rather than clinical diagnosis, to investigate how cognitive reserve predicts cognitive decline in the presence of neuropathology, results are also mixed. Proxy measures of cognitive reserve have either been found not to predict rate of future cognitive change (e.g., Early et al., 2013; Gross et al., 2015) or predict an acceleration in decline as pathology increases (e.g., Mungas et al., 2018; Soldan et al., 2017). These findings are contrary to what we would expect from measures of cognitive reserve, given that it is hypothesized to be a process that slows or delays cognitive decline due to age- and disease-related brain changes.

The research cited previously has used proxy measures of cognitive reserve, primarily years of education, which may be limited by a range of confounding variables and circular relationships (Jones, 2003; Jones et al., 2011; Reed et al., 2010). As an alternative to proxies, Reed et al created a novel method that uses structural equation modeling to operationalize cognitive reserve as a residual term representing the difference between observed cognitive performance and what would be predicted by brain integrity and demographics. We will refer to this residual term as the residual reserve index. An individual who performs better than expected based on their brain integrity and demographics has a positive residual reserve index, which represents high cognitive reserve.

An advantage of using the residual reserve index is that, unlike proxies based on mostly static life history variables such as education, it can be used dynamically to estimate cognitive reserve at any point along the continuum from healthy aging to severe dementia. Prior studies have found that better standing on the residual reserve index not only decreased the risk of conversion to dementia but moderated the relationship between brain integrity and cognitive decline. Brain integrity, represented by global brain matter, hippocampus, and white matter hyperintensity (WMH) volumes (the same structural brain measures used to decompose memory into the residual reserve index), became a weaker predictor of cognitive decline as the residual reserve index increased (Reed et al., 2010; Zahodne et al., 2015, 2013). These findings were expected based on cognitive reserve theory and provide initial validation for Reed and colleagues' residual method of estimating cognitive reserve.

Neuropathological changes are a common occurrence during aging, even among older adults with normal cognition (Rahimi and Kovacs, 2014). Beta-amyloid and tau biomarkers are primary indicators of Alzheimer's disease (AD; Jack et al., 2010) that are often observed in typically aging individuals and can affect cognition at a subclinical level (Wennberg et al., 2019). Cognitive reserve is theorized to confer resilience to age-associated and disease-associated brain changes (Stern, 2009; Stern et al., 2018). However, it is yet to be determined whether cognitive reserve—whether estimated using proxies or using the residual reserve index—buffers against the effects of brain pathology when it is at a level consistent with typical aging, as opposed to pathology that is at a level consistent with neurodegenerative disease.

The present study seeks to answer this question by comparing the ability of the residual reserve index to predict executive function change across 2 levels of brain pathology: one level that is consistent with AD pathology (labeled as AD biomarker−positive), and another level that is more consistent with typical aging (labeled as AD biomarker−negative). These pathology levels were defined using the ratio of total tau (t-tau) to beta-amyloid ($A\beta_{1-42}$) concentration in cerebrospinal fluid (CSF) (Shaw et al., 2009), which is separate from the brain variables used to create the residual reserve index. Executive function change was used as the outcome because executive functioning decline is a common consequence of aging and AD (Buckner, 2004), and it is the only nonmemory domain for which Alzheimer's Disease Neuroimaging Initiative (ADNI) has a valid and reliable composite score available (Crane et al., 2012; Gibbons et al., 2012). By comparing the effect of the residual reserve index on executive function change across the AD biomarker−positive and −negative groups, the present study will test the theory that cognitive reserve is a process that protects cognition against both age- and disease-related brain changes (Stern et al., 2018).

Two different patterns of association between cognitive reserve, pathology, and executive function change are considered most plausible, and are presented here as competing hypotheses. The first (null) hypothesis is that greater cognitive reserve is protective against future executive function decline regardless of whether individuals are positive or negative for AD pathology biomarkers in their cerebrospinal fluid. By contrast, the second (alternative) hypothesis posits that greater cognitive reserve is more protective against executive functioning decline in the AD biomarker−positive group compared with the AD biomarker−negative group. The absence or presence of a significant interaction between the residual reserve index and pathology group will be used as evidence for or against these hypotheses.

## 2. Method

Data used in this study were obtained from the ADNI database at http://adni.loni.usc.edu/data-samples/access-data/. ADNI was launched in 2003 as a public-private partnership and is led by Principal Investigator Michael W. Weiner, MD. The goal of ADNI is to test whether the progression of mild cognitive impairment and early AD can be measured by combining biological markers, such as magnetic resonance imaging (MRI), with clinical and neuropsychological assessment. For more information, please see http://adni.loni.usc.edu/.

### 2.1. Participants

Data from 1214 participants were collected by ADNI investigators at 59 sites in North America, for phases ADNI1, ADNIGO, and ADNI2. For inclusion in ADNI, participants needed to be aged 55−90 years, in generally good health, and willing to participate in a longitudinal study that included neuroimaging and blood collection. Full inclusion and exclusion criteria can be found at http://adni.loni.usc.edu/. As part of the ADNI protocol, written informed consent was obtained from each participant, per the research ethics requirements at each participating site.

### 2.2. Magnetic resonance imaging

Baseline measures of hippocampal, whole brain, WMH, and total intracranial volume, all derived from MRI, were used. Details of ADNI's neuroimaging protocols have been described previously (Jack et al., 2008). T1-weighted MP-RAGE scans obtained from 1.5-Tesla (1.5 T) and 3.0-Tesla (3T) scanners were downloaded from the ADNI database. The images were processed using FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/), and the hippocampal and whole brain volumes were computed. Total intracranial volume was estimated using an atlas-based spatial normalization procedure in FreeSurfer (Buckner et al., 2004). A subset of ADNI participants underwent both 1.5 T and 3T imaging concurrently; the correlations between the volumes obtained using 1.5 T and 3T scans were used to obtain an estimate of measurement error for each 3T

region of interest. Data from the 1.5 T scanners were not included in the final residual model.

Preprocessed WMH volumes were downloaded directly from the ADNI database. T2-weighted FLAIR scans were performed on ADNI2 participants using 3T scanners, and WMH volumes were estimated using a Bayesian approach. Further details about ADNI's FLAIR acquisition and WMH estimation procedures for ADNI2 participants have been described in prior studies (e.g., Scott et al., 2015), and ADNI's imaging protocols can be downloaded from http://adni.loni.usc.edu/.

### 2.3. CSF biomarkers

Baseline levels of $A\beta_{1-42}$ and t-Tau in the CSF were used as measures of brain pathology for the purpose of testing whether baseline pathology moderates the relationship between the baseline residual reserve index and change in executive functioning. ADNI CSF collection and analysis procedures have been previously described (Shaw et al., 2011, 2009). Briefly, CSF was collected via lumbar puncture using a 20- or 24-gauge spinal needle after the participant had fasted for ≥6 hours. Samples were stored and shipped according to the ADNI General Procedures manuals, accessible at http://adni.loni.usc.edu/methods/documents/. $A\beta_{1-42}$ and t-Tau levels were measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX, USA), with Innogenetics (INNO-BIA AlzBio3; Ghent, Belgium; for research use–only reagents) immunoassay kit–based reagents. Owing to the variability in measurements that can occur between AlzBio3 kits, baseline CSF measures from the ADNI1 study phase were used as the criterion standard by which to rescale each subsequent batch to ensure consistency in the data (Shaw et al., 2016). Each participant's $A\beta_{1-42}$ and t-Tau measurements were median rescaled measurements downloaded from the ADNI database.

A ratio of CSF t-Tau to $A\beta_{1-42}$ (t-Tau/$A\beta_{1-42}$) was used to group participants into the AD biomarker–positive and –negative groups. Participants were assigned to groups according to a t-Tau/$A\beta_{1-42}$ cutoff of 0.39 defined for ADNI by Shaw et al. Participants who were below this cutoff were considered more likely to be experiencing typical age-related changes: they were assigned to the AD biomarker–negative group and coded as 0. Participants at or above the cutoff were considered to have pathology consistent with AD and were assigned to the AD biomarker–positive group, which was coded as 1. To be considered a useful biomarker of AD pathology, an indicator should demonstrate sensitivity and specificity of ≥85%, and a positive predictive value of ≥80% (Frank et al., 2003; Shaw et al., 2007). t-Tau/$A\beta_{1-42}$ satisfied these requirements in ADNI participants and in an independent sample of autopsy-confirmed people with AD (Shaw et al., 2009).

### 2.4. Neuropsychological data

ADNI's composite memory measure, ADNI-Mem (Crane et al., 2012), was used as the source of variance to be decomposed in the residual reserve index model (Fig. 1). ADNI-Mem was created by factor analyzing all available tests of memory used by ADNI, such as the Rey Auditory Verbal Learning Test (Rey, 1964) and the Logical Memory subtest from the Wechsler Memory Scale Revised (Wechsler, 1987). ADNI-Mem is better or equal to its constituent tests at predicting conversion to AD (Crane et al., 2012).

ADNI's composite executive function measure, ADNI-EF (Gibbons et al., 2012), was used as the distal outcome variable from which to judge the effects of the baseline residual reserve index, the pathology group at the baseline, and their interaction in a longitudinal growth model. ADNI-EF is a combination of executive function measures, including Digit Span Backwards and Digit Symbol Substitution from the Wechsler Adult Intelligence Scale 3rd edition (Wechsler, 1997), and Trail Making Test parts A and B (Reitan and Wolfson, 1985). Importantly, Gibbons et al demonstrated that ADNI-EF is more sensitive to change over time than any of its constituent executive function measures. Five years' worth of ADNI-EF data (6 visits) were used in the current analysis: baseline visits plus 5 annual follow-ups. Data from each visit were

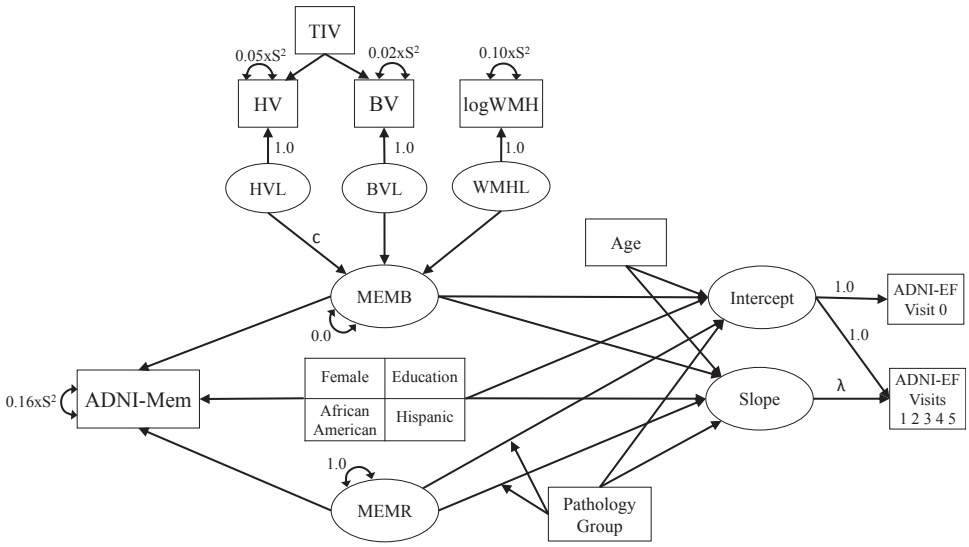


**Fig. 1.** Analytic model for decomposing memory variance and relating the variance components to longitudinal change in executive function. Rectangles represent observed variables and ovals represent latent variables. Observed demographic variables and executive function measurements at visits 1–5 have been condensed into single rectangles for simplicity. Paths are freely estimated unless labeled otherwise. Not shown: latent MRI and observed demographic variables were allowed to freely correlate, but nonsignificant correlations were constrained to zero to facilitate convergence. Correlations between MEMB, MEMR, and the demographic variables were constrained to zero to create independent memory variance components. Pathology group is the dichotomous variable representing the AD biomarker–positive and –negative groups, which were categorized according to t-Tau/$A\beta_{1-42}$ pathology cutoffs defined by Shaw et al. (2009). The interaction between pathology group and MEMR is indicated by arrows. MEMR represents the residual reserve index. $S^2$ represents sample variance. c represents a scaling constant used to fix MEMB variance to 1.0. λ represents the slope factor loadings for ADNI-EF visits 1–5.

standardized using the entire sample's mean and standard deviation at the baseline; therefore, any deviation from 0 could be interpreted as change from the sample average at the baseline.

Demographic variables were also used in the analysis. Quantitative years of education (full-time equivalent), and categorical variables for sex (1 = female, 0 = male), race (1 = African American, 0 = Caucasian), and ethnicity (1 = Hispanic, 0 = non-Hispanic) were used to define the residual reserve index. Age was included as a covariate of the ADNI-EF intercept and slope. To simplify interpretation of the results, years of education was centered on 12 years, and age was centered on the sample average of 72.65 years.

### 2.5. Statistical analyses

#### 2.5.1. Decomposition of ADNI-Mem

All analyses were completed using Mplus version 8 (Muthén and Muthén, 2017). A structural equation model (Fig. 1) was used to decompose ADNI-Mem variance into variance due to demographic variables, variance due to structural brain measures (MEMB), and residual variance (MEMR). MEMR, which is the residual reserve index, is conceptualized as cognitive reserve and represents the difference between observed memory performance and that which is predicted based on brain structure and demographics.

The variance in ADNI-Mem was decomposed as described by Reed et al. (2010), with one change: ADNI-Mem was regressed directly onto the observed demographic indicators, rather than being regressed onto a formative latent factor representing the demographic variables (reported as MEMD in prior studies). This did not impact the modeling of the residual reserve index, it simply allowed each demographic indicator to be used as a separate predictor of longitudinal change in ADNI-EF. This meant the influence of the residual reserve index on change in executive function could be compared directly with the influence of individual demographic predictors such as years of education.

MEMB is the variance in episodic memory explained by hippocampal volume, total brain volume, and WMH volume. Per Reed et al. (2010), these MRI volumes were transformed into single-indicator latent variables. To account for measurement error in the brain measures, the residual variances of the observed volumes were fixed to the product of their sample variance and an error estimate. The error estimates for the hippocampal and whole brain volumes were obtained by correlating 1.5 T and 3T scans performed on the same subjects at the same time point and subtracting these correlations from 1. Data from concurrent 1.5 T and 3T scans were not available for WMH volumes, so a conservative error estimate of 0.10 was used, which would correspond to a reliability estimate of 0.90. Hippocampal and total brain volumes were regressed onto total intracranial volume to control for the effect of head size. The distribution of WMH was positively skewed; therefore, it was log-transformed before being entered in the model.

The residual variance of ADNI-Mem was also fixed to account for measurement error. A conservative reliability estimate of 0.84 was obtained by correlating ADNI-Mem scores at the baseline and 6-month follow-up in people who were classed as healthy controls and negative for pathology at the baseline, as scores in this subsample would be expected to change very little because of aging or disease pathology over this length of time.

#### 2.5.2. Growth modeling of ADNI-EF

Analyses were conducted using maximum likelihood estimation with robust standard errors, as this estimator can handle missing values and non-normal distributions (Muthén and Muthén, 2017). Before being incorporated into the full model, change in ADNI-EF over five years was modeled with linear, quadratic, and logarithmic growth functions to find the best fitting model to be used in subsequent analyses.

Model fit was evaluated using the chi-square test of model fit, comparative fit index (CFI; Bentler, 1990), Tucker-Lewis Index (TLI; Tucker and Lewis, 1973), the root mean square error of approximation (RMSEA; Steiger, 1990), the standardized root mean square residual (SRMR; Jöreskog and Sörbom, 1993), the Akaike Information Criterion (AIC; Akaike, 1974), Bayesian Information Criterion (BIC; Schwarz, 1978), and adjusted BIC (aBIC; Sclove, 1987). Cutoffs for acceptable CFI, TLI, RMSEA, and SRMR indices were those recommended by Hu and Bentler (1999), and when comparing different models, a lower AIC, BIC, and aBIC were favored.

After selecting the best fitting growth function for ADNI-EF, the next step was to test the competing hypotheses regarding whether the effect of MEMR (the residual reserve index) on the ADNI-EF slope would change depending on whether participants are classed as being AD biomarker−positive or −negative at the baseline. This was achieved by regressing the latent ADNI-EF slope factor onto the interaction between the residual reserve index and pathology group (Fig. 1). A significant interaction term would indicate that pathology status moderates the effect of cognitive reserve on executive function change—that is, the effect of baseline cognitive reserve on the ADNI-EF trajectory is different between the AD biomarker−positive and AD biomarker−negative groups. As seen in Fig. 1, the remaining components of ADNI-Mem were entered as covariates. As there was a statistically significant difference in age between the AD biomarker−positive and −negative groups (Table 1), age was also entered as a covariate in the prediction of ADNI-EF intercept and slope.

## 3. Results

Of the 1214 participants whose data were used to select the most appropriate growth function for ADNI-EF, 344 were excluded from further analyses because of missing data for some predictor variables. These missing data primarily consisted of absent t-Tau/$A\beta_{1-42}$ values. The excluded participants did not differ from the included sample in terms of age, proportion of African American or Hispanic participants, years of education, or structural brain volumes. However, the excluded participants were more likely to be female, had higher baseline ADNI-Mem and ADNI-EF scores, and attended fewer follow-ups than the final sample (see Table S1 in supplementary information).

Descriptive statistics for the final sample of 870 participants are presented in Table 1. The AD biomarker−negative and AD biomarker−positive groups differed on all variables except sex. People in the AD biomarker−positive group were, on average, older, had less education, included a smaller proportion of African-American and Hispanic participants, and attended fewer visits. Their mean ADNI-Mem and ADNI-EF scores at the baseline were lower than the AD biomarker−negative group by almost one sample standard deviation.

### 3.1. Growth modeling of ADNI-EF

A linear growth model was selected as the best fitting model of ADNI-EF change, based on fit indices: CFI = 0.99; TLI = 0.99, RMSEA = 0.04, 90% C.I. 0.02−0.05; SRMR = 0.03; and lowest AIC, BIC, and aBIC. See Supplementary Table S2 for a comparison of all growth functions that were considered.

Next, the linear slope of ADNI-EF was regressed onto the residual reserve index, pathology group, their interaction, and covariates (Fig. 1). Of particular relevance to this study's hypotheses was the interaction between the residual reserve index and pathology group: a significant interaction would indicate that the residual

**Table 1**
Participant characteristics

| Variable | All ($N = 870$) | AD biomarker negative ($n = 402$) | AD biomarker positive ($n = 468$) | Difference[a] |
|---|---|---|---|---|
| Age (y) | | | | |
| Mean (SD) | 72.65 (7.26) | 71.23 (7.04) | 73.87 (7.23) | $t$ (868) = 5.44[d] |
| Clinical diagnosis | | | | |
| *n* (%) HC | 269 (30.92%) | 181 (45.02%) | 88 (18.80%) | |
| *n* (%) MCI | 458 (52.64%) | 212 (52.74%) | 246 (52.56%) | $X^2$ (2) = 139.74[d] |
| *n* (%) AD | 143 (16.44%) | 9 (2.24%) | 134 (28.63%) | |
| MMSE score | | | | |
| Mean (SD) | 27.49 (2.59) | 28.63 (1.52) | 26.51 (2.90) | $t$ (719.98) = 13.18[d] |
| Female gender | | | | |
| *n* (%) | 414 (47.6%) | 191 (47.50%) | 223 (47.60%) | $X^2$ (1) = 0.01 |
| Race/Ethnicity | | | | |
| *n* (%) African American | 32 (3.70%) | 21 (5.20%) | 11 (2.40%) | $X^2$ (1) = 5.11[c] |
| *n* (%) Hispanic | 31 (3.60%) | 20 (5.00%) | 11 (2.40%) | $X^2$ (1) = 4.26[c] |
| Education (y) | | | | |
| Mean (SD) | 16.19 (2.64) | 16.51 (2.57) | 15.91 (2.67) | $t$ (868) = 3.37[d] |
| ADNI-Mem score | | | | |
| Mean (SD) | 0.35 (0.91) | 0.81 (0.69) | −0.05 (0.88) | $t$ (860.59) = 16.13[d] |
| Baseline ADNI-EF score | | | | |
| Mean (SD) | 0.31 (1.05) | 0.73 (0.86) | −0.05 (1.07) | $t$ (864.39) = 12.00[d] |
| Hippocampal volume | | | | |
| Mean (SD) | 7023.63 (1245.36) | 7538.14 (1125.08) | 6672.16 (1202.56) | $t$ (858.95) = 10.63[d] |
| Whole brain volume | | | | |
| Mean (SD) | 894,333.83 (97,759.86) | 907,516.81 (94,113.20) | 880,941.58 (94,877.77) | $t$ (868) = 3.98[d] |
| WMH volume | | | | |
| Mean (SD) | 6.78 (9.62) | 5.10 (6.55) | 8.23 (11.45) | $t$ (609.31) = 4.52[d] |
| t-Tau/A$\beta_{1-42}$ ratio | | | | |
| Mean (SD) | 0.59 (0.49) | 0.24 (0.07) | 0.90 (0.48) | $t$ (490.13) = 29.46[d] |
| Min-max | 0.09–3.58 | 0.09–0.38 | 0.39–3.58 | |
| Number of visits | | | | |
| Mean (SD) | 3.70 (1.53) | 4.01 (1.40) | 3.43 (1.58) | $t$ (867.22) = 5.81[d] |
| *n* (%) with 1 visit[b] | 70 (8.00%) | 18 (4.50%) | 52 (11.10%) | |
| *n* (%) with 2 visits | 151 (17.40%) | 46 (11.40%) | 105 (22.40%) | |
| *n* (%) with 3 visits | 171 (19.70%) | 72 (17.90%) | 99 (21.20%) | |
| *n* (%) with 4 visits | 191 (22.00%) | 112 (27.90%) | 79 (16.90%) | |
| *n* (%) with 5 visits | 152 (17.50%) | 84 (20.90%) | 68 (14.50%) | |
| *n* (%) with 6 visits | 135 (15.50%) | 70 (17.40%) | 65 (13.90%) | |

The AD biomarker–negative group is defined by t-tau/A$\beta_{1-42}$ scores below AD pathology cutoffs defined by Shaw et al., 2009, and the AD biomarker–positive group is defined by t-tau/A$\beta_{1-42}$ scores at or above these cutoffs.
Key: HC, healthy control; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; WMH, white matter hyperintensity.
[a] The result of difference tests between the AD biomarker–positive and negative–groups.
[b] Baseline visit only.
[c] $p < .05$.
[d] $p < .001$.

reserve index exerted differential effects on ADNI-EF slope in the AD biomarker–negative group compared with the AD biomarker–positive group. The results of this analysis are presented in Table 2.

Predicted baseline ADNI-EF scores (i.e., the intercept) were influenced by both the residual reserve index and pathology group, as well as their interaction. All covariates also had significant effects on predicted baseline scores. Higher MEMB values (meaning better structural brain health), higher education, and being Caucasian, non-Hispanic, and female were all associated with a higher ADNI-EF intercept (Table 2).

The predicted rate of ADNI-EF change over five years (i.e., the slope) was not influenced by the main effect of the residual reserve index, but it was influenced by the main effect of pathology group; however, the interaction between the residual reserve index and pathology group was significant, meaning the effect of pathology group depends on the level of the residual reserve index, and vice versa. Of the covariates, only brain integrity (MEMB) and female sex had significant effects on the slope; better structural brain health and being female were both associated with slower ADNI-EF decline (Table 2).

Fig. 2 shows the expected rate of executive function change over 5 years as a function of pathology status and cognitive reserve for a reference person who is male, Caucasian, non-Hispanic, has completed 12 years of education, has average structural brain health, and is of average age (72.7 years) for this sample. For graphing purposes, the continuous residual reserve index was

**Table 2**
Predictors of the ADNI-EF intercept and slope over 5 y

| Variable | Intercept | | | Slope | | |
|---|---|---|---|---|---|---|
| | est | SE | *est/SE* | est | SE | *est/SE* |
| Constant (reference) | −0.30 | 0.08 | −3.67[b] | −0.36 | 0.13 | −2.69[a] |
| Years of education | 0.22 | 0.03 | 7.14[b] | 0.08 | 0.05 | 1.63 |
| Female | 0.10 | 0.03 | 3.08[a] | 0.11 | 0.05 | 2.28[a] |
| Age (y) | −0.15 | 0.04 | −3.84[b] | 0.09 | 0.06 | 1.50 |
| African American | −0.09 | 0.03 | −3.06[a] | 0.02 | 0.04 | 0.44 |
| Hispanic | −0.05 | 0.03 | −1.97[a] | −0.06 | 0.04 | −1.42 |
| MEMB | 0.45 | 0.04 | 11.31[b] | 0.40 | 0.06 | 6.42[b] |
| MEMR | 0.51 | 0.05 | 11.05[b] | 0.01 | 0.07 | 0.12 |
| Pathology group | −0.13 | 0.06 | −2.07[a] | −0.58 | 0.09 | −6.41[b] |
| MEMR × Pathology | 0.09 | 0.04 | 2.48[a] | 0.31 | 0.08 | 4.07[b] |

$n = 870$.
Key: *est*, standardized regression coefficient; *SE*, standard error; MEMR, the residual reserve index; Pathology group, categorical indicator of whether baseline t-tau/A$\beta_{1-42}$ values are positive or negative for AD-associated pathology (reference = AD biomarker–negative group); MEMB, variance in memory performance explained by structural brain variables.
[a] $p < .05$.
[b] $p < .001$.

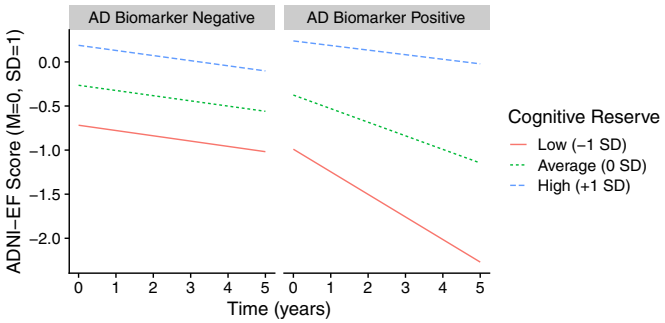


**Fig. 2.** Model-predicted change in executive function over time for a reference participant (i.e., 72.65-year-old non-Hispanic white male with 12 years of education and sample-average brain integrity [MEMB]), as a function of baseline cognitive reserve and pathology group. Executive function scores are in standard deviation units relative to baseline ADNI-EF scores. The interaction between cognitive reserve and pathology group was significant for the slope, $p < 0.001$, and the intercept, $p = 0.004$.

separated into high (one SD above average), average (0 SD), and low (one SD below average) levels. In the AD biomarker−negative group, cognitive reserve was not a strong predictor of rate of change in ADNI-EF scores.

In the AD biomarker−positive group, cognitive reserve had an important influence on how quickly ADNI-EF scores declined over 5 years, such that the predicted decline in ADNI-EF accelerated with increasingly lower levels of cognitive reserve. The slowest EF decline was seen when cognitive reserve was high: at higher levels of cognitive reserve, there was little difference in the rate of ADNI-EF decline between the AD biomarker−positive and −negative groups. These results suggest that the detrimental effect of pathology on the rate of ADNI-EF change is increasingly attenuated by higher cognitive reserve when the t-Tau/A$\beta_{1-42}$ ratio is consistent with AD, but not when the t-Tau/A$\beta_{1-42}$ ratio is more consistent with typical aging.

## 4. Discussion

The aim of the present study was to investigate whether the association between baseline cognitive reserve (when operationalized by the residual reserve index) and future executive function changes depends on whether individuals are CSF-biomarker−positive, suggesting the presence of AD-associated neuropathology. Two competing hypotheses were presented: the first (null) was that higher cognitive reserve would protect against executive function decline regardless of whether individuals are positive or negative for AD pathology; that is, there would be no significant interaction between the residual reserve index and pathology group when predicting the executive function slope. The second (alternative) hypothesis was that cognitive reserve would only protect against executive function decline in the presence of AD-associated pathology, such that there would be a significant interaction between the residual reserve index and pathology group when predicting executive function slope. These hypotheses allowed us to test the theory that cognitive reserve is an active process that protects against both age- and AD-related brain changes (Stern et al., 2018).

The current results failed to support the first hypothesis. The effect of baseline cognitive reserve on executive function decline was not uniform across both pathology groups. By contrast, the second hypothesis was supported, as there was a significant interaction between the baseline residual reserve index and baseline pathology group. When AD-associated pathology was present, cognitive reserve exerted a strong positive effect on executive function slope, such that higher standing on the residual reserve index was associated with slower decline, which is what we would expect from cognitive reserve as a process that provides resilience to brain pathology. Conversely, cognitive reserve was not predictive of change in executive function in the AD biomarker−negative group, suggesting cognitive reserve's protective effects are only active in the context of clinically significant pathological changes such as those seen in AD. This is inconsistent with theories of cognitive reserve that frame this construct as a process that delays or slows cognitive changes in response to both age- and disease-related brain changes (Stern, 2009; Stern et al., 2018).

This finding leads to the question of whether there must be a certain degree of neuropathological burden before cognitive reserve can influence future cognitive outcomes. Although our study demonstrated that the residual reserve index could not predict future change in executive function when the baseline t-Tau/A$\beta_{1-42}$ ratio was below the cutoff for AD pathology, it was beyond the scope of the study to determine whether this is a characteristic of the residual reserve index when measured cross-sectionally, or whether cognitive reserve processes are simply not engaged when pathology is below a certain threshold. Future research that tracks both the residual reserve index and AD-related pathology processes longitudinally can further investigate this issue. Over five years of follow-up, AD pathology burden would be expected to appear and/or increase in a proportion of participants (Jack et al., 2010), even among those who were AD biomarker−negative. It may be possible to identify a point at which AD-related pathology has accumulated sufficiently to provoke an effect of cognitive reserve on cognition, even in individuals who do not develop a clinically significant burden.

Although some studies have found that cognitive reserve is a less powerful predictor of cognition when brain volume changes are less pronounced (Reed et al., 2010; Zahodne et al., 2015, 2013), the present study adds to this literature by demonstrating that the ability of the residual reserve index to predict future cognitive outcomes depends on whether clinically significant AD CSF biomarkers are present at the baseline. As mentioned in the introduction, one advantage of the residual reserve index is that it is capable of measuring the dynamic nature of cognitive reserve as it changes over time. This feature makes it particularly amenable to the study of interventions to enhance cognitive reserve, which, in theory, should be most valuable when the interventions take place before the emergence of clinically meaningful pathological changes. However, if, as our current results suggest, the predictive ability of cognitive reserve depends on the extent of pathology present, it is unclear whether interventions aimed at boosting cognitive reserve in typically aging individuals can protect against future cognitive decline. Given that our results come from observational data, experimental studies aimed at enhancing reserve are needed to answer such questions.

Although baseline cognitive reserve and pathology status interact to affect executive function slope, executive function slope itself results from concomitant changes in brain integrity and cognitive reserve. Because this study used baseline measurements of cognitive reserve and brain pathology as predictors of future executive function change, it did not evaluate the degree to which these variables themselves changed over time, along with the observed executive function change. In other words, a negative executive function slope could be a consequence of accumulating pathological burden combined with maintenance of—or increase in—cognitive reserve, stable brain integrity combined with a depletion of cognitive reserve, or a combination of accumulating pathology and a depletion of cognitive reserve. Therefore, future research may benefit from separating observed cognitive outcomes such as executive function slope into their constituent cognitive reserve and brain maintenance (Stern et al., 2018) components to

better understand the interaction effect reported here. Such an approach could lead to a more nuanced understanding of whether the interaction between baseline cognitive reserve and baseline pathology is differentially predictive of changes in cognitive reserve versus changes in brain integrity over time. Although we did not attempt to measure brain reserve or brain maintenance per se, our results suggest a possible interaction between these variables, whereby cognitive reserve may only exert its protective effects in the context of low brain reserve or low brain maintenance (Nyberg et al., 2012).

Even though baseline cognitive reserve offered limited ability to predict future executive function decline in the context of AD-negative biomarker status, this does not mean that cognitive reserve is unimportant in the absence of neuropathology. Although there was a significant interaction between pathology group and cognitive reserve when predicting the intercept, Fig. 2 shows higher baseline cognitive reserve was associated with better executive function performance at the baseline in both the AD biomarker−positive and −negative groups, and this benefit extended to follow-up visits. This finding is consistent with past research that has found a protective effect of the residual reserve index on baseline cognition, but not rate of change, in nonclinical older adults (Zahodne et al., 2011). All else equal, the better baseline cognitive performance associated with higher cognitive reserve is likely to promote sustained cognitive health into late life.

Previous research using cognitive reserve proxies has suggested that individuals with high standing on the chosen proxy tend to decline more rapidly after a certain threshold of disease severity has been reached (e.g., Soldan, 2017). Our results suggest the opposite: that having higher baseline cognitive reserve is associated with less rapid cognitive decline after a certain threshold of disease severity has been reached. These seemingly contradictory patterns can be explained well in the context of 2 recent studies. First, Mungas et al. (2018) explained that the unexpectedly rapid decline in high cognitive reserve individuals is a consequence of using education—which interacts with brain atrophy rate to influence cognitive decline—as a proxy for cognitive reserve. This distinction between cognitive reserve and education was also made apparent by Bettcher et al. (2019), who found that rate of cognitive decline could be explained by how rapidly cognitive reserve was depleted, independent of brain atrophy rate and baseline levels of cognitive reserve; such an effect would be masked by static proxies such as years of education. Therefore, recent evidence, including the results of this study, appears to disconfirm the hypothesis that individuals with higher baseline cognitive reserve should be expected to decline more rapidly than individuals with lower baseline cognitive reserve once a disease severity threshold has been reached.

One limitation of this study is that most participants were Caucasian and highly educated, which limits our ability to generalize these findings to more demographically diverse samples. Furthermore, the findings only cover five years' worth of follow-up: it is possible that more time would be needed to elicit meaningful changes in executive function in typically aging older adults; therefore, the protective effect of cognitive reserve on executive function decline may have emerged in the AD biomarker−negative group with a longer period of follow-up. Finally, our results are specific to executive functioning decline and not decline in other cognitive domains. We used executive functioning as the primary outcome measure because the ADNI neuropsychological battery is heavily weighted toward the assessment of memory and executive functioning, and because of the availability of the reliable and valid ADNI-EF composite measure. Such a composite score was not available for other cognitive domains, preventing us from further generalizing these findings to other abilities. By contrast, strengths of this study include the use of a measure of pathology (t-Tau/$A\beta_{1-42}$) that was methodologically separate from the measures used to create the residual reserve index (global brain volume, hippocampal volume, and WMH), which augments previous studies using the residual method for measuring cognitive reserve (e.g., Zahodne et al., 2015, 2013), and adds to the growing body of research on the effect of cognitive reserve on cognitive change, which includes very few studies that measure pathology using biomarkers (Soldan et al., 2018).

A final limitation to consider is that we classified participants into groups based on one specific AD biomarker (the t-Tau/$A\beta_{1-42}$ ratio); therefore, we could not rule out the presence of non-AD disease pathologies across the entire sample, nor could we account for nonprogressive causes of neuronal injury that would not be expected to promote rapid cognitive decline. It is possible that for a small number of participants in the AD biomarker−negative group, it may be inaccurate to consider them typically aging if other neurodegenerative disease pathology is present. Although it is unlikely this biased our results—as the AD biomarker−negative group was, on average, cognitively intact and ADNI excludes participants thought to have non-AD pathology—the question of whether different biomarkers might have changed the predictive power of the residual reserve index remains unanswered in the present study.

As cognitive reserve must originate in the brain, the residual reserve index, which was used as our estimate of cognitive reserve, is almost certainly influenced by unmeasured brain variables, such as those that can be captured with microstructural imaging (e.g., diffusion imaging), functional imaging, and molecular imaging. Therefore, our current results suggest that baseline standing on those unmeasured brain variables may not be able to predict rate of cognitive decline in the absence of AD (or other neurodegenerative) pathology. This notion is consistent with the scaffolding theory of aging and cognition, which posits that supplemental neural structures and functions, built largely through lifestyle enrichment, are called on to support cognition when confronted by neuropathological changes (Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Park, 2014). The idea that the residual reserve index could be explained by these unmeasured brain variables (e.g., resting state connectivity, neural efficiency, white matter integrity) also suggests that, in theory, incorporating more brain imaging techniques, such as functional imaging, could eventually identify the neural basis of what we currently refer to as cognitive reserve. As such, defining cognitive reserve as the variance in episodic memory not explained by a set of brain variables allows for systematic study of how the residual reserve index functions when the set of brain variables changes. Estimating cognitive reserve in this way is therefore likely to be more successful than other approaches (e.g., years of education) at building cumulative scientific knowledge.

### 4.1. Summary and conclusions

The present study adds to the cognitive aging literature by providing new information about how cross-sectional cognitive reserve, as measured by the residual reserve index, predicts longitudinal executive function decline in a sample with wide variability in tau and beta-amyloid neuropathology. We sought to determine whether the residual reserve index could predict future executive functioning decline equally well in people who were positive and negative for AD-associated CSF biomarkers, and found that it could not, which supports the hypothesis that cognitive reserve is only predictive of cognitive decline when AD-associated pathology is present. Although typically aging people can vary in baseline cognitive reserve when measured using the residual reserve index, this variability appears to offer no value in predicting how rapidly their executive function will decline over the next five years. This

finding is inconsistent with the theory that cognitive reserve protects against brain changes due to typical aging as well as disease processes and suggests it may only be activated when disease pathology surpasses a particular threshold. Future studies investigating the interplay between concomitant changes in cognitive reserve and pathology over time can shed more light on at which point during the evolution of pathology cognitive reserve emerges as a process that buffers cognition against the effects of neurodegeneration.

## Disclosure statement

None of the authors have financial or personal conflicts of interest related to this work.

## CRediT authorship contribution statement

**Cathryn McKenzie:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Visualization, Validation, Investigation. **Romola S. Bucks:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration. **Michael Weinborn:** Conceptualization, Writing - review & editing, Supervision, Project administration. **Pierrick Bourgeat:** Methodology, Formal analysis, Writing - review & editing, Supervision, Validation, Project administration. **Olivier Salvado:** Methodology, Formal analysis, Writing - review & editing, Supervision, Validation, Project administration. **Brandon E. Gavett:** Conceptualization, Methodology, Formal analysis, Writing - review & editing, Visualization, Supervision, Validation, Investigation, Project administration.

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The research presented in this manuscript uses data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Written informed consent was obtained from each participant, and data collection was overseen by the human research review boards at each participating ADNI site. The authors used the data in accordance with ADNI's Data Use Agreement. ADNI's Data and Publication Committee has reviewed the manuscript and advised us it meets the requirements of their Agreement and is acceptable for submission. The manuscript has never been published, nor is it being considered for publication in another journal. All of the authors have contributed significantly to the manuscript and they agree with the presented findings.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.12.022.

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