

Background

- ❖ The development of amyloid-β plaques and tau tangles in the brain typically results in reduced brain volumes and cognitive impairment in Alzheimer’s disease.
- ❖ However, many individuals with amyloid and tau accumulation in the brain never proceed to experience cognitive decline or an Alzheimer’s disease (AD) diagnosis.
- ❖ Building high-quality metrics of resilience to pathology deposition is critical for studying the mechanisms of such protection.
- ❖ This study leverages multi-modal quantifications of amyloid and tau burden, harmonized cognitive scores, brain imaging, and diagnostic information to generate and evaluate resilience metrics.

Table 1. Participant Characteristics

	In-Vivo	Autopsy	Total
Cognitive N	4217	5487	9704
Age	72 (± 8.2)	80 (± 11)	76 (± 11)
Sex (Female)	2353 (56 %)	2470 (45 %)	4823 (50 %)
Education	16 (± 2.9)	16 (± 3.1)	16 (± 3.0)
Diagnosis			
CU	2378 (56 %)	813 (15 %)	3191 (33 %)
MCI	817 (19 %)	604 (11 %)	1421 (15 %)
AD	723 (17 %)	2888 (53 %)	3611 (37 %)
Missing	299 (7.1%)	1182 (21.5%)	1481 (15.3%)
Biomarker Status			
A-T-/A-/T-	2259 (54 %)	1222 (22 %)	3481 (36 %)
A-T+	73 (2 %)	916 (17 %)	989 (10 %)
A+T-	516 (12 %)	256 (5 %)	772 (8 %)
A+T+/A+/T+	1103 (26 %)	3093 (56 %)	4196 (43 %)
# of Cognitive Visits	3.1 (± 2.6)	4.0 (± 3.0)	3.6 (± 2.9)
Memory	0.43 (± 0.89)	-0.85 (± 1.1)	-0.29 (± 1.2)
Executive Functioning	0.35 (± 0.87)	-0.71 (± 0.94)	-0.20 (± 1.1)
Language	0.47 (± 0.82)	-0.65 (± 0.98)	-0.12 (± 1.1)
MRI Brain Volume Subset			
MRI N	871	254	1125
# of T1 Visits	2.6 (± 1.2)	2.7 (± 1.5)	2.6 (± 1.2)
Right HV	3700 (± 490)	3300 (± 520)	3700 (± 520)
Left HV	3500 (± 460)	3100 (± 490)	3400 (± 490)
SPARE-AD	-0.23 (± 0.60)	0.67 (± 0.76)	-0.082 (± 0.71)
Missing	225 (25.8%)	60 (23.6%)	285 (25.3%)

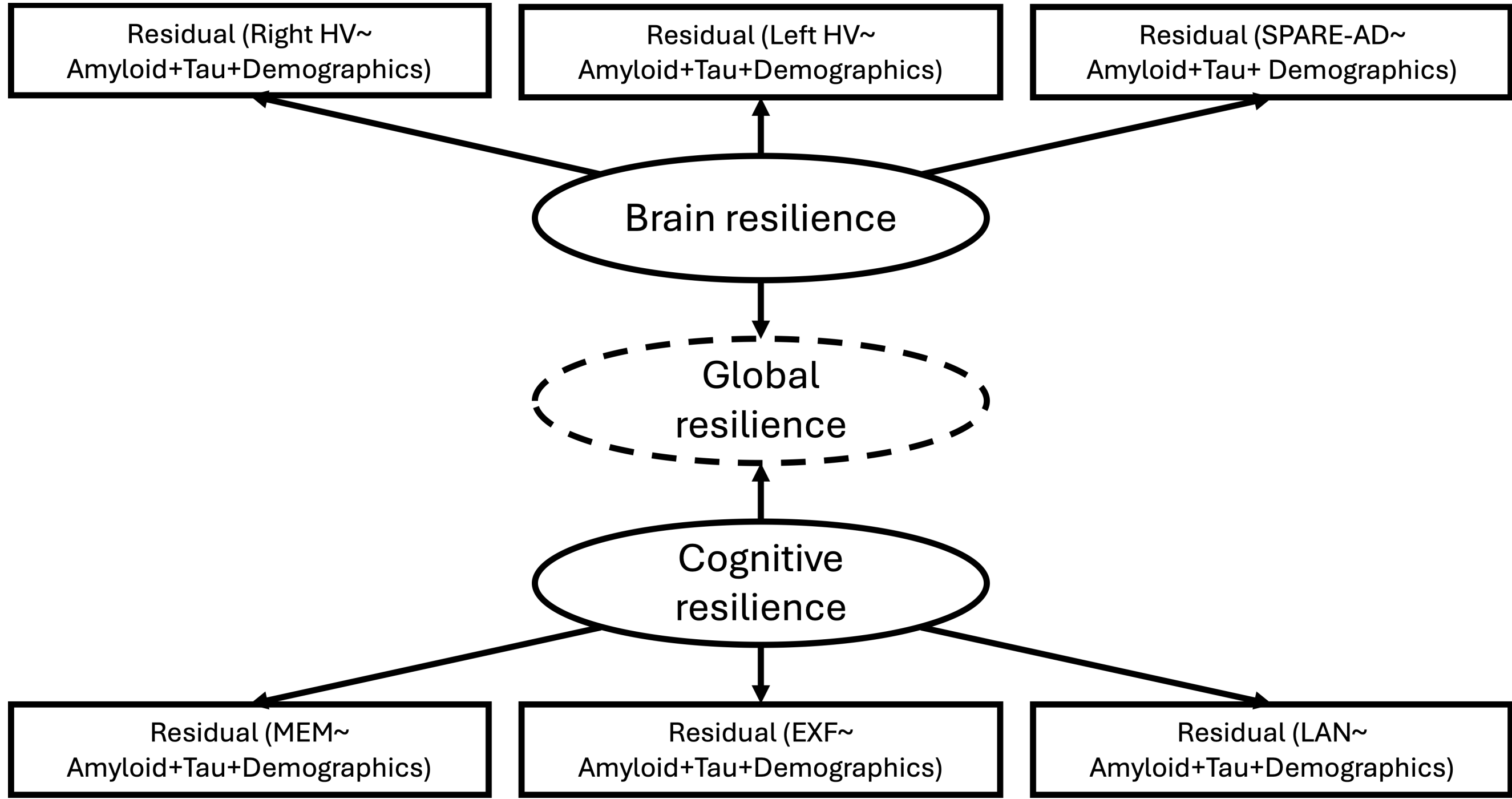
Continuous variables are presented in mean (standard deviation). Categorical variables are presented in N (%). **Abbreviations:** HV: hippocampal volume, MRI: magnetic resonance imaging, CU: cognitively unimpaired, MCI: mild cognitive impairment, AD: Alzheimer’s disease, A: amyloid, T: tau

Methods

- ❖ This project leveraged multi-modal data from the CLARiTi (ADRC Consortium for Clarity in ADRD Research Through Imaging) initiative of NACC (National Alzheimer’s Coordination Center) as well as harmonized phenotypes for NACC participants provided by the ADSP-PHC (Alzheimer’s Disease Sequencing Project – Phenotype Harmonization Consortium).

- ❖ Samples 50 years old and older were included if they had either a cognitive or a T1 visit within five years of an AD pathology measurement (**Table 1**).
- ❖ Harmonized cognitive scores were calculated across three domains (specifically memory, executive functioning, and language).
- ❖ MRI brain volumes were segmented either using FreeSurfer or MUSE. Left and right hippocampal volumes as well as the SPARE-AD signature were used for building brain resilience.
- ❖ Measures of amyloid and tau accumulation were drawn from amyloid and tau PET, cerebrospinal fluid (CSF) amyloid-β and total tau levels, and neuropathologically defined CERAD score and Braak stage at autopsy
- ❖ Resilience scores were calculated in two steps (**Figure 1**):
 - ❖ First, residuals were extracted from linear regression models of AD pathology on cognitive outcomes and on MRI outcomes. Covariates included: sex, *APOE-ε4* count, *APOE-ε2* positivity, age, diagnosis and age*diagnosis and ICV for MRI models. All residual models were run with and without a diagnosis covariate as well as in cognitively normal samples only.
 - ❖ Then, cognitive residuals were incorporated into cognitive resilience scores as were brain residuals into brain resilience. Second-order global resilience was constructed in samples with both cognitive and brain residuals.
- ❖ Resilience scores were evaluated based on their prediction of cognitive decline and of brain volume decline in linear mixed-effects regression, covarying for age, sex, and interval, with the intercept and interval entered as random effects. Further, prediction of diagnostic conversion was evaluated in logistic regression, covarying for age and sex.

Figure 1. Resilience Phenotype Model



Abbreviations: HV: hippocampal volume, MEM: memory performance, EXF: executive functioning, LAN: language performance

Results

- ❖ Autopsy resilience phenotypes
 - ❖ In autopsy resilience models, cognitive resilience calculated separately predicted cognitive decline in all three domains (see **Figure 2a**) but was inversely associated with diagnostic conversion antemortem (**Figure 2b**). This was the case whether or not diagnosis was included in the residual models.
- ❖ In-vivo resilience phenotypes
 - ❖ In-vivo global resilience predicted memory decline (**Figure 3A**) as well as diagnostic conversion (**Figure 3A**), although the first was only nominal after correction.
 - ❖ Interestingly, while brain resilience significantly predicted both diagnostic conversion and memory decline, cognitive resilience only significantly predicted diagnostic conversion but not memory decline and was in fact associated with slower decline in language performance (**Figure 3C-D**).

Figure 2. Autopsy Cognitive Resilience Predicts Better Cognitive Outcomes but Greater Likelihood of Conversion

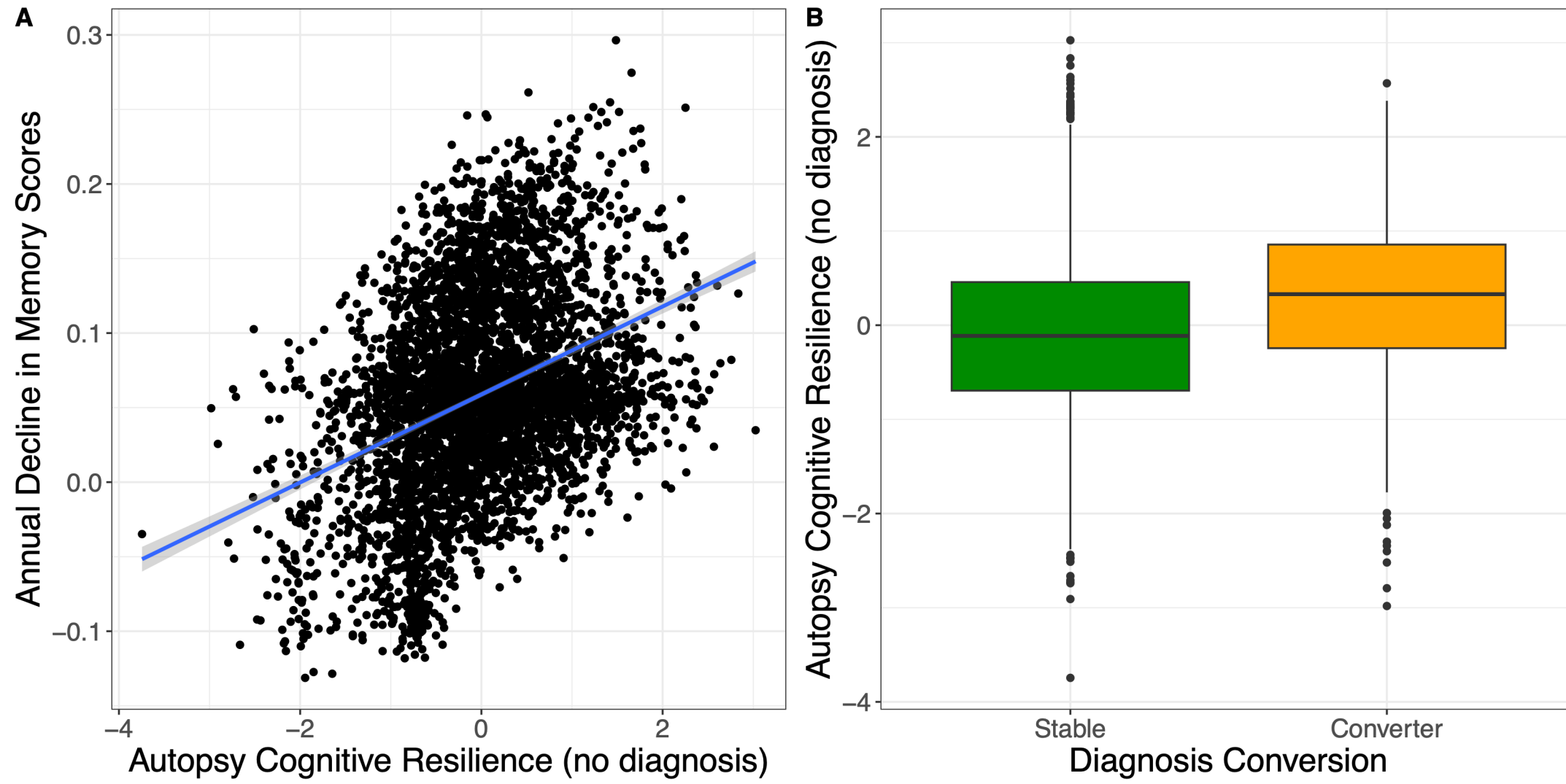


Figure 3. In-Vivo Brain and Global Resilience Phenotypes Predict Better Clinical Outcomes While Cognitive Resilience Predicts Faster Decline

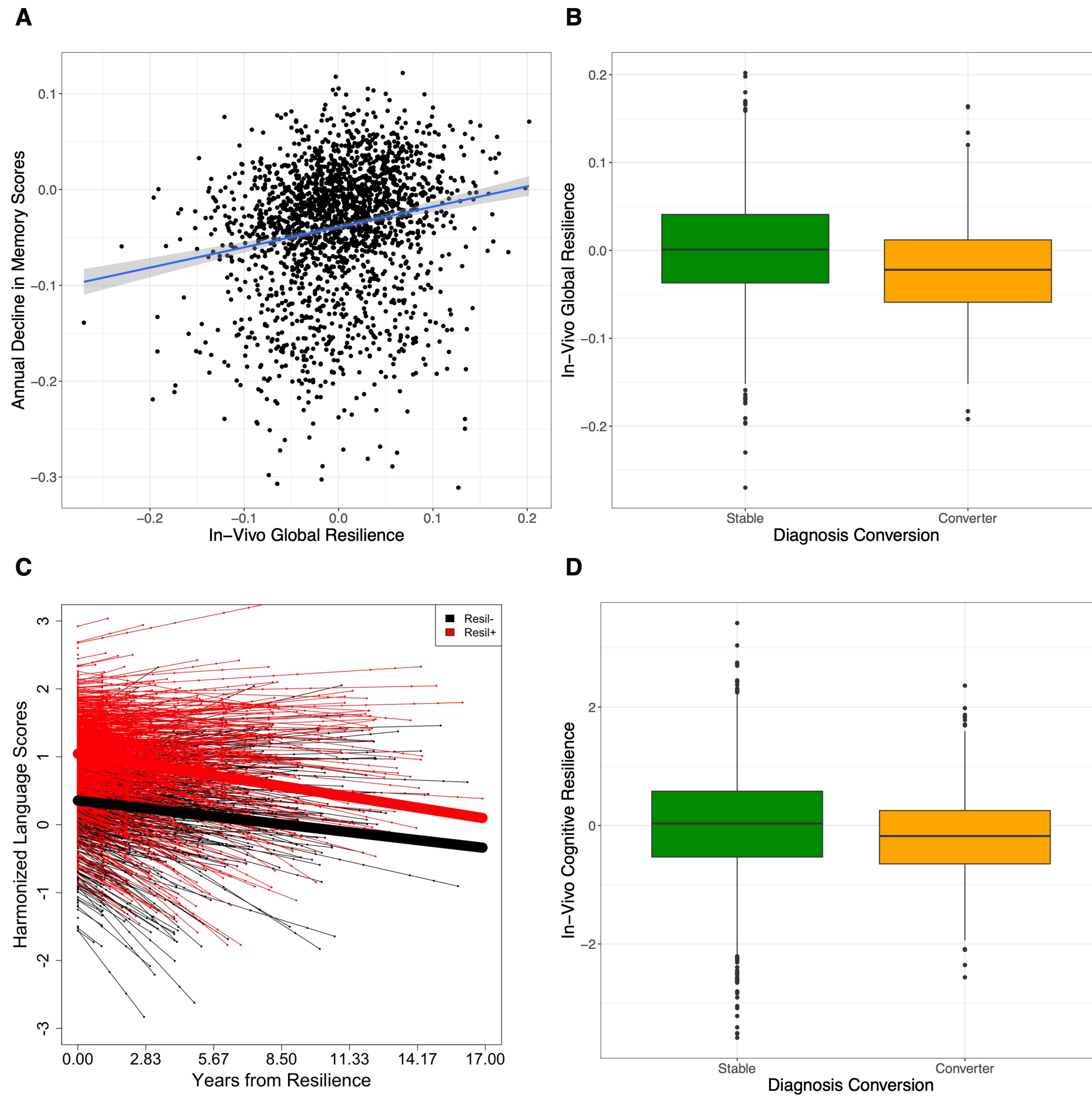


Fig 3 legend: In panel C, red indicates samples who have brain resilience scores above 0 while black indicates those who have scores less than zero.

Conclusions

- ❖ These results highlight the utility of incorporating larger or smaller than expected brain volumes to maximize clinical relevance of resilience quantifications.
- ❖ Further, the unique performance of resilience scores in in-vivo samples versus autopsy samples point to interesting differences in these phenotypes and qualify how these scores can be interpreted based on when the phenotype was generated.