Assessing distinct patterns of cognitive aging using tissue-specific brain age prediction based on diffusion tensor imaging and brain morphometry

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Abstract

Multimodal imaging enables sensitive measures of the architecture and integrity of the human brain, but the high-dimensional nature of advanced brain imaging features poses inherent challenges for the analyses and interpretations. Multivariate age prediction reduces the dimensionality to one biologically informative summary measure with potential for assessing deviations from normal lifespan trajectories. A number of studies documented remarkably accurate age prediction, but the differential age trajectories and the cognitive sensitivity of distinct brain tissue classes have to a lesser extent been characterized.

Exploring differential brain age models driven by tissue-specific classifiers provides a hitherto unexplored opportunity to disentangle independent sources of heterogeneity in brain biology. We trained machine-learning models to estimate brain age using various combinations of FreeSurfer based morphometry and diffusion tensor imaging based indices of white matter microstructure in 612 healthy controls aged 18-87 years. To compare the tissue-specific brain ages and their cognitive sensitivity we applied each of the 11 models in an independent and cognitively well-characterized sample (n=265, 20-88 years). Correlations between true and estimated age in our test sample were highest for the most comprehensive brain morphometry (r=0.83, CI:0.78-0.86) and white matter microstructure (r=0.79, CI:0.74-0.83) models, confirming sensitivity and generalizability. The deviance from the chronological age were sensitive to performance on several cognitive tests for various models, including spatial Stroop and symbol coding, indicating poorer performance in individuals with an over-estimated age. Tissue-specific brain age models provide sensitive measures of brain integrity, with implications for the study of a range of brain disorders.

Introduction

Increasing age is a major risk factor for cognitive decline and neurodegeneration, and deviating lifespan trajectories in brain structure and function is a sensitive marker in several common neurological and mental disorders (Cole & Franke 2017). The maturing and aging brain is highly heterogeneous in term of individual trajectories and in term of brain regions and mechanisms involved (Fjell et al. 2013; Westlye et al. 2010b). Understanding the individual determinants and heterogeneity of the developing and aging brain is imperative for identifying persons at risk for various brain disorders, and for developing and applying effective and targeted treatments.

Exploring different modalities acquired by magnetic resonance imaging (MRI) provide a powerful tool to investigate age-related differences in both gray- and white- matter tissue classes across brain regions. However, the richness and complexity of the information provided by advanced imaging pipelines challenges its interpretation. Together, the multifactorial age-related variability and the richness of imaging measures have motivated the development of biologically informative summary measures based on brain imaging data. Using machine-learning to estimate the biological age of the brain based on neuroimaging data is one such approach (Cole & Franke 2017; Cole et al. 2018; Kaufmann et al. 2018). Deviation from the normative trajectory is a highly relevant biomarker for the integrity of the brain in healthy and clinical populations (Marquand et al. 2016; Wolfers et al. in press). Brain age gap is a heritable trait showing regionally specific genetic overlaps with major brain disorders, including schizophrenia and multiple sclerosis (Kaufmann et al. 2018), and accumulating evidence supports increased brain age in several clinical groups, including patients with schizophrenia (Kaufmann et al. 2018; Schnack et al. 2016), Alzheimer's disease (Amoroso et al. 2017; Kaufmann et al. 2018), HIV (Cole et al. 2017b; Kuhn et al. 2018) multiple sclerosis (Kaufmann et al. 2018) and cardiovascular risk factors (Franke et al. 2013; Habes et al. 2016). Indeed, while individuals with brains estimated as younger than their chronological age have been shown to be more physically active (Steffener et al. 2016), augmented brain age has been associated with poor health (Ronan et al. 2016), poor cognitive performance (Liem et al. 2017), early neurodegenerative diseases (Gaser et al. 2013), and increased mortality (Cole et al. 2017a). Less is known about the regional heterogeneity, i.e. to which degree different brain regions, systems or compartments show differential aging patterns and sensitivity to cognitive performance. Brain gray and white matter compartments, which can be assessed and quantified using T1-weighted imaging and diffusion tensor

imaging (DTI), respectively, comprise distinct tissue classes with largely differential biological and environmental modifiers and age trajectories (Bennett et al. 2010; Cao et al. 2017; Fjell et al. 2013; Salat et al. 2005; Storsve et al. 2014; Westlye et al. 2010a; Westlye et al. 2010b). Therefore, allowing for differential brain age models for these distinct classes provides an opportunity to disentangle independent sources of heterogeneity in brain aging.

Thus, to identify common and unique aging patterns with potentially differential sensitivity to cognitive function, we aimed to test the complementary value of tissue-specific prediction by comparing brain age estimated using different combinations of FreeSurfer based morphometric measures (regional cortical thickness, surface area and volume) and white matter microstructure features (DTI based fractional anisotropy and mean, radial and axial diffusivity) across the brain. Based on previous studies on brain aging, we expected high accuracy and generalizability of the age prediction models (Cole & Franke 2017). Since tissue specific brain age models capture biologically distinct information, we anticipated that the different FreeSurfer based brain morphometry and white matter microstructure models would only partly reflect common variance, and therefore provide complementary information with differential sensitivity to cognitive performance. Given that brain age predictions might be sensitive to the overall integrity of the brain (Liem et al. 2017), we anticipated that individuals with an over-estimated brain age would show lower cognitive performance, in particular among the elderly, and that the tissue-specific brain age models would show partly differential cognitive sensitivity.

To ensure generalizability, we trained the models in a large publicly available training set (n=612, 18-87 years) and validated their performance using 10-fold cross-validation before applying to an independent and well characterized test set (n=265, 20-88 years). We assessed the cognitive sensitivity using linear and non-linear models with performance on a range of paper-and-pencil and computerized tests comprising different large-scale cognitive domains (processing speed, executive functioning, working memory, attention, and general intellectual abilities) and cognitive scores based on computational models as dependent variables and age, sex and brain age gap (BAG, estimated brain age minus chronological age) as independent variables. For transparency, we report results both at an uncorrected level and corrected using false discovery rate (FDR) and Bonferroni methods to control the error rate.

Materials and methods

Table 1 summarizes key demographics. We included data from healthy volunteers from two independent cohorts: (1) the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) sample (http://www.mrc-cbu.cam.ac.uk/datasets/camcan/; (Shafto et al. 2014; Taylor et al. 2017)) and (2) StrokeMRI, which is an ongoing study on the determinants of stroke recovery, brain health and successful aging (Dorum et al. 2016; Dorum et al. 2017). Figure 1 shows the age distribution for each sample.

Volunteers were recruited to Cam-CAN through a large-scale collaborative research project funded by the Biotechnology and Biological Sciences Research Council (BBSRC, grant number BB/H008217/1), the UK Medical Research Council and University of Cambridge. For more information, see www.cam-can.org. Among the 650 datasets made available, 17 were excluded based on missing or poor quality DTI data and 21 due to poor T1-weighted data quality. Data from the remaining 612 individuals (age 18-87, mean = 54.41, SD = 18.26, 314 females) were included.

Healthy individuals were recruited to StrokeMRI through advertisement in newspapers, social media and word-of-mouth. All participants completed a comprehensive cognitive assessment, multimodal MRI and blood sampling for clinical biochemical analysis, various biomarkers and genotyping. MRI and cognitive assessments were performed on two subsequent days. Exclusion criteria included history of stroke, dementia, or other neurologic and psychiatric diseases, alcohol- and substance abuse, medications significantly affecting the nervous system and counter indications for MRI. In addition, individuals scoring lower than 25 on the Montreal Cognitive Assessment (MoCA; Nasreddine et al. 2005) were assessed for inclusion based on their age, level of education and performance on other cognitive tests. No participants were excluded based on a single low score. A neuroradiologist reviewed all scans and 14 participants with clinically significant abnormalities were excluded. Additional exclusion criteria included missing or incomplete MRI or cognitive data (n=2), or poor quality images (n=20). The remaining 265 participants (age 20-88, mean = 56.95, SD = 14.84, 168 females) were included in further analyses. The study was approved by the Regional Committee for Medical and Health Research Ethics (South-East Norway), and conducted in accordance with the Helsinki declaration. All subjects signed an informed consent prior to participating and received a compensation for their participation.

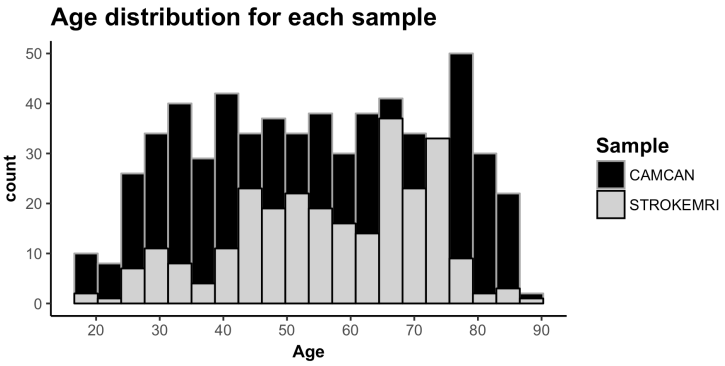

Fig. 1 Histogram of the age distribution for each sample.

Cognitive assessment in StrokeMRI

Cognitive performance was assessed with a set of neuropsychological and computerized tests assumed to be sensitive to cognitive aging, including the MoCA, the vocabulary and matrix subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler 1999), the California Verbal Learning Test (CVLT-II; Delis et al. 2000), and the Delis-Kaplan Executive Function System (D-KEFS) color word interference test (Stroop; Delis et al. 2001). We included several computerized tests from the Cognitive Assessment at Bedside for iPAD (CABPad; Willer et al. 2016), including motor speed, verbal fluency (phonological and semantic), working memory, spatial Stroop (executive control of attention), spatial attention span, and symbol digit coding tests. In addition, in order to assess the specificity of cognitive associations using computation modeling, we included three mathematically independent parameters based on the Theory of Visual Attention (TVA; Bundesen 1990; Bundesen & Habekost 2008), including short-term memory storage (K), processing speed (C), perceptual threshold (t_0). These parameters based on computational modeling of response patterns have been shown to be sensitive to age, brain structure and function in healthy individuals (Espeseth et al. 2014; Wiegand et al. 2018) and a range of brain disorders (Habekost 2015; Habekost & Starrfelt 2009). Here, we used a TVA-based modeling of a whole report (Sperling 1960), in which six letters were briefly presented for different exposure durations and the participant's task was to accurately report as many letters as possible. Task error rate was also assessed (i.e. number of incorrect letters out of reported letters).

MRI acquisition

Cam-CAN participants were scanned on a 3T Siemens TIM Trio scanner with a 32-channel head-coil at Medical Research Council (UK) Cognition and Brain Sciences Unit (MRC-

CBSU) in Cambridge, UK. DTI data was acquired using a twice-refocused spin echo sequence with the following parameters a repetition time (TR) of 9100 ms, echo time (TE) of 104 ms, field of view (FOV) of 192 x 192 mm, voxel size: 2 mm^3, 66 axial slices using 30 directions with b= 1000 s/mm^2, 30 directions with b= 2000 s/mm^2, and 3 b=0 images (Shafto et al. 2014). Only the b=[0,1000] were used in the current analysis. High-resolution 3D T1-weighted data was acquired using a magnetization prepared rapid gradient echo (MPRAGE) sequence with the following parameters: TR: 2250 ms, TE: 2.99 ms, inversion time (TI): 900 ms, flip angle (FA): 9°, FOV of 256 x 240 x 192mm; voxel size =1 mm^3 isotropic, GRAPPA acceleration factor of 2, scan time 4:32 minutes (Shafto et al. 2014).

StrokeMRI participants were scanned on a 3T GE 750 Discovery MRI scanner with a 32-channel head coil at Oslo University Hospital. Paddings were used to reduce head motion. DTI data were acquired using an echo planar imaging (EPI) sequence with the following parameters: TR/TE/flip angle: 8150 ms/83.1 ms/90°, FOV: 256 x 256 mm, slice thickness: 2 mm, in-plane resolution: 2 mm, 60 directions (b=1000 s/mm^2) and 5 b=0 volumes, scan time: 8:58 min. In addition, 7 b=0 volumes with reversed phase-encoding direction were acquired. High-resolution T1-weighted data was acquired using a 3D IR-prepared FSPGR (BRAVO) with the following parameters: repetition time: 8.16 ms, echo time: 3.18 ms, flip angle: 12º, voxel size: 1 × 1 × 1 mm, field of view: 256 x 256 mm, 188 sagittal slices, scan time: 4:43 minutes.

DTI processing and analysis

Diffusion MRI data from both samples were processed locally using the Oxford Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) (http://www.fmrib.ox.ac.uk/fsl). To correct for geometrical distortions, motion and eddy currents, data were preprocessed using topup (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/topup) and eddy (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/eddy) respectively (Andersson et al. 2003; Smith et al. 2004). Topup uses information from the reversed phase-encoded image, resulting in pairs of images (blip-up, blip-down) with distortions going in opposite directions. From these image pairs the susceptibility-induced off-resonance field was estimated and the two images were combined into a single corrected one (Andersson et al. 2003; Smith et al. 2004). This step was performed on StrokeMRI data only. Eddy detects and replaces slices affected by signal loss due to bulk motion during diffusion encoding, which is performed within an integrated framework along with correction for susceptibility induced distortions, eddy

currents and motion (Andersson & Sotiropoulos 2016). Although these processing steps have been shown to strongly increase the temporal signal-to-noise ratio (tSNR) (Doan et al. 2017), we performed additional visual inspection to identify and remove poor quality data.

Fractional anisotropy (FA), eigenvector, and eigenvalue maps were calculated using dtifit in FSL. Mean diffusivity (MD) was defined as the mean of all three eigenvalues, radial diffusivity (RD) as the mean of the second and third eigenvalue, and axial diffusivity (AD) as the principal eigenvalue.

Voxelwise analysis of FA, MD, AD and RD were carried out using Tract-Based Spatial Statistics (TBSS; Smith et al. 2006), part of FSL (Smith et al. 2004). First, all subjects' FA data were aligned to a common space using the nonlinear registration tool FNIRT (Andersson et al. 2007a; Andersson et al. 2007b). Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to all participants. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics. The same warping and skeletonization was repeated for MD, AD and RD. We thresholded and binarized the mean FA skeleton at FA>0.2. For each individual, we calculated the mean skeleton FA, MD, AD and RD, as well as mean values within 23 regions of interest (ROIs) based on two probabilistic white matter atlases provided with FSL, i.e. the CBM-DTI-81 white-matter labels atlas and the JHU white-matter tractography atlas (Hua et al. 2008; Mori et al. 2005; Wakana et al. 2007), yielding a total of 96 DTI features per individual.

T1 processing

T1-weighted images were processed using FreeSurfer 5.3 (http://surfer.nmr.mgh.harvard.edu; (Dale et al. 1999)) including brain extraction, intensity normalization, automated tissue segmentation, generation of white and pial surfaces (Dale et al. 1999). All reconstructions were visually assessed and corrected as appropriate. Cortical parcellation was performed using the Desikan–Killiany atlas (Desikan et al. 2006; Fischl et al. 2004) and subcortical segmentation was performed based on a probabilistic atlas (Fischl et al. 2002). In addition to global features (intracranial volume, total surface area, whole-cortex mean thickness), mean thickness, total surface area, and volume for each cortical ROI, as well as the volume of subcortical structures were computed yielding a set of 251 FreeSurfer based features.

Age prediction

Eleven different models were trained to estimate age based on the feature sets described above (one based on FreeSurfer T1 features, one based on WM DTI features, one including all T1 and DTI features, in addition to eight models based on a smaller subset of features, including models based on FA, MD, AD, RD, sub-cortical volume, volume, area and thickness to further explore the modality specificity of the estimations).

Due to the systematic differences in the brain features across scanners as well as non-linear effects of age, we fit a generalized additive model (GAM; Hastie 2017) for each feature and regressed out the effects of scanning site and age^2, accounting all models for age and sex. In addition, we regressed out the estimated total intracranial volume from the area and volume features. Next, for each model, we created a training data matrix by concatenating all the features for all participants in the training sample (Cam-CAN), which were used as input to estimate age. We used the *xgboost* framework in R (http://xgboost.readthedocs.io/en/latest/R-package/xgboostPresentation.html), an efficient and scalable implementation of gradient boosting machine learning techniques, to build the prediction models. The following parameters were used: learning rate (eta) = 0.1, nround = 5000, gamma = 1, max_depth = 6, subsample=0.5. To estimate the performance of our models, we used a 10-fold cross-validation procedure within the training sample and repeated the cross-validation step 1000 times to provide a robust estimate of model predictive accuracy. Next, we tested the performance of our trained models by predicting age in unseen healthy subjects in the test sample (StrokeMRI).

For each feature set, we calculated the correlation between the predicted and the chronological age as a measure of the model performance, in addition to the mean absolute error (MAE, in years). For each individual, we calculated the discrepancy between the estimated and the chronological age, i.e. the BAG, for each model. The MAE was calculated from the BAG for each model. Since we were interested in the effect of BAG independently of age, the effect of age was regressed out for each BAG using linear models.

Statistical analysis

Statistical analysis was performed using R (http://www.r-project.org). For cognitive data, we used *outlierTest* from the car package (Fox & Weisberg 2011) to identify the most extreme observations based on a linear model, including age and sex. Twenty-five observations were identified as outliers and treated as missing values based on a Bonferroni corrected $p < 0.05$.

To visualize the associations between the cognitive tests and to form cognitive domain scores based on the correlation patterns, we performed hierarchical clustering using the default setting of the heatmap.2 package in gplots (Warnes et al. 2016), which uses hclust (Müllner 2013) to form clusters based on the complete linkage method. Briefly, this is a step-wise clustering process that merges the two nearest clusters until only one single cluster remains, maximizing distance between individuals components between two clusters.

For each cognitive measure and summary score based on the clusters formed form the clustering step above, we used linear models to test for the effect of age and sex. Since cognitive performance may show non-linear associations with age, we performed an additional analysis including both age and age^2 in the models. Then, for each test showing a significant association with age, we tested whether adding BAG to the models lead to an improved model fit. More specifically, we tested for differential associations with cognitive function by comparing the parameter estimates for the different BAG models using Fisher z-transformation. To test the assumption that increased BAG is more relevant for cognitive function among the elderly, we tested for age by BAG interactions on cognitive performance. For transparency, we report both uncorrected p-values and p-values adjusted using FDR (Benjamini & Hochberg 1995; Wright 1992) and Bonferroni correction using a factor of 495 (11 brain gaps and 45 cognitive features).

Results

Brain age prediction

10-fold cross-validation on the training sample revealed high correlations between chronological and predicted age for the DTI based white matter microstructure (r=0.87) and FreeSurfer based morphometric (r=0.88) models. Likewise, the correlations for FA (r=.76), MD (r=.80), AD (r=.83), RD (r=78), sub-volume (r=.84), volume (r=.80), area (r=.70) and thickness (r=.79) based models also confirmed reasonable model performance.

Most models accurately predicted age in the independent test set. Figure 2A shows a correlation matrix for the 11 BAGs. Figure 2B shows the correlations between the chronological age and the predicted age in the test sample for each model with their confidence intervals, ranging from (r=.86, CI:.82-.89, MAE= 6.14) for the combined model to r=.58 (CI:.49-.65, MAE=10.24) for the model based on area. Figure 2 (D to F) show the estimated age from the three models that performed best among the 11 feature sets, i.e. the

combined DTI and T1 feature models (r=.86, CI:.82-.89, MAE= 6.14), the 251 FS T1 features (r=.83, CI:.78-.86, MAE= 6.76), and the 96 WM DTI features (r=.79, CI:.74-.83, MAE=7.28).

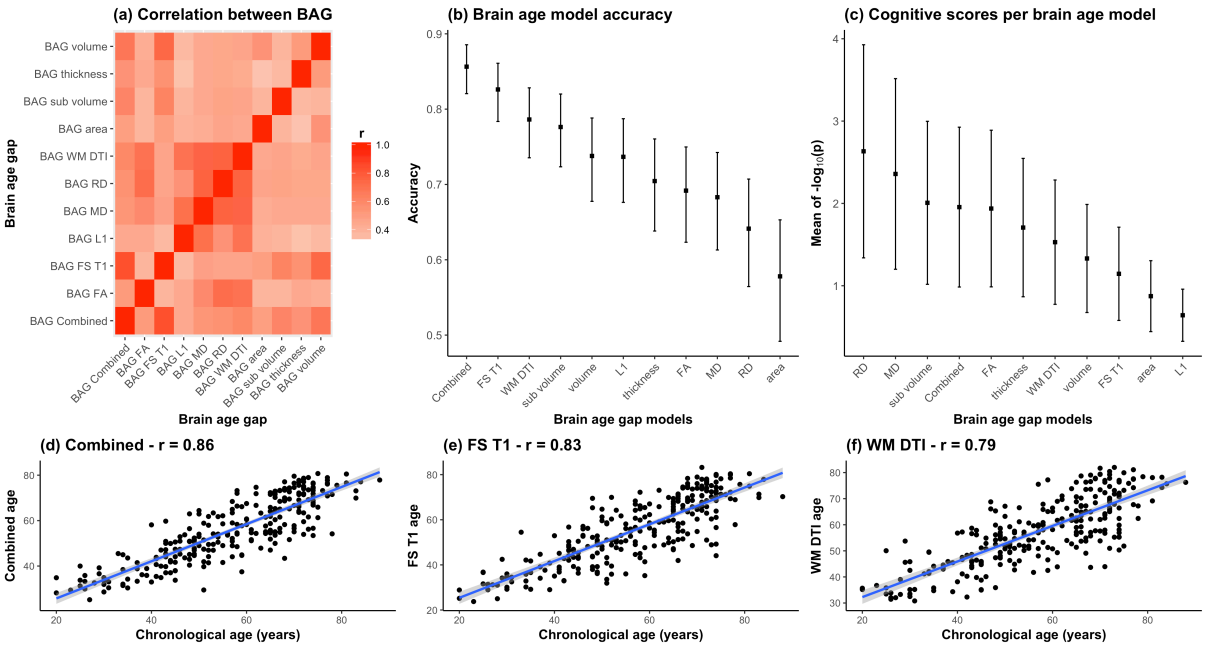

Fig. 2 Comparison between the 11 BAG models. (a) Heatmap of the correlation between different BAGs. (b) Correlations between the chronological age and the predicted age in the test sample for each model with their confidence intervals. (c) Mean and standard error of the 45 p-values ($-\log_{10}(p)$) for the cognitive scores and composite scores for each row (i.e. BAGs), with a higher mean representing a stronger global association across tests. (d) Correlation between the chronological age of each subjects and the combined age, (e) the brain morphometry age, and (f) the white matter microstructure age.

Cognitive assessments and associations with BAGs

Table 1 summarizes descriptive statistics and associations with age and sex for each of the 49 cognitive scores, derived features and domain scores. Linear models revealed 45 significant associations with age after correcting for multiple comparisons, with the strongest effect sizes for the symbol coding test, motor speed, spatial Stroop and spatial attention span. Since non-linear models revealed significant associations with age^2 only with the color word Stroop 3 (inhibition) and its derived scores (See supplementary Table S1), the main models presented here are linear in order to keep the model to its simplest form. Figure 3 shows a correlation matrix across all normalized cognitive scores with the variables sorted according to the

hierarchical clustering. Several variables were highly correlated, and the clustering solution generally suggested seven broad cognitive domains including (Cluster 1) memory and learning (CVLT, attention span, MoCA), (Cluster 2) visual processing speed (TVA processing speed and perceptual threshold), (Cluster 3) verbal skills (phonological and semantic flow), (Cluster 4) attentional control and speed (spatial Stroop), (Cluster 5) executive control and speed (color-word Stroop), (Cluster 6) reasoning and psychomotor speed (matrix, symbol coding and motor speed, short-term memory storage (TVA-parameter *K*)), and (Cluster 7) working memory.

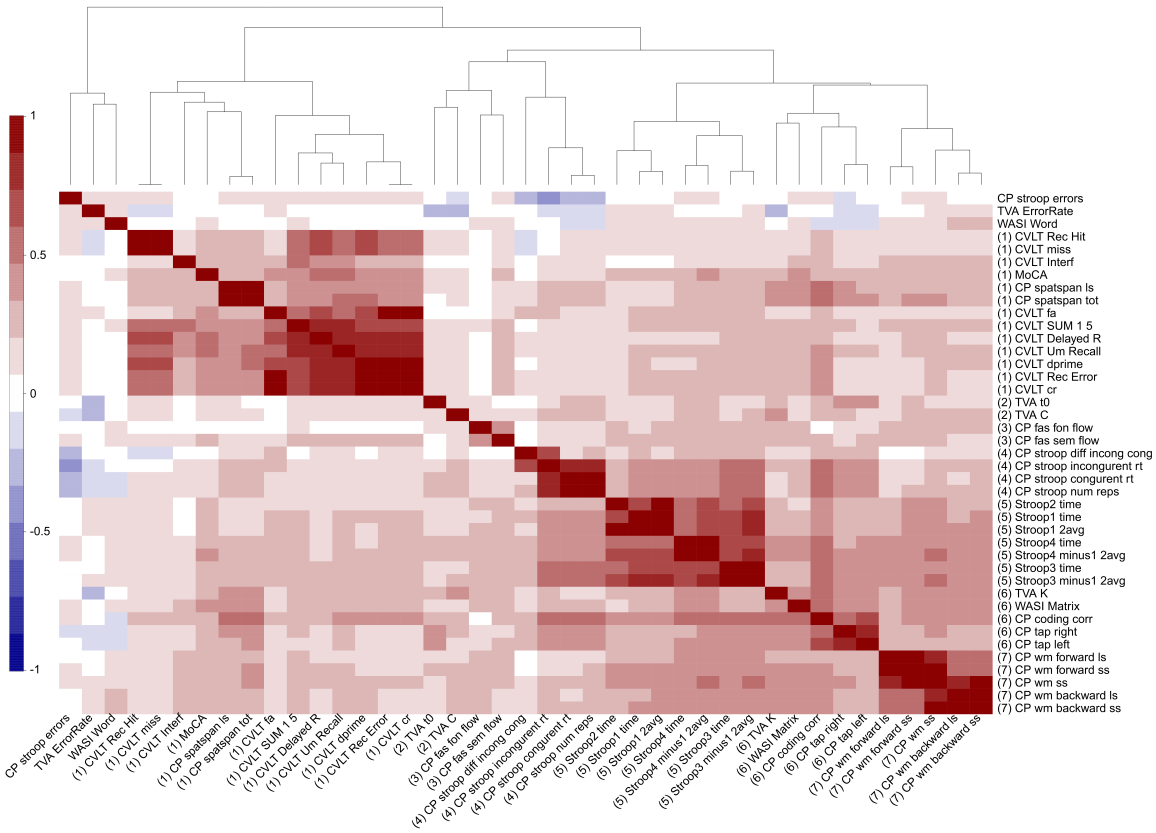

Fig. 3 Hierarchical clustering of the cognitive features. Each cognitive score was normalized and when required the scores were multiplied by -1 to ensure that positive scores represent good performance. The higher panel shows the dendrogram resulting from the hierarchical clustering of the scores in 7 cognitive domains.

Table 2 shows summary statistics for the associations between cognitive performance and BAG using linear models, including age and sex as covariates. Figure 4 shows a heatmap of the association between cognitive scores and brain age gaps for which the significant associations have been marked with an asterisk. Supplementary Table S1 and Fig. S1 shows

the summary statistics and the heatmap of the associations between cognitive performance and BAG using non-linear models. Figure 2C shows the mean and standard error of the 45 p-values ($-\log_{10}(p)$) for the cognitive scores and composite scores for each row (i.e. BAGs), with a higher mean representing a stronger cumulative association across tests.

Figure 5 shows a scatter plot of the 2 strongest associations, which were found between the most comprehensive model (all features combined) and spatial Stroop congruent trials and number of responses, respectively, indicating poorer performance with higher BAG. Fisher z-transformation revealed no statistically significant differences in the cognitive associations between linear models using tissue-specific BAG. No significant interactions were found between BAG and age on cognitive performance.

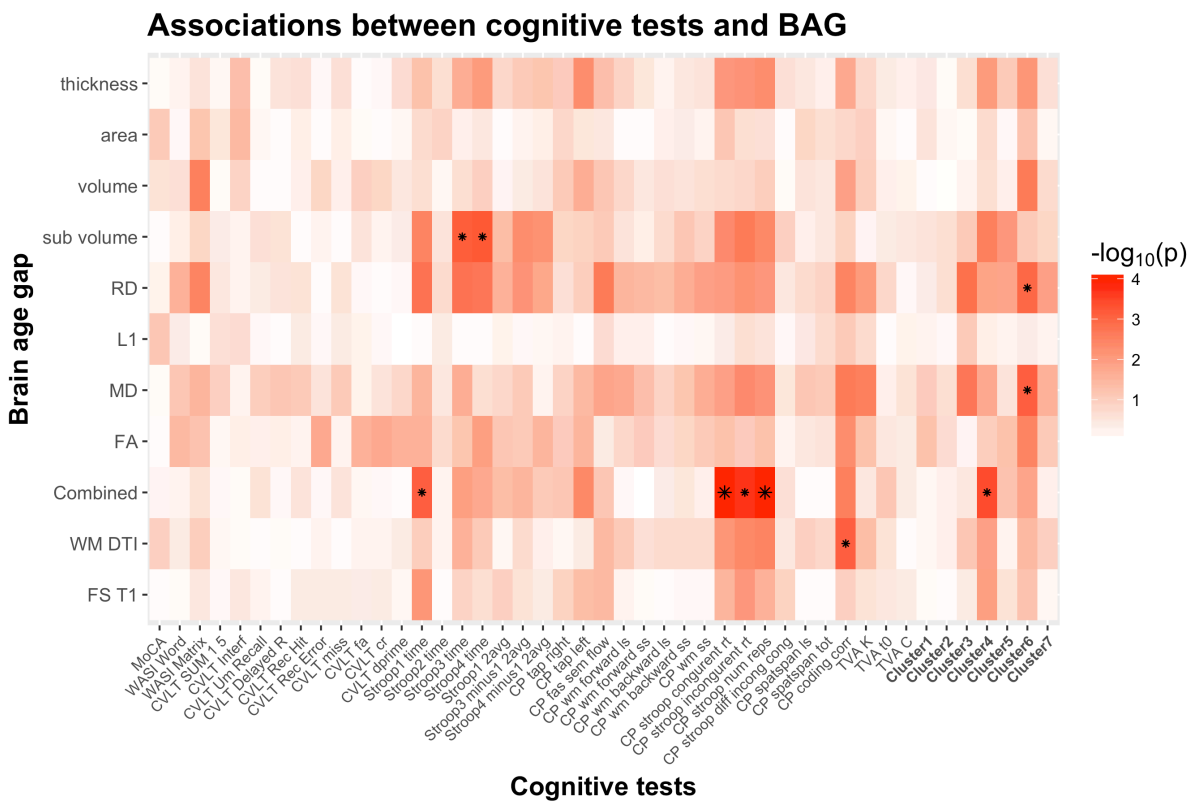

Fig. 4 Heatmap of the association between cognitive scores and brain age gaps. The color scale depicts the minus log of the p-values ($-\log_{10}(p)$) for each association. The association marked with a small star represents significant associations after FDR correction, and the one marked with a big star shows significant associations after Bonferroni correction.

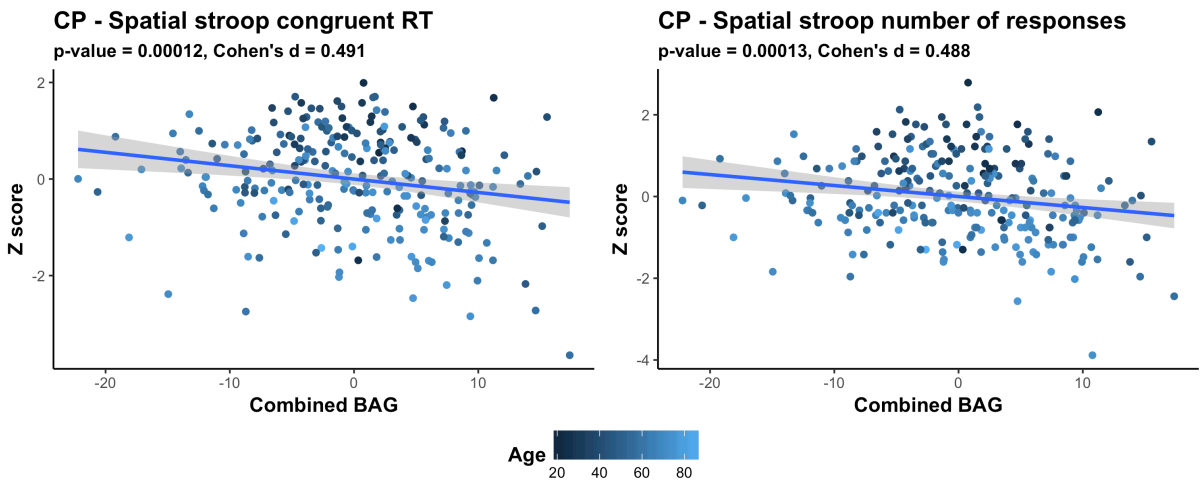

Fig. 5 Scatter plots of the 2 strongest associations between cognitive measures and BAG. The color gradient represents the age where lighter color is assigned to older individuals, and darker color to younger individuals. All associations indicate worse performance with higher brain age gap.

Discussion

Brain aging is highly heterogeneous, and expanding our understanding of the biological determinants of human aging is imperative for reducing the burden of age-related cognitive decline and neurodegenerative disorders. An estimate of an individual's deviation from the expected lifespan trajectory in brain structure and function may provide a sensitive measure of individual brain integrity and health, both in presumably healthy individuals and in patients suffering from various brain disorders.

The biological heterogeneity of the brain strongly suggests that the concept of a single brain age is too simple, and that tissue-specific brain age models may provide increased sensitivity and specificity in relation to cognitive and mental functions. In line with this view, our main findings demonstrate that different combinations of FreeSurfer based brain morphometry and DTI based white matter microstructural indices can be used to accurately predict the age of individuals, but that the shared variance from the different models suggest that they reflect partly non-overlapping processes of brain aging. Further, the results revealed partly differential sensitivity to cognitive performance; with the strongest cumulative associations across cognitive tests for brain age gaps estimated using RD. Even though our data provide no strong evidence of independent associations with cognitive performance in the current sample of healthy individuals, tissue specific age prediction models might better

379 inform us about the individual determinants and heterogeneity of the aging brain compared to
380 models collapsing several brain compartments by potentially capturing distinct measures of
381 brain aging.
382
383 *Brain age prediction*
384 For the age prediction models, our results demonstrated that the 11 different combinations of
385 FreeSurfer based morphometric measures (regional cortical thickness, surface area and
386 volume) and white matter microstructure features (diffusion tensor imaging (DTI) based
387 fractional anisotropy and mean, radial and axial diffusivity) across the brain age models
388 accurately predicted the age of an individual with a mean absolute error between 6.14 and
389 10.23 years. Brain morphometry and white matter microstructure models had a MAE of 6.76
390 and 7.28 respectively, which correspond with previous publications (Cole et al. 2016; Han et
391 al. 2014; Valizadeh et al. 2017). In general, combining features and modalities increased the
392 performance, and the highest performing model included a combination of both brain
393 morphometry and white matter microstructure (mean absolute error of 6.14 years). Moreover,
394 the correlations between the different brain age gaps suggested a relatively low level of shared
395 variance (mean correlation = 0.51, SD=0.13). Together these findings support the notion that
396 tissue specific brain age models capture biologically distinct information. This is in line with
397 the characteristic lifespan patterns of global linear decreases in gray matter volume and the
398 nonlinear trajectories of total white matter volume and DTI based metrics of white matter
399 microstructure (Cox et al. 2016; Fjell et al. 2013; Ge et al. 2002; Liu et al. 2017; Raz et al.
400 2010; Westlye et al. 2010b), highlighting that the different compartments carry unique
401 biological information and that combining different modalities lead to a better estimation the
402 age of individuals (Cherubini et al. 2016; Liem et al. 2017; Madan & Kensinger 2018).
403
404 *Cognitive associations*
405 We performed a comprehensive cognitive assessment of the test sample, confirming previous
406 evidence of substantial age-related differences in cognitive performance across a range of
407 tests and domains. Hierarchical clustering of the cognitive features indicated a characteristic
408 pattern of covariance, largely reflecting broad cognitive domains, including memory and
409 learning, visual processing speed, verbal skills, attentional and executive control, reasoning
410 and psychomotor speed, and working memory. Ninety percent of the included cognitive
411 features showed age-differences, with the largest effect sizes observed for speed-based

measures, such as symbol coding test, which measures mental and visuo-motor speed (Willer et al. 2016). This is in line with the well-established literature on age-related decline in information processing speed in healthy aging (Bennett et al. 2010; Craik & Salthouse 2008; Harada et al. 2013). Importantly, not only tasks measuring reaction time, but also various TVA measures based on computational modeling, such as short-term memory storage (*K*), processing speed (*C*), and perceptual threshold (t_0) showed strong associations with age, in line with previous studies (Espeseth et al. 2014; Habekost 2015; Habekost et al. 2013; McAvinue et al. 2012; Wiegand et al. 2018).

Based on the assumption that brain age captures variance related to the integrity of the brain, we anticipated that individuals with an over-estimated age would show lower cognitive performance, and that the tissue-specific brain age models would show partly differential sensitivity. To test these hypotheses, we used linear models to explore the associations between cognitive performance and BAG, with age and sex as covariates, and directly compared the parameter estimates from the different brain age models. We found a significant association between performance on several tests and BAG beyond the age associations, indicating lower performance in individuals with higher BAG. Briefly, one significant association was found for WM DTI, five for combined BAG, two for the sub-volume, one for the RD and one for the MD BAG. The strongest associations were found with the spatial Stroop congruent trials, and number of responses. These findings support that the deviance between the estimated age and the chronological age captures relevant biological information regarding the cognitive performance of an individual. Whereas we found no significantly different associations between brain age models, the association with symbol digit coding test was only seen for WM DTI BAG, while associations with Stroop 3 and 4 were observed only for sub-volume BAG, suggesting some specificity that should be investigated in future studies including larger samples and a broader spectrum of mental health, cognitive and brain phenotypes, both across healthy and clinical samples. We speculate that the contributions of the different modalities in predicting age and the associations with both cognitive performance, but also age-related illnesses vary across the age-span, as it does during maturational age (Brown et al. 2012). Thus, future studies might benefit from investigating modality specific brain-age estimation using specific age range.

Limitations

The present findings do not come without limitations. First, although reducing the dimensionality of complex brain imaging data to a biologically informative brain age is a powerful method to assess deviations from normal lifespan trajectories in brain health, findings from this data reduction method are limited in specificity. Here, we attempted to both reduce the complexity of the information while keeping some modality specificity measured by different MRI parameters. Finding a balance between specificity and precision represents an interesting challenge for future studies. Moreover, causality and individual level trajectories cannot be established based on cross-sectional data. Therefore, future longitudinal studies are needed to inform us about the relevance of the differential trajectories of the tissue-specific brain age prediction with implications for the study of a range of brain disorders. Next, although the age distribution of the test sample is irrelevant to the individual prediction accuracy, the relative overrepresentation of older individuals in the test sample is a limitation when investigating interactions between BAG and age. Thus, although the lack of brain by BAG interactions on cognitive function did not support our hypothesis that increased BAG is more relevant for cognitive function among the elderly, future studies including individuals across a broader range of function are needed to characterize the lifespan dynamics in the associations between brain and behavior. Although we covered a relatively broad spectrum of structural brain features, the link between imaging based indices of brain structure and brain function is elusive, and brain age models including other brain imaging features, including functional measures, might provide a sensitive supplement to the current models. Lastly, whereas the results showed some numerical differences in the cognitive sensitivity of the different combinations of FreeSurfer based morphometry and white matter microstructure models, these differences were not statistically significant, and the hypothesis that tissue specific models provide increased specificity in terms of cognitive associations remains to be further explored in future studies.

In conclusion, we have demonstrated that models based on different combinations of brain morphometry and white matter microstructural indices provide partly differential information about the aging brain, emphasizing the relevance of tissue-specific brain age models in the study of brain and mental function in health and disease.

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Figure legends

Fig. 1 Histogram of the age distribution for each sample.

Fig. 2 Comparison between the 11 BAG models. (a) Heatmap of the correlation between different BAGs. (b) Correlations between the chronological age and the predicted age in the test sample for each model with their confidence intervals. (c) Mean and standard error of the 45 p-values ($-\log_{10}(p)$) for the cognitive scores and composite scores for each row (i.e. BAGs), with a higher mean representing a stronger global association across tests. (d) Correlation between the chronological age of each subjects and the combined age, (e) the brain morphometry age, and (f) the white matter microstructure age.

Fig. 3 Hierarchical clustering of the cognitive features. Each cognitive score was normalized and when required the scores were multiplied by -1 to ensure that positive scores represent good performance. The higher panel shows the dendrogram resulting from the hierarchical clustering of the scores in 7 cognitive domains.

Fig. 4 Heatmap of the association between cognitive scores and brain age gaps. The color scale depicts the minus log of the p-values ($-\log_{10}(p)$) for each association. The association marked with a small star represents significant associations after FDR correction, and the one marked with a big star shows significant associations after Bonferroni correction.

Fig. 5 Scatter plots of the 2 strongest associations between cognitive measures and BAG. The color gradient represents the age where lighter color is assigned to older individuals, and darker color to younger individuals. All associations indicate worse performance with higher brain age gap.

Table legends

Table 1. Demographics and cognitive information. * significant associations between cognitive measures with age after FDR correction, ** significant associations between cognitive measures with age after Bonferroni correction

Table 2. Cognitive associations with Brain Age Gap (BAG) – statistics. * FDR significant ** Bonferroni significant

Supplementary Materials

Fig. S1. Heatmap of the association between cognitive scores and brain age gaps using non-linear models, including age, age^2 and sex as covariates. The color scale depicts the minus log of the p-values ($-\log_{10}(p)$) for each association. The association marked with a small star represents significant associations after FDR correction, and the one marked with a big star shows significant associations after Bonferroni correction.

Table S1. Cognitive associations with Brain Age Gap (BAG) using non-linear models, including age, age^2 and sex as covariates – statistics. * FDR significant ** Bonferroni significant.

Tables

Demographics and cognitive information

	Cam-CAN	StrokeMRI Mean (SD)	Range (IQR)	Main effect Age *t (p)*	Main effect Sex *t (p)*
Total N (% females)	612 (51.3%)	265 (63.4%)			
Mean age (SD)	54.41 (18.26)	56.95 (14.84)			
Age range	18-87	20-88			
MoCA	-	27.60 (1.72)	21 – 30 (2)	-4.57 (<0.001)**	-2.32 (0.021)
WASI words	-	65.27 (6.60)	44 – 79 (10)	4.72 (<0.001)**	0.10 (0.920)
WASI matrix	-	25.39 (5.64)	7 – 35 (6)	-7.60 (<0.001)**	-0.28 (0.776)
CVLT learning 1-5	-	48.92 (11.37)	17 – 73 (15.5)	-5.05 (<0.001)**	-5.26 (<0.001)
CVLT interference	-	5.53 (2.15)	0 – 13 (3)	-4.33 (<0.001)**	-0.41 (0.681)
CVLT recall	-	10.83 (3.42)	0 – 16 (5)	-6.50 (<0.001)**	5.94 (<0.001)
CVLT delayed recall	-	11.39 (3.44)	0 – 16 (5)	-4.97 (<0.001)**	-5.51 (<0.001)
CVLT recognition hit	-	14.70 (1.50)	8 – 16 (2)	-2.62 (0.0093)*	-2.68 (0.008)
CVLT recognition errors	-	3.79 (3.92)	0 – 18 (4)	5.22 (<0.001)**	4.18 (<0.001)
CVLT recog misses	-	1.30 (1.49)	0 – 8 (2)	2.62 (0.0093)*	2.68 (0.008)
CVLT recog false alarm	-	2.46 (3.48)	0 – 18 (3)	4.45 (<0.001)**	3.59 (0.0004)
CVLT recog correct rejection	-	44.20 (3.92)	30 – 48 (4)	-5.22 (<0.001)**	-4.18 (<0.001)
CVLT d’	-	2.97 (0.72)	0.97 – 3.90 (1.11)	-5.01 (<0.001)**	-4.50 (<0.001)
STROOP 1	-	31.14 (5.66)	21 – 50 (7)	5.05 (<0.001)**	2.44 (0.015)
STROOP 2	-	22.12 (3.49)	14 – 35 (4)	2.89 (0.004)*	2.27 (0.024)
STROOP 3	-	55.86 (14.13)	10 – 108 (15)	7.55 (<0.001)**	2.97 (0.003)
STROOP 4	-	61.74 (14.85)	33 – 117 (19)	7.51 (<0.001)**	1.77 (0.078)
STROOP mean 1 and 2	-	26.54 (4.16)	18.5 – 42 (5)	4.47 (<0.001)**	2.47 (0.014)
STROOP 3 minus mean 1 and 2	-	81.94 (16.51)	34.5 – 145 (18.5)	7.31 (<0.001)**	3.02 (0.003)
STROOP 4 minus mean 1 and 2	-	87.64 (16.73)	53.5 – 142 (24)	7.52 (<0.001)**	1.85 (0.066)
CP – Right motor speed	-	79.56 (23.34)	34 – 153 (32)	-12.25 (<0.001)**	-0.36 (0.716)
CP – Left motor speed	-	81.36 (17.80)	39 – 131 (26)	-12.07 (<0.001)**	0.20 (0.842)
CP – FAS Phonological flow	-	54.70 (14.53)	14 – 95 (19.75)	-0.61 (0.541)	-2.58 (0.011)
CP – FAS Semantic flow	-	51.00 (10.14)	27 – 81 (13)	-2.93 (0.004)*	-3.93 (<0.001)

CP – Visual WM forward ls	-	4.23 (1.01)	2 – 7 (2)	-5.31 (<0.001)**	0.29 (0.774)
CP – Visual WM forward ss	-	5.45 (1.87)	1 – 10 (3)	-6.59 (<0.001)**	-0.25 (0.803)
CP – Visual WM backward ls	-	3.80 (1.28)	0 – 8 (1)	-4.60 (<0.001)**	-1.85 (0.065)
CP – Visual WM backward ss	-	4.56 (2.08)	0 – 12 (3)	-5.48 (<0.001)**	-1.02 (0.309)
CP – Visual WM ss	-	9.96 (3.57)	1 – 21 (4)	-7.04 (<0.001)**	-0.95 (0.342)
CP – Spatial stroop congruent (ms)	-	674.42 (132.77)	410 – 1159 (181)	8.52 (<0.001)**	-1.03 (0.304)
CP – Spatial stroop incongruent (ms)	-	929.52 (198.01)	462 – 1827 (269)	9.41 (<0.001)**	-0.75 (0.451)
CP – Spatial stroop Errors	-	2.17 (2.41)	0 – 11 (3)	0.73 (0.463)	1.59 (0.113)
CP – Spatial stroop numb of reps	-	119.63 (16.64)	55 – 166 (22)	-9.67 (<0.001)**	1.23 (0.219)
CP – Spatial stroop incong – cong (ms)	-	252 (110)	20 – 678 (134.5)	5.73 (<0.001)**	-0.68 (0.498)
CP – Spatspan ls	-	5.37 (1.78)	1 – 10 (2)	-9.12 (<0.001)**	-4.88 (<0.001)
CP – Spatspan tot	-	29.87 (12.43)	3 – 55 (18)	-9.28 (<0.001)**	-4.66 (<0.001)
CP – Coding corr	-	54.50 (12.11)	24 – 88 (16)	-16.69 (<0.001)**	-2.46 (0.015)
CP – Coding error	-	0.67 (0.99)	0 – 5 (1)	-1.10 (0.271)	1.56 (0.121)
TVA – Short-term memory storage (*K*)	-	3.38 (0.77)	1.46 – 5.53 (1.09)	-7.75 (<0.001)**	-1.52 (0.129)
TVA – Processing speed (*C*)	-	31.55 (14.07)	5.99 – 89.67 (14.75)	-4.69 (<0.001)**	0.41 (0.6847)
TVA – Perceptual threshold (t_0)	-	23.01 (14.05)	0 – 79.75 (17.59)	5.72 (<0.001)**	-1.94 (0.053)
TVA – Error rate	-	0.10 (0.06)	0.0035 – 0.3316 (0.0983)	-1.35 (0.177)	0.67 (0.502)
Cluster 1	-	-	-	-7.19 (<0.001)**	-5.16 (<0.001)
Cluster 2	-	-	-	-7.28 (<0.001)**	1.61 (0.110)
Cluster 3	-	-	-	-2.01 (0.045)*	-3.99 (<0.001)
Cluster 4	-	-	-	-9.98 (<0.001)**	1.25 (0.212)
Cluster 5	-	-	-	-6.86 (<0.001)**	-2.56 (0.011)
Cluster 6	-	-	-	-15.79 (<0.001)**	-1.08 (0.282)
Cluster 7	-	-	-	-6.50 (<0.001)**	-0.77 (0.440)

Table 1. Demographics and cognitive information. * significant associations between cognitive measures with age after FDR correction, ** significant associations between cognitive measures with age after Bonferroni correction

843 Cognitive associations with Brain Age Gap (BAG) – statistics

Test	Adj R^2 no-BAG	BAG	Main effect Age *t (p)*	Main effect Sex *t (p)*	Main effect BAG *t (p)*	Adj R^2
MoCA	0.0907	T1	-4.5596 (<0.001)	-2.3145 (0.021)	-0.124 (0.901)	0.0878
		DTI	-4.5599 (<0.001)	-2.3155 (0.021)	1.5914 (0.113)	0.0966
		Combined	-4.5653 (<0.001)	-2.3176 (0.021)	-0.4626 (0.644)	0.0885
WASI words	0.0731	T1	4.7118 (<0.001)	0.1020 (0.919)	-0.2169 (0.828)	0.0704
		DTI	4.7056 (<0.001)	0.1121 (0.911)	-0.8126 (0.417)	0.0727
		Combined	4.7091 (<0.001)	0.1041 (0.917)	-0.4827 (0.630)	0.0711
WASI matrix	0.1791	T1	-7.6061 (<0.001)	-0.2785 (0.781)	-0.9158 (0.361)	0.1793
		DTI	-7.6610 (<0.001)	-0.2624 (0.793)	-1.6546 (0.099)	0.1854
		Combined	-7.6128 (<0.001)	-0.2726 (0.785)	-1.1102 (0.268)	0.1806
CVLT learning 1-5	0.1810	T1	-5.0373 (<0.001)	-5.2514 (<0.001)	-0.2505 (0.802)	0.1750
		DTI	-5.0418 (<0.001)	-5.2533 (<0.001)	-0.3608 (0.719)	0.1753
		Combined	-5.0387 (<0.001)	-5.2522 (<0.001)	-0.2492 (0.803)	0.1750
CVLT interference	0.0664	T1	-4.3256 (<0.001)	-0.4062 (0.685)	-0.9588 (0.339)	0.0626
		DTI	-4.3218 (<0.001)	-0.4104 (0.682)	-0.2391 (0.811)	0.0594
		Combined	-4.3202 (<0.001)	-0.4101 (0.682)	-0.1875 (0.851)	0.0594
CVLT recall	0.2438	T1	-6.4897 (<0.001)	-5.9257 (<0.001)	-0.4868 (0.627)	0.2397
		DTI	-6.4885 (<0.001)	-5.9257 (<0.001)	-0.1245 (0.901)	0.2391
		Combined	-6.5080 (<0.001)	-5.9373 (<0.001)	-1.1114 (0.268)	0.2427
CVLT delayed recall	0.1850	T1	-4.9636 (<0.001)	-5.4973 (<0.001)	0.1421 (0.887)	0.1808
		DTI	-4.9611 (<0.001)	-5.4969 (<0.001)	0.224 (0.823)	0.1809
		Combined	-4.9655 (<0.001)	-5.4954 (<0.001)	-0.3038 (0.762)	0.1810
CVLT recognition hits	0.0494	T1	-2.6125 (0.010)	-2.6822 (0.008)	-0.8586 (0.391)	0.0486
		DTI	-2.6144 (0.010)	-2.6786 (0.008)	0.0946 (0.925)	0.0459
		Combined	-2.6212 (0.009)	-2.6854 (0.008)	-1.0724 (0.285)	0.0501
CVLT recognition errors	0.1526	T1	5.2227 (<0.001)	4.1850 (<0.001)	-0.8471 (0.398)	0.1528
		DTI	5.2115 (<0.001)	4.1755 (<0.001)	-0.5651 (0.573)	0.1514
		Combined	5.2139 (<0.001)	4.1740 (<0.001)	-0.2537 (0.800)	0.1506
CVLT recog misses	0.0494	T1	2.6125 (0.010)	2.6822 (0.008)	0.8586 (0.391)	0.0486
		DTI	2.6144 (0.010)	2.6786 (0.008)	-0.0946 (0.925)	0.0459
		Combined	2.6212 (0.009)	2.6854 (0.008)	1.0724 (0.285)	0.0501
CVLT recog false alarm	0.1150	T1	4.4519 (<0.001)	3.5827 (<0.001)	-0.776 (0.439)	0.1146
		DTI	4.4378 (<0.001)	3.5803 (<0.001)	-0.5207 (0.603)	0.1134
		Combined	4.4418 (<0.001)	3.5788 (<0.001)	-0.3488 (0.728)	0.1129
CVLT recog correct rejection	0.1526	T1	-5.2227 (<0.001)	-4.1850 (<0.001)	0.8471 (0.398)	0.1528
		DTI	-5.2115 (<0.001)	-4.1755 (<0.001)	0.5651 (0.573)	0.1514
		Combined	-5.2139 (<0.001)	-4.1740 (<0.001)	0.2537 (0.800)	0.1506
CVLT d'	0.1566	T1	-5.0074 (<0.001)	-4.4914 (<0.001)	0.3628 (0.717)	0.1536
		DTI	-5.0021 (<0.001)	-4.4969 (<0.001)	0.8538 (0.394)	0.1556
		Combined	-5.0038 (<0.001)	-4.4902 (<0.001)	0.1699 (0.865)	0.1533
STROOP 1	0.1118	T1	5.1466 (<0.001)	2.4999 (0.013)	2.6939 (0.008)	0.1299

		DTI	5.0968 (<0.001)	2.4769 (0.014)	1.6664 (0.097)	0.1147
		Combined	5.2111 (<0.001)	2.5317 (0.012)	3.3767 (<0.001)*	0.1434
STROOP 2	0.0477	T1	2.8868 (0.004)	2.2619 (0.025)	0.1557 (0.876)	0.0433
		DTI	2.8768 (0.004)	2.2489 (0.025)	-0.4639 (0.643)	0.0440
		Combined	2.8949 (0.004)	2.2713 (0.024)	0.4976 (0.619)	0.0442
STROOP 3	0.2104	T1	7.5930 (<0.001)	2.9898 (0.003)	1.5092 (0.133)	0.2109
		DTI	7.6511 (<0.001)	3.0224 (0.003)	2.231 (0.027)	0.2190
		Combined	7.6793 (<0.001)	3.0233 (0.003)	2.5768 (0.011)	0.2240
STROOP 4	0.1887	T1	7.5403 (<0.001)	1.7884 (0.075)	1.2397 (0.216)	0.1906
		DTI	7.5847 (<0.001)	1.8121 (0.071)	1.7368 (0.084)	0.1953
		Combined	7.6387 (<0.001)	1.8247 (0.069)	2.3662 (0.019)	0.2033
STROOP mean 1 and 2	0.0949	T1	4.5089 (<0.001)	2.5033 (0.013)	1.5875 (0.114)	0.0978
		DTI	4.4750 (<0.001)	2.4760 (0.014)	0.3927 (0.695)	0.0894
		Combined	4.5432 (<0.001)	2.5399 (0.012)	2.0254 (0.044)	0.1034
STROOP 3 minus mean 1 and 2	0.2051	T1	7.3383 (<0.001)	3.0427 (0.003)	1.1397 (0.256)	0.2021
		DTI	7.3613 (<0.001)	3.0703 (0.002)	1.3546 (0.177)	0.2038
		Combined	7.4197 (<0.001)	3.1063 (0.002)	2.1881 (0.030)	0.2130
STROOP 4 minus mean 1 and 2	0.1936	T1	7.5360 (<0.001)	1.8671 (0.063)	0.8763 (0.382)	0.1919
		DTI	7.5297 (<0.001)	1.8697 (0.063)	0.6331 (0.527)	0.1907
		Combined	7.6081 (<0.001)	1.9215 (0.056)	1.7531 (0.081)	0.1993
CP – Right motor speed	0.3695	T1	-12.2893 (<0.001)	-0.3592 (0.720)	-1.5504 (0.122)	0.3676
		DTI	-12.2318 (<0.001)	-0.3612 (0.718)	-0.3435 (0.732)	0.3620
		Combined	-12.3125 (<0.001)	-0.3587 (0.720)	-1.8139 (0.071)	0.3697
CP – Left motor speed	0.3630	T1	-12.1437 (<0.001)	0.2100 (0.834)	-1.9945 (0.047)	0.3634
		DTI	-12.0669 (<0.001)	0.2081 (0.835)	-0.8704 (0.385)	0.3555
		Combined	-12.2516 (<0.001)	0.2149 (0.830)	-2.9047 (0.004)	0.3740
CP – FAS Semantic flow	0.0840	T1	-2.9562 (0.003)	-3.9454 (<0.001)	-2.0826 (0.038)	0.0960
		DTI	-2.9607 (0.003)	-3.9388 (<0.001)	-2.0997 (0.037)	0.0963
		Combined	-2.9513 (0.004)	-3.9389 (<0.001)	-1.8308 (0.068)	0.0926
CP – Visual WM forward ls	0.0936	T1	-5.3071 (<0.001)	0.2850 (0.776)	-0.5838 (0.560)	0.0906
		DTI	-5.3392 (<0.001)	0.2963 (0.767)	-1.7204 (0.087)	0.0999
		Combined	-5.3059 (<0.001)	0.2853 (0.776)	-0.3127 (0.755)	0.0897
CP – Visual WM forward ss	0.1416	T1	-6.5795 (<0.001)	-0.2502 (0.803)	-0.2158 (0.829)	0.1375
		DTI	-6.6000 (<0.001)	-0.2448 (0.807)	-1.1695 (0.243)	0.1420
		Combined	-6.5786 (<0.001)	-0.2496 (0.803)	-0.02 (0.984)	0.1373
CP – Visual WM backward ls	0.0852	T1	-4.5941 (<0.001)	-1.8511 (0.065)	-0.1047 (0.917)	0.0820
		DTI	-4.6170 (<0.001)	-1.8545 (0.065)	-1.3334 (0.184)	0.0884
		Combined	-4.6051 (<0.001)	-1.8550 (0.065)	-0.8013 (0.424)	0.0843
CP – Visual WM backward ss	0.1022	T1	-5.4741 (<0.001)	-1.0181 (0.310)	-0.2721 (0.786)	0.1015
		DTI	-5.4971 (<0.001)	-1.0179 (0.310)	-1.3043 (0.193)	0.1072
		Combined	-5.4898 (<0.001)	-1.0215 (0.308)	-1.0074 (0.315)	0.1048
CP – Visual WM ss	0.1607	T1	-7.0322 (<0.001)	-0.9515 (0.342)	-0.3013 (0.763)	0.1591
		DTI	-7.0622 (<0.001)	-0.9511 (0.342)	-1.3634 (0.174)	0.1649

		Combined	-7.0399 (<0.001)	-0.9528 (0.342)	-0.6665 (0.506)	0.1603
CP – Spatial stroop congruent	0.2288	T1	8.6156 (<0.001)	-1.0080 (0.314)	2.1921 (0.029)	0.2288
		DTI	8.6687 (<0.001)	-1.0021 (0.317)	2.6995 (0.007)	0.2362
		Combined	8.8278 (<0.001)	-0.9828 (0.327)	3.9007 (<0.001)**	0.2588
CP – Spatial stroop incongruent	0.2548	T1	9.5489 (<0.001)	-0.7429 (0.458)	2.6569 (0.008)	0.2700
		DTI	9.5931 (<0.001)	-0.7587 (0.449)	2.8817 (0.004)	0.2735
		Combined	9.7197 (<0.001)	-0.7378 (0.461)	3.8071 (<0.001)**	0.2903
CP – Spatial stroop numb of reps	0.2731	T1	-9.7755 (<0.001)	1.2211 (0.223)	-2.2212 (0.027)	0.2753
		DTI	-9.8507 (<0.001)	1.2328 (0.219)	-2.9614 (0.003)	0.2859
		Combined	-9.9891 (<0.001)	1.2198 (0.224)	-3.8816 (<0.001)**	0.3027
CP – Spatial stroop incong – cong	0.1012	T1	5.7663 (<0.001)	-0.6595 (0.510)	1.5611 (0.120)	0.1134
		DTI	5.7466 (<0.001)	-0.6678 (0.505)	0.9705 (0.333)	0.1081
		Combined	5.7568 (<0.001)	-0.6584 (0.511)	1.2056 (0.229)	0.1099
CP – Spatspan ls	0.3055	T1	-9.1038 (<0.001)	-4.8656 (<0.001)	-0.032 (0.975)	0.3009
		DTI	-9.1746 (<0.001)	-4.9104 (<0.001)	-1.5749 (0.117)	0.3077
		Combined	-9.1043 (<0.001)	-4.8663 (<0.001)	-0.075 (0.940)	0.3009
CP – Spatspan total	0.3057	T1	-9.2664 (<0.001)	-4.6439 (<0.001)	0.1074 (0.915)	0.3024
		DTI	-9.3260 (<0.001)	-4.6815 (<0.001)	-1.3773 (0.170)	0.3076
		Combined	-9.2686 (<0.001)	-4.6461 (<0.001)	-0.0612 (0.951)	0.3024
CP – Coding corr	0.5387	T1	-16.7647 (<0.001)	-2.5004 (0.013)	-1.6149 (0.108)	0.5352
		DTI	-17.0893 (<0.001)	-2.5467 (0.012)	-3.3998 (<0.001)*	0.5510
		Combined	-17.0071 (<0.001)	-2.5604 (0.011)	-3.0056 (0.003)	0.5467
TVA - Short-term memory storage (*K*)	0.2013	T1	-7.7691 (<0.001)	-1.5196 (0.130)	-1.1179 (0.265)	0.1981
		DTI	-7.8117 (<0.001)	-1.5383 (0.125)	-2.0302 (0.043)	0.2070
		Combined	-7.7525 (<0.001)	-1.5195 (0.130)	-0.9537 (0.341)	0.1970
TVA - Perceptual threshold (t_0)	0.0764	T1	5.7303 (<0.001)	-1.9470 (0.053)	0.9617 (0.337)	0.1141
		DTI	5.7333 (<0.001)	-1.9444 (0.053)	1.1066 (0.270)	0.1152
		Combined	5.7523 (<0.001)	-1.9587 (0.051)	1.8346 (0.068)	0.1226
TVA - Processing speed (*C*)	0.1304	T1	-4.6692 (<0.001)	0.3969 (0.692)	0.8093 (0.419)	0.0723
		DTI	-4.6800 (<0.001)	0.4053 (0.686)	0.1402 (0.889)	0.0699
		Combined	-4.6827 (<0.001)	0.3944 (0.694)	0.8916 (0.374)	0.0728
Cluster 1	0.2470	T1	-7.1741 (<0.001)	-5.1567 (<0.001)	-0.1927 (0.847)	0.2440
		DTI	-7.1623 (<0.001)	-5.1410 (<0.001)	0.3683 (0.713)	0.2443
		Combined	-7.1805 (<0.001)	-5.1641 (<0.001)	-0.3879 (0.699)	0.2443
Cluster 2	0.1720	T1	-7.2680 (<0.001)	1.6030 (0.110)	-0.1013 (0.919)	0.1687
		DTI	-7.2785 (<0.001)	1.6062 (0.110)	-0.6549 (0.513)	0.1701
		Combined	-7.2740 (<0.001)	1.6104 (0.109)	-0.6382 (0.524)	0.1700
Cluster 3	0.0698	T1	-2.0177 (0.045)	-3.9824 (<0.001)	-0.8103 (0.419)	0.0686
		DTI	-2.0337 (0.043)	-3.9969 (<0.001)	-1.84 (0.067)	0.0783
		Combined	-2.0185 (0.045)	-3.9877 (<0.001)	-0.9765 (0.330)	0.0697
Cluster 4	0.2783	T1	-10.1319 (<0.001)	1.2314 (0.219)	-2.5436 (0.012)	0.2937
		DTI	-10.1479 (<0.001)	1.2377 (0.217)	-2.5207 (0.012)	0.2933
		Combined	-10.3013 (<0.001)	1.2196 (0.224)	-3.6163 (<0.001)*	0.3113

Cluster 5	0.1772	T1	-6.8872 (<0.001)	-2.5902 (0.010)	-1.1084 (0.269)	0.1779
		DTI	-6.8667 (<0.001)	-2.5805 (0.010)	-0.5825 (0.561)	0.1750
		Combined	-6.9577 (<0.001)	-2.6481 (0.009)	-1.9103 (0.057)	0.1858
Cluster 6	0.5092	T1	-15.9345 (<0.001)	-1.1148 (0.266)	-1.8971 (0.059)	0.5145
		DTI	-15.9719 (<0.001)	-1.1080 (0.269)	-2.0875 (0.038)	0.5160
		Combined	-16.0156 (<0.001)	-1.1196 (0.264)	-2.459 (0.015)	0.5193
Cluster 7	0.1399	T1	-6.4852 (<0.001)	-0.7736 (0.440)	-0.3433 (0.732)	0.1369
		DTI	-6.5210 (<0.001)	-0.7689 (0.443)	-1.6007 (0.111)	0.1452
		Combined	-6.4926 (<0.001)	-0.7759 (0.439)	-0.63 (0.529)	0.1379

Table 2. Cognitive associations with BAG – statistics. * FDR significant ** Bonferroni significant.

Supplementary Figures

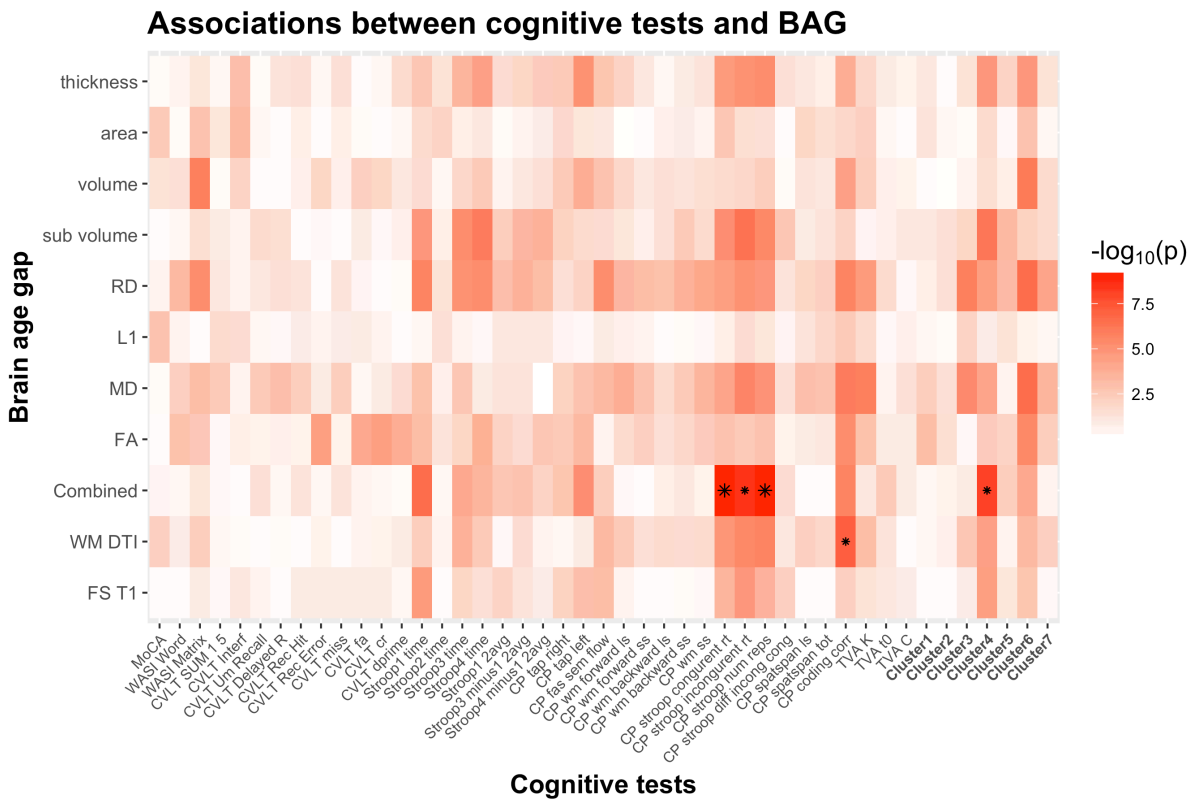

Fig. S1. Heatmap of the association between cognitive scores and brain age gaps using non-linear models, including age, age^2 and sex as covariates. The color scale depicts the minus log of the p-values ($-\log_{10}(p)$) for each association. The association marked with a small star represents significant associations after FDR correction, and the one marked with a big star shows significant associations after Bonferroni correction.

Supplementary Tables

Cognitive associations with Brain Age Gap (BAG) using non-linear models, including age, age^2 and sex as covariates – statistics.

Test	Adj R^2 no-BAG	BAG	Main effect Age *t(p)*	Main effect Age^2 *t(p)*	Main effect Sex *t(p)*	Main effect BAG *t(p)*	Adj R^2
MoCA	0.088	T1	-4.5563 (<0.001)	-0.2752 (0.7834)	-2.1792 (0.0302)	-0.1146 (0.9088)	0.0845
		DTI	-4.5575 (<0.001)	-0.3078 (0.7585)	-2.1727 (0.0307)	1.5937 (0.1122)	0.0934
		Combined	-4.561 (<0.001)	-0.2413 (0.8095)	-2.1894 (0.0295)	-0.4399 (0.6604)	0.0851
WASI words	0.0792	T1	4.7079 (<0.001)	-1.5614 (0.1197)	0.4698 (0.6389)	-0.1719 (0.8637)	0.0756
		DTI	4.7017 (<0.001)	-1.5532 (0.1216)	0.4775 (0.6334)	-0.7843 (0.4336)	0.0778
		Combined	4.7058 (<0.001)	-1.5325 (0.1266)	0.4655 (0.642)	-0.3554 (0.7226)	0.076
WASI matrix	0.1825	T1	-7.6085 (<0.001)	-1.3223 (0.1873)	0.048 (0.9618)	-0.8787 (0.3804)	0.1817
		DTI	-7.6627 (<0.001)	-1.311 (0.1911)	0.0606 (0.9517)	-1.6227 (0.1059)	0.1876
		Combined	-7.6132 (<0.001)	-1.2678 (0.206)	0.0407 (0.9676)	-1.0117 (0.3126)	0.1825
CVLT learning 1-5	0.1757	T1	-5.0181 (<0.001)	0.5198 (0.6036)	-5.2162 (<0.001)	-0.2662 (0.7903)	0.1727
		DTI	-5.0228 (<0.001)	0.5204 (0.6032)	-5.2181 (<0.001)	-0.3723 (0.71)	0.1729
		Combined	-5.0196 (<0.001)	0.5363 (0.5922)	-5.2205 (<0.001)	-0.2959 (0.7675)	0.1727
CVLT interference	0.0593	T1	-4.3175 (<0.001)	-0.062 (0.9506)	-0.3788 (0.7051)	-0.9545 (0.3407)	0.0589
		DTI	-4.3143 (<0.001)	-0.086 (0.9316)	-0.3772 (0.7064)	-0.2366 (0.8132)	0.0558
		Combined	-4.3124 (<0.001)	-0.075 (0.9403)	-0.3794 (0.7047)	-0.1796 (0.8576)	0.0557
CVLT recall	0.2401	T1	-6.4676 (<0.001)	0.6091 (0.543)	-5.8925 (<0.001)	-0.5048 (0.6141)	0.2379
		DTI	-6.4667 (<0.001)	0.5965 (0.5514)	-5.8892 (<0.001)	-0.1381 (0.8902)	0.2371
		Combined	-6.4859 (<0.001)	0.6973 (0.4863)	-5.9255 (<0.001)	-1.1682 (0.2438)	0.2412
CVLT delayed recall	0.1822	T1	-4.9433 (<0.001)	0.6624 (0.5083)	-5.4919 (<0.001)	0.1193 (0.9052)	0.179
		DTI	-4.9411 (<0.001)	0.6618 (0.5087)	-5.4912 (<0.001)	0.2079 (0.8354)	0.1791
		Combined	-4.9454 (<0.001)	0.6981 (0.4857)	-5.4986 (<0.001)	-0.3668 (0.7141)	0.1794
CVLT recognition hits	0.0464	T1	-2.615 (0.0095)	-0.3694 (0.7121)	-2.5144 (0.0125)	-0.8444 (0.3992)	0.0453
		DTI	-2.6175 (0.0094)	-0.3994 (0.6899)	-2.504 (0.0129)	0.1039 (0.9173)	0.0427
		Combined	-2.622 (0.0093)	-0.3004 (0.7641)	-2.5328 (0.0119)	-1.0382 (0.3002)	0.0467
CVLT recognition errors	0.1567	T1	5.2609 (<0.001)	1.4118 (0.1592)	3.7395 (<0.001)	-0.8964 (0.3709)	0.1561
		DTI	5.2485 (<0.001)	1.3947 (0.1643)	3.7336 (<0.001)	-0.5993 (0.5495)	0.1546
		Combined	5.2514 (<0.001)	1.4099 (0.1598)	3.7277 (<0.001)	-0.3837 (0.7015)	0.1539
CVLT recog misses	0.0464	T1	2.615 (0.0095)	0.3694 (0.7121)	2.5144 (0.0125)	0.8444 (0.3992)	0.0453
		DTI	2.6175 (0.0094)	0.3994 (0.6899)	2.504 (0.0129)	-0.1039 (0.9173)	0.0427
		Combined	2.622 (0.0093)	0.3004 (0.7641)	2.5328 (0.0119)	1.0382 (0.3002)	0.0467
CVLT recog false alarm	0.1191	T1	4.4883 (<0.001)	1.4053 (0.1612)	3.1557 (0.0018)	-0.8236 (0.411)	0.1179
		DTI	4.4728 (<0.001)	1.3906 (0.1656)	3.1567 (0.0018)	-0.5544 (0.5798)	0.1167
		Combined	4.4784 (<0.001)	1.4159 (0.158)	3.1475 (0.0018)	-0.4786 (0.6326)	0.1164
CVLT recog correct rejection	0.1567	T1	-5.2609 (<0.001)	-1.4118 (0.1592)	-3.7395 (<0.001)	0.8964 (0.3709)	0.1561
		DTI	-5.2485 (<0.001)	-1.3947 (0.1643)	-3.7336 (<0.001)	0.5993 (0.5495)	0.1546
		Combined	-5.2514 (<0.001)	-1.4099 (0.1598)	-3.7277 (<0.001)	0.3837 (0.7015)	0.1539
CVLT d’	0.1548	T1	-5.0157 (<0.001)	-0.7018 (0.4835)	-4.1938 (<0.001)	0.3855 (0.7002)	0.1519

		DTI	-5.0104 (<0.001)	-0.7106 (0.478)	-4.1973 (<0.001)	0.8695 (0.3854)	0.1539
		Combined	-5.0122 (<0.001)	-0.7079 (0.4796)	-4.1897 (<0.001)	0.2343 (0.8149)	0.1516
STROOP 1	0.1181	T1	5.2178 (<0.001)	1.8817 (0.061)	1.9786 (0.0489)	2.6477 (0.0086)	0.1385
		DTI	5.1698 (<0.001)	1.915 (0.0566)	1.9488 (0.0524)	1.6361 (0.103)	0.1239
		Combined	5.2707 (<0.001)	1.7146 (0.0876)	2.0444 (0.0419)	3.243 (0.0013)	0.1499
STROOP 2	0.0565	T1	2.955 (0.0034)	1.8769 (0.0617)	1.7273 (0.0853)	0.0898 (0.9286)	0.0528
		DTI	2.9455 (0.0035)	1.897 (0.059)	1.7093 (0.0886)	-0.5228 (0.6016)	0.0538
		Combined	2.9595 (0.0034)	1.8439 (0.0664)	1.7389 (0.0833)	0.3307 (0.7411)	0.0531
STROOP 3	0.2519	T1	7.9387 (<0.001)	4.0215 (<0.001)**	2.0391 (0.0425)	1.4584 (0.146)	0.2552
		DTI	8.0033 (<0.001)	4.0506 (<0.001)**	2.0666 (0.0398)	2.245 (0.0256)	0.2635
		Combined	8.0064 (<0.001)	3.9001 (<0.001)**	2.0915 (0.0375)	2.3542 (0.0193)	0.265
STROOP 4	0.2092	T1	7.727 (<0.001)	2.7144 (0.0071)	1.1078 (0.269)	1.1959 (0.2329)	0.2105
		DTI	7.7745 (<0.001)	2.7322 (0.0067)	1.1277 (0.2605)	1.7316 (0.0846)	0.2154
		Combined	7.8094 (<0.001)	2.5945 (0.01)	1.1659 (0.2448)	2.2006 (0.0287)	0.221
STROOP mean 1 and 2	0.1065	T1	4.6014 (<0.001)	2.1809 (0.0301)	1.8851 (0.0606)	1.5137 (0.1314)	0.1111
		DTI	4.5693 (<0.001)	2.2194 (0.0274)	1.8487 (0.0657)	0.3205 (0.7489)	0.1033
		Combined	4.6255 (<0.001)	2.0629 (0.0402)	1.9411 (0.0534)	1.8349 (0.0677)	0.1148
STROOP 3 minus mean 1 and 2	0.2486	T1	7.6928 (<0.001)	4.0734 (<0.001)**	2.0223 (0.0442)	1.0347 (0.3018)	0.2488
		DTI	7.7161 (<0.001)	4.0759 (<0.001)**	2.0485 (0.0416)	1.2741 (0.2038)	0.2504
		Combined	7.7517 (<0.001)	3.9419 (<0.001)**	2.0994 (0.0368)	1.8804 (0.0612)	0.2561
STROOP 4 minus mean 1 and 2	0.2225	T1	7.7912 (<0.001)	3.224 (0.0014)*	1.0274 (0.3052)	0.7875 (0.4317)	0.2213
		DTI	7.7853 (<0.001)	3.233 (0.0014)*	1.0273 (0.3053)	0.5573 (0.5778)	0.2203
		Combined	7.8437 (<0.001)	3.1135 (0.0021)*	1.0945 (0.2748)	1.4951 (0.1362)	0.2263
CP - Right motor speed	0.3621	T1	-12.2583 (<0.001)	0.4241 (0.6718)	-0.4499 (0.6532)	-1.56 (0.12)	0.3656
		DTI	-12.201 (<0.001)	0.3813 (0.7033)	-0.4415 (0.6592)	-0.3491 (0.7273)	0.3599
		Combined	-12.2818 (<0.001)	0.5259 (0.5994)	-0.4741 (0.6358)	-1.8479 (0.0658)	0.368
CP - Left motor speed	0.3586	T1	-12.1901 (<0.001)	-1.3758 (0.1701)	0.5329 (0.5946)	-1.9551 (0.0517)	0.3656
		DTI	-12.1163 (<0.001)	-1.4124 (0.159)	0.5396 (0.5899)	-0.8474 (0.3976)	0.3579
		Combined	-12.2849 (<0.001)	-1.2158 (0.2252)	0.4997 (0.6177)	-2.7995 (0.0055)	0.3752
CP - FAS semantic flow	0.1047	T1	-3.0413 (0.0026)	-2.5748 (0.0106)	-3.2544 (0.0013)	-2.0265 (0.0437)	0.1153
		DTI	-3.0473 (0.0025)	-2.6035 (0.0098)	-3.2424 (0.0013)	-2.0796 (0.0385)	0.116
		Combined	-3.0316 (0.0027)	-2.4889 (0.0134)	-3.2639 (0.0012)	-1.642 (0.1018)	0.1105
CP - Visual WM forward ls	0.0897	T1	-5.3048 (<0.001)	-0.2803 (0.7795)	0.3424 (0.7323)	-0.5645 (0.5729)	0.0873
		DTI	-5.3364 (<0.001)	-0.2747 (0.7838)	0.352 (0.7252)	-1.71 (0.0885)	0.0966
		Combined	-5.3039 (<0.001)	-0.2873 (0.7742)	0.3445 (0.7307)	-0.2836 (0.7769)	0.0864
CP - Visual WM forward ss	0.1388	T1	-6.5947 (<0.001)	-0.6439 (0.5202)	-0.0916 (0.9271)	-0.1756 (0.8608)	0.1355
		DTI	-6.6142 (<0.001)	-0.6289 (0.53)	-0.0903 (0.9281)	-1.1522 (0.2503)	0.1399
		Combined	-6.5945 (<0.001)	-0.657 (0.5118)	-0.0873 (0.9305)	0.0421 (0.9664)	0.1354
CP - Visual WM backward ls	0.0852	T1	-4.6076 (<0.001)	-0.9343 (0.351)	-1.567 (0.1184)	-0.068 (0.9458)	0.0816
		DTI	-4.6299 (<0.001)	-0.9132 (0.362)	-1.5757 (0.1163)	-1.3135 (0.1902)	0.0878
		Combined	-4.6163 (<0.001)	-0.8736 (0.3831)	-1.5842 (0.1144)	-0.7237 (0.4699)	0.0835
CP - Visual WM backward ss	0.1026	T1	-5.4768 (<0.001)	-0.619 (0.5365)	-0.8352 (0.4044)	-0.2473 (0.8049)	0.0993

		DTI	-5.4994 (<0.001)	-0.604 (0.5464)	-0.8389 (0.4023)	-1.2897 (0.1983)	0.105
		Combined	-5.4903 (<0.001)	-0.5466 (0.5852)	-0.8555 (0.3931)	-0.9558 (0.3401)	0.1023
CP - Visual WM ss	0.1618	T1	-7.0453 (<0.001)	-0.9494 (0.3433)	-0.6911 (0.4902)	-0.2639 (0.7921)	0.1588
		DTI	-7.0749 (<0.001)	-0.9354 (0.3504)	-0.6944 (0.4881)	-1.3432 (0.1804)	0.1645
		Combined	-7.051 (<0.001)	-0.9076 (0.365)	-0.7016 (0.4836)	-0.5866 (0.558)	0.1597
CP - Spatial stroop congruent	0.2152	T1	8.6103 (<0.001)	0.5061 (0.6132)	-1.099 (0.2728)	2.1677 (0.0311)	0.2265
		DTI	8.6646 (<0.001)	0.539 (0.5904)	-1.1012 (0.2719)	2.6844 (0.0078)	0.234
		Combined	8.8148 (<0.001)	0.27 (0.7874)	-1.0172 (0.3101)	3.8562 (<0.001)**	0.2561
CP - Spatial stroop incongruent	0.2498	T1	9.5215 (<0.001)	-0.3129 (0.7546)	-0.6399 (0.5228)	2.6625 (0.0083)	0.2674
		DTI	9.5663 (<0.001)	-0.2497 (0.803)	-0.6711 (0.5028)	2.8797 (0.0043)	0.2708
		Combined	9.6908 (<0.001)	-0.5285 (0.5976)	-0.5807 (0.5619)	3.8325 (<0.001)*	0.2883
CP - Spatial stroop numb of reps	0.2613	T1	-9.7578 (<0.001)	-0.1542 (0.8776)	1.2196 (0.2237)	-2.2091 (0.0281)	0.2725
		DTI	-9.8334 (<0.001)	-0.1782 (0.8587)	1.2369 (0.2173)	-2.951 (0.0035)	0.2831
		Combined	-9.967 (<0.001)	0.0905 (0.928)	1.1582 (0.2479)	-3.8672 (<0.001)**	0.2999
CP - Spatial stroop incong - cong	0.1076	T1	5.7387 (<0.001)	-0.9619 (0.337)	-0.4011 (0.6887)	1.5968 (0.1116)	0.1131
		DTI	5.7189 (<0.001)	-0.9105 (0.3635)	-0.4223 (0.6732)	0.9815 (0.3273)	0.1075
		Combined	5.7304 (<0.001)	-1.0014 (0.3176)	-0.3888 (0.6978)	1.2835 (0.2005)	0.1099
CP - Spatspan ls	0.3027	T1	-9.0803 (<0.001)	0.8225 (0.4116)	-4.9183 (<0.001)	-0.0628 (0.95)	0.3
		DTI	-9.1511 (<0.001)	0.8555 (0.3931)	-4.9703 (<0.001)	-1.5904 (0.113)	0.307
		Combined	-9.0818 (<0.001)	0.8301 (0.4073)	-4.9202 (<0.001)	-0.1448 (0.885)	0.3
CP - Spatspan total	0.3033	T1	-9.2413 (<0.001)	0.5919 (0.5545)	-4.6451 (<0.001)	0.085 (0.9324)	0.3006
		DTI	-9.3007 (<0.001)	0.6245 (0.5329)	-4.6899 (<0.001)	-1.3875 (0.1665)	0.3059
		Combined	-9.2443 (<0.001)	0.6028 (0.5472)	-4.6491 (<0.001)	-0.1118 (0.9111)	0.3006
CP - Coding corr	0.5307	T1	-16.7381 (<0.001)	-0.3279 (0.7433)	-2.3396 (0.0201)	-1.596 (0.1117)	0.5335
		DTI	-17.0629 (<0.001)	-0.3481 (0.7281)	-2.3804 (0.018)	-3.3875 (<0.001)*	0.5495
		Combined	-16.9736 (<0.001)	-0.1442 (0.8855)	-2.4411 (0.0153)	-2.976 (0.0032)	0.5449
TVA - Short-term memory storage (*K*)	0.1941	T1	-7.7533 (<0.001)	-0.0891 (0.9291)	-1.4529 (0.1475)	-1.1129 (0.2668)	0.1949
		DTI	-7.7958 (<0.001)	-0.0894 (0.9288)	-1.471 (0.1426)	-2.0247 (0.044)	0.2039
		Combined	-7.7352 (<0.001)	-0.0343 (0.9726)	-1.4655 (0.144)	-0.9449 (0.3456)	0.1938
TVA - Perceptual threshold (t_0)	0.1146	T1	5.7716 (<0.001)	0.9866 (0.3248)	-2.1312 (0.034)	0.9264 (0.3551)	0.1141
		DTI	5.7764 (<0.001)	1.0081 (0.3144)	-2.1342 (0.0338)	1.0951 (0.2745)	0.1153
		Combined	5.784 (<0.001)	0.8478 (0.3973)	-2.1074 (0.0361)	1.7412 (0.0829)	0.1217
TVA - Processing speed (*C*)	0.0699	T1	-4.66 (<0.001)	0.1122 (0.9107)	0.3556 (0.7225)	0.804 (0.4222)	0.0686
		DTI	-4.6708 (<0.001)	0.135 (0.8927)	0.3579 (0.7207)	0.1387 (0.8898)	0.0662
		Combined	-4.6734 (<0.001)	0.0619 (0.9507)	0.3657 (0.7149)	0.8815 (0.3789)	0.0691
Cluster 1	0.2446	T1	-7.1703 (<0.001)	-0.4829 (0.6296)	-4.8899 (<0.001)	-0.1702 (0.865)	0.2416
		DTI	-7.1589 (<0.001)	-0.5024 (0.6158)	-4.8709 (<0.001)	0.3825 (0.7024)	0.242
		Combined	-7.1752 (<0.001)	-0.4542 (0.6501)	-4.8989 (<0.001)	-0.3391 (0.7349)	0.2419
Cluster 2	0.1695	T1	-7.2665 (<0.001)	-0.5147 (0.6072)	1.6797 (0.0943)	-0.0814 (0.9352)	0.1662
		DTI	-7.2772 (<0.001)	-0.5154 (0.6068)	1.6829 (0.0937)	-0.6514 (0.5154)	0.1676
		Combined	-7.2707 (<0.001)	-0.4611 (0.6451)	1.6725 (0.0957)	-0.5914 (0.5548)	0.1674
Cluster 3	0.0767	T1	-2.065 (0.0399)	-1.6934 (0.0916)	-3.4589 (<0.001)	-0.7735 (0.4399)	0.0753

		DTI	-2.0812 (0.0384)	-1.693 (0.0917)	-3.4728 (<0.001)	-1.8207 (0.0698)	0.0849
		Combined	-2.0636 (0.0401)	-1.6405 (0.1021)	-3.4746 (<0.001)	-0.848 (0.3972)	0.0757
Cluster 4	0.2757	T1	-10.1014 (<0.001)	0.3766 (0.7068)	1.098 (0.2733)	-2.5518 (0.0113)	0.2912
		DTI	-10.118 (<0.001)	0.31 (0.7568)	1.1208 (0.2635)	-2.5199 (0.0124)	0.2908
		Combined	-10.2703 (<0.001)	0.5794 (0.5629)	1.0357 (0.3014)	-3.6468 (<0.001)*	0.3095
Cluster 5	0.2124	T1	-7.1604 (<0.001)	-3.4563 (<0.001)*	-1.6891 (0.0924)	-1.0197 (0.3089)	0.2125
		DTI	-7.1405 (<0.001)	-3.4709 (<0.001)*	-1.6759 (0.095)	-0.5011 (0.6167)	0.21
		Combined	-7.2104 (<0.001)	-3.3405 (0.001)*	-1.7586 (0.0799)	-1.6393 (0.1024)	0.2177
Cluster 6	0.51	T1	-15.9382 (<0.001)	-1.0984 (0.2732)	-0.8171 (0.4147)	-1.8518 (0.0653)	0.5149
		DTI	-15.9778 (<0.001)	-1.1226 (0.2627)	-0.8054 (0.4214)	-2.0589 (0.0406)	0.5165
		Combined	-16.0092 (<0.001)	-0.9591 (0.3385)	-0.8532 (0.3944)	-2.3608 (0.019)	0.5191
Cluster 7	0.1381	T1	-6.5016 (<0.001)	-0.6594 (0.5102)	-0.5961 (0.5516)	-0.3018 (0.7631)	0.135
		DTI	-6.5363 (<0.001)	-0.643 (0.5208)	-0.5958 (0.5518)	-1.5824 (0.1148)	0.1432
		Combined	-6.5065 (<0.001)	-0.6229 (0.5339)	-0.6062 (0.5449)	-0.5676 (0.5708)	0.1358

Table S1. Cognitive associations with Brain Age Gap (BAG) using non-linear models, including age, age^2 and sex as covariates – statistics. * FDR significant ** Bonferroni significant.