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The (Limited?) Utility of Brain Age as a Biomarker for Capturing Cognitive Decline

Alina Tetereva, Narun Pat

Department of Psychology, University of Otago, New Zealand, 9016

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Abstract

For decades, neuroscientists have been on a quest to search for a biomarker that can help capture age-related cognitive decline. One well-known candidate is Brain Age, or a predicted value based on machine-learning models built to predict chronological age from brain MRI data. Here we aim to formally evaluate the utility of Brain Age as a biomarker for capturing cognitive decline. Using 504 aging participants (36-100 years old) from the Human Connectome Project in Aging, we created 26 age-prediction models for Brain Age based on different combinations of MRI modalities. We first tested how much Brain Age from these age-prediction models added to what we had already known from a person's chronological age in capturing cognitive decline. Based on the commonality analyses, we found a large degree of overlap between Brain Age and chronological age, so much so that, at best, Brain Age could uniquely add only around 1.6% in explaining variation in cognitive decline. Next, the age-prediction models that performed better at predicting chronological age did NOT necessarily create better Brain Age for capturing cognitive decline over and above chronological age. Instead, better-performing age-prediction models created Brain Age that overlapped larger with chronological age, up to around 29% out of 32%, in explaining cognitive decline, thus not improving the models' ability to capture cognitive decline. Lastly, unlike Brain Age, Brain Cognition, or a predicted value based on machine-learning models built to predict cognitive abilities from brain MRI data, provided much higher unique effects. Brain Cognition added over 11% to explain variation in cognitive decline beyond chronological age, leading to around a 1/3-time improvement of the total variation explained. Accordingly, while demonstrating the limited utility of Brain Age, we provided a solution to improve our ability to use brain MRI data as a biomarker for cognitive decline.

eLife assessment

This **useful** manuscript challenges the utility of current paradigms for estimating brain-age with magnetic resonance imaging measures, but presents **inadequate** evidence to support the suggestion that an alternative approach focused on predicting cognition is more **useful**. The paper would benefit from a clearer explication of the methods and a more critical evaluation of the conceptual basis of the different models. This work will be of interest to researchers working on brain-age and related models.

Introduction

Older adults often experience declines in several cognitive abilities such as memory, attention and processing speed, collectively known as fluid cognition ($cognition_{fluid}$) (Salthouse, 2019; Weintraub et al., 2014). Having objective biomarkers to capture these declines in $cognition_{fluid}$ would give researchers and clinicians a tool to detect early cognitive impairments, monitor treatment/intervention efficacy and forecast cognitive prognosis (Frisoni et al., 2017). Over the past decade, Brain Age (Franke et al., 2010) has emerged as a potential biomarker to capture declines in $cognition_{fluid}$ (Cole, 2020; le et al., 2018; Liem et al., 2017; Richard et al., 2018; Wrigglesworth et al., 2022; Boyle et al., 2021). Yet, to justify the use of Brain Age as an informative biomarker for $cognition_{fluid}$, we still need to address many outstanding issues.

First, to what extent does having information on Brain Age improve our ability to capture declines in $cognition_{fluid}$ beyond knowing a person's chronological age? To compute Brain Age, researchers first built a prediction model that predicts the chronological age based on a person's brain neuroimaging data (Baecker et al., 2021). They then apply this prediction model to an unseen individual, not part of the model-building process. Brain Age is the predicted value of this model. Accordingly, by design, Brain Age is tightly close to chronological age. Because chronological age usually has a strong relationship with $cognition_{fluid}$, to begin with, it is unclear how much Brain Age adds to what is already captured by chronological age.

Note researchers often subtract chronological age from Brain Age, creating an index known as Brain Age Gap (Franke & Gaser, 2019). A higher value of Brain Age Gap is thought to reflect accelerated/premature aging. Yet, given that Brain Age Gap is calculated based on both Brain Age and chronological age, Brain Age Gap still depends on chronological age (Butler et al., 2021). If, for instance, Brain Age was based on prediction models with poor performance and made a prediction that everyone was 50 years old, individual differences in Brain Age Gap would then depend solely on chronological age (i.e., 50 minus chronological age). In addition to the dependency on chronological age, Brain Age is often overestimated in younger, but underestimated in older, individuals (Le et al., 2018). There are many adjustments proposed to correct for this estimation bias, but the outcomes tend to be similar, if not identical, to each other (Beheshti et al., 2019; de Lange & Cole, 2020; Liang et al., 2019; Smith et al., 2019). These adjustments can be applied to Brain Age and Brain Age Gap, creating Corrected Brain Age and Corrected Brain Age Gap, respectively. Corrected Brain Age Gap in particular is viewed as being able to control for both age dependency and estimation biases (Butler et al., 2021). Here we tested the ability of different Brain Age calculations in capturing $cognition_{fluid}$, over and above chronological age.

Second, do better-performing age-prediction models correspond to the improvement in an ability to capture $cognition_{fluid}$? Over the past decades, there has been a race to improve the performance of age-prediction models to be better at predicting chronological age, for instance, by combining different MRI/neuroimaging modalities features (Cole, 2020; Engemann et al., 2020; Liem et al., 2017) or by applying more sophisticated machinelearning algorithms (Baecker et al., 2021; Jonsson et al., 2019; Zhao & Zhao, 2021). However, the improvement in predicting chronological age may not necessarily make Brain Age to be better at capturing $cognition_{fluid}$. If, for instance, the age-prediction model had the perfect performance, Brain Age Gap would be exactly zero and would have no utility in capturing $cognition_{fluid}$ beyond chronological age. Few, if any, studies have examined the performance of age-prediction models as a function of their ability to capture $cognition_{fluid}$.

Third and finally, can we further improve our ability to capture the decline in $cognition_{fluid}$ by using, not only Brain Age and chronological age, but also another biomarker, Brain Cognition? Analogous to Brain Age, Brain Cognition is defined as a predicted value from prediction models that predict $cognition_{fluid}$ based on a person's brain data (Dubois et al., 2018; Pat, Wang, Anney, et al., 2022; Rasero et al., 2021; Sripada et al., 2020; Tetereva et al., 2022; Vieira et al., 2022). Age-related cognitive decline is not only related to the changes in age, but also to the changes in cognition. While Brain Age is about the former, Brain Cognition is about the letter. Brain Age and Brain Cognition are found to capture some overlapped variation in cognitive abilities (Jiang et al., 2022). Despite the overlap, there might still be unique effects contributed by each biomarker that, when combined, may collectively help capture $cognition_{fluid}$.

Our study set out to test the utility of Brain Age as a biomarker for capturing decline in $cognition_{fluid}$. Using aging participants (36-100 years old) from the Human Connectome Project in Aging, we computed different Brain Age indices (including Brain Age, Brain Age Gap, Corrected Brain Age and Corrected Brain Age Gap) and Brain Cognition from prediction models based on different sets of MRI features. These MRI features covered task, resting-state and structural MRI, creating 26 prediction models in total. We, then, tested the biomarkers' ability to explain $cognition_{fluid}$ in unseen participants. To test the ability of Brain Age by itself, we applied simple regression models with each Brain Age index as a sole regressor to explain $Cognition_{fluid}$. Next, to test the unique effects of Brain Age in explaining $Cognition_{fluid}$ beyond chronological age, we applied multiple regression models with both each Brain Age index and chronological age as regressors to explain $Cognition_{fluid}$. To reveal how much chronological age and Brain Age had in common in explaining $Cognition_{fluid}$ (i.e., common effects), we then applied the commonality analysis (Nimon et al., 2008) to these multiple regression models. Additionally, given that certain sets of MRI features led to prediction models that were better at predicting chronological age, we also examined if these better-performing age-prediction models improved the ability of Brain Age in explaining $cognition_{fluid}$. Finally, to test whether Brain Cognition could further improve the ability to capture $cognition_{fluid}$, beyond Brain Age and chronological age, we added Brain Cognition to the multiple regression models and tested its unique and common effects in explaining $Cognition_{fluid}$.

Results

Relationship between chronological age and $Cognition_{fluid}$

Figure 1a shows the negative relationship between chronological age and $Cognition_{fluid}$ ($r(502) = -.57$, $p < .001$, $R^2 = .32$). Older individuals tended to have a lower $Cognition_{fluid}$ score.

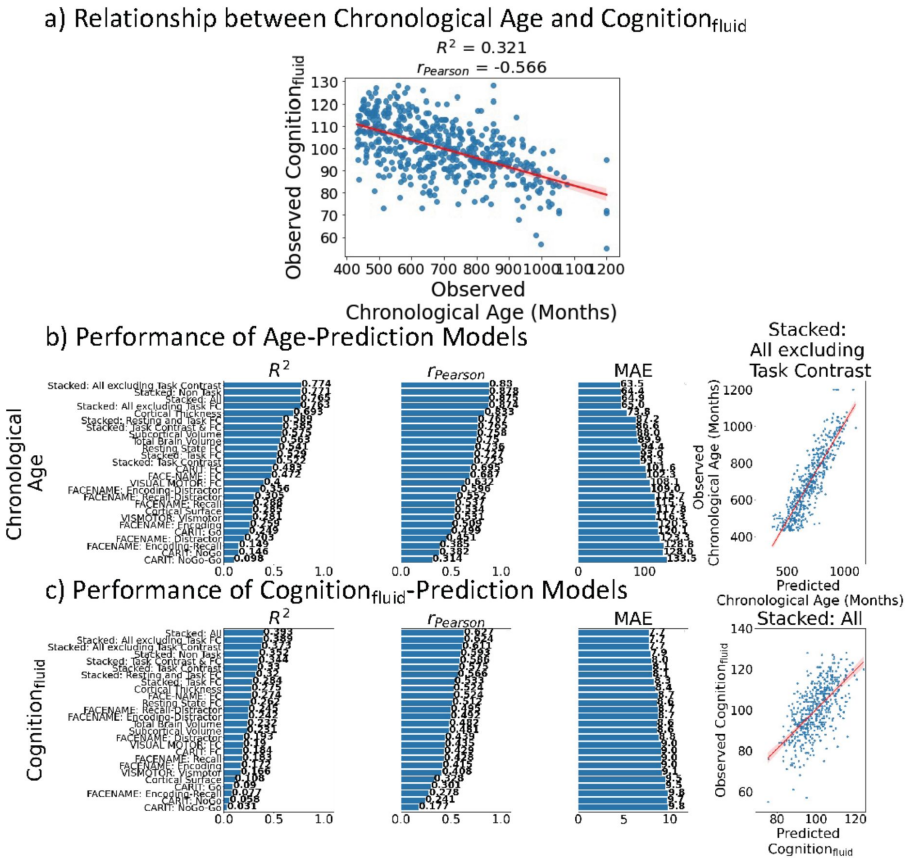

Figure 1.

Relationship between chronological age and Cognition$_{fluid}$ (a) and predictive performance of prediction models using Brain MRI from different sets of MRI features to predict chronological age (b) and Cognition$_{fluid}$ (c).

Note we only provided the scatter plots between observed and predicted values in the test sets from the best prediction models for each target here. See Supplementary Figures 1 and 2 for the scatter plots from other prediction models.

Predictive performance of prediction models for Brain Age and Brain Cognition

Figure 1b and 1c show the predictive performance of different sets of brain MRI features in predicting chronological age and Cognition$_{fluid}$, respectively. For age prediction, the top-four similarly performing models were 'stacked' models that included multiple sets of brain MRI features: "Stacked: All excluding Task Contrast", "Non Task", "All excluding Task FC" and "All" (R^2 > .76, r >.83, MAE < 65 months). For Cognition$_{fluid}$ prediction, the top-performing model was "Stacked: All" (R^2 = .393, r = .627, MAE = 7.7 points). The best set of features across age and Cognition$_{fluid}$ prediction was cortical thickness. Across sets of MRI features, the age-prediction models tended to provide higher R^2 and r than the Cognition$_{fluid}$-prediction models. Figure 2 shows the feature importance of prediction models based on each of the 18 sets of features. Figure 3 shows the feature importance of the eight stacked prediction models.

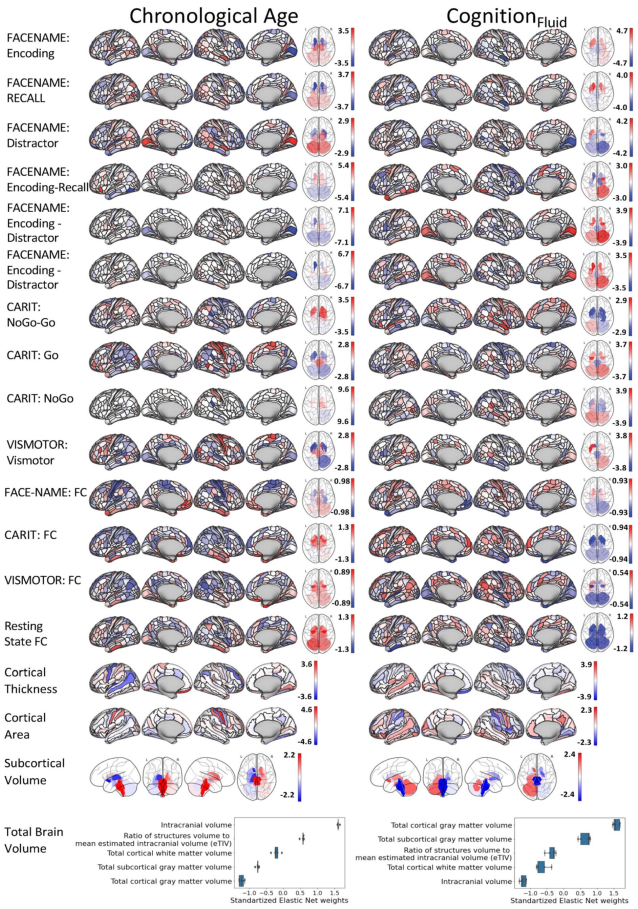

Figure 2.

Feature importance of prediction models based on each of the 18 sets of features.

We calculated feature importance by, first, standardising Elastic Net weights across brain features of each set of features from each test fold. We then plotted the averaged weights across the five test folds for each of the set of features. For functional connectivity (FC), we, first, multiplied the absolute PCA scores (extracted from the 'components_' attribute of 'sklearn.decomposition.PCA') with Elastic Net weights and, then, summed the multiplied values across the 75 components, leaving 71,631 ROI-pair indices. Thereafter, we standardised these indices from each test fold and averaged them across the five test folds. Finally, given that the 71,631 ROI-pair indices were based on correlations among 379 ROIs, we averaged the ROI-pair indices from each ROI and plotted them. Accordingly, our FC plots showed the contribution of each seeding area.

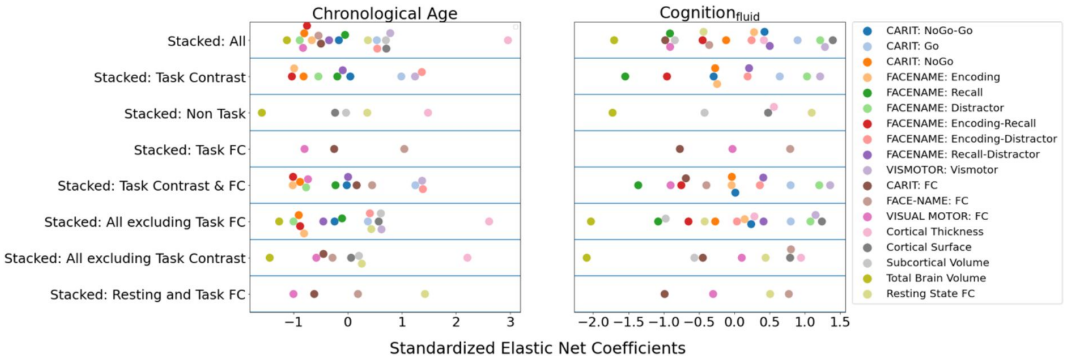

Figure 3.

Feature importance of the eight stacked prediction models.

Here we plotted the Elastic weights, standardised across predicted values from different sets of features and averaged across the five test folds.

Simple regression: Using each Brain Age index to explain $Cognition_{fluid}$

Figure 4a shows variation in $Cognition_{fluid}$ explained by Brain Age Indices when having each Brain Age index as the sole regressor in simple regression models. Brain Age and Corrected Brain Age created from higher-performing age-prediction models explained a higher amount of variation in $Cognition_{fluid}$. However, Brain Age Gap created from the *lower*-performing age-prediction models explained a higher amount of variation in $Cognition_{fluid}$. For instance, the top performing age-prediction model, "Stacked: All excluding Task Contrast", generated Brain Age and Corrected Brain Age that explained the highest amount of variation in $Cognition_{fluid}$, but, at the same time, produced Brain Age Gap that explained the least amount of variation in $Cognition_{fluid}$.

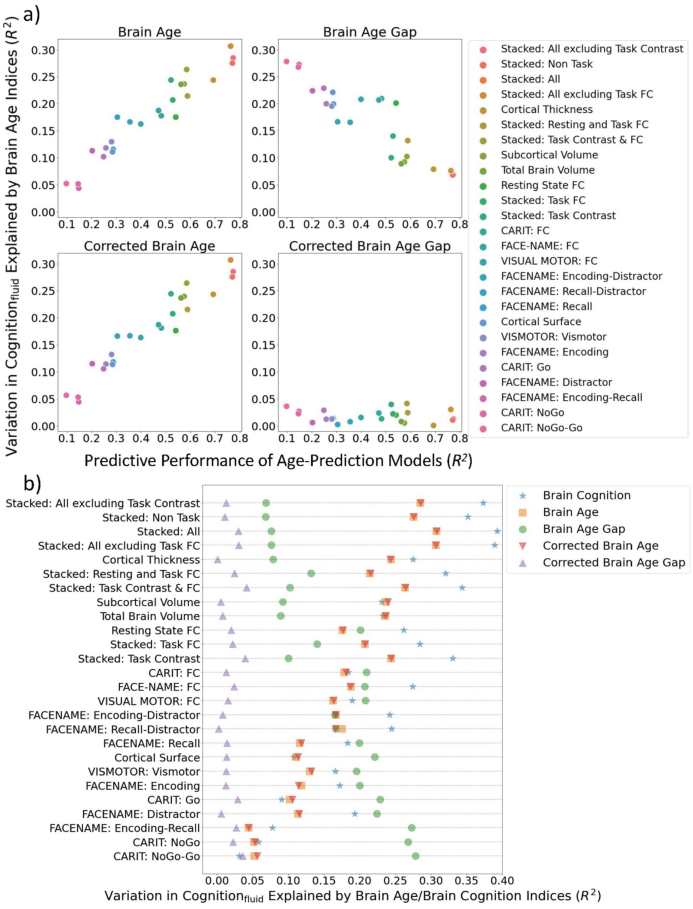

Figure 4.

Simple regression: using each Brain Age index or Brain Cognition to explain $Cognition_{fluid}$.

4a shows variation in $Cognition_{fluid}$ explained by each Brain Age index as a function of the predictive performance of age-prediction models. 4b plots variation in $Cognition_{fluid}$ explained by Brain Age indices and Brain Cognition.

On the contrary, an amount of variation in $Cognition_{fluid}$ explained by Corrected Brain Age Gap was relatively small (maximum at R^2=.041) across age-prediction models and did not relate to the predictive performance of the age-prediction models. Figure 4b shows variation in $Cognition_{fluid}$ explained by Brain Cognition, as compared to Brain Age indices. Brain Cognition appeared to explain a higher amount of variation in $Cognition_{fluid}$ than any Brain Age indices, especially for top-performing age/cognition-prediction models (e.g., Stacked: All).

Multiple regression: Using chronological age and each Brain Age index to explain $Cognition_{fluid}$

Figure 5 shows the commonality analysis of multiple regression models, having both chronological age and each Brain Age index as the regressors for $Cognition_{fluid}$. We found R^2 for these models at M = .326 (SD = 005). The unique effects of Brain Age indices were all relatively small (maximum at $\Delta R^2_{\text{Brain Age index}}$ = .0161, with statistically significant at *p-value* < .05 in 10 out of 26 models) across the four Brain Age indices and across different ageprediction models.

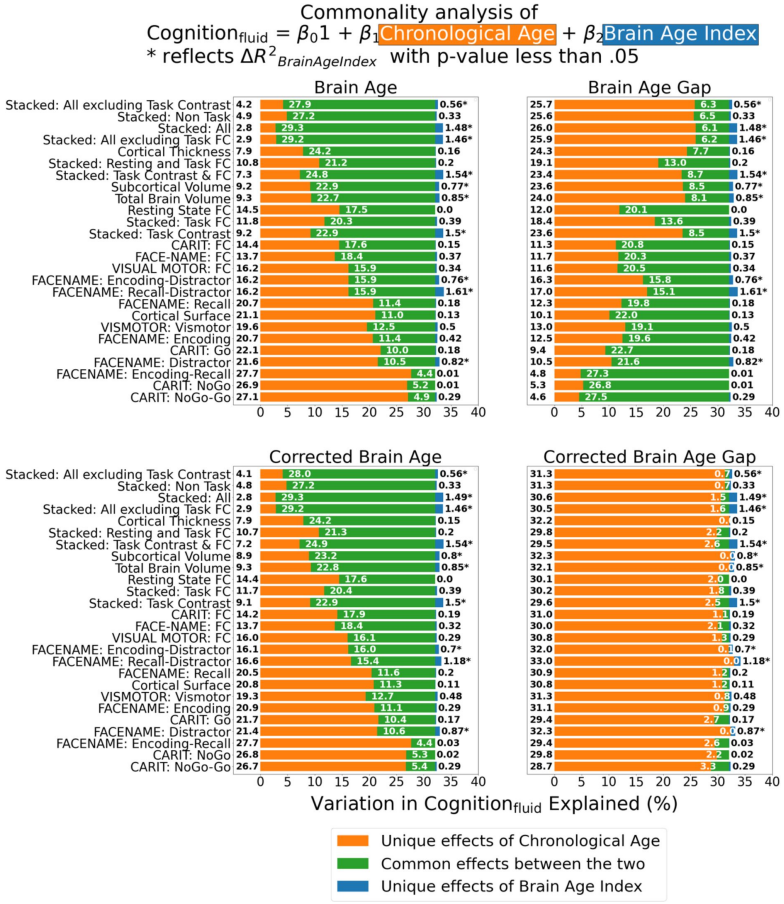

Figure 5.

Commonality analysis of a multiple regression model, having both chronological age and each Brain Age index as the regressors for $Cognition_{fluid}$.

However, it is clear that different Brain Age indices led to different levels of the unique effects of chronological age and the common effects between chronological age and Brain Age indices. For the top-performing age-prediction models (e.g., Stacked: All excluding Task Contrast), the unique effects of chronological age were low for Brain Age and Corrected Brain Age, but high for Brain Age Gap. On the contrary, the lower-performing age-prediction models provided high common effects for Brain Age and Corrected Brain Age, but low for Brain Age Gap. Nonetheless, for Corrected Brain Age Gap, the unique effects of chronological age were much higher than the common effects across all age-prediction models.

Multiple regression: Using chronological age, each Brain Age index and Brain Cognition to explain Cognition$_{fluid}$

Figure 6 shows the commonality analysis of multiple regression models, having chronological age, each Brain Age index and Brain Cognition as the regressors for Cognition$_{fluid}$. We found R^2 for these models at M=.385 (SD=.042). As before, the unique effects of Brain Age indices were all relatively small across the four Brain Age indices and across different prediction models. On the contrary, the unique effects of Brain Cognition appeared much larger (maximum at ΔR^2cognition = .1183, statistically significant *p-value* at .05 in 24 out of 26 models).

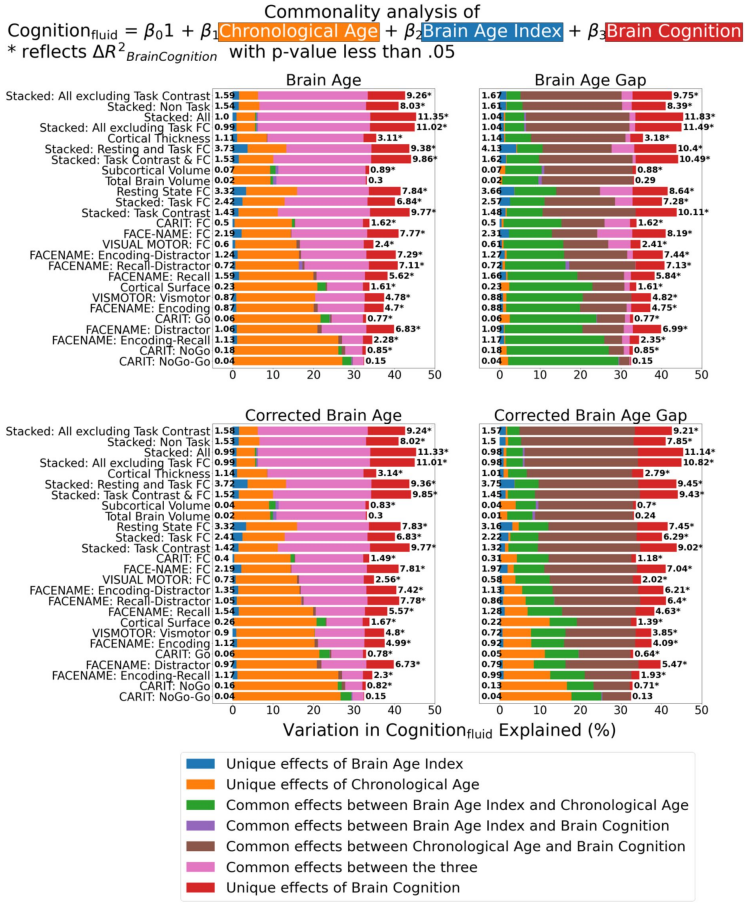

Figure 6.

Commonality analysis of a multiple regression model, having chronological age and each Brain Age index and Brain Cognition as the regressors for Cognition$_{fluid}$.

For top-performing age/cognition-prediction models (e.g., Stacked All), the largest proportion of Cognition$_{fluid}$ was attributed to a) the common effects among the three for Brain Age and Corrected Brain Age and b) the common effects between chronological age and Brain Cognition for Brain Age Gap and Corrected Brain Age Gap.

Discussion

To demonstrate the utility of Brain Age as a biomarker for cognition$_{fluid}$, we investigated three unsettling issues. First, how much does Brain Age add to what is already captured by chronological age? The short answer is very little. Second, do better-performing age-prediction models improve the ability of Brain Age to capture cognition$_{fluid}$? Unfortunately,

the answer is no. Third, do we have a solution that can improve our ability to capture $\text{cognition}_{\text{fluid}}$ from brain MRI? The answer is, fortunately, yes. Using Brain Cognition as a biomarker, along with chronological age, seemed to capture a higher amount of variation in $\text{cognition}_{\text{fluid}}$ than only using Brain Age.

First, Brain Age itself did not add much more information to help us capture $\text{cognition}_{\text{fluid}}$ than what we had already known from a person's chronological age. This can clearly be seen from the small unique effects of Brain Age indices in the multiple regression models having Brain Age and chronological age as the regressors. While the unique effects of some Brain Age indices from certain age-prediction models were statistically significant, there were all relatively small. Without Brain Age indices, chronological age by itself already explained around 32% of variation in $\text{cognition}_{\text{fluid}}$. Including Brain Age indices only added around 1.6% at best.

Investigating the simple regression models and the commonality analysis between each Brain Age index and chronological age provided additional insights. In the simple regression models, higher-performing age-prediction models, such as stacked models, created Brain Age and Corrected Brain Age that captured a higher amount of variation in $\text{Cognition}_{\text{fluid}}$. Because both Brain Age and Corrected Brain Age from higher-performing age-prediction models were closer to the real chronological age of participants, their ability to capture $\text{cognition}_{\text{fluid}}$ mirrored the ability of chronological age. The commonality analysis confirmed this by showing higher common effects between (Corrected) Brain Age and chronological age from higher-performing age-prediction models. In contrast, lower-performing (as opposed to higher-performing) age-prediction models, such as CARIT NoGo-Go, created Brain Age Gap that explained a higher amount of variation in $\text{Cognition}_{\text{fluid}}$. Brain Age Gap was a result of subtracting a real chronological age from Brain Age. And when Brain Age was a poor indicator of the real chronological age, the ability of Brain Age Gap is driven more by the real chronological age (Butler et al., 2021). The commonality analysis confirmed this by showing higher common effects, therefore more similarity in variance, between Brain Age Gap and chronological age from lower-performing, than higher-performing, age-prediction models.

Corrected Brain Age Gap, on the other hand, showed weak effects in the simple regression models across all age-prediction models (max at around 4.1% of variation explained). Corrected Brain Age Gap was the only index among the four that appeared to deconfound the influences of chronological age on the relationship between brain aging and $\text{cognition}_{\text{fluid}}$ (Butler et al., 2021). This can be seen in the small common effects between Corrected Brain Age Gap and chronological age in the multiple regression models with chronological age and each Brain Age index as regressors. Note while these common effects between Corrected Brain Age Gap and chronological age were small, most were not zero (max at around 3.3% of variation explained). This means that the correction done to deconfound the influences of chronological age on Corrected Brain Age Gap (de Lange & Cole, 2020) may not be perfect. Perhaps this is because the estimation of the influences of chronological age was done in the training set, which might not fully be applicable to the test sets. Still, weak effects of Corrected Brain Age Gap in the simple regression indicate that, after controlling for the influences of chronological age, this Brain Age index could only account for a small amount of variation in $\text{cognition}_{\text{fluid}}$. In other words, the weak effects of Corrected Brain Age Gap shown by the simple regression are consistent with the small unique effects across the four Brain Age indices shown by the multiple regression models having a Brain Age index and chronological age as regressors.

Second, the predictive performance of age-prediction models did not correspond to the ability of Brain Age to capture $\text{cognition}_{\text{fluid}}$ over and above chronological age. For instance, while the best-performing age-prediction model was "Stacked: All excluding Task Contrast"

(R^2=.775), the unique effects of Brain Age indices from this model in the two-regressor multiple regressions were weak ($\Delta R^2_{\text{Brain Age index}} \leq .0048$) and not statistically significant. The highest unique effects of Brain Age indices in the two-regressor multiple regression models were from the FACENAME: Distractor model ($\Delta R^2_{\text{Brain age index}} \leq .0135$, $p < .05$) that had a poorer performance in predicting chronological age (R^2=.204). Accordingly, a race to improve the performance of age-prediction models (Baecker et al., 2021) does not necessarily enhance the utility of Brain Age indices as a biomarker for $\text{cognition}_{\text{fluid}}$. This calls for a new paradigm. Future research should aim to build prediction models for Brain Age indices that are not necessarily good at predicting age, but at capturing phenotypes of interest, such as $\text{cognition}_{\text{fluid}}$ and beyond.

Third, while Brain Age indices may not add much to capture $\text{cognition}_{\text{fluid}}$, over and above chronological age, Brain Cognition did as shown by its unique effects. Adding Brain Cognition as a regressor along with chronological age and a Brain Age index allowed us to explain as much as 11% more of the variation in $\text{cognition}_{\text{fluid}}$ (i.e., around 1/3 times better than the multiple regression models without Brain Cognition). Based on the commonality analyses, the multiple regression models that explained higher variation were driven predominantly by the common effects involving Brain Cognition. This overlapped variation was consistent with a recent study (Jiang et al., 2022). Altogether, while both the effects of Brain Age and Brain Cognition overlapped with chronological age, Brain Cognition offered additional unique effects that helped improve the ability to capture $\text{cognition}_{\text{fluid}}$.

What does it mean then for researchers/clinicians who would like to use Brain Age as a biomarker? First, they have to be aware of the overlap in variation between Brain Age and chronological age and should focus on the contribution of Brain Age over and above chronological age. Using Brain Age Gap will not fix this. Similar to a previous recommendation (Butler et al., 2021), we suggest focusing on Corrected Brain Age Gap or, better, unique effects of Brain Age indices in multiple regressions. In the case of $\text{cognition}_{\text{fluid}}$, the unique effects might be too small to be clinically meaningful. While our emphasis was on $\text{cognition}_{\text{fluid}}$, we suspect that the unique effects of Brain Age might also be small for other phenotypes, especially if those phenotypes vary with age (e.g., neurodegenerative risks). Next, researchers/clinicians should not select the MRI modalities or machine-learning algorithms based on age-prediction performance, but rather select them based on the unique effects of Brain Age indices. Finally, beyond Brain Age, researchers/clinicians should explore the unique effects of other biomarkers that may tap closer into the phenotypes of interest. One straightforward approach tested here is to build the model using the phenotype of interest as a target (i.e., $\text{cognition}_{\text{fluid}}$). This approach significantly improved our ability to capture $\text{cognition}_{\text{fluid}}$ in the current study.

Methods and Materials

Dataset

We used the Human Connectome Project in Aging (HCP-A) (Bookheimer et al., 2019) Release 2.0 (24-February-2021). HCP-A's 'typical-aging' participants (36-100 years old) may have prevalent health conditions (e.g., hypertension and different forms of vascular risks) but did not have identified pathological causes of cognitive decline (e.g., stroke and clinical dementia). In this Release, HCP-A provided data from 725 participants. HCP-A offered quality control flags, and here, we removed participants with the flag 'A' anatomical anomalies or 'B' segmentation and surface (n= 117). Following further removal of participants with missing values in any of MRI modalities (n=15) or cognitive measurements (n= 111), we ultimately included 504 individuals (293 females, M= 57.83 (SD=14.25) years old) in our analyses. For

ethical procedures including informed consent, please see Bookheimer and colleagues' (2019).

Sets of brain MRI features

HCP-A provides details of parameters for brain MRI elsewhere (Bookheimer et al., 2019; Harms et al., 2018). Here we used MRI data that were pre-processed by the HCP-A with recommended methods, including the MSMALL alignment (Glasser et al., 2016; Robinson et al., 2018) and ICA-FIX (Glasser et al., 2016) for functional MRI. We used multiple brain MRI modalities, covering task functional MRI (task fMRI), resting-state functional MRI (rsfMRI) and structural MRI (sMRI), and organised them into 19 sets of features.

Sets of Features 1-10: Task fMRI contrast (Task Contrast)

Task contrasts reflect fMRI activation relevant to events in each task. (Bookheimer and colleagues (2019)) provided detailed information about the fMRI in HCP-A. Here we focused on the pre-processed task fMRI files with a suffix, "_PA_Atlas_MSMAll_hp0_clean.dtserïes.nii." To extract Task Contrasts, we regressed the fMRI time series on the convolved task events using a double-gamma canonical hemodynamic response function via FMRIB Software Library (FSL)'s FMRI Expert Analysis Tool (FEAT) (Woolrich et al., 2001). We then parcellated the contrast 'cope' files, using the Glasser atlas (Gordon et al., 2016) for cortical surface regions and the Freesurfer's automatic segmentation (aseg) (Fischl et al., 2002) for subcortical regions. This resulted in 379 regions, which was, in turn, the number of features for each Task Contrast set of features.

HCP-A collected fMRI data from three tasks: Face Name (Sperling et al., 2001), Conditioned Approach Response Inhibition Task (CARIT) (Somervil(le et al., 2018)) and VISual MOTOR (VISMOTOR) (Ances et al., 2009). First, the Face Name task (Sperling et al., 2001) taps into episodic memory. The task had three blocks. In the encoding block [Encoding], participants were asked to memorise the names of faces shown. These faces were then shown again in the recall block [Recall] when the participants were asked if they could remember the names of the previously shown faces. There was also the distractor block [Distractor] occurring between the encoding and recall blocks. Here participants were distracted by a Go/NoGo task. We computed six contrasts for this Face Name task: [Encode], [Recall], [Distractor], [Encode vs. Distractor], [Recall vs. Distractor] and [Encode vs. Recall].

Second, the CARIT task (Somervil(le et al., 2018)) was adapted from the classic Go/NoGo task and taps into inhibitory control. Participants were asked to press a button to all [Go] but not to two [NoGo] shapes. We computed three contrasts for the CARIT task: [NoGo], [Go] and [NoGo vs. Go].

Third, the VISMOTOR task (Ances et al., 2009) was designed to test simple activation of the motor and visual cortices. Participants saw a checkerboard with a red square either on the left or right. They needed to press a corresponding key to indicate the location of the red square. We computed just one contrast for the VISMOTOR task: [Vismotor], which indicates the presence of the checkerboard vs. baseline.

Sets of Features 11-13: Task fMRI functional connectivity (Task FC)

Task FC reflects functional connectivity (FC) among the brain regions during each task, which is considered an important source of individual differences (Elliott et al., 2019; Fair et al., 2007; Gratton et al., 2018). Unlike Task Contrasts, here we treated the double-gamma, convolved task events as regressors of no interest and focused on the residuals of the regression from each task (Fair et al., 2007). Using the same atlases as Task Contrast (Fischl et

al., 2002; Glasser et al., 2016), we computed Pearson's correlations of each pair of 379 regions, resulting in a table of 71,631 non-overlapping FC indices for each task. We then applied r-to-z transformation and principal component analysis (PCA) of 75 components (Rasero et al., 2021; Sripada et al., 2019; 2020). Note to avoid data leakage, we conducted the PCA on each training set and applied its definition to the corresponding test set. Accordingly, there were three sets of 75 features for Task FC, one for each task.

Set of Features 14: Resting-state functional MRI functional connectivity (Rest FC)

Similar to Task FC, Rest FC reflects functional connectivity (FC) among the brain regions, except that Rest FC occurred during the resting (as opposed to task-performing) period. HCP-A collected Rest FC from four 6.42-min (488 frames) runs across two days, leading to 26-min long data (Harms et al., 2018). On each day, the study scanned two runs of Rest FC, starting with anterior-to-posterior (AP) and then with posterior-to-anterior (PA) phase encoding polarity. We used the "rfMRI_REST_Atlas_MSMAll_hp0_clean.dscalar.nii" file that was pre-processed and concatenated across the four runs. We applied the same computations (i.e., parcellation, Pearson's correlations, r-to-z transformation and PCA) with the Task FC.

Sets of Features 15-18: Structural MRI (sMRI)

sMRI reflects individual differences in brain anatomy. The HCP-A used an established preprocessing pipeline for sMRI (Glasser et al., 2013). We focused on four sets of features: cortical thickness, cortical surface area, subcortical volume and total brain volume. For cortical thickness and cortical surface area, we used Destrieux's atlas (Destrieux et al., 2010; Fischl, 2012) from FreeSurfer's "aparc.stats" file, resulting in 148 regions for each set of features. For subcortical volume, we used the aseg atlas (Fischl et al., 2002) from FreeSurfer's "aseg.stats" file, resulting in 19 regions. For total brain volume, we had five FreeSurfer-based features: "FS_IntraCranial_Vol" or estimated intra-cranial volume, "FS_TotCort_GM_Vol" or total cortical grey matter volume, "FS_Tot_WM_Vol" or total cortical white matter volume, "FS_SubCort_GM_Vol" or total subcortical grey matter volume and "FS_BrainSegVol_eTIV_Ratio" or ratio of brain segmentation volume to estimated total intracranial volume.

Cognitive abilities: $\text{Cognition}_{\text{fluid}}$

We measured $\text{Cognition}_{\text{fluid}}$ via the NIH Toolbox (Weintraub et al., 2014), using the "fluidcogcomp_unadj" variable. $\text{Cognition}_{\text{fluid}}$ summarises scores from five tests assessed outside of the MRI: Dimensional Change Card Sort, Flanker Inhibitory Control and Attention, Picture Sequence Memory, List Sorting Working Memory and Pattern Comparison Processing Speed.

Prediction models for Brain Age and Brain Cognition

To compute Brain Age and Brain Cognition, we ran two separate prediction models. These prediction models either had chronological age or $\text{Cognition}_{\text{fluid}}$ as the target and standardised brain MRI as the features (Denissen et al., 2022). We used nested cross-validation (CV) to build these models. We first split the data into five folds (i.e., outer CV). One of these outer-CV folds was treated as a test set, and the rest was treated as a training set, which was further divided into five folds (i.e., inner CV). We used the inner CV to tune for hyperparameters of the models and the outer CV to evaluate the predictive performance of the models. We controlled for the potential influences of biological sex on the brain features by first residualising biological sex from brain features in the training set. We then

applied the regression of this residualisation based on the training set to the test set. We also standardised the brain features in the training set and then used the mean and standard deviation of the training set to standardise the test set.

To demonstrate the predictive performance, we assessed the similarity between the observed values and the predicted values of each model across test sets, using Pearson's *r*, coefficient of determination (R^2) and mean absolute error (MAE). Note that for R^2, we used the sum of squares definition (i.e., R^2 = 1 – (sum of squares residuals/total sum of squares)) per a previous recommendation (Poldrack et al., 2020). We considered the predicted values from the test sets of models predicting age or $Cognition_{fluid}$, as Brain Age and Brain Cognition, respectively.

In addition to using each of the 18 sets of features in separate prediction models, we drew information across these sets via stacking. Specifically, we computed predicted values from each of the 18 sets of features in the training sets. We then treated different combinations of these predicted values as features to predict the targets in separate "stacked" models. We specified eight stacked models: "All" (i.e., including all 18 sets of features), "All excluding Task FC", "All excluding Task Contrast", "Non-Task" (i.e., including only Rest FC and sMRI), "Resting and Task FC", "Task Contrast and FC", "Task Contrast" and "Task FC". Accordingly, in total, there were 26 prediction models for Brain Age and Brain Cognition.

For the machine learning algorithm, we used Elastic Net (Zou & Hastie, 2005) as implemented in sklearn (Pedregosa et al., 2011). Not only does Elastic Net provide a relatively good predictive performance for fMRI (Dubois et al., 2018; Pat, Wang, Anney, et al., 2022; Pat, Wang, Bartonicek, et al., 2022; Tetereva et al., 2022), but it also offers easy-to-interpret feature importance (Molnar, 2019). In our grid search, we tuned two Elastic Net hyperparameters: a using 70 numbers in log space, ranging from .1 and 100, and ℓ_1-ratio using 25 numbers in linear space, ranging from 0 and 1.

Brain Age calculations: Brain Age, Brain Age Gap, Corrected Brain Age and Corrected Brain Age Gap

In addition to Brain Age, which is the predicted value from the models predicting chronological age in the test sets, we calculated three other indices to reflect the estimation of brain aging. First, Brain Age Gap reflects the difference between the age predicted by brain MRI and the actual, chronological age. Here we simply subtracted the chronological age from Brain Age.

Next, to correct for the estimation biases (i.e., overestimation in younger, but underestimation in older, individuals (Le et al., 2018)), we applied (de Lange and Cole's (2020)) 5^{th} equation. Specifically, we first fit a regression line predicting the Brain Age from a chronological age in a training set. We then used the slope and intercept of this regression line to adjust Brain Age in a test set, resulting in Corrected Brain Age.

Lastly, we computed Corrected Brain Age Gap by subtracting the chronological age from the Corrected Brain Age (Butler et al., 2021; Le et al., 2018).

The ability of Brain Age indices to capture $Cognition_{fluid}$

We first combined Brain Age, Brain Cognition, chronological age and $Cognition_{fluid}$ across test sets into one table. We then conducted three sets of regression analyses to demonstrate the ability of different Brain Age indices, calculated from 26 different prediction models based on different sets of brain MRI features, to capture $Cognition_{fluid}$.

1. Simple Regression: Using each Brain Age index to explain $Cognition_{fluid}$

Here using simple regression, we simply had each Brain Age index as the sole regressor for $Cognition_{fluid}$:

$$Cognition_{fluid} \sim \beta_0 + \beta_1 \text{ Brain Age Index}_i, \quad (1)$$

where i is the index for the four Brain Age indices. Because different Brain Age indices differ in the adjustments applied, this simple regression could reveal the extent to which each adjustment influences variation in $Cognition_{fluid}$ explained. Additionally, Brain Age calculated from 26 different prediction models would have different levels of predictive performance in predicting chronological age. Accordingly, this simple regression could also reveal if Brain Age from a better-performing age-prediction model was able to capture more variation in $Cognition_{fluid}$.

In addition to Brain Age indices, we also used simple regression to test how well Brain Cognition as a sole regressor explains $Cognition_{fluid}$:

$$Cognition_{fluid} \sim \beta_0 + \beta_1 \text{ Brain Cognition}, \quad (2)$$

This allows us to compare the ability of Brain Age Indices vs. Brain Cognition as a sole regressor for predicting $Cognition_{fluid}$.

2. Multiple Regression: Using chronological age and each Brain Age index to explain $Cognition_{fluid}$

Here using multiple regression, we had both chronological age and each Brain Age index as the regressors for $Cognition_{fluid}$:

$$Cognition_{fluid} \sim \beta_0 + \beta_1 \text{ Chonological Age} + \beta_2 \text{ Brain Age Index}_i, \quad (3)$$

Having chronological age in the same regression model as a Brain Age index allowed us to control for the effects of chronological age on the Brain Age index, thereby, revealing the unique effects of the Brain Age index (Butler et al., 2021; Le et al., 2018). To formally determine the unique effects of a Brain Age index on $Cognition_{fluid}$ along with the effects it shared with chronological age (i.e., common effects), we applied the commonality analysis (Nimon et al., 2008). For the unique effects, we computed ΔR^2. ΔR^2 is the increase in R^2 when having an additional regressor in the regression model:

$$\begin{aligned} \text{Unique Effects}_{\text{chronological age}} &= \Delta R^2_{\text{chronological age}} = R^2_{\text{chronological age, Brain Age index}} - R^2_{\text{Brain Age index}} \\ \text{Unique Effects}_{\text{Brain Age index}} &= \Delta R^2_{\text{Brain Age index}} = R^2_{\text{chronological age, Brain Age index}} - R^2_{\text{chronological age}}, \quad (4) \end{aligned}$$

We determined the statistical significance of ΔR^2 by:

$$F_{Change} = \frac{(N-k_2-1)\Delta R^2}{k_{change}(1-R_2^2)}, \quad (5)$$

where F_{Change} is the F-ratio (with the degree of freedom of k_{Change} and $N - k_2 - 1$), N is the number of observations, 2 is the model with more regressors, k is the number of regressors,

k_{Change} is the difference between the number of regressors.

As for the common effects between chronological age and each Brain Age index, we used the below calculation:

$$\text{Common Effects}_{\text{chronological age, Brain Age index}} = R^2_{\text{chronological age, Brain Age index}} - \Delta R^2_{\text{chronological age}} - \Delta R^2_{\text{Brain Age index}}, \quad (6)$$

These common effects indicate the extent to which variation in $\text{Cognition}_{\text{fluid}}$ explained by each Brain Age index was shared with chronological age. Note the common effects can be negative, especially with a high multicollinearity (Ray-Mukherjee et al., 2014). To deal with this, we treated negative common effects as zero (Frederick, 1999) and then scaled variation explained by other effects to be proportional to the total effects of the full regression model.

3. Multiple Regression: Using chronological age, each Brain Age index and Brain Cognition to explain $\text{Cognition}_{\text{fluid}}$

Similar to the above multiple regression model, we had chronological age, each Brain Age index and Brain Cognition as the regressors for $\text{Cognition}_{\text{fluid}}$:

$$\text{Cognition}_{\text{fluid}} \sim \beta_0 + \beta_1 \text{Chronological Age} + \beta_2 \text{Brain Age Index}_i + \beta_3 \text{Brain Cognition}, \quad (7)$$

Applying the commonality analysis here allowed us, first, to investigate the addictive, unique effects of Brain Cognition, over and above chronological age and Brain Age indices. More importantly, the commonality analysis also enabled us to test the common, shared effects that Brain Cognition had with chronological age and Brain Age indices in explaining $\text{Cognition}_{\text{fluid}}$. We calculated the commonality analysis as follows (Nimon et al., 2017):

$$\text{Unique Effects}_{\text{chronological age}} = \Delta R^2_{\text{chronological age}} = R^2_{\text{chronological age, Brain Age index, Brain Cognition}} - R^2_{\text{Brain Age index, Brain Cognition}}$$

$$\text{Unique Effects}_{\text{Brain Age index}} = \Delta R^2_{\text{Brain Age index}} = R^2_{\text{chronological age, Brain Age index, Brain Cognition}} - R^2_{\text{chronological age, Brain Cognition}}$$

$$\text{Unique Effects}_{\text{Brain Cognition}} = \Delta R^2_{\text{Brain Cognition}} = R^2_{\text{chronological age, Brain Age index, Brain Cognition}} - R^2_{\text{chronological age, Brain Age Index}}$$

$$\text{Common Effects}_{\text{chronological age, Brain Age index}} = R^2_{\text{chronological age, Brain Cognition}} + R^2_{\text{Brain Age index, Brain Cognition}} - R^2_{\text{Brain Cognition}} - R^2_{\text{chronological age, Brain Age index, Brain Cognition}}$$

$$\text{Common Effects}_{\text{chronological age, Brain Cognition}} = R^2_{\text{chronological age, Brain Age Index}} + R^2_{\text{Brain Age index, Brain Cognition}} - R^2_{\text{Brain Age Index}} - R^2_{\text{chronological age, Brain Age index, Brain Cognition}}$$

$$\text{Common Effects}_{\text{Brain Age index, Brain Cognition}} = R^2_{\text{chronological age, Brain Age Index}} + R^2_{\text{chronological age, Brain Cognition}} - R^2_{\text{chronological age}} - R^2_{\text{chronological age, Brain Age index, Brain Cognition}}$$

$$\text{Common Effects}_{\text{chronological age, Brain Age index, Brain Cognition}} = R^2_{\text{chronological age}} + R^2_{\text{Brain Age Index}} + R^2_{\text{Brain Cognition}} - R^2_{\text{chronological age, Brain Age Index}} - R^2_{\text{chronological age, Brain Cognition}} - R^2_{\text{Brain Age Index, Brain Cognition}} - R^2_{\text{chronological age, Brain Age index, Brain Cognition}}, \quad (8)$$

Conflict of interest statement

The authors declare no competing interests.

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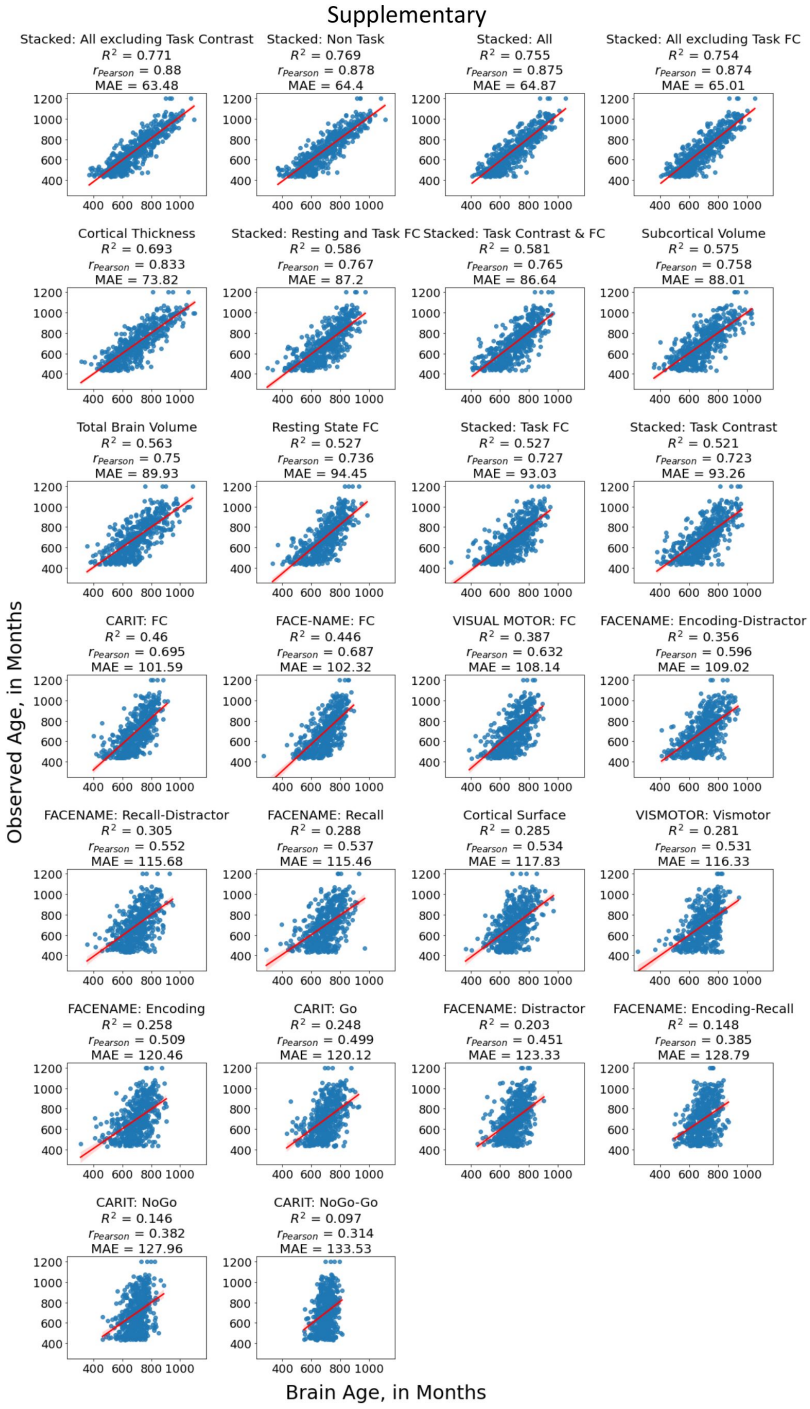
Code Accessibility

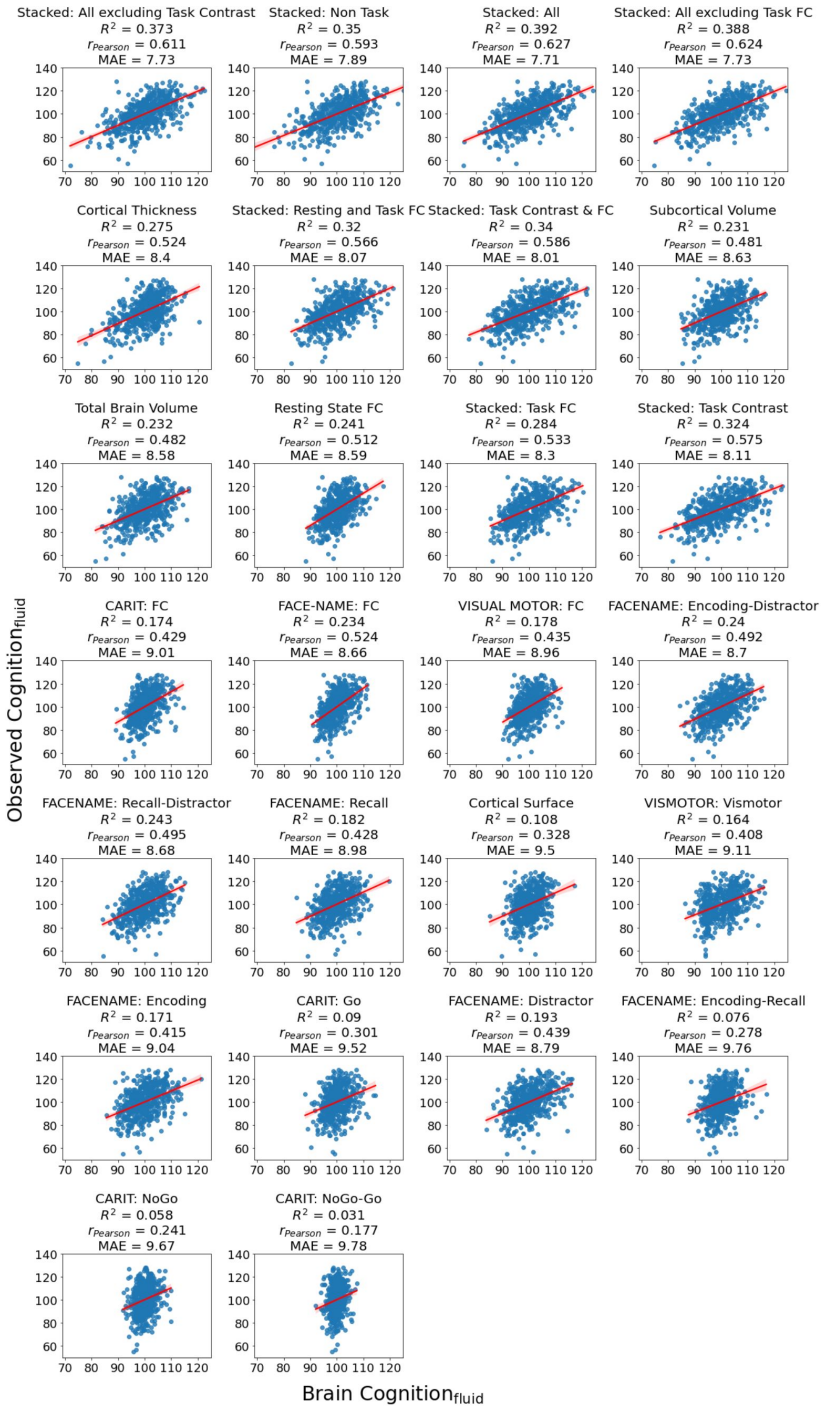
The shell and Python scripts used in the analyses are made available here: https://github.com/HAM-lab-Otago-University/HCP-Aging_commonality

Supplementary



Supplementary Figure 1.

The scatter plots between observed and predicted values in the test sets from age-prediction models.



Supplementary Figure 2.

The scatter plots between observed and predicted values in the test sets from cognition-prediction models

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Author information

Alina Tetereva
Department of Psychology, University of Otago, New Zealand, 9016
ORCID iD: 0000-0003-2077-628X

Narun Pat
Department of Psychology, University of Otago, New Zealand, 9016
For correspondence: narun.pat@otago.ac.nz
ORCID iD: 0000-0003-1459-5255

Editors

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Reviewer 1 (Public Review):

This is a reasonably good paper and the use of a commonality analysis is a nice contribution to understanding variance partitioning across different covariates. I have some comments that I believe the authors ought to address which mostly relate to clarity and interpretation.

First, from a conceptual point of view, the authors focus exclusively on cognition as a downstream outcome. I would suggest the authors nuance their discussion to provide broader considerations of the utility of their method and on the limits of interpretation of brain-age models more generally. Further, I think that since brain-age models by construction confound relevant biological variation with the accuracy of the regression models used to estimate them, there may be limits to the interpretation of (e.g.) the brain-age gap is as a dimensionless biomarker. This has also been discussed elsewhere (see e.g. https://academic.oup.com/brain/article/143/7/2312/5863667). I would suggest that the authors consider and comment on these issues.

Second, from a methods perspective, there is not a sufficient explanation of the methodological procedures in the current manuscript to fully understand how the stacked regression models were constructed. Stacked models can be prone to overfitting when combined with cross-validation. This is because the predictions from the first-level models (i.e. the features that are provided to the second level 'stacked' models) contain information about the training set *and* the test set. If cross-validation is not done very carefully (e.g. using multiple hold-out sets), information leakage can easily occur at the second level. Unfortunately, there is not a sufficient explanation of the methodological procedures in the current manuscript to fully understand what was actually done. Please provide more information to enable the reader to better understand the stacked regression models. If the authors are not using an approach that fully preserves training and test separability, they need to do so.

Please also provide an indication of the different regression strengths that were estimated across the different models and cross-validation splits. Also, how stable were the weights across splits?

Please provide more details about the task designs, MRI processing procedures that were employed on this sample in addition to the regression methods, and bias-correction methods used. For example, there are several different parameterisations of the elastic net, please provide equations to describe the method used here so that readers can easily determine how the regularisation parameters should be interpreted.

Reviewer 2 (Public Review):

In this study, the authors aimed to evaluate the contribution of brain-age indices in capturing variance in cognitive decline and proposed an alternative index, brain-cognition, for consideration. The study employs suitable data and methods, albeit with some limitations, to address the research questions. A more detailed discussion of methodological limitations in relation to the study's aims is required. For instance, the current commonality analysis may not sufficiently address potential multicollinearity issues, which could confound the findings. Importantly, given that the study did not provide external validation for the indices, it is unclear how well the models would perform and generalize to other samples. This is particularly relevant to their novel index, brain-cognition, given that brain-age has been validated extensively elsewhere. In addition, the paper's rationale for using

elastic net, which references previous fMRI studies, seemed somewhat unclear. The discussion could be more nuanced and certain conclusions appear speculative.

The authors aimed to evaluate how brain-age and brain-cognition indices capture cognitive decline (as mentioned in their title) but did not employ longitudinal data, essential for calculating 'decline'. As a result, 'cognition-fluid' should not be used interchangeably with 'cognitive decline,' which is inappropriate in this context.

In their first aim, the authors compared the contributions of brain-age and chronological age in explaining variance in cognition-fluid. Results revealed much smaller effect sizes for brain-age indices compared to the large effects for chronological age. While this comparison is noteworthy, it highlights a well-known fact: chronological age is a strong predictor of disease and mortality. Has the brain-age literature systematically overlooked this effect? If so, please provide relevant examples. They conclude that due to the smaller effect size, brain-age may lack clinical significance, for instance, in associations with neurodegenerative disorders. However, caution is required when speculating on what brain-age may fail to predict in the absence of direct empirical testing. This conclusion also overlooks extant brain-age literature: although effect sizes vary across psychiatric and neurological disorders, brain-age has demonstrated significant effects beyond those driven by chronological age, supporting its utility.

The second aim's results reveal a discrepancy between the accuracy of their brain-age models in estimating age and the brain-age's capacity to explain variance in cognition-fluid. The authors suggest that if the ultimate goal is to capture cognitive variance, brain-age predictive models should be optimized to predict this target variable rather than age. While this finding is important and noteworthy, additional analyses are needed to eliminate potential confounding factors, such as correlated noise between the data and cognitive outcome, overfitting, or the inclusion of non-healthy participants in the sample. Optimizing brain-age models to predict the target variable instead of age could ultimately shift the focus away from the brain-age paradigm, as it might optimize for a factor differing from age.

While a primary goal in biomarker research is to obtain indices that effectively explain variance in the outcome variable of interest, thus favouring models optimized for this purpose, the authors' conclusion overlooks the potential value of 'generic/indirect' models, despite sacrificing some additional explained variance provided by ad-hoc or 'specific/direct' models. In this context, we could consider brain-age as a 'generic' index due to its robust out-of-sample validity and significant associations across various health outcome variables reported in the literature. In contrast, the brain-cognition index proposed in this study is presumed to be 'specific' as, without out-of-sample performance metrics and testing with different outcome variables (e.g., neurodegenerative disease), it remains uncertain whether the reported effect would generalize beyond predicting cognition-fluid, the same variable used to condition the brain-cognition model in this study. A 'generic' index like brain-age enables comparability across different applications based on a common benchmark (rather than numerous specific models) and can support explanatory hypotheses (e.g., "accelerated ageing") since it is grounded in its own biological hypothesis. Generic and specific indices are not mutually exclusive; instead, they may offer complementary information. Their respective utility may depend heavily on the context and research or clinical question.

The study's third aim was to evaluate the authors' new index, brain-cognition. The results and conclusions drawn appear similar: compared to brain-age, brain-cognition captures more variance in the outcome variable, cognition-fluid. However, greater context and discussion of limitations is required here. Given the nature of the input variables (a large proportion of models in the study were based on fMRI data using cognitive tasks), it is perhaps unsurprising that optimizing these features for cognition-fluid generates an index better at explaining variance in cognition-fluid than the same features used to predict age. In

other words, it is expected that brain-cognition would outperform brain-age in explaining variance in cognition-fluid since the former was optimized for the same variable in the same sample, while brain-age was optimized for age. Consequently, it is unclear if potential overfitting issues may inflate the brain-cognition's performance. This may be more evident when the model's input features are the ones closely related to cognition, e.g., fMRI tasks. When features were less directly related to cognitive tasks, e.g., structural MRI, the effect sizes for brain-cognition were notably smaller (see 'Total Brain Volume' and 'Subcortical Volume' models in Figure 6). This observation raises an important feasibility issue that the authors do not consider. Given the low likelihood of having task-based fMRI data available in clinical settings (such as hospitals), estimating a brain-cognition index that yields the large effects discussed in the study may be challenged by data scarcity.

This study is valuable and likely to be useful in two main ways. First, it can spur further research aimed at disentangling the lack of correspondence reported between the accuracy of the brain-age model and the brain-age's capacity to explain variance in fluid cognitive ability. Second, the study may serve, at least in part, as an illustration of the potential pros and cons of using indices that are specific and directly related to the outcome variable versus those that are generic and only indirectly related.

Overall, the authors effectively present a clear design and well-structured procedure; however, their work could have been enhanced by providing more context for both the brain-age and brain-cognition indices, including a discussion of key concepts in the brain-age paradigm, which acknowledges that chronological age strongly predicts negative health outcomes, but crucially, recognizes that ageing does not affect everyone uniformly. Capturing this deviation from a healthy norm of ageing is the key brain-age index. This lack of context was mirrored in the presentation of the four brain-age indices provided, as it does not refer to how these indices are used in practice. In fact, there is no mention of a more common way in which brain-age is implemented in statistical analyses, which involves the use of brain-age delta as the variable of interest, along with linear and non-linear terms of age as covariates. The latter is used to account for the regression-to-the-mean effect. The 'corrected brain-age delta' the authors use does not include a non-linear term, which perhaps is an additional reason (besides the one provided by the authors) as to why there may be small, but non-zero, common effects of both age and brain-age in the 'corrected brain-age delta' index commonality analysis. The context for brain-cognition was even more limited, with no reference to any existing literature that has explored direct brain-cognitive markers, such as brain-cognition.

While this paper delivers intriguing and thought-provoking results, it would benefit from recognizing the value that both approaches--brain-age indices and more direct, specific markers like brain-cognition--can contribute to the field.

Reviewer 3 (Public Review):

The main question of this article is as follows: "To what extent does having information on brain-age improve our ability to capture declines in fluid cognition beyond knowing a person's chronological age?" While this question is worthwhile, considering that there is considerable confusion in the field about the nature of brain-age, the authors are currently missing an opportunity to convey the inevitability of their results, given how brain-age and the brain-age gap are calculated. They also argue that brain-cognition is somehow superior to brain-age, but insufficient evidence is provided in support of this claim.

Specific comments follow:

- "There are many adjustments proposed to correct for this estimation bias" (p3). Regression to the mean is not a sign of bias. Any decent loss function will result in over-predicting the age of younger individuals and under-predicting the age of older individuals. This is a direct result of minimizing an error term (e.g., mean squared error). Therefore, it is inappropriate to refer to regression to the mean as a sign of bias. This misconception has led to a great deal of inappropriate analyses, including "correcting" the brain age gap by regressing out age.

- "Corrected Brain Age Gap in particular is viewed as being able to control for both age dependency and estimation biases (Butler et al., 2021)" (p3). This summary is not accurate as Butler and colleagues did not use the words "corrected" and "biases" in this context. All that authors say in that paper is that regressing out age from the brain age gap - which is referred to as the modified brain age gap (MBAG) - makes it so that the modified brain age gap is not dependent on age, which is true. This metric is meaningless, though, because it is the variance left over after regressing out age from residuals from a model that was predicting age. If it were not for the fact that regression on residuals is not equivalent to multiple regression (and out of sample estimates), MBAG would be a vector of zeros. Upon reading the Methods, I noticed that the authors use a metric from Le et al. (2018) for the "Corrected Brain Age Gap". If they cite the Butler et al. (2021) paper, I highly recommend sticking with the same notation, metrics and terminology throughout. That would greatly help with the interpretability of the present manuscript, and cross-comparisons between the two.

- "However, the improvement in predicting chronological age may not necessarily make Brain Age to be better at capturing Cognitionfluid. If, for instance, the age-prediction model had the perfect performance, Brian Age Gap would be exactly zero and would have no utility in capturing Cognitionfluid beyond chronological age" (p3). I largely agree with this statement. I would be really careful to distinguish between brain-age and the brain-age gap here, as the former is a predicted value, and the latter is the residual times -1 (i.e., predicted age - age). Therefore, together they explain all of the variance in age. Changing the first sentence to refer to the brain-age gap would be more accurate in this context. The brain-age gap will never be exactly zero, though, even with perfect prediction on the training set, because subjects in the testing set are different from the subjects in the training set.

- "Can we further improve our ability to capture the decline in cognitionfluid by using, not only Brain Age and chronological age, but also another biomarker, Brain Cognition?". This question is fundamentally getting at whether a predicted value of cognition can predict cognition. Assuming the brain parameters can predict cognition decently, and the original cognitive measure that you were predicting is related to your measure of fluid cognition, the answer should be yes. Upon reading the Methods, it became clear that the cognitive variable in the model predicting cognition using brain features (to get predicted cognition, or as the authors refer to it, brain-cognition) is the same as the measure of fluid cognition that you are trying to assess how well brain-cognition can predict. Assuming the brain parameters can predict fluid cognition at all, it is then inevitable that brain-cognition will predict fluid cognition. Therefore, it is inappropriate to use predicted values of a variable to predict the same variable.

- "However, Brain Age Gap created from the lower-performing age-prediction models explained a higher amount of variation in Cognitionfluid. For instance, the top performing age-prediction model, "Stacked: All excluding Task Contrast", generated Brain Age and Corrected Brain Age that explained the highest amount of variation in Cognitionfluid, but, at the same time, produced Brian Age Gap that explained the least amount of variation in Cognitionfluid" (p7). This is an inevitable consequence of the following relationship between predicted values and residuals (or residuals times -1): $y=(y-\hat{y})+\hat{y}$. Let's say that age explains 60% of the variance in fluid cognition, and predicted age ($\hat{y}$) explains 40% of the variance in

fluid cognition. Then the brain age gap (-(y-ŷ)) should explain 20% of the variance in fluid cognition. If by "Corrected Brain Age" you mean the modified predicted age from Butler et al (2021), the "Corrected Brain Age" result is inevitable because the modified predicted age is essentially just age with a tiny bit of noise added to it. From Figure 4, though, this does not seem to be the case, because the lower left quadrant in panel (a) should be flat and high (about as high as the predictive value of age for fluid cognition). So it is unclear how "Corrected Brain Age" is calculated. It looks like you might be regressing age out of brain-age, though from your description in the Methods section, it is not totally clear. Again, I highly recommend using the terminology and metrics of Butler et al (2021) throughout to reduce confusion. Please also clarify how you used the slope and intercept. In general, given how brain-age metrics tend to be calculated, the following conclusion is inevitable: "As before, the unique effects of Brain Age indices were all relatively small across the four Brain Age indices and across different prediction models" (p10).

"On the contrary, the unique effects of Brain Cognition appeared much larger" (p10). This is not a fair comparison if you do not look at the unique effects above and beyond the cognitive variable you predicted in your brain-cognition model. If your outcome measure had been another metric of cognition other than fluid cognition, you would see that brain-cognition does not explain any additional variance in this outcome when you include fluid cognition in the model, just as brain-age would not when including age in the model (minus small amounts due to penalization and out-of-sample estimates). This highlights the fact that using a predicted value to predict anything is worse than using the value itself.

"First, how much does Brain Age add to what is already captured by chronological age? The short answer is very little" (p12). This is a really important point, but the paper requires an in-depth discussion of the inevitability of this result, as discussed above.

"Third, do we have a solution that can improve our ability to capture Cognitionfluid from brain MRI? The answer is, fortunately, yes. Using Brain Cognition as a biomarker, along with chronological age, seemed to capture a higher amount of variation in Cognitionfluid than only using Brain Age" (p12). I suggest controlling for the cognitive measure you predicted in your brain-cognition model. This will show that brain-cognition is not useful above and beyond cognition, highlighting the fact that it is not a useful endeavor to be using predicted values.

"Accordingly, a race to improve the performance of age-prediction models (Baecker et al., 2021) does not necessarily enhance the utility of Brain Age indices as a biomarker for Cognitionfluid. This calls for a new paradigm. Future research should aim to build prediction models for Brian Age indices that are not necessarily good at predicting age, but at capturing phenotypes of interest, such as Cognitionfluid and beyond" (p13). I whole-heartedly agree with the first two sentences, but strongly disagree with the last. Certainly your results, and the underlying reason as to why you found these results, calls for a new paradigm (or, one might argue, a pre-brain-age paradigm). As of now, your results do not suggest that researchers should keep going down the brain-age path. While it is difficult to prove that there is no transformation of brain-age or the brain-age gap that will be useful, I am nearly sure this is true from the research I have done. If you would like to suggest that the field should continue down this path, I suggest presenting a very good case to support this view.