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

Cathryn McKenzie[1], Romola S. Bucks[1], Michael Weinborn[1], Pierrick Bourgeat[2], Olivier Salvado[3], Brandon E. Gavett[1], for the Alzheimer's Disease Neuroimaging Initiative*

[1]School of Psychological Science, The University of Western Australia, Perth, WA, 6009, Australia

[2]Australian e-Health Research Centre, CSIRO Health and Biosecurity, Brisbane, QLD, 4006, Australia

[3]Data61, CSIRO, Sydney, NSW, 2015, Australia

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Corresponding author: Brandon E. Gavett, brandon.gavett@uwa.edu.au, School of Psychological Science (M304), The University of Western Australia, 35 Stirling Highway, Perth, WA, Australia, 6056. Phone: +61 6488 2977 Fax: +61 6488 1006.

Supplementary Materials

The following sections describe aspects of our method and results in further detail.

S1. MRI Methods

Baseline measures of hippocampal, whole brain, white matter hyperintensity, and total intracranial volume, all derived from MRI, were used. Details of ADNI's neuroimaging protocols have been described previously (Jack et al., 2008). Pre-processed T1-weighted MP-RAGE scans obtained from 1.5-Tesla (1.5T) and 3.0-Tesla (3T) scanners were downloaded directly from the ADNI database. 1.5T images from ADNI1 were processed by ADNI using Freesurfer version 4.3; all other volumes were processed by ADNI using version 5.1 (http://surfer.nmr.mgh.harvard.edu/). Total intracranial volume was estimated using an atlas-based spatial normalisation procedure in Freesurfer (Buckner et al., 2004). 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.

Pre-processed white matter hyperintensity volumes were downloaded directly from the ADNI database. T2-weighted FLAIR scans were performed on ADNI2 participants using 3T scanners, and white matter hyperintensity volumes were estimated using a Bayesian approach. Further details about ADNI's FLAIR acquisition and 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/.

S2. Statistical Analyses

Model fit was evaluated using the comparative fit index (CFI) (Bentler, 1990), Tucker-Lewis Index (TLI) (Tucker & Lewis, 1973), the root mean square error of approximation (RMSEA) (Steiger, 1990), and the standardized root mean square residual (SRMR) (Jöreskog & Sörbom, 1993), using the cut-offs for acceptable fit recommended by Hu and Bentler (1999).

S2.1. Decomposition of ADNI-Mem

A structural equation model (Figure 1A in main text) was used to decompose ADNI-Mem variance into variance due to demographic variables, variance due to structural MRI measures (MEMB; our index for structural brain integrity), and residual variance (MEMR; our residual reserve index). Reed and colleagues (2010) conceptualised MEMR as cognitive reserve, and it represents the difference between observed memory performance and that which is predicted based on structural brain volumes 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 variance in ADNI-Mem explained by demographics. This allowed us to test hypotheses regarding the contribution of years of education to our outcome variables, independent of the effects of MEMB and MEMR.

MEMB is the variance in episodic memory explained by hippocampal, whole brain, and white matter hyperintensity volume. Per Reed and colleagues, these observed 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 1.5T and 3T scans performed on the same subjects at the same time point and subtracting these correlations from 1. Data from concurrent 1.5T and 3T scans were not available for white matter hyperintensity volumes, so a conservative reliability estimate of 0.90 was used (Reed et al., 2010). Hippocampal and total brain volumes were regressed onto total intracranial volume to control for the effect of head size. Although white matter intensity volume was not regressed onto intracranial volume, the two variables were allowed to correlate in the model. The distribution of white matter

hyperintensity volume was positively skewed, therefore it was log-transformed prior to analyses. The residual variance of ADNI-Mem was fixed to account for measurement error. A conservative reliability estimate of 0.84 was used, based on the correlation between baseline and 6-month follow-ups in t/Aβ- participants who were classed as healthy controls by ADNI (McKenzie et al., 2020).

The decomposition model fit well: X^2 (11) = 12.65, p = 0.317; CFI = 0.99; TLI = 0.99; RMSEA = 0.01, 90% CI 0.00 – 0.02; SRMR = 0.01.

S2.2. Longitudinal Growth Modelling of ADNI-EF and ECog

This section details the process by which we arrived at the longitudinal growth model shown in the main text (Figure 1B). To remain consistent with past work using similar models, we estimated a linear growth function over five years for all growth models. See Figure S1 for model diagrams.

First the ADNI-EF and ECog growth models were created separately (Figure S1A and S1B). The results of the two separate growth models are shown in Table S1. Next the parallel growth model was created (Figure S1C). The within-domain intercept and slope terms were not correlated as in previous models, as any shared variance was accounted for via the other correlation and regression paths in the model (Muthén & Muthén, 2017). Model fit was as follows: X^2 (66) = 270.13, p <0.001; CFI = 0.98; TLI = 0.98; RMSEA = 0.04, 90% CI 0.03 – 0.04; SRMR = 0.06. The parameters estimated from this model are shown in Table S2.

Finally, the ECog intercept and slope were regressed onto the ADNI-EF intercept and slope, respectively, to account for a possible predictive relationship that is likely to exist between ADNI-EF and ECog (See Figure S1D). Correlations between the within-domain intercepts and slopes were added back to the model, as shared variance was no longer being accounted for by other paths. Model fit was as follows: X^2 (64) = 201.76, p <.001; CFI = 0.99;

TLI = 0.99; RMSEA = 0.03, 90% CI 0.03 – 0.04; SRMR = 0.05. The parameters estimated from this model are shown in Table S2.

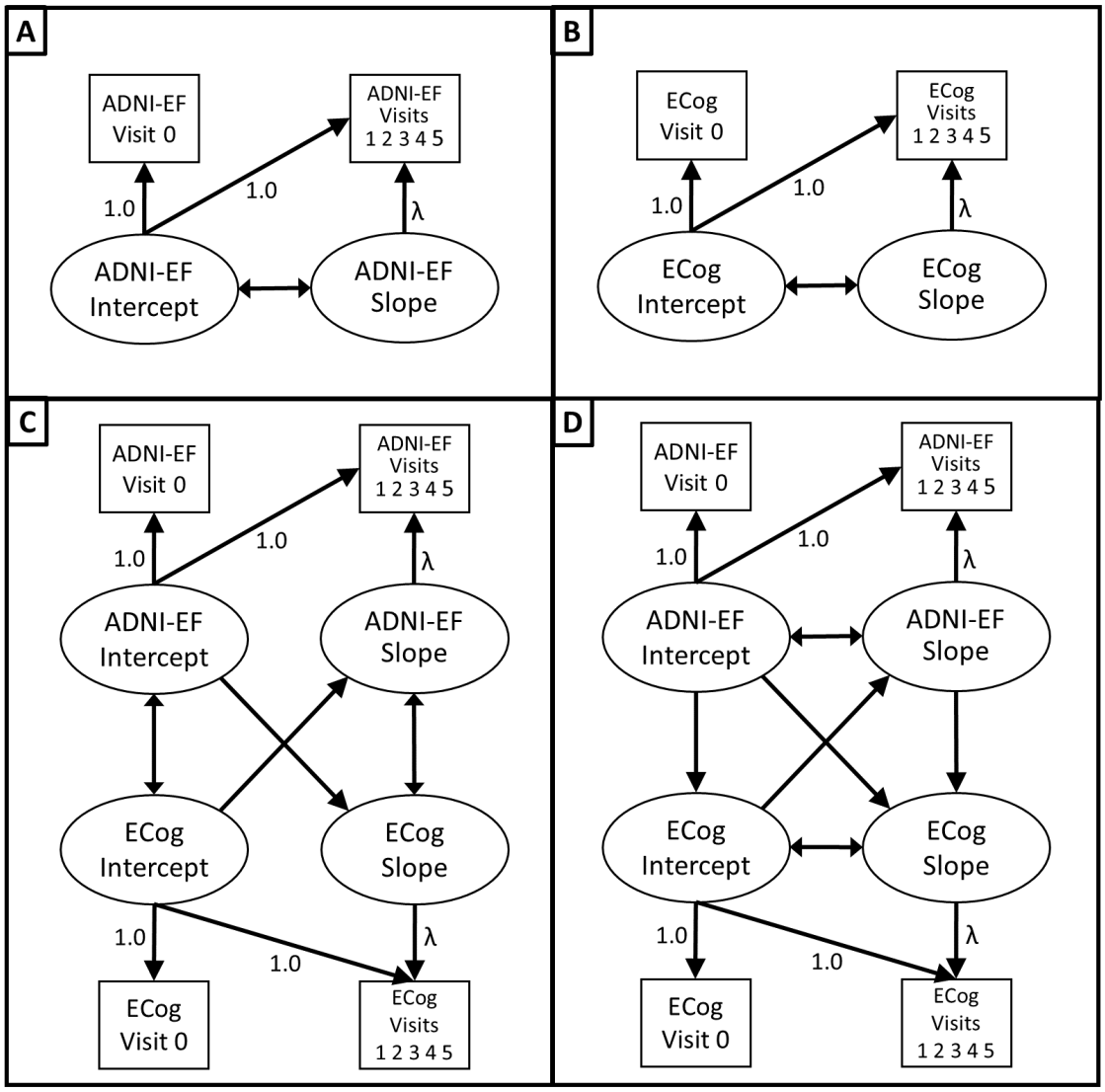

Figure S1. **Schematic model diagrams for each latent growth model used to model longitudinal change in executive function and/or daily function**. Rectangles represent observed variables and ovals represent latent variables. Observed outcome measurements at visits 1-5 have been condensed into single rectangles for ease of interpretation. Paths are freely estimated unless labelled otherwise. Double-ended arrows represent correlations. ECog scores were recoded such that higher scores represented better independent functioning. λ represents the slope factor loadings. **A.** The growth model used to obtain an intercept and linear slope for executive function (ADNI-EF) over five years. **B**. The growth model used to obtain an intercept and linear slope for daily function (ECog) over five years. **C**. The parallel growth model used to simultaneously estimate intercepts and linear slopes for ADNI-EF and ECog. **D**. The parallel growth model from **C**, with the ECog intercept and slope regressed onto the ADNI-EF intercept and slope, respectively.

Table S1. Model fit and parameter estimates for the separate ADNI-EF and ECog models.

Model	X^2	df	RMSEA (90% CI)	SRMR	CFI	TLI	Growth parameter estimates			
							Intercept		Linear Slope	
							Mean	Variance	Mean	Variance
ADNI-EF Growth Model (Supplementary Fig. 1A)[a]	84.92*	16	0.05 (0.04 – 0.05)	0.02	0.99	0.99	0.29*	1.04*	-0.10*	0.03
2. ECog Growth Model (Supplementary Fig. 1B)[b]	61.32*	16	0.04 (0.03 – 0.05)	0.11	0.98	0.98	3.34*	0.47*	-0.08*	0.02*

Note: Six time points (five years) of data were used. Parameter estimates are unstandardized. Recommended cut-offs (Hu & Bentler, 1999) are: CFI ≥0.95, TLI ≥0.95, RMSEA <.05, SRMR <0.06.

[a] N = 2,128

[b] N = 1,666

*p <0.001

Table S2. Parameter estimates for the parallel ADNI-EF and ECog growth models

Parallel Growth Model (Supplementary Fig. 1C)	Outcome	Growth parameter estimates		Correlation parameter estimates			Regression parameter estimates		
							Predictor variable:		
		Mean	Variance	ADNI-EF Slope	ECog Intercept	ECog Slope	ADNI-EF intercept	ADNI-EF Slope	ECog Intercept
	1. ADNI-EF Intercept	0.28*	1.09*	-	0.61*	-	-	-	-
	2. ADNI-EF Slope	-0.10*	0.03*		-	0.58*	-	-	0.51*
	3. ECog Intercept	3.26*	0.52*			-	-	-	-
	4. ECog Slope	-0.10*	0.02*				0.48*	-	-
Regression of ECog on ADNI-EF within Parallel Growth Model (Supplementary Fig. 1D)	Outcome	Growth parameter estimates		Correlation parameter estimates			Regression parameter estimates		
							Predictor variable:		
		Mean	Variance	ADNI-EF Slope	ECog Intercept	ECog Slope	ADNI-EF intercept	ADNI-EF Slope	ECog Intercept
	1. ADNI-EF Intercept	0.29*	1.04*	0.38*	-	-	-	-	-
	2. ADNI-EF Slope	-0.11*	0.03*		-	-	-	-	0.37*
	3. ECog Intercept	3.27*	0.48*			-0.02	0.62*	-	-
	4. ECog Slope	-0.11*	0.02*				0.21*	0.71*	-

Note: $N = 2{,}224$. Six time points (five years) of data were used. Growth parameter estimates are unstandardised. Correlation and regression parameter estimates are standardised. Recommended cut-offs (Hu & Bentler, 1999) are: CFI ≥0.95, TLI ≥0.95, RMSEA <.05, SRMR <0.06.
*p <0.001

S2.3. Hypothesis Testing

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

S3. Sample Characteristics

Descriptive statistics for the whole sample, including those with missing CSF biomarker data, are shown in Table S3. Of the 2238 participants whose data were downloaded from the ADNI database, 1037 were excluded from the final analyses due to missing CSF biomarker data. On average, the excluded participants had a smaller proportion of males and African Americans, and a higher proportion of people diagnosed as cognitively normal at baseline. They also averaged higher baseline ADNI-Mem and ADNI-EF performance, less functional impairment (indicated by higher recoded ECog scores and lower CDR sum of boxes), as well as smaller hippocampal and whole brain volumes, smaller white matter hyperintensity volumes, and larger intracranial volume. Excluded participants also had a lower mean number of visits.

Table S3. Participant characteristics of the whole sample

Variable	All (N = 2238)	Included (n=1201)	Excluded (n = 1037)	Difference
Age (years)				
M (SD)	73.20 (7.40)	73.32 (7.26)	73.07 (7.55)	$t(2234)=0.80$
Sex				
N (%) male	1188 (2.08)	663 (55.20)	525 (50.62)	$X(1)=4.68$†
Race/ethnicity				
N (%) African American	107 (4.78)	44 (3.7)	63 (6.08)	$X(1)=7.11$†
N (%) Hispanic	84 (3.75)	34 (2.8)	50 (4.82)	$X(1)=6.10$†
Education (Years)				
M (SD)	16.05 (2.77)	16.04 (2.78)	16.06 (2.75)	$t(2236)=.20$
Baseline Diagnosis				
N (%) CN	810 (36.19)	369 (30.72)	441 (44.10)	$X(2)=42.32$‡
N (%) MCI	1005 (44.91)	606 (50.46)	399 (39.90)	
N (%) Dementia	386 (17.25)	226 (18.82)	160 (16.00)	
ADNI-Mem				
M (SD)	0.31 (0.90)	0.26 (0.90)	0.38 (0.89)	$t(2130)=3.26$†
ADNI-EF				
M (SD)	0.27 (1.08)	0.18 (1.05)	0.37 (1.11)	$t(2126)=3.94$‡
ECog score				
M (SD)	1.66 (0.72)	3.27 (0.73)	3.43 (0.71)	$t(1382)=3.86$‡
CDR sum of boxes				
M (SD)	1.49 (1.79)	1.59 (1.78)	1.37 (1.79)	$t(2236)=3.01$†
Hippocampal volume (cm^3)				$t(1490)=3.05$†
M (SD)	6.790.13 (1.19)	6.85 (1.18)	6.65 (1.18)	
Whole brain volume (cm^3)		1031.14	999.14	$t(1690)=5.53$‡
M (SD)	1021.08 (111.52)	(110.94)	(109.74)	
White matter hyperintensity volume (cm^3)				
M (SD)	3.83 (7.37)	4.80 (8.74)	2.67 (5.06)	$t(1674.75)=6.57$‡
Total intracranial volume (cm^3)		1527.33	1540.79	$t(1723)=1.55$
M (SD)	1531.52 (166.59)	(166.61)	(166.32)	
Number of visits				
M (SD)	3.82 (2.366)	4.50 (2.22)	3.03 (2.29)	$t(2236)=15.42$‡

Note: 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.

†$p < 0.05$

‡$p < 0.001$