SUPPLEMENTARY MATERIAL

Progression Score Model

For clarity, vector-valued variables are in bold and matrices are capitalized. The affine transformation between the age t_{ij} of subject i at visit j and the Cog-PS s_{ij} is given by

$$s_{ij} = \alpha_i t_{ij} + \beta_i,$$

where α_i and β_i are the subject-specific variables assumed to be independent and identically distributed across subjects with a bivariate normal distribution $N(\mathbf{m}, V)$. α_i and β_i model the rate of change and baseline level of Cog-PS, respectively.

The trajectory of cognitive measure k is assumed to be a sigmoid in Cog-PS, and is given by

$$g_k(s; \boldsymbol{\omega}_k) = \frac{a_k}{1 + e^{-b_k(s-c_k)}} + d_k,$$

where $\boldsymbol{\omega}_k = (a_k, b_k, c_k, d_k)$ are trajectory parameters to be estimated. d_k and $a_k + d_k$ correspond to the minimum and maximum values of the sigmoid, respectively. c_k is the inflection point (the Cog-PS value at which the second derivative is zero) and $a_k b_k / 4$ is the slope at the inflection point.

The observed cognitive measures y_{ijk} stacked into the vector $\mathbf{y}_{ij}$ are assumed to have additive normally distributed noise, and are described by

$$\mathbf{y}_{ij} = \mathbf{g}(s; \boldsymbol{\omega}) + \boldsymbol{\epsilon}_{ij},$$

where $\mathbf{g}$ is the vector obtained by stacking g_k, and $\boldsymbol{\epsilon}_{ij}$ is noise, assumed to be independent and identically distributed with a multivariate normal distribution $N(\mathbf{0}, R)$. R is an unstructured covariance matrix that represents the variance of noise for each cognitive measure as well as the correlations among them, and is estimated during the model fitting procedure.

Model fitting is performed using a Monte Carlo expectation-maximization (MC-EM) algorithm. The subject-specific variables and missing cognitive measures constitute the hidden variables in this framework. Model parameters include $\boldsymbol{\omega}$, $\mathbf{m}, V$, and R. The EM approach is an iterative procedure where the most likely values of the hidden variables are computed given the data and current parameter estimates, and then the model parameters are estimated using these most likely values for the hidden variables. Since the integral in the E-step for our model does not have an analytical form, we approximate it using Monte Carlo samples.

After model fitting, we compute the cross-sectional mean and variance of the Cog-PS among cognitively normal individuals:

$$\mu = \frac{1}{|\Omega_{\text{normal}}|} \sum_{i \in \Omega_{\text{normal}}} s_{ij_0} ,$$

$$\sigma^2 = \frac{1}{|\Omega_{\text{normal}}|} \sum_{i \in \Omega_{\text{normal}}} (s_{ij_0} - \mu)^2$$

where j_0 is the visit index at which the mean and variance are computed and Ω_{normal} is the set of individuals who are cognitively normal at visit j_0. We selected j_0 as the baseline visit in both BLSA and WRAP. We calibrate the Cog-PS scale as $s_{ij}^* = \frac{s_{ij} - \mu}{\sigma}$, which corresponds to the following changes in the subject-specific variables:

$$\begin{pmatrix} \alpha_i^* \\ \beta_i^* \end{pmatrix} = \frac{1}{\sigma} \begin{pmatrix} \alpha_i \\ \beta_i - \mu \end{pmatrix}.$$

This calibration is accompanied by the following standardization of the model parameters:

$$b_k^* = \sigma b_k,$$

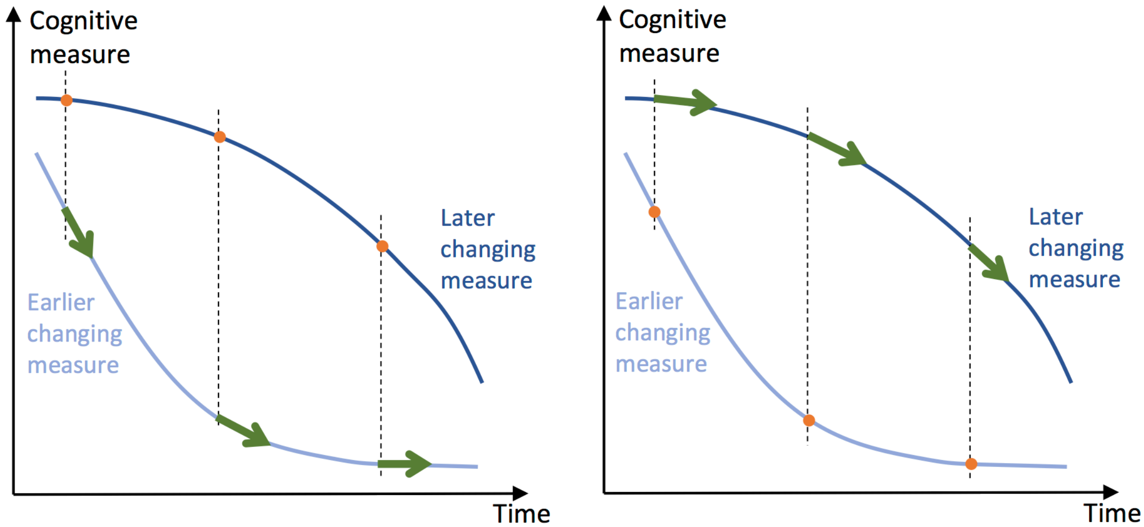
$$c_k^* = \frac{c_k - \mu}{\sigma},$$

$$\mathbf{m}^* = \frac{1}{\sigma}\left[\mathbf{m} - \binom{0}{\mu}\right],$$

$$V^* = \frac{1}{\sigma^2} V.$$

Let the minimum and maximum progression scores observed in the data set after model fitting be $s_{\min}$ and $s_{\max}$. We scale the trajectory of each marker so that fitted values at these values correspond across markers. Scaled values are given by

$$g_k^{(\text{scaled})}(s; \boldsymbol{\omega}_k) = \frac{g_k(s; \boldsymbol{\omega}_k) - g_k(s_{\min}; \boldsymbol{\omega}_k)}{g_k(s_{\max}; \boldsymbol{\omega}_k) - g_k(s_{\min}; \boldsymbol{\omega}_k)}.$$



a) Expected *negative* association between baseline values of the later changing measure and the rate of change of the earlier changing measure: at higher baseline values of the later changing measure, rate of change in earlier changing measure is smaller (more negative).

b) Expected *positive* association between baseline values of the earlier changing measure and the rate of change of the later changing measure: at higher baseline values of the earlier changing measure, rate of change in later changing measure is greater (less negative).

Figure S1. Illustration of the expected associations between two cognitive measures given their temporal ordering.

Predictors of CVLT imm.	Estimate	SE	*p*-value
Intercept	43.0170	1.9700	0.000
Education	0.4289	0.1038	0.000
Time	-0.4359	0.0926	0.000
Baseline age	-0.5529	0.0382	0.000
Sex	-7.2161	0.5735	0.000
Baseline digit span forward	0.4209	0.1279	0.001
Time × base age	-0.0019	0.0041	0.651
Time × sex	-0.0022	0.0467	0.962
Time × base digit span forward	**0.0268**	**0.0107**	**0.012**
Predictors of CVLT imm.	Estimate	SE	*p*-value
Intercept	41.9780	1.8479	0.000
Education	0.3231	0.1039	0.002
Time	-0.3324	0.0832	0.000
Baseline age	-0.5309	0.0377	0.000
Sex	-7.1160	0.5666	0.000
Baseline digit span backward	0.8422	0.1285	0.000
Time × base age	-0.0025	0.0041	0.545
Time × sex	-0.0112	0.0466	0.810
Time × base digit span backward	0.0156	0.0102	0.125
Predictors of CVLT delayed	Estimate	SE	*p*-value
Intercept	8.5992	0.5894	0.000
Education	0.1183	0.0311	0.000
Time	-0.0951	0.0258	0.000
Baseline age	-0.1513	0.0114	0.000
Sex	-1.4995	0.1708	0.000
Baseline digit span forward	0.0897	0.0381	0.018
Time × base age	0.0001	0.0012	0.962
Time × sex	-0.0170	0.0130	0.191
Time × base digit span forward	**0.0066**	**0.0030**	**0.026**
Predictors of CVLT delayed	Estimate	SE	*p*-value
Intercept	7.9821	0.5540	0.000
Education	0.0906	0.0312	0.004
Time	-0.0167	0.0232	0.470
Baseline age	-0.1438	0.0112	0.000
Sex	-1.4840	0.1688	0.000
Baseline digit span backward	0.2431	0.0383	0.000
Time × base age	-0.0002	0.0011	0.890
Time × sex	-0.0172	0.0129	0.185
Time × base digit span backward	-0.0030	0.0028	0.292

Predictors of digit span forward	Estimate	SE	*p*-value
Intercept	5.2572	0.5393	0.000
Education	0.0832	0.0255	0.001
Time	0.0211	0.0355	0.552
Baseline age	-0.0178	0.0100	0.074
Sex	0.5308	0.1455	0.000
Baseline CVLT imm.	0.0343	0.0072	0.000
Time × base age	0.0001	0.0011	0.924
Time × sex	0.0004	0.0130	0.978
Time × base CVLT imm.	-0.0009	0.0007	0.155
Predictors of digit span forward	Estimate	SE	*p*-value
Intercept	6.09630	0.47992	0.000
Education	0.08855	0.02568	0.001
Time	0.02130	0.02483	0.391
Baseline age	-0.02578	0.00984	0.009
Sex	0.41390	0.14179	0.004
Baseline CVLT delayed	0.07984	0.02356	0.001
Time × base age	0.00010	0.00109	0.929
Time × sex	0.00167	0.01286	0.897
Time × base CVLT delayed	**-0.00426**	**0.00211**	**0.043**
Predictors of digit span backward	Estimate	SE	*p*-value
Intercept	3.4228	0.5136	0.000
Education	0.1004	0.0242	0.000
Time	-0.0124	0.0353	0.726
Baseline age	-0.0136	0.0095	0.153
Sex	0.3193	0.1389	0.022
Baseline CVLT imm.	0.0462	0.0069	0.000
Time × base age	-0.0011	0.0011	0.311
Time × sex	-0.0183	0.0130	0.160
Time × base CVLT imm.	-0.0006	0.0007	0.336
Predictors of digit span backward	Estimate	SE	*p*-value
Intercept	4.3338	0.4563	0.000
Education	0.1039	0.0244	0.000
Time	-0.0164	0.0248	0.509
Baseline age	-0.0197	0.0094	0.036
Sex	0.1959	0.1353	0.148
Baseline CVLT delayed	0.1333	0.0225	0.000
Time × base age	-0.0010	0.0011	0.335
Time × sex	-0.0175	0.0128	0.173
Time × base CVLT delayed	-0.0026	0.0021	0.216

Table S1. Results of the linear mixed effects models investigating the temporal ordering of digit span and CVLT measures in the BLSA. Results described in the text are in bold. SE = Standard error, CVLT = California Verbal Learning Test, BLSA = Baltimore Longitudinal Study of Aging.