S1. Supplemental Results

S.1 Results among Individuals with Normal Cognition

Among individuals with normal cognition, higher cognitive resilience (Hazard Ratio [95% confidence interval]=0.60 [0.39-0.93], p=0.024) and global resilience (HR=0.56 [0.34-0.90], p=0.016) predicted a decreased risk of diagnostic conversion. Similarly, higher brain resilience (β=0.03, t(986)=2.47, p=0.014) predicted better trajectories of memory performance. Conversely, higher cognitive resilience predicted worse trajectories of memory (β=-0.03, t(986)=-2.82, p=0.005) and executive function (β=-0.03, t(986)=-2.36, p=0.019) performance likely reflecting a regression to the mean artifact (cognitive resilience strongly predicts baseline cognition, and baseline cognitive scores show a comparable inverse association with longitudinal change in this cohort consistent with previous regression to the mean artifacts reported in cognitively normal older adults).[1] Cognitive reserve and brain reserve did not predict a decreased risk of diagnostic conversion or slower trajectories of cognitive performance among NC participants (p-values>0.28). Additionally, none of the latent variables of resilience or reserve predicted slower rates of left or right ventricular dilation (p-values>0.12).

S.2 Results when Controlling for Baseline Biomarker Levels, Baseline Hippocampal Volume, and Baseline Cognitive Performance

In analyses adjusting for baseline hippocampal volume, baseline CSF biomarker levels, and baseline cognitive performance, higher levels of brain resilience (HR=0.45 [0.29-0.68], $p=1.5x10^{-4}$), cognitive resilience (HR=0.48 [0.34-0.67], $p=2.7x10^{-5}$), and

global resilience (HR=0.47 [0.34-0.67], $p=1.8x10^{-5}$) continued to predict a decreased risk of diagnostic conversion. Similarly, brain resilience, cognitive resilience, and global resilience predicted better trajectories of performance in both memory and executive function (p-values<0.001) and inferior lateral ventricle volume (p-values<0.02). Brain reserve and cognitive reserve did not predict slower rates of diagnostic conversion (p-values>0.42), and brain reserve again predicted worse trajectories of memory and executive function performance (p-values<0.003) and faster rates of ventricular dilation (p-values<$3.0x10^{-7}$), suggesting brain reserve had particularly poor predictive value after adjusting for strong predictors of cognitive decline.

It should also be noted that we did observe the expected evidence of collinearity among brain resilience (variance inflation factor (VIF)=8.6 for memory, VIF=8.5 for executive function) and hippocampal volume (VIF=10.2 for memory, VIF=10.2 for executive function), cognitive resilience (VIF=4.3 for memory, VIF=5.5 for executive function) and baseline cognitive performance (VIF=5.7 for memory, VIF=5.1 for executive function), and global resilience (VIF=5.6 for memory, VIF=6.7 for executive function) and both hippocampal volume (VIF=3.7 for memory, VIF=4.5 for executive function) and baseline cognitive performance (VIF=3.9 for memory, VIF=3.2 for executive function).

S.3 Results when Restricting to 3T or 1.5T Data Points

When restricting the sample to individuals who were scanned on a 3T scanner, we observed a comparable fit for the PLS model with a goodness of fit of 0.75. Brain resilience, cognitive resilience, and global resilience continued to predict diagnostic conversion (HRs<0.51, p-values<$2x10^{-9}$), longitudinal change in memory

(p-values<0.004), and ventricle dilation (p-values<$1.4x10^{-6}$). Only brain resilience predicted longitudinal change in executive function (β=0.03, t(1395), p=0.03), perhaps due to the restricted follow-up period in ADNI-2/GO. Similarly, among individuals who were scanned on a 1.5T scanner (excluding all individuals with 3T scans), we observed a comparable overall fit for the PLS model with a goodness of fit of 0.76. Brain resilience, cognitive resilience, and global resilience all predicted diagnostic conversion (HRs<0.57, p-values<$2x10^{-5}$), longitudinal change in memory (p-values<0.04), longitudinal change in executive function (p-values<$7x10^{-8}$), and ventricle dilation (p values<$4.3x10^{-8}$).

S.4 Results when Using Dichotomized CSF Metrics

We reran all analyses by recalculating the residuals used as indicators in our original analysis. Instead of a continuous measure of amyloid in the regression models, we used a binary variable of Amyloid Positive (Aβ-42≤192 pg/mL). Similarly, instead of a continuous measure of total tau, we used a binary variable of Tau Positive (total tau≥93 pg/mL). These cut-off definitions are more commonly applied in clinical settings and thus maybe more applicable to clinical care. Our results were consistent with those identified using continuous metrics. Higher levels of brain resilience (HR=0.54 [0.46-0.63], p=$3x10^{-14}$), cognitive resilience (HR=0.42 [0.34-0.51], p<$2x10^{-16}$), and global resilience (HR=0.41 [0.34-0.49], p<$2x10^{-16}$) continued to predict a decreased risk of diagnostic conversion. Similarly, brain resilience, cognitive resilience, and global resilience predicted better trajectories of performance in both memory and executive function (p-values<$8.3x10^{-5}$) and inferior lateral ventricle volume (p-values<$3.9x10^{-17}$). Brain reserve and cognitive reserve did not predict slower rates of diagnostic conversion

(p-values>0.15), and brain reserve again predicted worse trajectories of executive function performance (p=0.047) and faster rates of ventricular dilation (p-values<4.6×10^{-7}).

S.5 Results to Address Potential Circularity

We performed two additional analyses to address potential circularity. First, we removed the composite memory measure from the cognitive resilience calculation and reassessed the association between resilience and longitudinal memory performance. We then repeated this procedure removing executive function performance from the cognitive resilience calculation and reassessing the association between all resilience phenotypes and longitudinal change in executive function. When restricting the cognitive resilience calculation to only include memory performance, we observed a comparable goodness of fit for the latent variable model (0.78) and all three resilience metrics continued to successfully predict slower rates of longitudinal decline in executive function performance (all p-values<5×10^{-5}). Similarly, when restricting the cognitive resilience calculation to only include executive function performance, we observed a comparable goodness of fit for the latent variable model (0.77) and all three resilience metrics continued to successfully predict slower rates of longitudinal decline in memory performance (all p-values<0.0005).

S.6 Alternative Cognitive Resilience Calculations

Previous work using a comparable approach has defined cognitive resilience based on residual variance after adjusting for MRI measures of brain volume.[2] Therefore we evaluated two additional methods of calculating residual cognitive variance to determine whether the simplified model leveraging CSF biomarkers

provides any additional predictive power over leveraging of MRI measures. Both additional metrics were calculated in the subset of individuals included in our original analysis. First, we calculated the “resilience in executive function” score (as outlined previously[2]) adjusting for age, sex, education, Hachinski score, cortical volume adjusting for intracranial volume, hippocampal volume adjusting for intracranial volume, and baseline memory performance. We did not include white-matter hyperintensity volume or presence of lacunes as included previously[2] because these metrics were not available at baseline for all participants evaluated. Second, we calculated cognitive resilience in the context of our PLS framework by calculating residuals for memory performance and executive performance separately (as in our original model) adjusting for the demographic and structural MRI variables listed above. We observed a comparable goodness of fit for the PLS model when leveraging these new residuals (goodness of fit=0.73).

To evaluate these metrics, we calculated the correlation between our cognitive resilience metric based on residual variance after adjusting for CSF biomarker levels to both the resilience in executive function variable and the cognitive resilience variable calculated using MRI predictors instead of CSF predictors. Then we assessed the ability of each measure to predict diagnostic conversion using the same survival analysis outlined in the present manuscript.

The three calculations of cognitive resilience were correlated, with the cognitive resilience metrics calculated in the PLS framework showing the strongest correlation (Pearson’s $R=0.82$, $p<0.0001$). The resilience in executive functioning variable showed a more modest correlation with cognitive resilience calculated based on CSF biomarker

levels (Pearson's R=0.46, p<0.0001) and cognitive resilience calculated based on MRI measures (Pearson's R=0.58, p<0.0001).

When evaluating the ability of each metric to predict diagnostic conversion, we observed the best performance for cognitive resilience calculated based on CSF biomarker levels (HR=0.42 [0.34-0.51], p<0.0001), followed by cognitive resilience calculated based on structural MRI variables (HR=0.61 [0.51-0.73], p<0.0001). Resilience in executive functioning did not successfully predict protection from diagnostic conversion (HR=0.84 [0.66-1.07], p=0.166).

S.7 Additional Detail on PLS Path Model

The PLS path model was implemented using the *plspm* package (https://cran.r-project.org/web/packages/plspm/plspm.pdf) in R. Additional documentation and examples for the use of *plspm* are available online (https://cran.r-project.org/web/packages/plspm/vignettes/plspm_introduction.pdf). For the present analysis, we built an outer model with four first-level and one second-level latent variable. Building a PLS path model requires a dataset and the following three variables: 1) a path variable which represents the inner model, 2) a blocks variable that identifies the indicator variables, and 3) a mode variable that represents the type of measurement to use in the outer model. We will walk through how each component of the model was built in the following text so that others may implement a similar methodology.

The outer model was built following the specifications of the *plspm* documentation as follows:

```
#Build Inner Model
brain_resilience <- c(0,0,0,0,0)
```

```
cognitive_resilience <- c(0,0,0,0,0)
cognitive_reserve <- c(0,0,0,0,0)
brain_reserve <- c(0,0,0,0,0)
global_resilience <- c(1,1,1,1,0)
```

These values were then assigned to the path variable as follows:

```
#Build Path Variable
resil_path <-
rbind(brain_resilience,cognitive_resilience,cognitive_reserve,brain_reserve,
global_resilience)
```

Next, we built a data frame that included the variables of interest for cognitive resilience (residuals from cognition regression models), brain resilience (residuals from hippocampal volume regression models), cognitive reserve (education, reading score), and brain reserve (height, ICV). The blocks were set by assigning the proper column numbers to the latent variable in the order specified in the path model as follows:

```
#Identify indicator variables
resil_blocks <- list(15:18,11:14,9:10,7:8,7:18)
```

We then set the mode of measurement to reflective in the following way:

```
#Specify the type of measurement (reflective)
resil_modes <- c("A","A","A","A","A")
```

Finally, the dataset, path, blocks, and modes were all used to build the final model using the following code:

```
#Run plspm path model
resil_pls <- plspm(dataset,resil_path, resil_blocks, modes=resil_modes,
maxiter=500)
```

The individual scores that result from this model calculation were then pulled from the scores table in the resil_pls output.

S.8 References

1. Pudas S, Persson J, Josefsson M, de Luna X, Nilsson L-G, Nyberg L. Brain characteristics of individuals resisting age-related cognitive decline over two decades. The Journal of Neuroscience 2013;33:8668-8677.

2. Mukherjee S, Kim S, Gibbons LE, Nho K, Risacher SL, Glymour MM, et al. Genetic architecture of resilience of executive functioning. Brain Imaging and Behavior 2012;6:621-633.