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Research Article

Tau and amyloid biomarkers modify the degree to which cognitive reserve and brain reserve predict cognitive decline

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Abstract

Objective: Brain reserve, cognitive reserve, and education are thought to protect against late-life cognitive decline, but these variables have not been directly compared to one another in the same model, using future cognitive and functional decline as outcomes. We sought to determine whether the influence of these protective factors on executive function (EF) and daily function decline was dependent upon Alzheimer's disease (AD) pathology severity, as measured by the total tau to beta-amyloid (T-τ/A$\beta_{1\text{-}42}$) ratio in cerebrospinal fluid (CSF). **Method:** Participants were 1201 older adult volunteers in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. Brain reserve was defined using a composite index of structural brain volumes (total brain matter, hippocampus, and white matter hyperintensity). Cognitive reserve was defined as the variance in episodic memory performance not explained by brain integrity and demographics. **Results:** At higher levels of T-τ/A$\beta_{1\text{-}42}$, brain and cognitive reserve predicted slower decline in EF. Only brain reserve attenuated decline at lower levels of T-τ/A$\beta_{1\text{-}42}$. Education had no independent association with cognitive decline. **Conclusions:** These results point to a hierarchy of protection against aging- and disease-associated cognitive decline. When pathology is low, only structural brain integrity predicts rate of future EF decline. The ability of cognitive reserve to predict future EF decline becomes stronger as CSF biomarker evidence of AD increases. Although education is typically thought of as a proxy for cognitive reserve, it did not show any protective effects on cognition after accounting for brain integrity and the residual cognitive reserve index.

Keywords: Alzheimer disease; Amyloid beta-peptides; Tau proteins; educational achievement; neuropsychological tests; cognitive aging

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Reserve is commonly invoked to explain why some individuals are more resilient to the cognitive effects of brain aging and neuropathology than others (Arenaza-Urquijo & Vemuri, 2020). Two independent types of reserve have been proposed: brain reserve, which represents passive neurobiological "capital," and cognitive reserve, which represents the capacity for cognitive processes to adapt to disease-related change (Stern, 2009). Brain reserve may be estimated as the neural resources available at any one time (e.g., gray matter volume) or using proxies for "peak" capital (e.g., total intracranial volume). Cognitive reserve is traditionally defined using proxy measures, such as years of education (Opdebeeck et al., 2016; Stern et al., 2020); such proxies are not, however, synonymous with cognitive reserve (Jones et al., 2011; Reed et al., 2010). An alternative method for measuring cognitive reserve, the residual reserve index, is to define it as the residual variance in memory performance after accounting for the variance explained by brain structure and demographic variables (Reed et al., 2010).

Despite the finding that cognitive reserve, measured by the residual reserve index, is associated with better baseline executive function (EF), it is not able to predict future changes in EF unless tau and amyloid biomarkers in cerebrospinal fluid (CSF) are consistent with Alzheimer's disease (AD; McKenzie et al., 2020). This leads to an important question: If cognitive reserve does not predict the rate of future EF decline in people without CSF evidence of AD pathology, what does? The current study seeks to answer this question by considering two candidate predictors: structural brain integrity and years of education.

Existing literature supports the role of structural brain integrity as a predictor of cognitive functioning in older adults with and without dementia. Cortical and hippocampal volumes predict cognitive performance in typically aging older adults, as well as those with AD (Adak et al., 2004; Fletcher et al., 2018; Kaup et al., 2011; Mungas et al., 2002; 2005). Further, neuroimaging studies show that changes in regional brain volumes can be detected over as little as one year in cognitively healthy participants, including those at low risk of

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developing AD (Fjell et al., 2013; Fjell & Walhovd, 2010). Together, these findings indicate that structural brain volumes can predict cognitive decline regardless of whether AD neuropathology has developed, which suggests structural brain integrity may be a robust predictor of future cognitive decline.

Our second candidate predictor is education, a common proxy for cognitive reserve (Opdebeeck et al., 2016), which we model as statistically independent from the residual reserve index. Higher education is associated with reduced risk of dementia (e.g., Brayne et al., 2010), but findings are mixed regarding its association with cognitive decline: some studies find no association between education and rate of cognitive decline, others find higher education predicts faster decline (Soldan et al., 2017; Zahodne et al., 2011), and others report that the direction of the association depends on brain atrophy (Mungas et al., 2018). Other recent work has revealed that education does not moderate the effect of brain pathology on baseline or longitudinal cognition in participants with mild cognitive impairment or AD (Bauer et al., 2019). Thus, education does not appear to meet a necessary criterion for cognitive reserve proxies, which is that a proxy should uniformly protect against cognitive decline in the presence of brain pathology (Stern et al., 2020). Most studies using education as a cognitive reserve proxy have not examined its independent association with cognition after accounting for brain reserve and other indicators of cognitive reserve, such as the residual reserve index. Thus, it is important to directly compare the independent effects of education, structural brain integrity, and the residual reserve index on cognitive decline, in participants with and without CSF evidence of AD pathology, to best understand how, together, these variables promote late-life cognitive health.

The aim of this study was to quantify the extent to which baseline structural brain integrity, the baseline residual reserve index, and years of education independently predict rate of change in two outcomes relevant to dementia: EF performance and informant-rated daily function. We sought to understand whether the strength of association between these variables and future cognitive and functional decline depends on the level of AD pathology, as measured by the ratio of total tau to beta-amyloid (T-τ/A$\beta_{1\text{-}42}$) in the CSF at baseline. Education and the residual reserve index will be defined as statistically independent from one another, thus allowing us to determine whether education has incremental validity as a predictor of outcomes after accounting for the residual reserve index. If education is a significant predictor, that would mean it has unique value as a proxy for cognitive reserve above and beyond its contribution to episodic memory performance.

This study explores three hypotheses. First, given our previous findings (McKenzie et al., 2020), we hypothesize that the residual reserve index will interact with T-τ/A$\beta_{1\text{-}42}$ such that it is a poorer predictor of future EF and daily function change at lower levels of T-τ/A$\beta_{1\text{-}42}$ and a stronger predictor of future EF and daily function change at higher levels of T-τ/A$\beta_{1\text{-}42}$. Second, given that structural brain integrity appears to be a robust predictor of cognitive decline in the literature, we hypothesize that structural brain integrity will predict EF and daily function decline at all levels of T-τ/A$\beta_{1\text{-}42}$. Third, considering recent findings by Bauer and colleagues (2019), our third hypothesis is that education will not be a significant predictor of change in EF and daily function after the effects of the residual reserve index and structural brain integrity are accounted for.

Method

Data were obtained from the ADNI database at https://adni.loni.usc.edu/data-samples/access-data/. ADNI was launched in 2003. A public-private partnership led by Michael W. Weiner, the goal of ADNI is to test whether the progression of mild cognitive impairment and early AD can be measured by combining biological markers with clinical and neuropsychological assessment (see https://adni.loni.usc.edu/).

Participants

Data from 2238 participants, aged 55–90 years, were collected by ADNI investigators at 59 sites in North America; the current study uses data from phases ADNI1, ADNIGO and ADNI2. Full inclusion criteria can be found at https://adni.loni.usc.edu/. Written informed consent was obtained from each participant, per the research ethics requirements at each ADNI site. Because the current study used de-identified archival data from ADNI, it was exempted from human subjects review by our institutional ethics committee.

Magnetic resonance imaging

Baseline measures of hippocampal, whole brain, and white matter hyperintensity (WMH) volumes obtained from 1.5-Tesla (1.5T) and 3.0-Tesla (3T) scanners were downloaded directly from the ADNI database (neuroimaging protocols have been described previously; Jack et al., 2008). 1.5T MRI data were used to obtain an estimate of measurement error in each 3T region of interest; only 3T MRI data were used to test this study's hypotheses. Further details regarding the MRI data can be found in Supplementary Materials, with ADNI's imaging protocols downloadable from https://adni.loni.usc.edu/.

Cerebrospinal fluid biomarkers

Baseline levels of A$\beta_{1\text{-}42}$ and total tau (T-tau) in the CSF were used as biomarkers for AD pathology. ADNI CSF collection and analysis procedures have been previously described (Shaw et al., 2016; Shaw et al., 2009; 2011). Each participant's A$\beta_{1\text{-}42}$ and T-tau measurements were downloaded directly from the ADNI database. The T-τ/A$\beta_{1\text{-}42}$ ratio was used as a continuous measure of neuropathological burden. This variable was standardized when used in analyses.

Neuropsychological data

ADNI's composite measure of memory performance, ADNI-Mem (Crane et al., 2012), was used as the source of variance to be decomposed to create the baseline residual reserve index, per the original decomposition model by Reed et al. (2010). Crane and colleagues (2012) demonstrated that ADNI-Mem is equal to or better than its constituent memory tests when predicting conversion to dementia due to AD.

ADNI's composite measure of EF tests, ADNI-EF, was used as one longitudinal outcome variable. Gibbons and colleagues (2012) demonstrated that change over time can be detected more sensitively using ADNI-EF compared to its constituent EF measures. The second distal outcome variable used in the analysis was the informant-rated Everyday Cognition questionnaire (ECog; Tomaszewski Farias et al., 2008). The ECog measures changes in cognitively-loaded everyday tasks across domains such as memory and EF. The informant-rated ECog is a valid measure of clinical outcomes (Rueda et al., 2015). The ECog is scored on a scale of 1–4, where 1 = better or no change compared to 10 years earlier, and 4 = consistently much worse. To facilitate interpretation of the results, ECog scores were reverse coded such that

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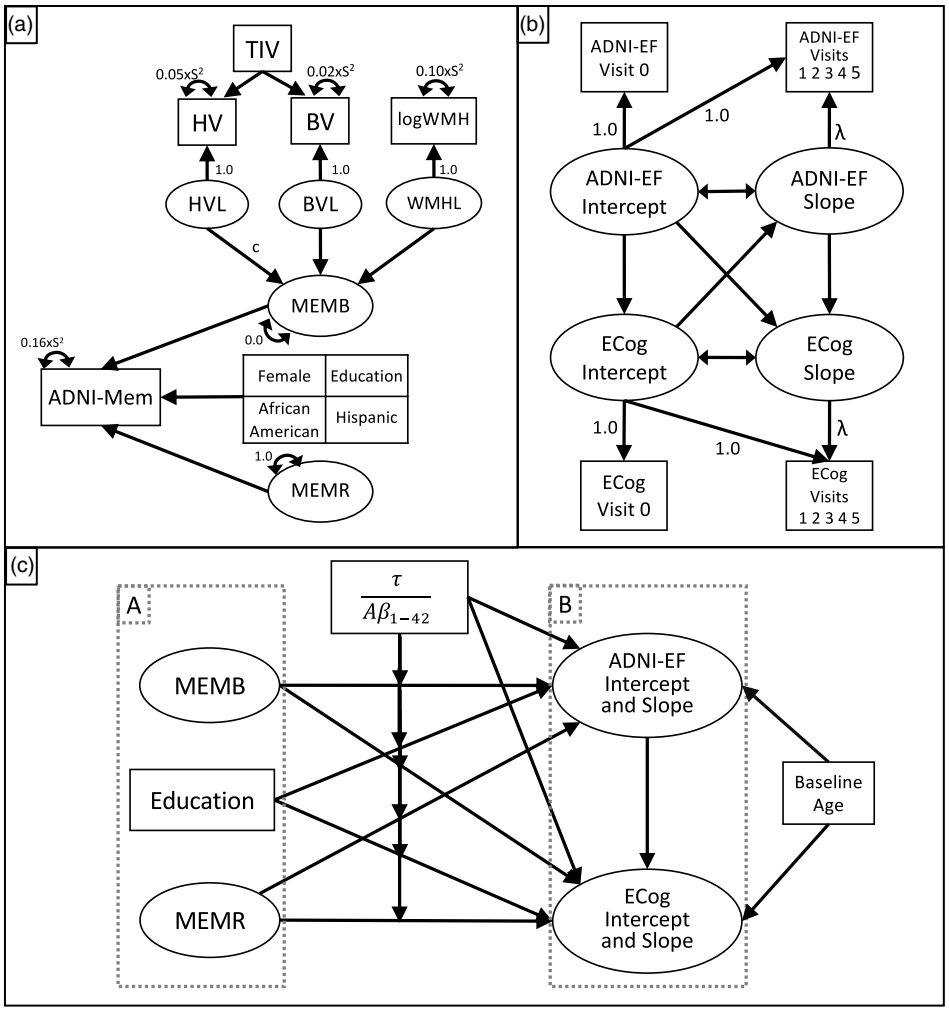

Figure 1. Schematic diagram for decomposing memory variance and relating the variance components to longitudinal change in executive function and daily function. Rectangles represent observed variables and ovals represent latent variables. Observed demographic variables and outcome measurements at visits 1–5 have been condensed into single rectangles for ease of interpretation. Paths are freely estimated unless labeled otherwise. Double-ended arrows represent correlations. A. the decomposition model used to define the latent variables representing structural brain integrity (MEMB) and the residual reserve index (MEMR). S^2 = sample variance (fixed to account for measurement error). c = scaling constant used to fix MEMB variance to 1.0. Not shown: latent MRI and observed demographic variables were allowed to freely correlate, but non-significant correlations were constrained to zero to facilitate convergence. Correlations between MEMB, MEMR, and the demographic variables were constrained to zero in order to create independent memory variance components. B. The parallel growth model used to obtain intercepts and linear slopes for ADNI-EF and ECog over five years. λ represents the slope factor loadings. C. Vertical arrows represent the interactions between the T-τ/A$\beta_{1\text{-}42}$ ratio and MEMB, MEMR, and education, when predicting ADNI-EF and ECog intercepts and slopes. Not shown: indicators of sex, race, and ethnicity were also entered as covariates of the intercepts and slopes.

1 = consistently much worse, and 4 = better or no change compared to 10 years earlier. The 39 ECog items are averaged to obtain the ECog total score. ADNI-EF and ECog data were collected at baseline and over five annual follow-ups.

Demographic variables were used as predictors of ADNI-Mem performance to ensure that the residual reserve index was not capturing variance explained by these factors. In particular, years of education (full-time equivalent), and categorical variables for sex (1 = male, 0 = female), race (1 = African American, 0 = Caucasian), and ethnicity (1 = Hispanic, 0 = non-Hispanic) were used to define the residual reserve index. Baseline age was included as a covariate of the ADNI-EF and ECog intercepts and slopes. Years of education was centered on 12 years and age was centered on 72 years.

Statistical analyses

All analyses were completed in Mplus version 8 (Muthén & Muthén, 2017) using maximum likelihood estimation with robust standard errors. Missing data was handled using full information maximum likelihood, which uses all available data to estimate model parameters. The three primary analysis steps are shown in Figure 1. Supplementary Materials contain a full description of the statistical analyses.

Figure 1A shows the structural equation model, adapted from Reed and colleagues (2010), used to decompose ADNI-Mem variance into variance due to demographic variables, variance due to structural MRI measures (MEMB; an index of structural brain integrity), and residual variance (MEMR; the residual reserve index). We accounted for measurement error in the observed MRI volumes and ADNI-Mem scores by fixing their residual variance to the product of their sample variance and an error estimate obtained using test-retest correlations. Such a correlation was not available for WMH volume, so a conservative reliability estimate of .90 was chosen to be consistent with Reed et al.'s (2010) work. The distribution of WMH volume was strongly positively skewed, so it was log-transformed prior to analysis. Hippocampal and total brain volumes were regressed onto total intracranial volume to control for the effect of head size. WMH and total intracranial volume were allowed to correlate, to account for shared variance between them.

Figure 1B shows the growth model used to model change in ADNI-EF and ECog (the outcome variables) over five years. Linear slopes were chosen as our previous work found linear growth provided the best and most parsimonious fit to the data (McKenzie et al., 2020). Both ADNI-EF and ECog were entered as separate outcomes within the growth model; however, given that prior research has established a directional association between EF and daily function abilities (e.g., Tomaszewski Farias et al., 2009),

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Table 1. Participant characteristics at baseline

Variable	All (N = 1201)	t/Aβ- (n = 523)	t/Aβ+ (n = 678)	Difference
Age (years) M (SD)	73.32 (7.26)	72.14 (7.15)	74.23 (7.23)	$t(1199) = 4.99$†
Sex N (%) male	663 (55.20)	288 (55.10)	375 (55.31)	$X(1) = 0.01$
Race/ethnicity N (%) African American	44 (3.7)	29 (5.54)	15 (2.21)	$X(1) = 9.29$†
N (%) Hispanic	34 (2.8)	20 (3.82)	14 (2.06)	$X(1) = 3.32$
Education (Years) M (SD)	16.04 (2.78)	16.28 (2.71)	15.86 (2.82)	$t(1199) = 2.63$†
Baseline Diagnosis				$X(2) = 188.52$‡
N (%) CN	369 (30.72)	246 (47.04)	123 (18.14)	
N (%) MCI	606 (50.46)	256 (48.95)	350 (51.62)	
N (%) Dementia	226 (18.82)	21 (4.01)	205 (30.24)	
ADNI-Mem M (SD)	0.26 (0.90)	0.72 (0.73)	−0.10 (0.86)	$t(1186.26) = 17.86$‡
ADNI-EF M (SD)	0.18 (1.05)	0.62 (0.89)	−0.15 (1.04)	$t(1184.68) = 13.75$‡
ECog score M (SD)	3.27 (0.73)	3.58 (0.47)	3.00 (0.81)	$t(668.59) = 12.18$‡
CDR sum of boxes M (SD)	1.59 (1.78)	0.82 (1.15)	2.19 (1.95)	$t(1127.04) = 15.15$‡
Hippocampal volume (cm^3) M (SD)	6.85 (1.18)	7.32 (1.08)	6.48 (1.12)	$t(996.86) = 12.34$‡
Whole brain volume (cm^3) M (SD)	1031.14 (110.94)	1048.70 (108.87)	1017.50 (110.68)	$t(1158) = 4.80$‡
White matter hyperintensity volume (cm^3) M (SD)	4.80 (8.74)	3.84 (6.03)	5.46 (10.15)	$t(995.79) = 3.20$†
Total intracranial volume (cm^3) M (SD)	1527.33 (166.61)	1524.34 (164.74)	1529.68 (168.14)	$t(1125.91) = 0.55$
CSF t-tau (pg/mL) M (SD)	90.79 (54.90)	51.60 (16.50)	121.02 (55.06)	$t(829.26) = 31.07$‡
CSF $A\beta_{1\text{-}42}$ (pg/mL) M (SD)	174.62 (54.55)	219.34 (41.47)	140.13 (34.80)	$t(1012.65) = 35.16$‡
T-τ/$A\beta_{1\text{-}42}$ ratio M (SD)	0.62 (0.51)	0.24 (0.07)	0.92 (0.51)	$t(709.60) = 34.02$‡
Range	[0.086, 4.459]	[0.086, 0.39]	(0.39, 4.459]	–
Number of visits M (SD)	4.50 (2.22)	5.03 (2.20)	4.09 (2.14)	$t(1199) = 13.49$‡

Note: T-τ/$A\beta_{1\text{-}42}$ groupings are based on Shaw et al. (2009); t/Aβ- refers to participants with CSF biomarkers levels that are consistent with typical aging, whereas t/Aβ+ refers to participants with CSF biomarkers levels that are consistent with AD. ECog scores are recoded such that lower scores represent greater functional impairment relative to 10 years prior. CN = cognitively normal; MCI = mild cognitive impairment; CDR = Clinical Dementia Rating Scale.
†$p < 0.05$.
‡$p < 0.001$.

we modeled change in ADNI-EF as an additional predictor of change in ECog.

To test this study's hypotheses, the latent ADNI-EF and ECog slope factors were regressed onto the interactions between the T-τ/$A\beta_{1\text{-}42}$ ratio and structural brain integrity, the T-τ/$A\beta_{1\text{-}42}$ ratio and the residual reserve index, and the T-τ/$A\beta_{1\text{-}42}$ ratio and education (Figure 1C). A significant interaction term would indicate that the effect of the independent variable on EF or daily function change differed depending on participants' baseline T-τ/$A\beta_{1\text{-}42}$ ratio.

Results

Of 2238 participants, data from 1201 were used (CSF biomarker data were unavailable for 1037). All 1201 participants had ADNI-EF scores available at baseline. There were 1028 (85.6%) participants with ADNI-EF data available at visit 2, 911 (75.9%) participants with ADNI-EF data available at visit 3, 549 (45.7%) participants with data available at visit 4, 497 (41.4%) with data available at visit 5, and 280 (23.3%) with data available at visit 6. For ECog, there were 785 (65.4%) participants with data available at baseline, 638 (53.1%) participants with data available at visit 2, 573 (47.7%) with data available at visit 3, 319 (26.6%) with data available at visit 4, 430 (35.8%) with data available at visit 5, and 293 (24.4%) with data available at visit 6. Participant characteristics are presented in Table 1. When categorizing T-τ/$A\beta_{1\text{-}42}$ into high (typical for AD) and low (typical for normal aging) groups using an established threshold (Shaw et al., 2009), the two groups differed on all variables except sex, proportion of Hispanic participants, and total intracranial volume. Table 2 shows the results obtained from regressing the ADNI-EF and ECog slopes onto our variables of interest and their interactions with CSF pathology (Figure 1C).

Daily functioning

The ECog intercept was influenced by the residual reserve index, T-τ/$A\beta_{1\text{-}42}$, and their interaction, as well as structural brain integrity, but not its interaction with T-τ/$A\beta_{1\text{-}42}$. The ADNI-EF slope was the only significant predictor of the ECog slope, such that a more positive ADNI-EF slope predicted a slower ECog decline.

Executive functioning

The ADNI-EF intercept was influenced by the residual reserve index and its interaction with the T-τ/$A\beta_{1\text{-}42}$ ratio, as well as the main effects of years of education and structural brain integrity. Because the latter two variables, education and brain integrity,

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Table 2. Predictors of the ADNI-EF and ECog intercepts and slopes over 5 years

	Outcome: ADNI-EF						Outcome: ECog					
	Intercept			Slope			Intercept			Slope		
Predictor Variable	*est*	*SE*	*est/SE*	*est*	*SE*	*est/SE*	*est*	*SE*	*est/SE*	*est*	*SE*	*est/SE*
Constant (reference)	1.13	0.28	3.98†	−1.02	0.45	−2.26†	−1.04	0.35	−2.94†	−1.04	0.47	−2.24†
T-τ/A$\beta_{1\text{-}42}$	0.01	0.04	0.88	−0.30	0.08	−3.83†	−0.19	0.06	−3.38†	−0.05	0.08	−0.58
Years of Education	0.23	0.04	6.30†	0.08	0.06	1.44	0.05	0.05	0.89	0.03	0.06	0.50
MEMR	0.50	0.04	11.79†	0.01	0.08	0.93	0.36	0.07	5.42†	−0.04	0.09	−0.43
MEMB	0.48	0.04	11.73†	0.39	0.08	5.04†	0.48	0.06	7.74†	0.05	0.09	0.58
MEMR x T-τ/A$\beta_{1\text{-}42}$	0.08	0.03	2.82†	0.33	0.06	5.91†	0.09	0.04	2.10†	0.11	0.08	1.50
MEMB x T-τ/A$\beta_{1\text{-}42}$	−0.02	0.03	0.60	0.06	0.05	1.16	0.03	0.04	0.76	0.04	0.05	0.77
Education x T-τ/A$\beta_{1\text{-}42}$	−0.07	0.05	−1.34	0.09	0.68	0.14	0.09	0.06	1.46	−0.08	0.09	−0.91
ADNI-EF Intercept							0.00	0.07	0.04	0.18	0.09	1.94
ECog Intercept				−0.05	0.08	−0.62						
ADNI-EF slope										0.56	0.09	6.04†

Note. $n = 1201$. est = standardized regression coefficient; SE = standard error; MEMR = the residual reserve index; MEMB = an index of memory-relevant structural brain integrity. ECog scores are reverse coded such that lower scores represent greater functional impairment relative to 10 years prior.
†$p < 0.05$.

did not interact with the T-τ/A$\beta_{1\text{-}42}$ ratio, their effect on the executive functioning intercept was constant across all levels of pathology.

When predicting the ADNI-EF slope, there were significant main effects of structural brain integrity and the T-τ/A$\beta_{1\text{-}42}$ ratio. In addition, there was a significant residual reserve index by T-τ/A$\beta_{1\text{-}42}$ ratio interaction term. The T-τ/A$\beta_{1\text{-}42}$ ratio did not interact with structural brain integrity, meaning that the main effect of this variable on ADNI-EF slope was consistent across all levels of CSF pathology. Similarly, the T-τ/A$\beta_{1\text{-}42}$ ratio did not interact with years of education, but because there was also no main effect of education on ADNI-EF slope, these results show that education did not offer any unique ability to predict future executive functioning changes.

Figure 2 shows model-predicted ADNI-EF scores for a reference individual as a function of the interactions between T-τ/A$\beta_{1\text{-}42}$ and (2A) structural brain integrity, (2B) the residual reserve index, and (2C) education. For graphing purposes, structural brain integrity and the residual reserve index were split into low (1 SD below sample average), average (0 SD), and high (1 SD above average) levels; similarly, the T-τ/A$\beta_{1\text{-}42}$ ratio was split into low (−1 SD; less pathology than average) and high (+1 SD; more pathology than average) categories.

Figure 2A shows that higher baseline structural brain integrity predicted higher ADNI-EF at baseline, and that this effect on the intercept did not significantly differ based on T-τ/A$\beta_{1\text{-}42}$. Similarly, higher baseline structural brain integrity was protective against rapid ADNI-EF decline in both groups; this protective effect against rapid ADNI-EF decline was not dependent upon baseline T-τ/A$\beta_{1\text{-}42}$ levels.

In contrast, the relationship between the residual reserve index and ADNI-EF performance was dependent upon the T-τ/A$\beta_{1\text{-}42}$ ratio, as shown in Figure 2B. In general, higher standing on the residual reserve index predicted higher baseline ADNI-EF and less rapid ADNI-EF decline, but these effects were more pronounced at higher levels of T-τ/A$\beta_{1\text{-}42}$.

To facilitate interpretation of the interaction effects reported above, simple slopes were calculated (Preacher et al., 2006). Figure 3 shows the average rate of change in ADNI-EF slope for low (−1 SD) and high (+1 SD) levels of T-τ/A$\beta_{1\text{-}42}$, as predicted by (A) baseline structural brain integrity, (B) the residual reserve index, and (C) years of education. Predicted rate of ADNI-EF decline was attenuated by better structural brain integrity, regardless of the level of CSF pathology (Figure 3A).

The results in Figure 3B indicate that, when T-τ/A$\beta_{1\text{-}42}$ was low, rate of ADNI-EF decline was the same regardless of whether the residual reserve index was high or low. In contrast, the residual reserve index was strongly related to rate of ADNI-EF decline in the context of more extensive brain pathology. More specifically, higher levels of the residual reserve index were increasingly protective against rapid ADNI-EF decline at high levels of T-τ/A$\beta_{1\text{-}42}$. The simple slopes in Figure 3C show that years of education had no influence over the rate at which cognition declined as a function of the T-τ/A$\beta_{1\text{-}42}$ ratio.

When comparing panels 3B and 3C, the simple slopes depicted by the dashed blue lines are almost identical (and statistically indistinguishable from 0), suggesting that neither the residual reserve index nor years of education moderate the effect of AD pathology on ADNI-EF decline when the T-τ/A$\beta_{1\text{-}42}$ ratio is low (consistent with typical aging). This is in stark contrast to the simple slopes depicted in the solid red lines. The steep positive slope in panel 3B shows that higher levels of the residual reserve index are clearly associated with increasingly greater protection against cognitive decline when AD pathology is high, whereas the largely horizontal red line in panel 3C suggests no significant protection offered by high education against the effects of AD pathology, when the T-τ/A$\beta_{1\text{-}42}$ ratio is high, on EF decline.

Discussion

This study investigated the extent to which the residual reserve index, structural brain integrity, and education could uniquely predict longitudinal change in cognitive and functional outcomes across the spectrum of CSF T-τ/A$\beta_{1\text{-}42}$ levels. The first hypothesis was that the residual reserve index will interact with T-τ/A$\beta_{1\text{-}42}$ such that it is a poorer predictor of future EF and daily function change at lower levels of T-τ/A$\beta_{1\text{-}42}$ and a stronger predictor of future EF and daily function change at higher levels of T-τ/A$\beta_{1\text{-}42}$. The second hypothesis was that structural brain integrity will predict EF and daily function decline at all levels of T-τ/A$\beta_{1\text{-}42}$. The third hypothesis was that education would not be a significant predictor of change in EF and daily function.

Our first and second hypotheses were partially supported: structural brain integrity and the residual reserve index both predicted change in EF (ADNI-EF), and the residual reserve index interacted with T-τ/A$\beta_{1\text{-}42}$ such that it only predicted EF change at higher levels of T-τ/A$\beta_{1\text{-}42}$. On the other hand, the only

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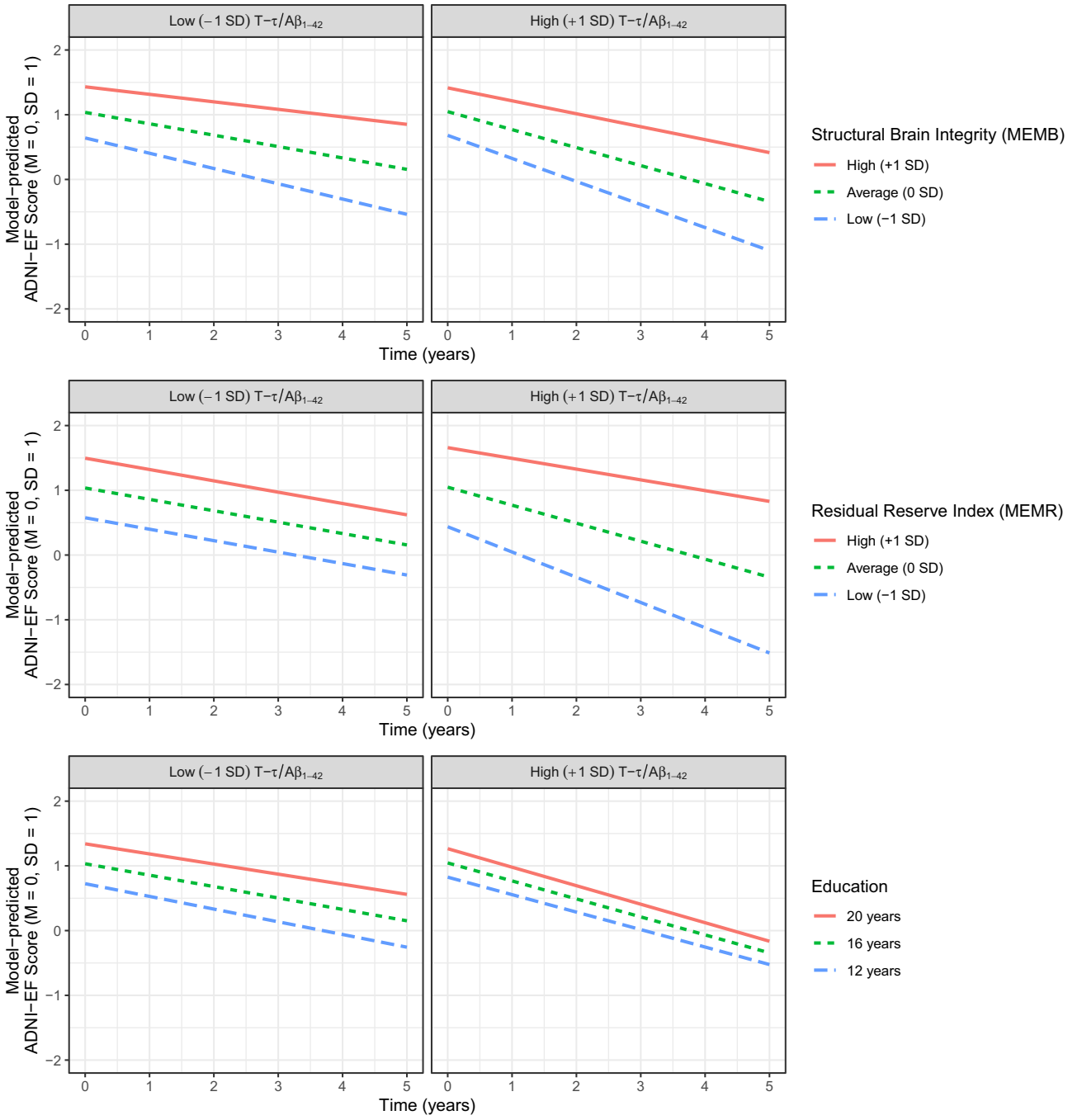

Figure 2. The interaction effects between T-τ/$A\beta_{1-42}$ and (A) baseline structural brain integrity, (B) the baseline residual reserve index, and (C) years of education when predicting change in ADNI-EF over five years. ADNI-EF scores are in standard deviation units relative to baseline scores. A. Model-predicted ADNI-EF scores over time for a reference participant (i.e., 72-year-old non-Hispanic white male with 12 years of education and sample average residual reserve index), as a function of structural brain integrity and T-τ/$A\beta_{1-42}$ ratio. B. Model-predicted ADNI-EF scores over time for a reference participant, as a function of residual reserve index and T-τ/$A\beta_{1-42}$ ratio. C. Model-predicted ADNI-EF scores over time for a reference participant, as a function of years of education and T-τ/$A\beta_{1-42}$ ratio. The interaction between the residual reserve index and T-τ/$A\beta_{1-42}$ was significant for the slope ($p < .001$) and the intercept ($p = .005$).

significant predictor of change in daily function (ECog) was change in EF. Our third hypothesis was supported, as education did not predict change in either EF or daily function after accounting for the other predictors in the model.

Our primary results show that, when CSF markers of brain pathology are low (i.e., consistent with the absence of AD), the best predictor of future rate of EF change is structural brain integrity, which may be interpreted to represent brain reserve. But as CSF biomarkers become increasingly abnormal, the residual reserve index, which may be interpreted to represent cognitive reserve, becomes a comparable predictor of future EF decline. These findings build upon prior research by demonstrating that the benefits of having high cognitive reserve are directly proportional to the amount of brain pathology that has accumulated. On the other hand, the benefits of having high brain reserve are apparent regardless of pathology (McKenzie et al., 2020). In other words, these

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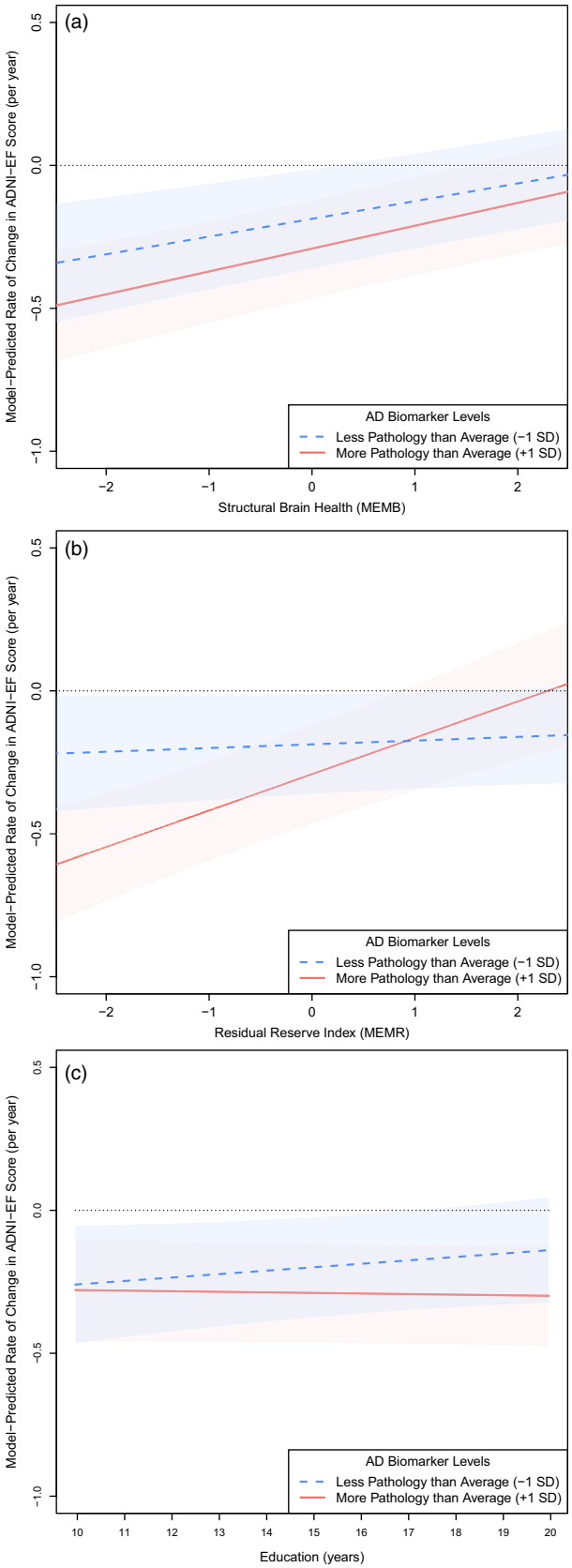

Figure 3. Simple slopes depicting expected rate of change in ADNI-EF over 5 years, as predicted by the interactions between T-τ/A$\beta_{1\text{-}42}$ and (A) structural brain integrity, (B) the residual reserve index, and (C) years of education. Structural brain integrity and the residual reserve index are represented in sample-based SD units. Rate of change in ADNI-EF is in SD units per year. The shaded areas around the lines represent 95% confidence intervals; where these cross the horizontal line marking zero, the predicted change in ADNI-EF slope is not reliably different from zero. A. Rate of change in ADNI-EF as a function of structural brain integrity and the T-τ/A$\beta_{1\text{-}42}$ ratio. B. Rate of change in ADNI-EF as a function of the residual reserve index and the T-τ/A$\beta_{1\text{-}42}$ ratio. C. Rate of change in ADNI-EF as a function of years of education and the T-τ/A$\beta_{1\text{-}42}$ ratio.

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results point to a hierarchy of protection against aging- and disease-associated cognitive decline, where high brain reserve may act as a first line of defense, and cognitive reserve may only be "activated" when pathology becomes increasingly evident in the CSF. Thus, preserving brain reserve later into life – via a mechanism known as brain maintenance (Nyberg et al., 2012) – could potentially reduce the need to rely on cognitive reserve to promote dementia-free survival. This finding may be especially beneficial for promoting healthy cognitive aging in populations who have decreased access to enriching early- (e.g., education) and mid-life (e.g., occupational complexity) opportunities that are thought to contribute to building cognitive reserve. If brain reserve and brain maintenance are amenable to late-life interventions (e.g., improving sleep and increasing physical activity; Brown et al., 2016; Livingston et al., 2020), such findings could lead to more targeted health interventions and public health initiatives to prioritize older adults' brain reserve. These results also suggest that interventions to promote structural brain health could potentially be beneficial regardless of the degree of AD pathology present in CSF, whereas interventions to promote cognitive reserve may only be beneficial if that high cognitive reserve can be maintained at high levels as AD pathology increases. These are topics for future research.

Although the residual reserve index did not predict EF change at low levels of T-τ/A$\beta_{1\text{-}42}$, it nevertheless exerted an influence over long-term EF performance via its association with baseline EF. Figure 2B shows that a higher residual reserve index predicted higher baseline EF performance at high and low levels of T-τ/A$\beta_{1\text{-}42}$, and this resulted in a higher predicted score after five years, independent of the rate of change. A similar result was found for education: although it did not predict the rate of change in EF, higher education independently predicted higher baseline EF scores. These findings are consistent with other studies that have found an association between static cognitive reserve proxies and improved clinical outcomes (e.g., reduced risk of conversion to dementia), but no association between such proxies and rate of cognitive decline over time (e.g., Soldan et al., 2020). As seen in Figure 2C, the rates of EF change between low and high T-τ/A$\beta_{1\text{-}42}$ levels did not significantly differ by education. Visually, the data in Figure 2C show somewhat non-parallel lines, but with confidence intervals that are too wide to reject the null hypothesis of no difference in the slopes. If a similar pattern of non-parallel lines, representing the education x T-τ/A$\beta_{1\text{-}42}$ interaction, were to be estimated with increased precision (e.g., with a larger sample size or using a sample with better representation of low-education individuals), it may be interpreted to suggest that higher education is protective against cognitive decline when AD pathology is low, but associated with more rapid decline when pathology is high; a similar pattern was the focus of another recent study (Mungas et al., 2018).

Our study demonstrates the importance of baseline structural brain integrity when predicting future EF decline, which has implications for the importance of brain reserve: those who have greater structural brain capital available at baseline are predicted to experience slower EF decline over five years relative to people with less capital, and this is true regardless of baseline T-τ/A$\beta_{1\text{-}42}$ levels. However, our findings should be interpreted with the caveat that we did not estimate "peak" brain reserve. An ideal measure of brain reserve would be one that allows for the separation of atrophy secondary to AD or other neurodegeneration from structural characteristics of brain reserve (Stern et al., 2020). Therefore, study designs that can estimate a peak level of brain reserve may be most suitable for identifying the unique contributions of brain reserve to protecting future cognition. Laubach and colleagues (2018) recently reported a novel method of estimating peak brain reserve by using regression to correct gray matter volume for atrophy. This method can estimate lifetime brain reserve even when structural MRI is obtained after the onset of atrophy and may allow future research to examine associations between estimated lifetime brain reserve and cognition, while accounting for the rate of accumulation of AD pathology, and rate of atrophy.

The concordance between current and peak estimates of brain reserve is a consequence of brain maintenance, which is the process of maintaining structural brain integrity during aging, such that the impact of any pathology on brain structure and function is reduced. Although we found that higher baseline structural brain integrity predicted slower EF decline over time, longitudinal brain volume measurements are needed to determine to what extent brain maintenance contributes to slower EF decline. In addition, while better brain maintenance has been associated with preserved cognitive function (Nyberg et al., 2012), it is currently unknown whether brain maintenance could also predict longitudinal change in cognitive reserve, via the preservation of neurological systems underpinning cognitive reserve. Research has found that the rate of depletion of the residual reserve index over time predicts cognitive decline independently of brain atrophy rate (Bettcher et al., 2019), highlighting the need to understand the causes and consequences of depleting cognitive reserve and brain reserve.

Several potential limitations may impact the interpretation of our findings. First, ADNI participants tend to be non-Hispanic and White; recent work shows that education differentially contributes to cognitive reserve across different racial/ethnic groups (Avila et al., 2021) which limits our ability to generalize our findings to more diverse populations. A proxy that measures the quality of education, such as word-reading ability, may provide a more appropriate alternative to education in future studies (e.g., Manly et al., 2002). Second, with more years of follow-up data, the longitudinal outcomes and their associations with the predictor variables may have differed. Finally, given that our sample consists of ADNI participants, our findings are limited to pathology biomarkers specific to Alzheimer's disease. We are therefore unable to determine whether the associations between brain and cognitive reserve and future cognitive outcomes demonstrated in this study would manifest differently in other neurodegenerative and non-degenerative pathologies.

The residual reserve index is defined as the variance remaining in episodic memory performance after removing variance due to structural MRI variables (hippocampal, whole brain, and WMH volume), demographics, and measurement error (Reed et al., 2010). The residual reserve index is therefore likely to contain unmeasured aspects of brain structure and function underlying memory performance (Mungas et al., 2021). Given that cognitive reserve must have a neurophysiological basis (Stern et al., 2020), we can assume that the unmeasured characteristics of brain function inherent within the residual reserve index must be capturing, in some part, processes underlying cognitive reserve (e.g., neural efficiency). Our results suggest that, once variance in whole brain, hippocampal, and WMH volumes are accounted for, these unmeasured aspects of brain function do not predict future EF change when T-τ/A$\beta_{1\text{-}42}$ levels are low.

Conclusion

The present study provides a novel addition to the cognitive aging literature by comparing how structural brain integrity (brain

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reserve) and two candidate measures of cognitive reserve (the residual reserve index and education) differentially predict future EF and daily function decline, and how their ability to predict these outcomes depends on the degree of AD pathology. Although past research has suggested that all three of these variables can predict dementia-relevant outcomes, the current study is novel in that it compares all three predictors to one another – using both cognitive and functional status as outcomes – within in the same model, while ensuring that the predictors are statistically independent from one another. Our findings suggest that – in the context of low AD pathology – a composite measure of hippocampal, whole brain, and WMH volume has a greater ability to predict future EF decline than does the residual reserve index. However, in the context of high AD pathology, the structural brain composite and the residual reserve index were comparable in their ability to predict future decline in EF. Finally, when controlling for the influence of brain integrity and the residual reserve index, education, which is commonly used as a proxy for cognitive reserve, was not found to have incremental predictive validity. Our study highlights the importance of brain reserve in predicting future executive and everyday function decline regardless of CSF pathology levels and supports the use of the residual reserve index as a measure of cognitive reserve to predict future rate of cognitive decline in the context of pathological brain aging. Further research using longitudinal biomarker and MRI collection is needed to understand more about the interplay between pathology, brain maintenance, and the reserve constructs during aging.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1355617722000546

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Conflicts of interest. None.

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