Supplementary Material: Rethinking the residual approach: Leveraging statistical learning to operationalize cognitive resilience in Alzheimer's disease

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Simulating data

Except for our experiments exploring the effects of correlated predictors and nonlinear associations, we simulated the predictor matrix *X* using the 'make_regression' function from the sklearn package. Here, variables are drawn from multiple univariate standard Gaussian distributions if no correlation between predictors is desired, otherwise it generates a low-rank-fat-tail matrix to simulate variable correlations.

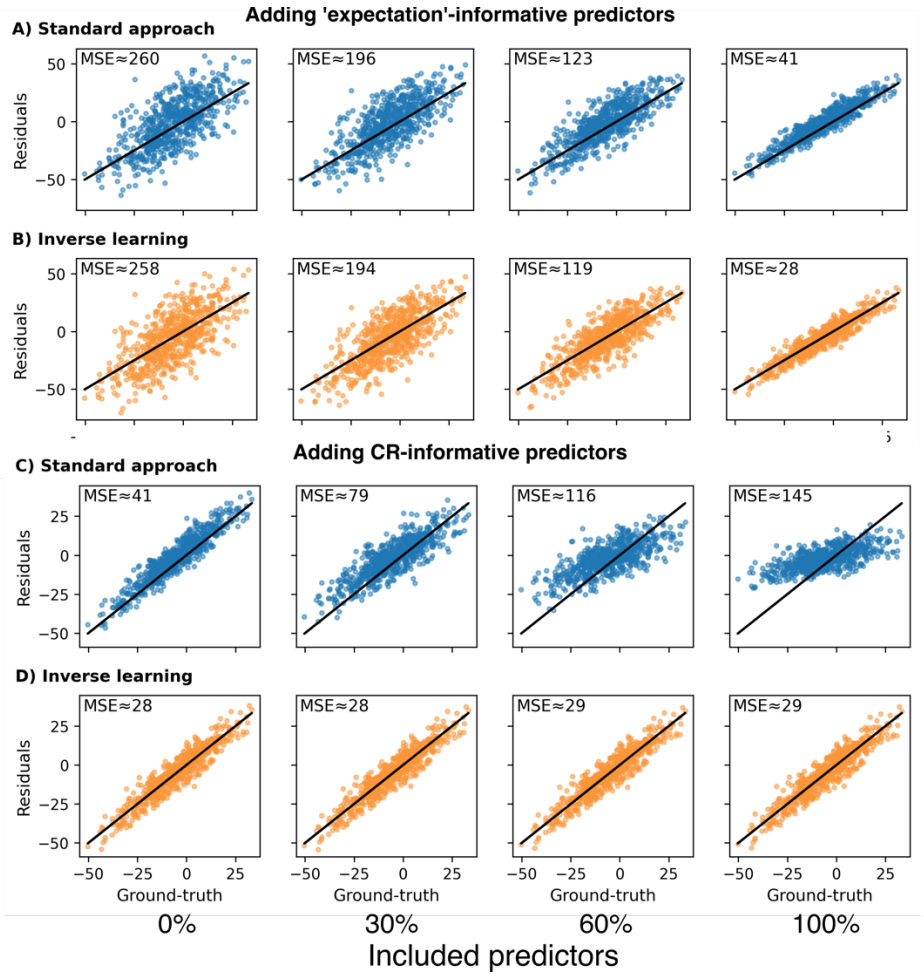
Our correlation experiments required us to specifically set the correlation strength. We therefore sampled the predictor matrix from a multivariate Gaussian distribution with a compound symmetric covariance matrix.

Below, we present the nonlinear transformation used to simulate a non-linear relationship between predictors, the expectation component, and the cognitive resilience (CR) component of the observed outcome. We used the function as implemented in scikit-learn[1] and presented in Friedman et al.[2]:

$$y(x) = 10 * \sin(\pi * x_1 * x_2) + 20 * (x_2 - 0.5)^2 + 10 * x_3 + 5 * x_4 + noise * N(0,1)$$

Effect of noise in the simulated outcome measure

Supplementary Figure 1 highlights that adding noise to our generated data has no influence on the observed trends in the behavior of the standard approach and the inverse learning approach. In Supplementary Figure 1, the same analysis was repeated that produced Figure 2 in the main text, with the only difference being that we added random Gaussian noise with mean 0 and a standard deviation of 5 to our simulated outcome value.



Supplementary Figure 1: Estimation of CR using the standard and inverse learning approach while including varying proportions of informative predictors for either the CR or 'expectation' component of the observed cognition. This figure is equivalent to the one presented in the main text as Figure 2, however, here Gaussian noise was added to the outcome. A linear regression was used as the expectation model for the inverse learning approach. **A, B:** Estimation without including any CR-informative predictors and varying proportions of 'expectation'-informative predictors for the standard approach (A) and inverse learning approach (B). **C, D:** Estimation while including all 'expectation'-informative predictors and varying proportions of CR-informative predictors for the standard approach (C) and inverse learning approach (D). MSE: Mean squared error between the simulated CR ground-truth and estimated CR.

Contrasting the inverse learning approach from the standard approach

Both, the standard approach and inverse learning approach estimate CR by solving Eq. 1 in the main text for cr:

S.Eq. 1: $cr = cog_{obs} - \widehat{cog_{exp}}$

Where, $\widehat{cog_{exp}}$ denotes the prediction for the expectation of a sample, cog_{exp} (i.e., the cognitive function an individual would have if they were unaffected by CR). The shift in cognition caused by CR is denoted by cr. In the standard approach, $\widehat{cog_{exp}}$ is predicted using a linear regression model $M: X \rightarrow \mathbb{R}$ that was fitted on the entire dataset X. Analogous to S.Eq. 1, CR is estimated as

S.Eq. 2: $cr = cog_{obs} - M(X)$

In our proposed inverse learning approach, CR is estimated using an 'expectation' model $E: X \rightarrow \mathbb{R}$ that predicts cog_{exp} and was only trained on samples, X_{nr}, that follow a specific definition of what the 'expectation' of individuals is:

S.Eq. 3: $\theta = arg\min_{\theta} L(E(X_{nr}, \theta), cog_{nr})$

where L denotes any loss function for optimizing regression models and θ represents the learnable parameters of the model. cog_{nr} denotes the observed cognition for samples in X_{nr}.

We further introduce the 'error correction' model, $C: X \rightarrow \mathbb{R}$, which predicts the innate error of the expectation model, aiming to remove it from the achieved CR estimates. The model learns to predict the error of the expectation model by training it on the empirical errors observed during cross-validation on X_{nr}, denoted by e_{nr}:

S.Eq. 4: $\varphi = arg\min_{\varphi} L(C(X_{nr}, \varphi), e_{nr})$

where φ denotes the learnable parameters of C and e_{nr} can be calculated as

S.Eq. 5: $e_{nr} = cog_{nr} - E(X_{nr}, \theta)$

CR is then estimated for the samples not used during training, X_{res} as

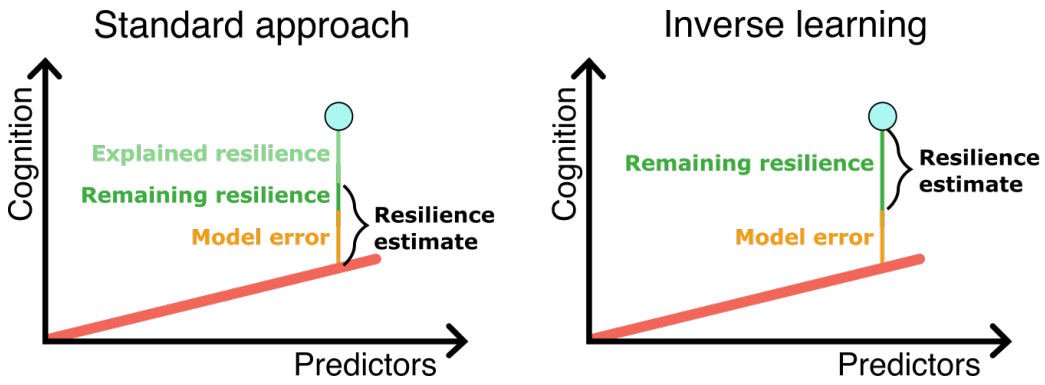
S.Eq. 6: $cr = cog_{res} - E(X_{res}, \theta) - C(X_{res}, \varphi)$

Hyperparameter tuning

We tuned the following hyperparameters in the employed xgboost models using Optuna, a package for Bayesian hyperparameter optimization[3] with the following distributions to sample them from:

- gamma: FloatDistribution(1, 8)
- learning_rate: FloatDistribution(1e-7, 1, log=True)
- max_depth: IntDistribution(3,8)
- subsample: FloatDistribution(0.7, 1, 0.1)

Schematic comparing CR estimates across residual approaches



Supplementary Figure 2: Difference between the CR estimates achieved by the standard approach and the proposed inverse learning approach. The standard approach will 'learn away' parts of the resilience component in the observed cognition due to either direct inclusion of associated predictors or correlation. Further, the linear regression will not perfectly predict the observed cognition and thus introduces model error. The residual achieved by the standard approach will thus contain an unknown proportion of error and have lost a proportion of the sought-after information (resilience). The inverse learning approach will not learn any of the predictor-resilience associations and the model error can be quantified and reduced using the 'error correction' model, thus leading to more reliable estimates of cognitive resilience.

Supplementary References

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