DOI: 10.1002/alz70862_109741

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NEUROIMAGING

Lifestyle and health signatures of brain pathological and cognitive aging

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Abstract

Background: While aging almost inevitably leads to some degree of cognitive decline, the interindividual heterogeneity in the trajectories of decline raises the question of the extent to which resistance against pathology and cognitive resilience are involved. Using a multimodal approach including neuroimaging, fitness assessment, questionnaire data, and Alzheimer's disease (AD) genetic risk and plasma biomarkers (Figure 1), we aimed to characterize latent structures of lifestyle, mental and bodily health, estimate indices of brain (pathological) and cognitive aging, and relate lifestyle/health profiles and AD genetic risk to these indices.

Method: We analyzed a subsample of 211 cognitively normal older adults aged ≥ 60 years from an ongoing study (CRC1436) (age=71.0±7.4years, 46% female). Using principal component analysis, we derived seven principal components (PCs) that capture latent structures of lifestyle and general health from thirty variables (Figure 2B). To characterize successful brain/cognitive aging, we calculated a brain (BAG) and cognitive age gap (CAG) as the difference between brain pathology-/cognition-predicted age and chronological age (Figure 2A). Our novel BAG estimate incorporated also AD pathology, white matter hyperintensities and enlarged perivascular spaces. We regressed the first seven principal components (PC) on BAG and CAG to estimate the association of lifestyle/health profiles with successful brain/cognitive aging. We further assessed whether APOE4 carriers had higher BAG/CAG using a two-sample t-test.

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Result: We named the PCs according to their main factor loadings (Figure 2B). PC1 (*Low Mental Health*), PC2 (*Active Life*), and PC5 (*Mentally Inactive & Physically Active*) were significantly associated with CAG, whereas only PC2 was significantly associated with BAG (Figure 3A). BAG partly explained the relationship between PC2 and CAG (partial mediation of 18.0% of total effect, $p = 0.027$; Figure 3B). Finally, APOE e4 carrier had significantly higher BAG ($p = 0.049$), but not CAG ($p = 0.155$).

Conclusion: Our results suggest that factors of cognitive resilience and brain maintenance are to some extent unified in an active lifestyle described by physical fitness, mental leisure activities, and lower cardiovascular risk. In addition, engagement in mental leisure activities may explain cognitive resilience independent of brain pathology. Finally, genetic risk for AD may also accelerate brain aging in cognitively healthy older adults.

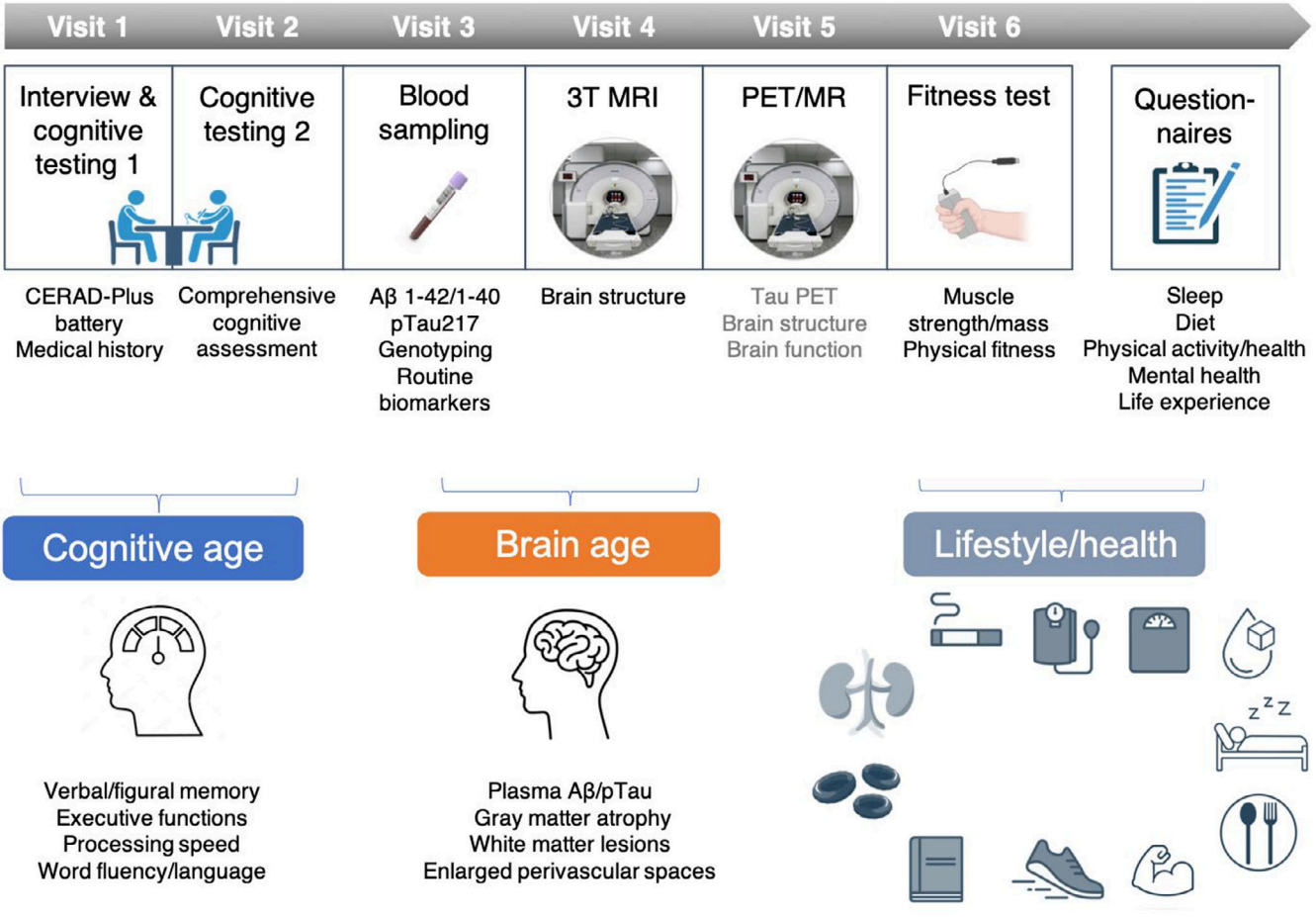

Figure 1 - Study overview and key measures. The study (Central Project 03 of CRC1436) included up to 6 visits. All participants underwent two comprehensive cognitive tests, and blood sampling. Most participants (~80%) underwent a 3T MR scan, including a T1- and T2-weighted sequences. A sub-sample also underwent tau PET imaging on a 3T MR-PET scanner with PI-2620 while additional structural and functional sequences were acquired. Most participants underwent a fitness test to assess physical fitness. Finally, participants completed several health and lifestyle questionnaires.

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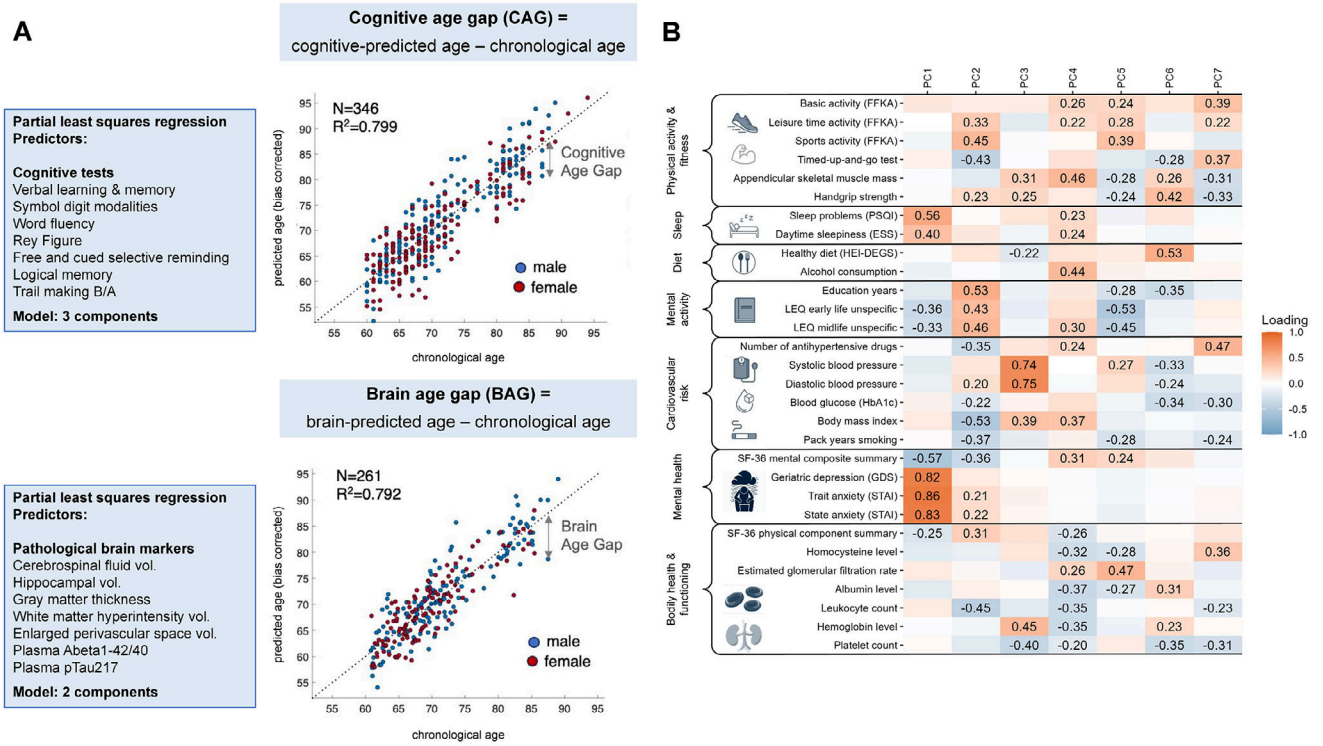

Figure 2 - Estimation of cognitive age gap, brain age gap, and lifestyle & health signatures. (A) Cognitive and brain age predicted from the partial least squares regression models based on cognitive scores and brain pathology-related markers, respectively. Scatter plots show predicted age after age bias correction against chronological age. Arrows indicate the difference between chronological and predicted age (i.e., cognitive age gap and brain age gap) **(B)** Lifestyle and health variables were transformed to normality and checked for extreme outliers (listwise exclusion of n = 3 subjects). Afterwards the variables were residualized if there was a significant association with age and/or sex. Missing values were imputed with *missForest* and all values were z-transformed before performing a principal component analysis with parallel analysis (5000 iterations). The loadings of the 30 lifestyle and health variables on the 7 retained components are shown.

A

	Cognitive age gap			Brain age gap		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	-0.64	-1.39 – 0.11	0.095	-0.74	-1.55 – 0.07	0.074
PC1	**0.36**	**0.09 – 0.64**	**0.010**	-0.00	-0.29 – 0.28	0.993
PC2	**-0.66**	**-0.98 – -0.34**	**<0.001**	**-0.52**	**-0.86 – -0.18**	**0.003**
PC3	0.13	-0.22 – 0.48	0.474	-0.06	-0.43 – 0.32	0.770
PC4	-0.18	-0.55 – 0.20	0.354	0.35	-0.03 – 0.73	0.073
PC5	**0.57**	**0.18 – 0.96**	**0.004**	-0.04	-0.45 – 0.36	0.833
PC6	0.23	-0.20 – 0.66	0.293	-0.23	-0.68 – 0.22	0.323
PC7	0.13	-0.31 – 0.57	0.557	-0.08	-0.54 – 0.39	0.750
Sex [male]	**1.54**	**0.50 – 2.57**	**0.004**	**1.10**	**0.00 – 2.20**	**0.050**
	Observations: 206			Observations: 171		
	R^2 = 0.180			R^2 = 0.097		

B

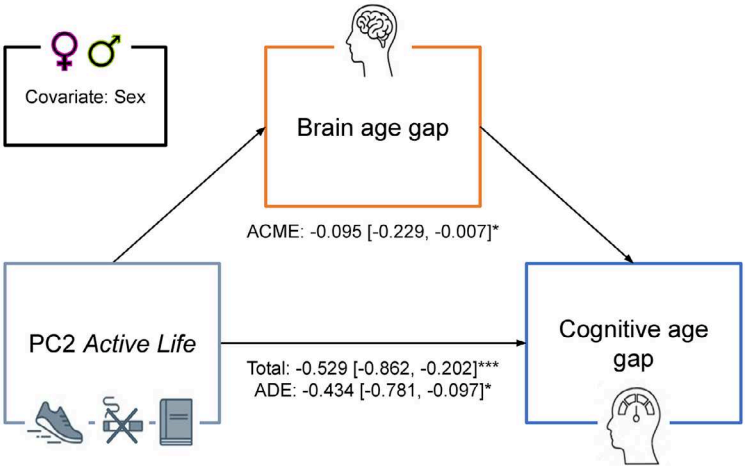

Figure 3 - Association of cognitive age gap and brain age gap with the lifestyle and health principal components (A) Results of linear regression models with cognitive age gap and brain age gap as target variables and the lifestyle and health signatures as predictors (sex as covariate). Sample sizes depended on available cognitive and imaging data. **(B)** Causal mediation analysis (10,000 simulations) of the effect of principal component (PC) 2 via brain age gap on cognitive age gap in n = 171 participants suggests partial mediation.